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Bivalirudin, the new kid on the block in coronary interventions

Summary

Bivalirudin is an interesting new intravenous direct thrombin inhibitor with already well-documented efficacy. It is predominantly used in the cardiac catheterisation laboratory during percutaneous coronary interventions. In contrast to hirudin, which failed in this setting, bivalirudin has a shorter half-life and much less immunogenicity. Bivalirudin lacks the risk of heparin-induced thrombocytopenia and shows a tendency to lower bleeding risks without reduction of efficacy when compared with combining unfractionated heparin and glycoprotein IIb/IIIa inhibitors (common in the United States but not in Europe). Improved efficacy compared with the use of unfractionated heparin without glycoprotein IIb/IIIa inhibitors (the rule in Europe) is likely but not proved.

Due to its short half-life, and some data showing its safety during cardiac surgery, there is no particular concern for patients needing immediate heart surgery after a percutaneous coronary intervention. Bivalirudin can be used on the background of any other anticoagulant save vitamin K antagonists, which have not been examined in this context.

The ideal doses have been sufficiently determined as have been the dosage reductions recommended in patients with mild to moderate renal failure. Safety in patients without renal function has not been assessed. The metabolism of bivalirudin occurs by proteolysis and no interactions with drugs employing cytochrome P 450 are to be expected. No other interactions with common drugs in cardiovascular disease have been observed to date.

Bivalirudin is a real asset for patients with thrombocytopenia or a history thereof undergoing coronary interventions. Some interventional cardiologists may take advantage of the slightly more favourable outcome in patients with bivalirudin compared with patients with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors but most will probably continue to use glycoprotein IIb/IIIa inhibitors in

risky cases, thereby eliminating this theoretical advantage of bivalirudin. Safety concerns are not to be expected. Considering policies in European catheterisation laboratories, an increase in cost will occur if bivalirudin replaces unfractionated heparin in routine cases of interventional cardiology.

The compound bivalirudin

Chemical action and dosage

Bivalirudin (Angiox[®], Nycomed) is an analogue of hirudin. It is a short acting anticoagulant which bivalently and directly inhibits thrombin (coagulation factor II). It binds the active (catalytic) site and the fibrinogen-binding site (exosite I). This provides high affinity and specificity for thrombin. Its excretion is less kidney-dependent (predominant enzymatic metabolism) than that of hirudin and it is less immunogenic. The half-life is about 25 minutes rather than the 80 minutes of hirudin.

The recommended dosage schedule during percutaneous catheter-based coronary interventions is 0.75 mg/kg as an intravenous bolus and 1.75 mg/kg/h as an intravenous infusion for the duration of the catheter intervention. The dosage has to be adapted in patients with renal impairment due to partial renal excretion of the compound. In patients with moderate renal impairment the bolus is maintained at 0.75 mg/kg but the infusion is reduced to 1.4 mg/kg/h (20% reduction). In patients with severe renal insufficiency, the excretion pattern is variable. Bivalirudin may still be used but the dose has to be adjusted to coagulation parameters such as activated clotting time

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(ACT). In clinical practice, creatinine clearance <30 ml/min is considered a contraindication against the use of bivalirudin.

Anticoagulant effect

Bivalirudin binds both to the anion binding site and the active site of thrombin and thereby inhibits activation of fibrinogen to fibrin by thrombin. Slow cleavage at the Arg³-Pro⁴ bond results in recovery of thrombin activity after discontinuation of bivalirudin. During treatment with the mentioned doses, bivalirudin produces rapid, dose-dependent anticoagulation. This can be documented and monitored by ACT assessments. The activated prothrombin time (aPTT) is less useful, as the anticoagulation stage achieved with these doses and considered necessary during therapeutic catheter interventions is in a range above that reliably assessed with aPTT.

In the catheterisation trials the desirable lower threshold of ACT was set at 280 sec. The patients all had concomitant platelet inhibition with acetylsalicylic acid, thienopyridines, or intravenous glycoprotein IIb/IIIa inhibitors. The median ACT achieved in the various studies varied between 300 and 360 sec. The ACT did not correlate with ischaemic or haemorrhagic complications. This led to the conclusion that ACT monitoring is not required in clinical practice (with the exception of patients with renal impairment as mentioned above).

Bivalirudin was also evaluated in patients with unstable angina. In these patients it was used for 72 hours at various doses ranging from 0.02 to 1.0 mg/kg/h. These doses were significantly lower than those used during catheter interventions. Hence aPTT was used for monitoring.

In patients with unstable angina and prolonged treatment, aPTT values remained at about 300 sec during the three day regimen with both 0.5 and 1.0 mg/kg/h and decreased similarly to about 120 sec (nontherapeutic range) 12 hours after discontinuation of bivalirudin.

The effects in patients with hepatic impairment or in the elderly have not been specifically analysed yet.

Bivalirudin following heparin (unfractionated or low molecular weight)

The achieved ACT levels were not different from those achieved in patients without pretreatment with heparin. This, however, has only been assessed in patients in whom low molecular weight heparin was discontinued

for at least 8 hours. When switching healthy volunteers from unfractionated heparin to bivalirudin, the aPTT values were significantly higher than under bivalirudin without preceding heparin.

Concomitant platelet inhibitors

The co-administration of acetylsalicylic acid, thienopyridines, or intravenous glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatid, or tirofiban) had no influence on ACT levels or clinical outcome.

Immunological aspects

The relatively simple random folding beta-sheet configuration of bivalirudin provides for a nonallergic profile. Antibodies against bivalirudin were found in a few percent of the patients but had no clinical implication. Re-exposure to bivalirudin has not been evaluated. Cross-reaction with lepirudin has been observed but there are no data on the efficacy of bivalirudin in patients with lepirudin antibodies.

Clinical efficacy of bivalirudin

Design of trials

Clinical efficacy was assessed and proved in over 20 published mostly consecutive patient series focussing on all comers with coronary artery disease, patients with acute coronary artery disease [1, 2], patients during myocardial infarction, patients with percutaneous coronary interventions [3–10], and patients with various adjunctive medications, or patients undergoing cardiac surgery [11–13].

The clinical feasibility for the use of bivalirudin, documented in nonrandomised trials on patients undergoing coronary artery bypass grafting [11–13], is beyond the scope of this review.

Randomised data in the context of percutaneous coronary intervention were reported under the heading of the “Randomised Evaluation of PCI Linking Bivalirudin to reduce Clinical Events” trials with the acronyms REPLACE-1 [14] and REPLACE-2 [15–17].

Further study populations encompass about 12 000 patients matching the baseline criteria of typical patients undergoing percutaneous coronary interventions. The stent use increased in these studies from 0% to about 90% in parallel to policy changes occurring over time. Unfractionated heparin had been used prior to bivalirudin in 12% and low molecular weight heparin in 10% of patients.

General exclusion criteria in these trials were increased bleeding risk and ongoing ST-segment elevation myocardial infarction. The endpoints included death, myocardial infarction, abrupt vessel closure, and major bleeding but varied among the trials. In more recent trials, a triple ischaemic endpoint (cardiovascular death, myocardial infarction, or urgent revascularisation) was employed according to the contemporary trends in trials on percutaneous coronary interventions.

The doses used ranged from a bolus of 0.15–1.00 mg/kg and subsequent infusions of 0.6–2.5 mg/kg/h for the duration of the procedure or up to 3 days in patients with unstable angina.

Results of trials

The randomised trials [14–17] unequivocally showed in about 7000 patients that bivalirudin, used in lieu of unfractionated heparin, resulted in comparable major adverse cardiac and cerebral events with some reduction in significant bleeding. The noninferiority to heparin treatment could also be proved at 1 year of follow-up [16]. The use of glycoprotein IIb/IIIa inhibitors, ie, the intravenous agents abciximab, tirofiban, or eptifibatid, did not influence these results, irrespective of whether they were used a priori [14] or selectively at the discretion of the operator [15, 16]. Death, myocardial infarction, or urgent revascularisation were significantly reduced by bivalirudin with an odds ratio of 0.62 (95% confidence interval 0.47–0.82) when compared with the outcome of patients randomised to heparin who did not receive glycoprotein IIb/IIIa inhibitors. This was, however, not a pre-specified subanalysis. None of the individual endpoints showed a significant difference between bivalirudin and heparin plus glycoprotein IIb/IIIa inhibitors except for major bleeding which was 2.4% with bivalirudin compared with 4.1% with heparin plus glycoprotein IIb/IIIa inhibitors ($p < 0.01$). The mortality at one year was 2.5% in the control group and 1.9% in the bivalirudin group ($p = 0.16$).

The REPLACE-1 trial [14] showed that bivalirudin mirrored the results of unfractionated heparin in terms of death, myocardial infarction, repeat revascularisation, or major bleeding in patients undergoing percutaneous coronary interventions when glycoprotein IIb/IIIa inhibitors were administered routinely at the discretion of the operators. Stents were used in roughly 85% of patients. In the remainder of patients (about $\frac{1}{3}$) in whom no glycoprotein IIb/IIIa inhibitors were used,

death, myocardial infarction, or repeat revascularisation were significantly reduced by bivalirudin from 6.2% to 4.5% and major bleedings from 2.0% to 0%.

In the REPLACE-2 trial [15] (6,010 patients), using glycoprotein IIb/IIIa inhibitors conditionally (ie, in 7.2%) in patients randomised to bivalirudin and routinely in patients randomised to unfractionated heparin, the results in terms of death, myocardial infarction, repeat revascularisation, or bleeding were highly comparable, proving the hypothesis of noninferiority of bivalirudin with low use of additional glycoprotein IIb/IIIa inhibitors compared with the ticket unfractionated heparin plus glycoprotein IIb/IIIa inhibitors. This equality was also seen at one year [16]. This finding was particularly important for the US market, where the average use of glycoprotein IIb/IIIa inhibitors ranged way above 50% of coronary catheter interventions. The reduction of this usage to 10% calculated out to an economical advantage of the use of bivalirudin which in itself is more expensive than unfractionated heparin. In Europe in contrast, the percentage of coronary catheter interventions with glycoprotein IIb/IIIa inhibitors varies between 10% and 25%, already rendering the economical projections of American papers inapplicable. It was also examined, whether pretreatment with the thienopyridine clopidogrel could be omitted when bivalirudin was used [17]. However, it was found, that pretreatment with clopidogrel benefited both groups alike (the one treated with bivalirudin with a 10% use of glycoprotein IIb/IIIa inhibitors and the one treated with unfractionated heparin and default use of glycoprotein IIb/IIIa inhibitors).

Additional interesting data have been presented but not yet published, in particular the ACUTY trial [18]. It encompassed 13 819 patients with moderate to high risk acute coronary syndrome undergoing coronary intervention. The patients were randomised into three groups, one being treated with bivalirudin alone, one with unfractionated heparin or enoxaparin plus glycoprotein IIb/IIIa inhibitors, and one with bivalirudin and glycoprotein IIb/IIIa inhibitors. The last group was sub-randomised into use of glycoprotein IIb/IIIa inhibitors upstream or intra catheterisation laboratory use. Overall the bivalirudin alone group fared best. However, the difference was only significant for bleeding but not for the prognostic endpoints. In addition it was limited to low risk patients with no enzyme elevation before the intervention and with

Table 1
ACUITY results [18].

Endpoints	bivalirudin	UFH/enoxaparin + GP IIb/IIIa inhibitors	bivalirudin + GP IIb/IIIa inhibitors	significance
Death (%)	1.6	1.3	1.5	ns
Myocardial infarction (%)	5.4	4.9	5.0	ns
Unplanned revascularisation (%)	2.4	2.3	2.7	ns
Major bleeding (%)	3.0*	5.7*	5.3	p* = 0.0001
Any of the above (%)	10.1**	11.7**	11.8	p** = 0.015

* Difference significant only pertaining to access site bleeding.
** Difference entirely due to bleeding in patients pretreated with clopidogrel, and with normal troponin and creatine kinase as well as low risk score at the outset.
UFH = unfractionated heparin; ns = no significant difference.

clopidogrel pre-treatment. The results are summarised in table 1.

Safety of bivalirudin

Based on clinical data on roughly 16 000 patients receiving bivalirudin during their treatment for coronary artery disease within strict study protocols and over 300 000 patients treated outside of protocols, the compound has proved safe. Bleeding occurred as with any anticoagulant but was equally and in some cases even less frequent than with traditional drug regimens. Major bleeding was reported between 2% and 6% across all studies with the figures of the bivalirudin arms being consistently lower albeit to a nonsignificant degree in most trials. Considering any kind of bleeding in studies only encompassing patients undergoing percutaneous coronary interventions, the figures were 33% for bivalirudin and 49% for heparin. This was clearly in favor of bivalirudin. The overall high figures are explained by the use of fairly large arterial access sheaths in all patients. An advantage for bivalirudin was also found when only protocol-defined bleedings were considered with bleeding at the puncture site for catheterisation prevailing (0.9% with bivalirudin versus 2.4% with heparin, $p < 0.001$).

Backpain was the most common side-effect reported by patients in trials. It was not linked to the type of anticoagulant used but to the duration of bed rest. Nausea dominated the side-effects possibly related to the drug in the bivalirudin cohorts and thrombocytopenia in the heparin (\pm glycoprotein IIb/IIIa inhibitor) cohorts.

Serious adverse events possibly related to the drug occurred as follows: thrombocytopenia 0.7% versus 1.7% in the bivalirudin and heparin groups, respectively, others 0.5% versus 1.2%, respectively. Mortality was 0.9% versus

1.3%, respectively (difference not significant). The difference remained nonsignificant with 6% and 7%, respectively, at one year, later events being almost exclusively due to the underlying disease and not to the drug treatment.

Adverse effects increased with age as in all trials but were not linked to the type of treatment. The same held true for an increased percentage of side effects in females compared with males. Renal insufficiency also increased adverse events without predilection of treatment randomisation.

A report on two cases issued a caveat that bivalirudin may increase the risk of abrupt stent closure after brachytherapy [19].

Conclusions

Bivalirudin is an interesting and already well documented new direct thrombin inhibitor to be exclusively used intravenously. This report focuses on its use in the cardiac catheterisation laboratory during percutaneous coronary interventions. In contrast to hirudin which failed in this setting, bivalirudin has a shorter half-life and much less immunogenicity. In contrast to the well established unfractionated heparin, bivalirudin lacks the risk of heparin-induced thrombocytopenia and shows a tendency to lower bleeding risks without reduction of efficacy when compared with the two-pronged treatment unfractionated heparin and glycoprotein IIb/IIIa inhibitors which is more common in the United States than in Europe. Improved efficacy compared with the use of unfractionated heparin without glycoprotein IIb/IIIa inhibitors (the rule in Europe) is suggested by the REPLACE-I trial [15]. However, there is no proof for it and respective studies are neither planned nor en route.

The community of interventional cardiologists in Europe welcome the arrival of bi-

valirudin in routine practice, primarily as an alternative for patients with thrombocytopenia or a history thereof. Some may bank on the slightly more favorable outcome in patients with bivalirudin compared with patients with nonfractionated heparin plus glycoprotein IIb/IIIa inhibitors but most will probably continue to use glycoprotein IIb/IIIa inhibitors in risky cases, thereby eliminating this theoretical advantage of bivalirudin. Based on the excellent record of the compound, safety concerns among the users have not to be expected. Considering policies in European catheterisation laboratories, an increase in cost will occur if bivalirudin replaces unfractionated heparin in routine cases of interventional cardiology.

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