

Theme Issue Article

Bivalirudin

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Summary

Bivalirudin is a direct thrombin inhibitor (DTI) frequently used for anticoagulation in the setting of invasive cardiology, particularly percutaneous coronary intervention (PCI). Bivalirudin has a unique pharmacologic profile: unlike other marketed DTIs, it undergoes predominant non-organ elimination (proteolysis), and has the shortest half-life (~25 min). Its affinity for thrombin is intermediate between that of lepirudin (highest) and argatroban (lowest) — this helps explain why it interferes with functional clotting assays to an extent intermediate between that achieved by these two other DTIs. This effect is best known for the PT (INR) — higher affinity for thrombin corresponds to lower molar DTI requirements to prolong the APTT; in turn, lower concentrations required for APTT prolongation (and, presumably, in-vivo effect) result in reduced PT (INR) prolongation. Bivalirudin is primarily used for its first FDA-approved indi-

cation, namely anticoagulation during percutaneous transluminal coronary angioplasty ("balloon angioplasty"), the most frequent type of PCI. Bivalirudin is also indicated for PCI with provisional use of glycoprotein IIb/IIIa antagonist therapy, and for patients with, or at risk of, heparin-induced thrombocytopenia (HIT), or HIT with thrombosis syndrome (HITTS), undergoing PCI. The bivalirudin development program has used a "quadruple" endpoint comprising a "triple" efficacy endpoint plus major bleeding — this approach anticipated the subsequent emphasis on strategies to improve clinical outcomes through bleeding reduction. Besides summarizing the key trials evaluating bivalirudin use for acute coronary syndrome (especially employing PCI), we review also the studies of bivalirudin as anticoagulant for "on-" and "off-pump" cardiac surgery, including both HIT and non-HIT situations.

Keywords

Bivalirudin, direct antithrombin agents, direct thrombin inhibitors

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Bivalirudin

Bivalirudin is a direct thrombin inhibitor (DTI) that is frequently used for anticoagulation in the mainstream setting of invasive cardiology. This contrasts with the other three marketed DTIs, with their "niche" indication of heparin-induced thrombocytopenia (HIT) — lepirudin, argatroban — or with a minor role in a pharmaceutically competitive arena — desirudin for post-orthopedic surgery thromboprophylaxis.

Pharmacology

Bivalirudin (Angiomax, The Medicines Company, Parsippany, NJ, USA) is an oligopeptide analogue of hirudin, i.e. a "hirulog". However, it is only about one-third the size of hirudin (20 vs. 65 amino acids): it combines a carboxy-terminal segment of 12

amino acids (dodecapeptide) derived from native hirudin (residues 53–64, the fibrin[ogen] binding site, also known as exosite 1), to an active site-binding tetrapeptide sequence (d-Phe-Pro-Arg-Pro) at its amino-terminus; four glycine residues bridge these two segments together (Fig. 1) (1–3). Thus, like hirudin, bivalirudin is a *bivalent* DTI that binds specifically to thrombin at two sites, without the need for a cofactor. Its affinity for human thrombin ($K_i = 2$ nM) is intermediate between hirudin ($K_i = 0.0001$ nM) and the synthetic DTI, argatroban (40 nM) (4, 5). Whereas hirudin binding to thrombin is irreversible, the binding of bivalirudin to the active site of thrombin is transient. The molecular mass of bivalirudin is 2,180 Da.

Bivalirudin has important pharmacologic differences versus heparin. It inhibits thrombin irrespective of whether the thrombin is free in solution or bound to fibrin; in contrast, heparin binds fibrin-bound thrombin poorly. Bivalirudin also has low —

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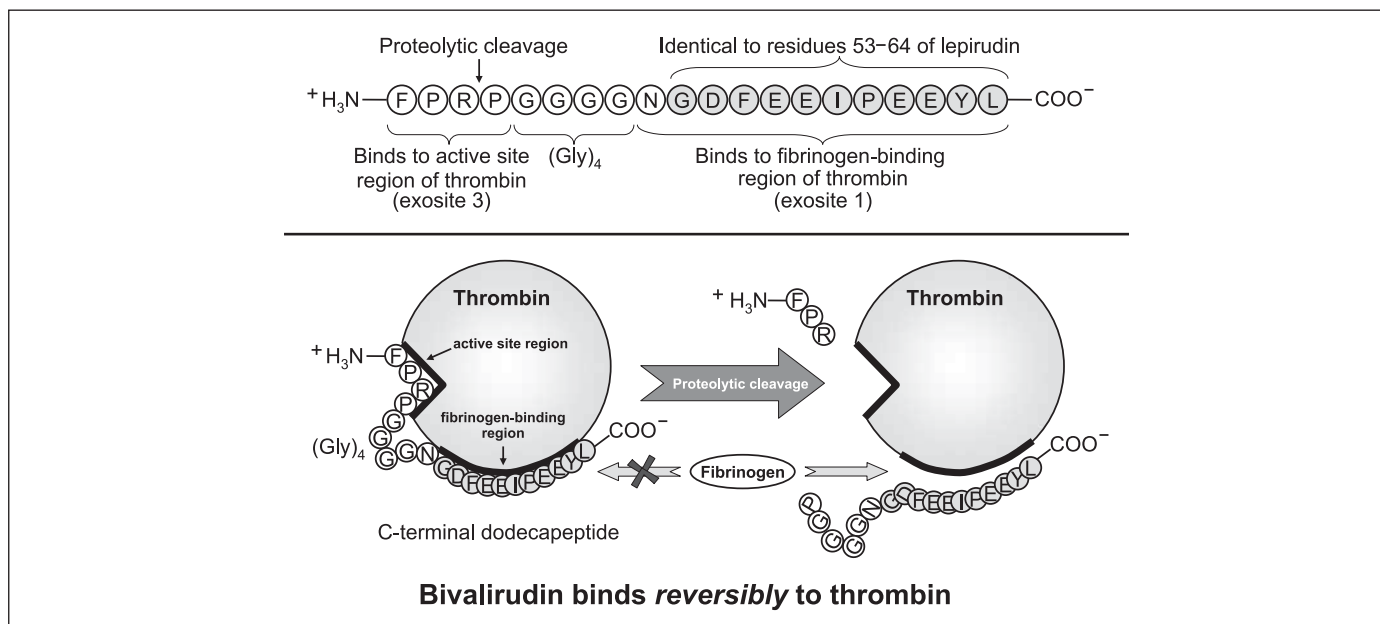


Figure 1: The structure of bivalirudin. Top: Bivalirudin is comprised of 20 amino acids, with an N- (amino-) terminal d-Phe-Pro-Arg-Pro (F-P-R-P) region that binds with high affinity to the active site region –(exosite 3) of thrombin; a (gly)₄ (G₄) “spacer” region; and a C- (carboxy-) terminal Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu dodecapeptide (N-G-D-F-E-E-I-P-E-E-Y-L) that binds to the fibrin(ogen)-binding region (exosite 1) of thrombin. The eleven C-terminal amino acids (shaded circles) correspond exactly to the 53–64 amino acid sequence of lepirudin. Highly-specific, non-competitive binding between bivalirudin and thrombin results. (Not shown is the heparin-binding region [exosite 2] of thrombin.) However, proteases such as thrombin cleave the Arg₃-Pro₄ of bivalirudin, leading to loss of antithrombin

activity. Bottom: Initially, there is bivalent binding of bivalirudin to thrombin, as shown. Following cleavage at Arg₃-Pro₄, the N-terminal sequence of bivalirudin no longer binds to thrombin, leaving the residual C-terminal dodecapeptide with greatly-reduced binding affinity for exosite 1 of thrombin. Thus, the bivalirudin remnant transforms to a competitive inhibitor of thrombin. Other substrates, e.g. fibrinogen, can compete with, and displace, bivalirudin, thus allowing thrombin to resume its prohaemostatic functions. Arg (R), arginine; Asn (N), asparagine; Asp (D), aspartic acid; Glu (E), glutamic acid; Gly (G), glycine; Ile (I), isoleucine; Leu (L), leucine; Phe (F), phenylalanine; Pro (P), proline; Tyr (Y), tyrosine. Reprinted with permission (3).

perhaps negligible – immunogenic potential; in contrast, immune HIT is a major drawback of heparin therapy. Bivalirudin also differs from the DTIs, hirudin and argatroban, with respect to route of elimination; whereas lepirudin is renally-excreted, and argatroban is excreted via hepatobiliary mechanisms, bivalirudin is predominantly excreted by a non-organ mechanism (proteolysis), with only a minor (20%) component of renal clearance. In addition, the half-life of bivalirudin (approximately 25 minutes [min]) is shorter than the other marketed DTIs (argatroban, 45 min; lepirudin, 80 min or greater).

The prothrombin time (PT)/international normalized ratio (INR), activated clotting time (ACT), activated partial thromboplastin time (APTT), and thrombin time (TT) all rise in a linear fashion with increasing doses of bivalirudin (6). Upon stopping bivalirudin infusion, its anticoagulant effects reverse rapidly, with coagulation times approaching baseline within 1 to 2 hours (h) after stopping the infusion. The ACT is generally used to confirm that bivalirudin has been received during interventional cardiology, as well as for monitoring during cardiac surgery. In contrast, the APTT has been used for monitoring in patients treated for HIT. In this situation, the target APTT generally is a 1.5– to 2.5-fold increase in the patient’s baseline APTT (3). However, APTT monitoring may not be reliable if the patient has additional factors that can contribute to APTT prolongation (e.g. hepatic dysfunction, warfarin administration, severe HIT-associ-

ated disseminated intravascular coagulation [DIC]), non-specific inhibitor, and so forth).

Among the commercially-available DTI’s, the prolongation of the INR by bivalirudin is intermediate between that seen with lepirudin (lowest) and that of argatroban (highest) (4, 5) (Fig. 2). Notably, the affinity of bivalirudin for thrombin is intermediate between that of lepirudin (highest) and argatroban (lowest) – this helps explain why bivalirudin interferes with functional clotting assays to an extent intermediate between that achieved by these two other DTIs. This effect is best known for the PT (INR) – higher affinity for thrombin corresponds to lower (molar) DTI requirements to prolong the APTT; in turn, lower (molar) concentrations required for APTT prolongation (and, presumably, for in-vivo effect) result in reduced INR prolongation (4). These effects are particularly evident in critically ill patients, as DTI levels tend to be higher (due to reduced drug elimination), and concomitant reductions in coagulation factor levels (e.g. due to liver dysfunction or consumptive coagulopathies) are common.

Bivalirudin is administered by intravenous (i.v.) route, and produces a rapid anticoagulant effect. It has an average volume of distribution of 0.24 l/kg, i.e. the majority of bivalirudin distributes extracellularly. Its rapid plasma clearance rate (~4 ml/min/kg) greatly exceeds average glomerular filtration rate (~1.0–1.7 ml/min/kg), reflecting its dual clearance by proteolysis (~80%) and kidneys (~20%) (6, 7). The half-life of bivaliru-

din in severe renal dysfunction is prolonged to about 1 h, and in the setting of dialysis-dependent renal failure, the half-life approaches 4 h; thus, patients with renal insufficiency require lower initial bivalirudin dosing and more frequent anticoagulant monitoring. This approximate eight-fold increase in the half-life of bivalirudin (and corresponding approximate eight-fold decrease in its initial infusion rate) in the setting of dialysis-dependent renal failure contrasts with the 100-fold increase in half-life (and 100-fold decrease in the initial infusion rate) seen with hirudin.

Reversal

There is no specific antidote for bivalirudin. Mechanical devices including haemodialysis, haemofiltration, and plasmapheresis can remove significant amounts of bivalirudin (especially, when compared with lepirudin) (8), and may be helpful in some situations of overdosing.

Clinical use of bivalirudin

Bivalirudin is primarily used for its first FDA-approved indication, namely anticoagulation during percutaneous transluminal coronary angioplasty (PTCA, or "balloon angioplasty"), the most frequent type of percutaneous coronary intervention (PCI), and a procedure that has been performed since 1977 (9). Bivalirudin is also indicated for PCI with provisional use of glycoprotein (GP) IIb/IIIa antagonist therapy, and for patients with, or at risk of HIT (or HIT with thrombosis syndrome [HITTS]) undergoing PCI. (In Canada, bivalirudin is also indicated for patients with, or at risk of HIT/HITTS, undergoing cardiac surgery.)

Bivalirudin has also been evaluated for non-interventional treatment of acute coronary syndrome (ACS) and myocardial infarction (MI), as well as for anticoagulation during cardiac surgery, both for "routine" use as well as in situations where heparin therapy is contraindicated. Treatment and prevention of thrombosis complicating HIT is another evolving clinical application. This section will discuss primarily the efficacy of bivalirudin in PTCA and other PCI procedures (e.g. stenting), as well as certain

"off-label" situations, including interventional management of ACS/MI and cardiac surgery (both "off-" and "on-pump"). We will also discuss use of bivalirudin for treatment of acute HIT, including specialized situations such as cardiac surgery and PCI. We will not discuss use of bivalirudin in other clinical situations, such as non-interventional treatment of ACS/MI, peripheral percutaneous interventions (PPI), and the prevention and treatment of venous thromboembolism.

Percutaneous coronary intervention (PCI)

The first report describing use of bivalirudin during cardiac catheterization employing angioplasty appeared in 1993, and represented a multicenter, open-label, dose-finding trial of 279 patients undergoing this procedure (10). Efficacy appeared greatest at the highest doses employed, and subsequently, an even higher dose regimen (bolus, 1.0 mg/kg; infusion, 2.5 mg/kg/h) was selected for subsequent study (11).

Bivalirudin was compared with unfractionated heparin (UFH) for patients requiring urgent angioplasty because of unstable angina, and who had not received thrombolytic therapy within the last 24 h. In this Hirulog Angioplasty Study (HAS), which reported on 4,098 patients who underwent angioplasty, bivalirudin (n=2,059) was given as an i.v. bolus (1.0 mg/kg), followed by a 4 h infusion at a rate of 2.5 mg/kg/h; thereafter, an additional infusion (at a rate of 0.2 mg/kg/h) for 14 to 20 h was given. The comparator, UFH (n=2,039), was given as an i.v. bolus of 175 U/kg, followed by an 18 to 24 h infusion at a rate of 15 U/kg/h. The primary endpoint was any of the following complications during hospitalization: death, MI, or abrupt vessel closure within 24 h of PCI, or rapid clinical deterioration of cardiac origin requiring bypass surgery, intra-aortic balloon pump use, or repeated PCI. In the original publication (12), the authors reported that – as compared with high-dose UFH – bivalirudin did not reduce significantly the incidence of the primary efficacy endpoint (11.4% vs. 12.2%; p=0.44) but lowered the incidence of major bleeding (3.8% vs. 9.8%; p<0.001). In a prospectively stratified cohort of 704 patients with post-infarction angina (a subset of HAS), bivalirudin resulted in a lower rate of the pri-

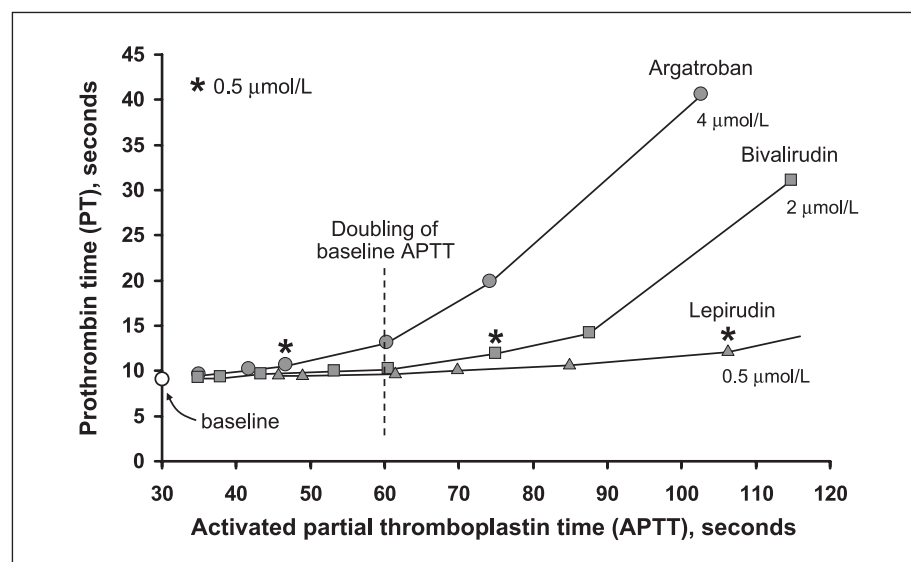


Figure 2: Prothrombin time (PT) versus activated partial thromboplastin time (APTT) relationship for three direct thrombin inhibitors (DTIs). Normal human plasma was supplemented with serial two-fold increases in the concentrations of each DTI. The asterisk (*) indicates the concentration of 0.5 µM for argatroban, bivalirudin, and lepirudin. For a two-fold increase in the APTT (the range shown by the vertical dotted line, i.e. a "therapeutic" concentration of DTIs), and higher, the DTIs differ considerably in their ability to prolong the INR, as follows: argatroban > bivalirudin > lepirudin. APTT, activated partial thromboplastin time; DTI, direct thrombin inhibitor; INR, international normalized ratio. Reprinted, with modifications, with permission (5).

mary efficacy endpoint (9.1% vs. 14.2%; $p=0.04$) and bleeding (3.0% vs. 11.1%; $p<0.001$) (12). These results, among other considerations, led the sponsor (Biogen) to cease further drug development.

Subsequently, the compound was transferred to The Medicines Company. A reanalysis of the trial data (13) was performed that included an additional 214 enrolled patients who had not undergone angioplasty, and who therefore had been excluded in the original per-protocol analysis, but who were now included (per intention-to-treat principle) in the subsequent report now comprising 4,312 subjects (4,098 + 214). The reanalysis was also based on contemporary definitions of adjudicated endpoints, and actuarial analysis with greater follow-up compliance. In this (renamed) Bivalirudin Angioplasty Trial (BAT), the frequencies of several important *secondary* endpoints were found to be significantly reduced with bivalirudin. For example, among all study patients, the composite endpoint (at day 7) of death, MI, or revascularization ("triple" efficacy endpoint) occurred in 6.2% of bivalirudin-treated patients, and 7.9% of UFH-treated patients ($p=0.039$). These differences were greater in the post-infarction angina cohort (4.9% vs. 9.9%; $p=0.009$). Further, major bleeding occurred in 3.5% of bivalirudin-treated patients, but 9.3% of heparin-treated patients ($p<0.001$). Thus, bivalirudin appeared to be at least as effective as heparin in preventing ischemic complications in patients who underwent angioplasty for unstable angina, but was associated with fewer episodes of major haemorrhage (14).

Based on this study, bivalirudin was approved by the FDA in the following dose regimen: an i.v. bolus dose of 1.0 mg/kg followed by a 4 h i.v. infusion at a rate of 2.5 mg/kg/h; after completion of the initial 4 h dose, an additional infusion could be initiated (rate, 0.2 mg/kg/h) for up to 20 h, if needed. In 2005, based upon subsequent studies, the approved dose was reduced to a smaller bolus (0.75 mg/kg) and a smaller infusion rate (1.75 mg/kg/h) given for the duration of the procedure, rather than for a 4 h period.

PCI in the glycoprotein IIb/IIIa antagonist era

Bivalirudin underwent subsequent evaluations to bring it into the contemporary era of stents, clopidogrel, and GPIIb/IIIa antagonist therapy. The pilot study, CACHET (Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial), also evaluated different bivalirudin regimens (15): phase A (bolus, 1.0 mg/kg; infusion, 2.5 mg/kg/h for 4 h), phase B (bolus, 0.50 mg/kg; infusion 1.75 mg/kg/h for duration of procedure), and phase C (bolus, 0.75 mg/kg; infusion, 1.75 mg/kg/h for duration of procedure). CACHET helped to identify the dosing regimen (phase C) that eventually became "standard". In addition, later phases of CACHET evaluated provisional ("rescue") abciximab use for indications such as coronary dissection, new or suspected thrombus formation, impaired or slow coronary flow, and distal embolization. Approximately 25% of bivalirudin-treated patients received abciximab on such a provisional basis. The efficacy endpoint was a composite ("triple" endpoint) of death, MI, or surgical/interventional revascularization by hospital discharge or within seven days of randomization (whichever came first). Whereas this endpoint was observed in none of 59 patients receiving the standard bivalirudin dosing regimen, it occurred in

6.4% of controls. When the three bivalirudin dosing regimens studied in phases A through C were pooled in a post-hoc analysis, bivalirudin was found to be significantly more effective than the heparin-treated controls when the "triple" efficacy endpoint was combined with major bleeding to produce a "quadruple" endpoint (3.4% vs. 10.6%; $p=0.018$). These pilot data prompted the subsequent evaluation of bivalirudin for PCI in much larger phase III trials.

In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-1 trial, heparin was compared to bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/h infusion) in patients undergoing elective or urgent PCI with any one of the GPIIb/IIIa inhibitors (72% use in both groups at the discretion of the physician) in 1,056 patients (16). Bivalirudin use was required only for the duration of the PCI procedure itself (although it could be given for up to 4 h post-procedure at the discretion of the investigator). The composite "triple" efficacy endpoint showed a non-significant reduction in bivalirudin-treated patients at 48 h (5.6% vs. 6.9%; $p=0.40$). A similar non-significant reduction in the "quadruple" endpoint (that included major bleeding) also favored bivalirudin (7.1% vs. 8.8%; $p=0.32$). These results set the stage for the subsequent large-scale study, REPLACE-2.

The REPLACE-2 trial was a double-blind RCT of 6,010 patients that compared bivalirudin ($n=2,999$) with provisional use of GPIIb/IIIa inhibition (administered to 7.2% of patients) or heparin with planned GPIIb/IIIa inhibition (abciximab or eptifibatid; $n=3,011$) given for anticoagulation during PCI (17). All patients received aspirin, and most also an ADP receptor antagonist (usually clopidogrel). The dosing of bivalirudin was the same as per REPLACE-1, and thus its administration was usually limited to the duration of the PCI procedure itself (median duration of bivalirudin infusion in REPLACE-2, 0.73 h).

The "quadruple" composite endpoint (death, MI, urgent repeat revascularization, or in-hospital major bleeding by 30 days) occurred in 9.2% of bivalirudin-treated patients and 10.0% of controls (odds ratio [OR] 0.92; 95% confidence interval [CI] 0.77–1.09; $p=0.32$). The secondary "triple" composite endpoint occurred in 7.6% of bivalirudin-treated patients, and 7.1% of controls (OR, 1.09; 95% CI, 0.90–1.32; $p=0.40$). Prespecified statistical criteria for non-inferiority to heparin plus GPIIb/IIIa blockade were met for each endpoint. In addition, significantly less major bleeding was observed in bivalirudin-treated patients, compared with controls (2.4% vs. 4.1%; $p<0.001$). As well, significantly fewer bivalirudin-treated patients developed a platelet count fall to below $100 \times 10^9/l$ (0.7 vs. 1.7%; $p<0.001$). Clopidogrel therapy did not influence the relative efficacy of bivalirudin versus UFH plus GPIIb/IIIa blockade, though it did reduce the primary (quadruple) endpoint in patients receiving bivalirudin (8.7% pretreatment vs. 12.9% no pretreatment; $p=0.0007$) (18). Thus, whereas clopidogrel pretreatment appeared to improve clinical outcomes without compromising safety, its use was not required for bivalirudin to achieve efficacy similar to UFH plus GPIIb/IIIa blockade.

The benefits of bivalirudin appear to be durable, as the 6-month and 1-year follow-up results of REPLACE-2 (19) found the incidences of death, MI, and repeat vascularization to be similar between the patient groups. Thus, long-term clinical out-

comes with bivalirudin and provisional GPIIb/IIIa blockade were comparable to that of heparin plus planned GPIIb/IIIa inhibition, with non-significant trends toward lower one-year mortality with bivalirudin present in all patient subgroups analyzed that were of greatest magnitude among high-risk patients. Further, a meta-analysis of the BAT, CACHET, REPLACE-1, and REPLACE-2 studies by Dr. John A. Bittl, reported in (2), showed that the use of bivalirudin significantly reduced the "triple" efficacy endpoint (OR, 0.87 [95% CI, 0.77–0.99]) and bleeding (OR, 0.42 [95% CI, 0.35–0.51]).

Acute coronary syndrome (ACS)—ACUITY Trial

Medical management of ACS typically includes a combination of ADP receptor antagonism (clopidogrel), GPIIb/IIIa receptor antagonism, and heparin (UFH or low-molecular-weight heparin [LMWH]). To determine whether bivalirudin – in conjunction with acute catheterization and urgent intervention – might provide further improvement over these strategies, the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial was performed (20). Unlike the REPLACE-2 patient population, which comprised mainly low-risk ACS patients, the ACUITY trial enrolled moderate- and high-risk ACS patients.

The ACUITY trial randomized 13,819 patients with ACS in whom early invasive strategy was planned (i.e. angiography within 72 h) to one of three therapies: (A) UFH or LMWH (enoxaparin) plus a GPIIb/IIIa inhibitor versus (B) bivalirudin plus a GPIIb/IIIa inhibitor versus (C) bivalirudin alone (with provisional GPIIb/IIIa inhibition). Bivalirudin was administered as a 0.1 mg/kg bolus, then 0.25 mg/kg/h infusion continued through angiography; if PCI was performed, then an additional bolus of 0.5 mg/kg was given, and the infusion increased to 1.75 mg/kg/h until end of procedure (with the option to continue bivalirudin at 0.25 mg/kg/h for up to 12 h at the discretion of the investigator). The primary study efficacy endpoint was a "composite ischemia endpoint" (death, MI, unplanned revascularization at 30 days) and the primary safety endpoint was major bleeding. These endpoints were also combined, yielding a "net clinical outcome endpoint".

The ACUITY trial found that bivalirudin plus a GPIIb/IIIa inhibitor, as compared with heparin plus a GPIIb/IIIa inhibitor, was associated with a non-inferior rate of the composite ischemic endpoint (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%, respectively), and the net clinical outcome endpoint (11.8% and 11.7%, respectively). Thus, the nominal decrease in bleeding events seen with bivalirudin plus a GPIIb/IIIa inhibitor offset the nominal increase in ischemic events, which resulted in a similar net clinical outcome endpoint (21). The main study conclusion, however, focused on the following result: bivalirudin alone, as compared with heparin plus a GPIIb/IIIa inhibitor, was also associated with a non-inferior rate of the composite ischemic endpoint (7.8% and 7.3%, respectively), but with a significantly reduced rate of major bleeding (3.0% vs. 5.7%; relative risk [RR] 0.53, 95% CI 0.43 to 0.65; $p < 0.001$), and a net clinical outcome endpoint (10.1% vs. 11.7%; $P = 0.02$; RR 0.86, 95% CI, 0.77 to 0.97; $p = 0.02$).

One caveat of the ACUITY study (21) was that the patients who received bivalirudin monotherapy, but not clopidogrel, had a trend to increased ischemic events compared with those treated with a GPIIb/IIIa antagonist. This was a prespecified subgroup

analysis, and the result suggests that patients treated with bivalirudin alone could benefit from pretreatment with clopidogrel prior to PCI (21).

In order to determine the optimum strategy for use of GPIIb/IIIa inhibitors, patients in the ACUITY trial also underwent a second randomization procedure, as follows (22). Patients assigned to receive GPIIb/IIIa inhibitors (groups A and B) were subrandomized (in a 2x2 factorial design) to upfront initiation of the GPIIb/IIIa antagonist (immediately after randomization), as compared with deferring GPIIb/IIIa inhibitor initiation for selective use in the catheterization laboratory starting immediately prior to PCI. The GPIIb/IIIa inhibitors allowed for upfront use were eptifibatid or tirofiban, whereas abciximab or eptifibatid could be used at PCI (all at the investigator's choice).

In total, 7,789 of the 13,918 patients in ACUITY underwent a PCI after angiography. Little effect was seen whether the GPIIb/IIIa inhibitor was given upstream versus whether its use was deferred. As in the main ACUITY trial, the rates of composite ischemia, major bleeding, and the net clinical outcome among the patients who underwent PCI did not differ significantly between those who received bivalirudin plus GPIIb/IIIa inhibitors versus those who received heparin plus a GPIIb/IIIa inhibitor. However, although rates of the composite ischemia endpoint were much the same in those who received bivalirudin alone versus those who received heparin plus GPIIb/IIIa inhibitors, there were significantly fewer patients who experienced major bleeding among those who received bivalirudin alone than among those who received heparin plus GPIIb/IIIa inhibitors (3.5% vs. 6.8%; RR 0.52, 95% CI 0.40–0.66; $p < 0.0001$). This was associated with a trend towards better 30-day net clinical outcomes (11.6 vs. 13.3; RR 0.87, 95% CI 0.75–1.00; $p = 0.057$). Although these findings mirrored those of ACUITY and REPLACE-2, they occurred here in a more complex patient population (23).

Impact of bleeding in mortality in ACS

In the bivalirudin development program, major bleeding was defined as intracranial or retroperitoneal haemorrhage, or clinically-overt bleeding resulting in a decrease in haemoglobin level by more than 3 g/dl, or clinically-overt bleeding leading to transfusion of two or more units of blood (15–17, 20); other criteria also defining major bleeding in specific trials included any decrease in haemoglobin level by more than 4 g/dl without an overt bleeding site (REPLACE-1 and -2, ACUITY), haemorrhage at the access site requiring intervention (ACUITY), hematoma with a diameter of at least 5 cm (ACUITY), reoperation for bleeding (ACUITY), or any transfusion of a blood product (ACUITY) (17, 20). Moreover, in the REPLACE-2 and ACUITY trials, major bleeding was assessed up until 25 to 35 days post-randomization (earlier studies had used shorter assessment periods), and also were prospectively assessed using TIMI criteria (17, 20).

The clinical relevance of reduced bleeding in patients receiving bivalirudin alone versus the control group (heparin plus GPIIb/IIIa inhibitor) should not be underestimated. An analysis from the ACUITY trial (24) showed that patients with major bleeding had a higher 30-day mortality rate compared with patients who did not have major bleeding (7.3% vs. 1.2%; $p < 0.0001$), and was an independent predictor of 30-day mortal-

ity (OR 7.55, 95% CI, 4.68 to 12.18; $p < 0.0001$). Similar findings were observed in a recent analysis (25) of data from REPLACE-2: patients with major bleeding had a higher 30-day mortality rate, compared with patients without major haemorrhage (5.1% vs. 0.2%; $p < 0.001$). This difference in mortality remained significant at 1 year (8.7% vs. 1.9%; $p < 0.001$). Furthermore, major haemorrhage was an independent predictor of 1-year mortality (OR 2.66, 95% CI, 1.44 to 4.92; $p = 0.002$).

In this context, it is worth noting that the issue of major bleeding and increased mortality was also evident in an randomized controlled trial (RCT) comparing (low-dose) fondaparinux with (therapeutic-dose) enoxaparin for the treatment of ACS. In that study, the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) (26), a higher major bleeding rate with enoxaparin appeared to explain the higher mortality rate among patients receiving enoxaparin. Nevertheless, it remains an open question to what extent the advantages of avoiding bleeding with bivalirudin monotherapy are offset by potential compromise in therapeutic efficacy, particularly in certain high-risk patients. Indeed, it is important to point out that the lower mortality rate seen with fondaparinux (vs. enoxaparin) in the treatment of ACS was not mirrored in any of the bivalirudin trials to date, despite the consistent reduction in major bleeding seen with bivalirudin monotherapy.

Cardiac surgery (non-HIT settings)

Bivalirudin has been studied for intraoperative anticoagulation during cardiac surgery, both for surgery utilizing cardiopulmonary bypass (CPB), as well as "off-pump" coronary artery bypass graft (OPCAB) surgery. The rationale for using bivalirudin for anticoagulation during cardiac surgery (2) includes: its relatively short half-life (~25 min); its largely organ-independent clearance, its direct inhibition of thrombin without need for a cofactor (thus, avoiding potential for heparin "resistance" due to congenital or acquired antithrombin deficiency); its rapid, dose-dependent effect; its lack of structural similarity to heparin (thus, avoidance of HIT); no need for protamine (thus avoiding its adverse effects); and no need for dose reduction in settings of mild or moderate renal dysfunction.

In the first RCT involving OPCAB surgery, bivalirudin revealed comparable results with regard to safety (especially perioperative blood loss and transfusion requirements) and efficacy, with less graft occlusion versus UFH (with protamine reversal) (27), suggesting the possibility of superior graft patency due to more effective thrombus prevention within nascent sutured grafts (28). Subsequently, four prospective evaluations were performed evaluating bivalirudin for anticoagulation during cardiac surgery (29–32). Two studies (EVOLUTION-ON and -OFF) involved CPB and OPCAB surgery, respectively, in patients who did not have contraindications to use of UFH, whereas the other two studies (CHOOSE-ON and -OFF) included patients in whom heparin was considered contraindicated because of acute or previous HIT, or because of the presence of anti-PF4/heparin antibodies. The acronym, "EVOLUTION", denotes Evaluation of Patients during coronary artery bypass graft Operations: Linking Ut ilization of bivalirudin to Improved Outcomes and New anticoagulant strategies; in contrast, "CHOOSE" refers to CABG HIT/TS On- and Off-Pump Safety and Efficacy (33).

The four clinical situations evaluated in the two EVOLUTION and two CHOOSE studies differ considerably. For example, during CPB surgery, anticoagulation must be sufficient not only for the surgical procedure itself but also for inhibiting contact activation triggered by the large non-endothelial surfaces of the CPB apparatus as well as by the reinfusion of tissue factor-enriched blood aspirated from the operative field. Also, the hypercoagulability state of patients with acute HIT, and the comorbidities often encountered in this special patient population, may adversely affect outcomes compared with non-HIT patients (although relatively few patients in the CHOOSE studies actually had acute HIT).

Off-pump coronary artery bypass surgery

As already noted, Merry et al. (27) compared bivalirudin to UFH for OPCAB surgery in a semi-open label (surgeon-blinded) prospective study of 100 patients (half receiving bivalirudin). Dosing was identical to that currently used in PCI (0.75 mg/kg bolus with intraoperative infusion at 1.75 mg/kg/h). The target ACT was a minimum of 300 seconds (s). This regimen was employed because it results in bivalirudin concentrations during OPCAB between 7–10 µg/ml (3.2–4.6 µM); a minimum level of 6.5 µg/ml is believed to be the threshold for preventing thrombosis during PCI (34). The primary endpoint was 12 h blood loss, and secondary endpoints were ischemic complications and coronary artery patency at 12 weeks. No deaths were reported. Although the ACT took longer to return to normal after stopping bivalirudin, compared to UFH (with protamine reversal), total blood loss was similar in both groups, however. An intriguing finding was that graft patency (by angiography reviewer-blinded assessment) was improved in the patients receiving bivalirudin.

The EVOLUTION-OFF study was an open-label, multicenter, phase III study of OPCAB involving non-HIT patients (29). Of the 157 study patients, 105 received bivalirudin, and 52 received heparin with protamine reversal (2:1 randomization). Bivalirudin dosing was 0.75 mg/kg bolus and 1.75 mg/kg/h for the duration of the procedure, with the option to increase/decrease the infusion (by 0.25 mg/kg/h), or to administer additional boluses (from 0.1 to 0.5 mg/kg) if the ACT fell below 300 s. The primary efficacy endpoint – acute procedural success (defined as absence of death, Q-wave MI, repeat coronary revascularization, and stroke at day 7 or discharge, whichever came first) – occurred in 93% of patients in both study groups. No other significant differences occurred, although the frequency of stroke was somewhat greater (5.5% vs. 0%) in the heparin group. Total blood loss and reoperations for bleeding were not significantly different.

On-pump cardiac surgery

Koster and colleagues performed a pilot study of 20 patients (6 with moderate renal dysfunction) who underwent bivalirudin anticoagulation for normothermic CPB (35). A commercial device to measure the ecarin clotting time (ECT) intraoperatively was used to target bivalirudin to a concentration of 10–15 µg/ml, which corresponded to an ECT range of 400–500 s (36). Bivalirudin was administered as an i.v. bolus dose (1.5 mg/kg) and initial i.v. infusion of 2.5 mg/kg/h, plus 50 mg into the pump prime. Additional intraoperative bivalirudin boluses (0.25 mg/kg) and/or adjustments of 0.25 mg/kg/h in the infusion were permitted to

maintain the target ECT. The primary endpoint (death, Q-wave MI, need for revascularization, or stroke during hospitalization) occurred in two of 20 patients (10%), both non-fatal MIs. Median total (12 h) blood loss was 700 ml; 60% of patients received blood products. No patient required reoperation for persistent bleeding. The ECT remained above 400 s, and mean bivalirudin concentrations during CPB were approximately 16 µg/ml. Use of zero-balanced ultrafiltration lowered the elimination half-life of bivalirudin from about 35 min to 24 min. This pilot study demonstrated clinical feasibility of bivalirudin anticoagulation for CPB.

In view of the high bivalirudin concentrations achieved in this pilot study, and the predictable and stable concentrations observed throughout CPB, a second pilot study was performed to evaluate an even simpler regimen (37). In this 10-patient study, the initial pre-CPB bolus was reduced (to 1.0 mg/kg); the dose of bivalirudin (50 mg) added to the pump prime was unchanged. A constant fixed-dose i.v. infusion of bivalirudin was commenced as before (2.5 mg/kg/h), except that no intraoperative adjustments were made (however, rebolusing at 0.1–0.5 mg/kg was allowed to maintain the ECT value above 400 s). As before, the bivalirudin infusion was discontinued 15 min before expected separation from CPB. In all 10 patients, the target bivalirudin concentration was maintained, despite the use of a simpler, constant infusion rate. Moreover, the study showed that the bivalirudin, when used with a closed CPB system and without cardiomy suction, effectively attenuated haemostatic activation during CPB, based on measurements of fibrin d-dimer, prothrombin fragment 1+2, and thrombin-antithrombin complexes, thus demonstrating the effectiveness of the current dosing protocol for anticoagulation during CPB surgery.

Technical considerations

Unlike heparin, bivalirudin undergoes progressive enzymic metabolism, leading to reactivation of thrombin. Thus, bivalirudin-anticoagulated blood that lies stagnant (i.e. without ongoing source of bivalirudin) will eventually clot (38). Thus, clotting of stagnant blood (e.g. in pericardial spaces) does *not* indicate lack of adequate systemic anticoagulation, but rather ongoing metabolism of bivalirudin in pooled blood. The cardiac surgical/anaesthesiology/perfusionist team that is planning to utilize bivalirudin for cardiac surgery is urged to consult literature regarding the technical issues relating to the safe use of this anticoagulant during cardiac surgery, particularly when utilizing CPB (2, 32, 33).

Based on the two aforementioned pilot studies, the EVOLUTION-ON study for CPB was designed using the protocol shown in Table 1 (30, 38). Twenty-one institutions enrolled 101 patients randomized to bivalirudin and 49 to heparin with protamine reversal (2:1 randomization). In this small RCT, no significant difference in the primary endpoint of acute procedural success (absence of death, Q-wave MI, stroke, repeat coronary revascularization) was seen: 94.9% (bivalirudin) versus 96.2% (heparin/protamine) at 7-day follow-up. There was greater early postoperative blood loss with bivalirudin (median at 2 h, 238 vs. 160 ml; $p=0.0009$) and a numerically higher rate of reoperation for bleeding (5.1% vs. 1.9%; $p=0.67$), but an offsetting tendency to less perioperative non-Q-wave MI (5.1% vs. 9.6%; $p=0.32$). These data at least suggest the possibility that bivalirudin is a plausible candidate eventually to displace heparin from its half-century dominance in the cardiac operating suite (39).

Initial bivalirudin dosing (pre-CPB)	
Initial i.v. bivalirudin bolus:	1.0 mg/kg
and begin continuous i.v. infusion:	2.5 mg/kg/h (42 µg/kg/min)
Bivalirudin added to pump circuit:	50 mg
Target anticoagulant monitoring*:	At least 2.5-times baseline ACT, using either the ACT-Kaolin (Hemochron®), ACT-Plus®, ACT-T (International Technidyne), or ECT
If subtherapeutic ACT (or ECT):	give additional bolus (0.1–0.5 mg/kg)
Bivalirudin dosing and monitoring while on CPB	
Continue fixed-rate i.v. infusion:	2.5 mg/kg/h until 15 min prior to expected separation from CPB (if CPB <i>not</i> terminated in 20 min, then an additional 0.5 mg/kg bolus is given, and infusion at 2.5 mg/kg/h is restarted)
Frequency of anticoagulant monitoring:	every 15–30 min
If subtherapeutic ACT (or ECT):	give additional bolus (0.1–0.5 mg/kg)
Special steps at end of CPB	
Stop bivalirudin infusion 15 min prior to expected separation from CPB, then:	
Promptly (within 10 min) empty pump volume into cell saver** (replacing with crystalloid, e.g., sodium citrate), thus avoiding need for post-separation bivalirudin boluses to circuit; process blood for reinfusion with cell saver to remove bivalirudin; Or, <i>Alternative approach used by author [AK]</i> : After separation from CPB, promptly reconnect arterial and venous lines, clamp out arterial filter, give residual blood to the patient, refill the CPB with saline, recirculate, add 50 mg bivalirudin, and thereafter start a continuous infusion at 50 mg/h into the circuit. Later, this volume may be processed by cell saver (for reinfusion) or discarded.	
*The minimum target bivalirudin concentration (~10 µg/ml) corresponds approximately to the minimum threshold levels (>2.5-times baseline) for the 4 different monitoring assays listed above. **The Evolution-ON study protocol required the use of a cell saver.	

Table 1: Protocol for bivalirudin anti-coagulation during CPB (EVOLUTION-ON trial). Reprinted, with modifications, with permission (38).

Heparin-induced thrombocytopenia (HIT)

Off-label use of bivalirudin to treat HIT began with the report of Chamberlin et al. (40) describing this treatment in three patients with acute HIT. A subsequent report (41, 42) described 39 patients with HIT treated with bivalirudin, 17 of whom had acute HIT, the remainder with previous HIT. Four patients died due to complications of HIT, suggesting these deaths occurred among the subgroup with acute, rather than previous, HIT. Dosing depended upon the clinical situation, which most often was PCI (n=17) and thrombosis (including DVT or PE; n=10); one (non-PCI) regimen consisted of an optional initial i.v. bolus (1.0 mg/kg) with i.v. infusion starting at 0.25 mg/kg/h.

Francis et al. (43) presented their experience using bivalirudin to treat 52 patients with suspected HIT (82.6% of patients with positive enzyme immunoassay [EIA]). Initial bivalirudin infusion rates (without starting bolus) usually ranged from 0.15 to 0.20 mg/kg/h; the overall mean infusion rate was about 0.165 mg/kg/h, with the target APTT a 1.5- to 2.5-fold prolongation of the baseline value. Bivalirudin was given for a mean of 8.0 days, with transition to warfarin (mean overlap, 5 days) performed in 44 of 52 patients. The authors noted minimal increase in the INR on bivalirudin alone (mean increase, 0.33). Minor bleeding was seen in only a few patients. Antithrombotic efficacy was believed by the authors to be acceptable, but detailed results were not presented.

The issue of INR prolongation during DTI therapy is of clinical relevance because during overlapping DTI-coumarin (warfarin) therapy, there is the potential for provoking warfarin-associated microthrombosis (e.g. venous limb gangrene syndrome) during treatment of HIT-associated deep vein thrombosis (DVT), if warfarin is prematurely initiated and/or the DTI is prematurely discontinued (44).

Two recent retrospective studies evaluated use of bivalirudin for management of clinically-suspected HIT. Both studies focused on intensive care unit (ICU) patients, as this patient population may be ideally suited for bivalirudin, given its clearance largely independent of specific organ function. One study performed at the University of Colorado Health Sciences Center (Denver, CO, USA) reported 18 patients with clinically-diagnosed HIT in the ICU setting (45). All patients had either hepatic dysfunction (n=4) or renal compromise (n=2) or both (n=12). Only six of 15 patients tested positive in the EIA (none underwent testing by serotonin release assay [SRA]), and just four had thrombosis preceding bivalirudin therapy, indicating that most patients likely did not have HIT. The median dose of bivalirudin required to obtain a therapeutic aPTT was 0.05 mg/kg/h, although the dose requirement was somewhat greater (~0.15 mg/kg/h) among the four patients with isolated hepatic dysfunction. The mean (\pm SD) INR value increased from 1.4 ± 0.3 to 2.2 ± 0.8 during bivalirudin treatment. No patients had clinically significant bleeding, and only one patient had thrombosis progression while receiving bivalirudin.

A report by Dang et al. (46) from the Medical University of South Carolina (Charleston, SC, USA) evaluated 42 patients with clinically diagnosed HIT or a history of HIT requiring anticoagulation, of whom 24 patients were treated with bivalirudin (half with combined hepatic and renal dysfunction); the remaining patients were treated with argatroban (n=13) and lepirudin

(n=5). Only eight of the 24 bivalirudin-treated patients had a positive EIA for PF4-dependent antibodies. The median time to reaching a therapeutic aPTT in the bivalirudin-treated patients was 8.5 h. Fourteen (58%) of the bivalirudin patients were reported as having "major bleeding". Seven thrombosis-associated events (DVT, MI, stroke, amputation) occurred, but whether these occurred in seven or fewer patients (due to multiple events) was not clear, as well as the timing of thrombosis in relation to heparin and subsequent bivalirudin therapy. Information on bivalirudin dosing was not provided.

In summary, although bivalirudin is a promising therapy for treatment of acute HIT, no studies have employed a comparator group of non-bivalirudin-treated patients. Further, its preferential use in the critically-ill (a setting where thrombocytopenia is usually explained by non-HIT factors) and the failure to document HIT (through use of high-quality laboratory assays for HIT antibodies) means that its efficacy and safety in HIT remains conjectural.

PCI and HIT

The Anticoagulant Therapy with Bivalirudin to Assist in the Performance of PCI in patients with Heparin-induced Thrombocytopenia (ATBAT) trial evaluated by prospective, open-label methodology the safety and efficacy of bivalirudin in patients with a "new diagnosis of HIT" (n=19), or a past history of HIT (n=33), undergoing PCI (47). The initial dosing regimen (bolus, 1.0 mg/kg; infusion, 2.5 mg/kg/h for 4 h) was later changed to reflect dosing in non-HIT patients (bolus, 0.75 mg/kg; infusion, 1.75 mg/kg/h for 4 h). The primary efficacy endpoint was defined as procedural success (<50% stenosis) and clinical success without death, emergency bypass surgery, or Q-wave MI. The primary safety endpoint was major bleeding within 48 h after completion of bivalirudin. Only one of 52 patients required a blood transfusion (1 U) and procedural and clinical success were achieved in 98% and 96% of the patients, respectively. There were no abrupt closures, nor was thrombus formation reported during or after PCI. One patient died of cardiac arrest about 46 h after successful PCI.

HIT and cardiac surgery

Bivalirudin has been used off-label for cardiac surgery in a number of patients with acute or previous HIT. Both on- and off-pump use has been reported.

Off-pump coronary artery bypass surgery

Although some anecdotal experience using bivalirudin for OPCAB surgery in patients with putative HIT has been reported (48), the main published experience is in the CHOOSE-OFF study (31), an open-label, multicenter trials that enrolled 51 patients. However, only five patients had a diagnosis of "HIT and thrombosis", with most patients in the trial included because of positive antibody status. Bivalirudin dosing was as per EVOLUTION-OFF. The primary study endpoint was in-hospital procedural success (absence of death, MI, stroke, or repeat revascularization by postoperative day 7 or hospital discharge, whichever occurred first). Procedural success was seen in 47 of 51 (92%) patients (3 patients had MI, 1 had stroke). Blood transfusion (to day 7/discharge) was administered to 53% of study pa-

tients, and two patients required reexploration for persistent haemorrhage.

On-pump cardiac surgery

Several patients have been reported anecdotally as having received bivalirudin for CPB in the context of previous HIT (36, 49–55) or heparin allergy (56). None of the patients appeared to have had acute HIT when cardiac surgery was performed, although at least four patients had subacute HIT (i.e. platelet count recovery but residual positive test for anti-PF4/heparin antibodies) at the time of surgery (52–55). Except for one early study (36) reporting use of the ECT, all used an ACT for monitoring of bivalirudin. In some cases, excess bleeding and/or need for blood transfusions were observed. No deaths were reported.

CHOOSE-ON, an open-label, multicenter trial, enrolled 50 patients with confirmed or suspected HIT and/or presence of anti-PF4/heparin antibodies for bivalirudin anticoagulation during CPB. As in CHOOSE-OFF, the primary study endpoint was in-hospital procedural success (absence of death, Q-wave MI, stroke, or repeat revascularization by postoperative day 7 or hospital discharge, whichever occurred first). Procedural success was achieved in 46 (94%) of 49 patients who received bivalirudin for CPB. Most (83.7%) of patients required one or more blood products by day 7. A limitation of the study is that the number of patients with acute HIT or those in whom functionally-active antibodies were still present at the time of surgery was not reported.

To date, no anticoagulant other than UFH is approved for use during cardiac surgery. In the special situation of acute HIT – where UFH use is contraindicated – a number of different non-heparin anticoagulants (e.g. lepirudin, argatroban, danaparoid) or modified heparin-containing protocols (UFH plus the short-acting platelet GPIIb/IIIa antagonist, tirofiban; or UFH plus a prostacyclin analogue, iloprost or epoprostenol) have been employed, sometimes with severe complications, particularly bleeding. The CHOOSE (and parallel EVOLUTION studies) were the first clinical investigations assessing an alternative anticoagulant for HIT patients requiring cardiac surgery. Although comparative data are lacking, bivalirudin appears to be the main alternative strategy with a reasonable safety profile in this special situation (57). For patients with a previous history of HIT in whom antibodies subsequently become undetectable or lack biological activity, use of heparin at CPB is another important option (57).

Safety and tolerability

Bleeding is the major adverse effect of bivalirudin, and occurs more commonly in patients with renal impairment. In the Hirulog Angioplasty Study (HAS), the most frequent adverse effects included back pain, nausea, hypotension, pain, and headache. Ap-

proximately 5–10% of patients reported insomnia, hypertension, vomiting, anxiety, dyspepsia, bradycardia, abdominal pain, fever, nervousness, pelvic pain and pain at the injection site (12, 58).

No evidence of fetal harm has been ascribed to bivalirudin in animal teratogenicity studies. However, well-controlled studies in pregnant women are lacking. Caution is advised when giving bivalirudin to nursing women, as it is not known whether bivalirudin crosses the placenta, or whether it is excreted in breast milk.

Antibivalirudin antibodies and allergic reactions

Bivalirudin is a relatively small polypeptide and may therefore have minimal antigenicity. In a study of plasma samples from seven patients, no evidence for antibody formation (IgG, IgM, or IgE) was found with plasma samples obtained at days 7 and 14 after i.v. administration (6). Further, no evidence for changes in the pharmacokinetics or pharmacodynamics of bivalirudin was seen over time.

In another review of 494 bivalirudin-treated patients from nine different studies, 11 subjects initially tested positive for antibivalirudin antibodies (59). However, nine of these were found to be false positives on repeat testing. The remaining two (who could not be retested) did not develop any anaphylactic or other allergic reactions. In clinical trials of bivalirudin performed from 1993 to 1995, only one of 3,639 patients (0.03%) experienced an allergic reaction considered by the investigator to be related to study drug. This experience differs somewhat from that described using lepirudin, in which several fatal post-bolus anaphylactic reactions have been reported, usually in a setting of re-exposure following recent use (60). However, it remains possible that longer duration therapy with bivalirudin might be associated with risk of anaphylaxis with drug reexposure.

Since bivalirudin shares an 11-amino acid sequence with hirudin, it is at least theoretically possible that patients with anti-lepirudin antibodies resulting from treatment with lepirudin could cross-react with bivalirudin. Eichler et al. (61) found that 22 of 43 (51%) sera containing antilepirudin antibodies showed reactivity *in vitro* against bivalirudin. This suggests that if bivalirudin is used in patients previously treated with lepirudin, extra caution should be used, e.g. careful anticoagulant monitoring as antilepirudin antibodies sometimes influence pharmacokinetics.

Conclusion

Bivalirudin is an oligopeptide DTI with unique and favorable pharmacologic features. It is widely used in the setting of invasive cardiology (particularly PCI), where it offers similar anti-thrombotic efficacy but lower bleeding rates compared with other therapies. It is also suitable for off-label use in certain specialized situations, such as cardiac surgery in a patient in whom heparin therapy is contraindicated because of HIT.

References

1. Maraganore JM, et al. Design and characterization of hirulogs: a novel class of bivalent peptide inhibitors of thrombin. *Biochemistry* 1990; 29: 7095–7101.
2. Warkentin TE, Koster A. Bivalirudin: a review. *Expert Opin Pharmacother* 2005; 6: 1349–1371.
3. Bartholomew JR. Bivalirudin for the treatment of heparin-induced thrombocytopenia. In: *Heparin-Induced Thrombocytopenia*, 4th edn. New York: Informa Healthcare USA, Inc.; 2007: 409–439.
4. Warkentin TE, et al. Differences in the clinically effective molar concentrations of four direct thrombin inhibitors explain their variable prothrombin time prolongation. *Thromb Haemost* 2005; 94: 958–964.

5. Warkentin TE. Bivalent direct thrombin inhibitors. *Best Pract Res Clin Haematol* 2004; 17: 105–125.
6. Fox I, et al. Anticoagulant activity of HirulogTM, a direct thrombin inhibitor, in humans. *Thromb Haemost* 1993; 69: 157–163.
7. Robson R. The use of bivalirudin in patients with renal impairment. *J Invasive Cardiol* 2000; 12 (Suppl F): 33F–36F.
8. Koster A, et al. An assessment of different filter systems for extracorporeal elimination of bivalirudin: an in vitro study. *Anesth Analg* 2003; 96: 1316–1319.
9. Gruentzig AR. Seven years of coronary angioplasty. *Z Cardiol* 1984; 73 (Suppl 2): 159–160.
10. Topol EJ, et al. Use of a direct antithrombin, hirulog, in place of heparin during coronary angioplasty. *Circulation* 1993; 87: 1622–1629.
11. Bittl JA. Bivalirudin for percutaneous coronary interventions: development perspective. *J Invasive Cardiol* 2000; 12 (Suppl F): 2F–6.
12. Bittl JA, et al. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. *N Engl J Med* 1995; 333: 764–769.
13. Bittl JA, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J* 2001; 142: 952–959.
14. Antman EM, Braunwald E. A second look at bivalirudin. *Am Heart J* 2001; 142: 929–931.
15. Lincoff AM, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CA-CHET). *Am Heart J* 2002; 143: 847–853.
16. Lincoff AM, et al.; for the REPLACE-1 investigators: Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduce Clinical Events [REPLACE]-1 trial). *Am J Cardiol* 2004; 93: 1092–1096.
17. Lincoff AM, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *J Am Med Assoc* 2003; 289: 853–863.
18. Saw J, et al. Lack of clopidogrel pretreatment effect on the relative efficacy of bivalirudin with provisional glycoprotein IIb/IIIa blockade compared to heparin with routine glycoprotein IIb/IIIa blockade. A REPLACE-2 substudy. *J Am Coll Cardiol* 2004; 44: 1194–1199.
19. Lincoff AM, et al.; for the REPLACE-2 investigators: Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization. *J Am Med Assoc* 2004; 292: 696–703.
20. Stone GW, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355: 2203–2216.
21. Bittl JA. Accounting for ACUITY. *N Engl J Med* 2006; 355: 2249–2250.
22. Stone GW, et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007; 369: 907–919.
23. Waksman R. ACUITY-PCI: one drug does not fit all. *Lancet* 2007; 369: 881–882.
24. Manoukian SV, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes. *J Am Coll Cardiol* 2007; 49: 1362–1368.
25. Feit F, et al. Predictors and impact of major haemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. *Am J Cardiol* 2007; 100: 1364–1369.
26. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; 354: 1464–1476.
27. Merry AF, et al. Bivalirudin versus heparin and protamine in off-pump coronary artery bypass surgery. *Ann Thorac Surg* 2004; 77: 925–931.
28. Warkentin TE. Invited commentary. *Ann Thorac Surg* 2004; 77: 931.
29. Smedira NG, 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: 686–692.
30. Dyke CM, et al. A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. *J Thorac Cardiovasc Surg* 2006; 131: 533–539.
31. Dyke CM, et al. Off-pump coronary artery bypass with bivalirudin for patients with heparin-induced thrombocytopenia or antiplatelet factor four/heparin antibodies. *Ann Thorac Surg* 2007; 84: 836–840.
32. Koster A, et al. Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: results of the CHOOSE-ON trial. *Ann Thorac Surg* 2007; 83: 572–577.
33. Koster A, et al. Management of intraoperative anticoagulation in patients with heparin-induced thrombocytopenia undergoing cardiovascular surgery. In: *Heparin-Induced Thrombocytopenia*, 4th edn. New York: Informa Healthcare USA, Inc.; 2007: 487–502.
34. Merry AF. Bivalirudin, blood loss, and graft patency in coronary artery bypass surgery. *Semin Thromb Haemost* 2004; 30: 337–346.
35. Koster A, et al. Effectiveness of bivalirudin as a replacement for heparin during cardiopulmonary bypass grafting. *Am J Cardiol* 2004; 93: 356–359.
36. Koster A, et al. Bivalirudin monitored with the ecarin clotting time for anticoagulation during cardiopulmonary bypass. *Anesth Analg* 2003; 96: 383–386.
37. Koster A, et al. Assessment of haemostatic activation during cardiopulmonary bypass for coronary artery bypass grafting with bivalirudin: results of a pilot study. *J Thorac Cardiovasc Surg* 2005; 129: 1391–1394.
38. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg* 2003; 76: 2121–2131.
39. Warkentin TE. Anticoagulation for cardiopulmonary bypass: is a replacement for heparin on the horizon? *J Thorac Cardiovasc Surg* 2006; 131: 515–516.
40. Chamberlin JR, et al. Successful treatment of heparin-associated thrombocytopenia and thrombosis using Hirulog. *Can J Cardiol* 1995; 11: 511–514.
41. Campbell KR, et al. Bivalirudin in patients with heparin-induced thrombocytopenia undergoing percutaneous coronary intervention. *J Invasive Cardiol* 2000; 12 (Suppl F): 14F–19F.
42. Berkowitz SD. Bivalirudin in heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITS) patients. *Blood* 1999; 94 (Suppl 1): 101b Abstract.
43. Francis JL, et al. Successful use of bivalirudin in the treatment of patients suspected, or at risk of, heparin-induced thrombocytopenia. *Blood* 2004; 104 (Suppl): 105b Abstract.
44. Smythe MA, et al. Venous limb gangrene during overlapping therapy with warfarin and a direct thrombin inhibitor for immune heparin-induced thrombocytopenia. *Am J Hematol* 2002; 71: 50–52.
45. Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. *Pharmacotherapy* 2006; 26: 452–460.
46. Dang CH, et al. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. *Pharmacotherapy* 2006; 26: 461–468.
47. Mahaffey KW, et al. The Anticoagulant Therapy with Bivalirudin to Assist in the performance of percutaneous coronary intervention in patients with heparin-induced Thrombocytopenia (ATBAT) study: main results. *J Invasive Cardiol* 2003; 15: 611–616.
48. Bott JN, Reddy K, Krick S. Bivalirudin use in off-pump myocardial revascularization in patients with heparin-induced thrombocytopenia. *Ann Thorac Surg* 2003; 76: 1778.
49. Vasquez JC, et al. Anticoagulation with bivalirudin during cardiopulmonary bypass in cardiac surgery. *Ann Thorac Surg* 2002; 74: 2177–2179.
50. Davis Z, et al. Favorable outcome with bivalirudin anticoagulation during cardiopulmonary bypass. *Ann Thorac Surg* 2003; 75: 264–265.
51. Jabr K, et al. Plasma-modified ACT can be used to monitor bivalirudin (Angiomax[®]) anticoagulation for on-pump cardiopulmonary bypass surgery in a patient with heparin-induced thrombocytopenia. *J Extra Corpor Technol* 2004; 36: 174–177.
52. Clayton SB, et al. Cardiopulmonary bypass with bivalirudin in type II heparin-induced thrombocytopenia. *Ann Thorac Surg* 2004; 78: 2167–2169.
53. Baker T, et al. Anticoagulant monitoring techniques in a heparin-induced thrombocytopenia patient undergoing cardiopulmonary bypass using bivalirudin anticoagulant. *J Extra Corpor Technol* 2004; 36: 371–374.
54. Mann MJ, et al. Use of bivalirudin, a direct thrombin inhibitor, and its reversal with modified ultrafiltration during heart transplantation in a patient with heparin-induced thrombocytopenia. *J Heart Lung Transplant* 2005; 24: 222–225.
55. Wasowicz M, et al. Bivalirudin anticoagulation for cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. *Can J Anesth* 2005; 52: 1093–1098.
56. Pappalardo F, et al. Successful use of bivalirudin for cardiopulmonary bypass in a patient with heparin allergy. *Perfusion* 2007; 22: 67–69.
57. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126 (3 Suppl.): 311S–337S.
58. Sciulli TM, Mauro VF. Pharmacology and clinical use of bivalirudin. *Ann Pharmacother* 2002; 36: 1028–1041.
59. Berkowitz SD. Antigenic potential of bivalirudin. *Blood* 1999; 94 (Suppl 1): 102b Abstract.
60. Greinacher A, et al. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; 108: 2062–2065.
61. Eichler P, et al. Antibodies against lepirudin are polyspecific and recognize epitopes on bivalirudin. *Blood* 2004; 103: 613–616.