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Editorial

Bivalirudin: The relevance in today's interventional practice

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Today many areas of concern in coronary interventions are fairly addressed with the advent of new anti-platelet agents, low profile balloon catheters, drug eluting stents and a variety of guide-wires. However one problem that continues to haunt the cardiologists is the considerable incidence of bleeding complications following PCI.¹ We are now well aware that bleeding complications following PCI not only increased mortality and morbidity pre-discharge but also in the long term. The reasons for this could be several including the physical effects of blood loss, bleeding into critically important areas like brain, the need to discontinue anti-platelet therapy and the need for blood transfusions with its attendant adverse effects like reduced ability of blood to transfer oxygen, TRIM (transfusion related immune modulation) and so on.¹

Therefore any new modalities adopted to reduce bleeding complications are welcome like radial route for PCI. The recently published RIVAL study randomized patients of acute coronary syndromes to radial or femoral access during PCI.² This multi-centric trial randomized 7021 patients and showed that trans-radial access has lower rate of local vascular complications [Fig. 1]. But there was no difference in primary and secondary outcomes. The reason for lack of difference in primary outcomes is due to the fact that the non-access site bleeding complications contributed significantly to the primary outcome [Fig. 2]. This goes on to show that adopting radial route will only partly address the problem.

Today the patient of acute coronary syndrome is bombarded with a variety of anti-thrombotics including anti-coagulants, two P2Y₁₂ antagonists and often Glycoprotein IIb/IIIa receptor inhibitors during PCI. Naturally the risk of bleeding is high. The intensive pharmacological therapy may reduce the benefit of mechanical reperfusion as bleeding related mortality/morbidity increase.³

We require an anti-thrombotic agent during PCI which is efficacious and at the same time is associated with least chances of bleeding complications. One agent which comes close to being a nearly satisfactory answer to our requirements is the intravenous direct thrombin inhibitor – Bivalirudin.

We reviewed earlier this wonderful molecule and its pharmacokinetic properties and adverse effects in Indian Heart Journal.⁴ This molecule has been tried during PCI in a variety of settings of acute coronary syndrome including Primary PCI, high risk PCI, CABG and other interventions.

The advantages of Bivalirudin over conventional Heparin include action being independent of anti-thrombin III levels, better bioavailability, capacity to inhibit both soluble and clot-bound thrombin, absence of inhibition by platelet factor 4 and absence of stimulation of platelet activation.⁵ The drug has a biological half-life of 25 min which makes it an ideal anti-coagulant in Cath labs, as it allows almost on/off use during the procedure particularly in complex angioplasties like CTO interventions.⁶

One indication which is very clear for Bivalirudin is the 5% of patients who develop Heparin induced thrombocytopenia (HIT) while on Heparin.⁷ At least one trial has clearly established safety and efficacy of Bivalirudin in these patients.

Elliott Antman and Eugene Braunwald in their editorial 'A second look at Bivalirudin' have reviewed this molecule and the story of the struggle to establish it.⁸

It has been studied extensively in a variety of settings.

REPLACE-2 trial evaluated the safety and efficacy of Bivalirudin in patients with stable angina or ACS without ST-segment elevation,⁹ the ACUTY trial evaluated patients with NSTEMI undergoing PCI.¹⁰ It is apparent from both these trials that the use of Bivalirudin alone is as effective as UFH with GP inhibitors while reducing bleeding complications. However neither of these trials have shown a reduction in mortality.

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	Radial (n=3507)	Femoral (n=3514)	HR(95%CI)	p value
Major vascular complications at 30 days				
Large haematoma	42 (1.2%)	106 (3.0%)	0.40 (0.28–0.57)	<0.0001
Pseudoaneurysm needing closure	7 (0.2%)	23 (0.6%)	0.30 (0.13–0.71)	0.006
Arteriovenous fistula	0 (0%)	5 (0.1%)	"	"
Ischaemic limb needing surgery	1 (0%)*	0 (0%)	"	"

Fig. 1 – Procedural complications of patients enrolled in RIVAL study.²

HORIZONS-AMI trial compared Bivalirudin alone with unfractionated heparin combined with GP inhibitors for “high-risk” STEMI patients undergoing primary PCI.¹¹ This trial clearly showed a reduction in mortality with Bivalirudin. But the flip side of this trial was that Bivalirudin was associated with a small increase in acute stent thrombosis in the first 24 h. Despite this Bivalirudin has reduced late (>30 days) cardiac mortality and re-infarction rates. This result was maintained even after 3 years and treatment with Bivalirudin alone compared to heparin plus a GP IIb/IIIa inhibitor resulted in significantly reduced rates of all-cause mortality (5.9% vs. 7.7%), cardiac mortality (2.9% vs. 5.1%), re-infarction (6.2% vs. 8.2%) and major bleeding not related to bypass graft surgery (6.9% vs. 10.5%).¹² The

reported reduction in all-cause mortality seen in the trial equates to 18 lives saved per 1000 patients treated with Bivalirudin.

Rassen et al in a retrospective analysis studied 127,185 number of real world patients in United States who were given Bivalirudin plus provisional GP inhibitors or Heparin with GP inhibitors involving both elective and primary PCI.¹³ Those patients given Bivalirudin were generally of higher risk as they had Diabetes Mellitus and Hypertension more often. This study showed a 33% reduction in need for blood transfusions with Bivalirudin. Also a 49% reduction of in-hospital deaths was shown.

In ISAR REACT 4 trial, patients with acute NSTEMI undergoing PCI were randomized to receive abciximab plus

	Radial (n=3507)	Femoral (n=3514)	Hazard ratio (95% CI)	p value
Primary outcome				
Death, MI, stroke, or non-CABG bleeding at 30 days	128 (3.7%)	139 (4.0%)	0.92 (0.72–1.17)	0.50
Secondary outcomes at 30 days				
Death, MI, stroke, or stroke	112 (3.2%)	114 (3.2%)	0.98 (0.76–1.28)	0.90
Non-CABG major bleeding	24 (0.7%)	33 (0.9%)	0.73 (0.43–1.23)	0.23
Death	44 (1.3%)	51 (1.5%)	0.86 (0.58–1.29)	0.47
MI	60 (1.7%)	65 (1.9%)	0.92 (0.65–1.31)	0.65
Stroke	20 (0.6%)	14 (0.4%)	1.43 (0.72–2.83)	0.30
Secondary outcomes at 48h				
Death, MI, stroke, or non-CABG bleeding	50 (1.4%)	65 (1.8%)	0.77 (0.53–1.11)	0.17
Non-CABG major bleeding	11 (0.3%)	18 (0.5%)	0.61 (0.29–1.30)	0.20
Death	9 (0.3%)	15 (0.4%)	0.60 (0.26–1.37)	0.23
MI	29 (0.8%)	31 (0.9%)	0.94 (0.56–1.56)	0.80
Stroke	7 (0.2%)	6 (0.2%)	1.17 (0.39–3.48)	0.78
Other secondary outcomes				
PCI success*	2204 (95.4%)	2235 (95.2%)	1.01 (0.95–1.07)	0.83
Access site crossover	265 (7.36%)	70 (2.0%)	3.82 (2.93–4.97)	<0.0001
Major vascular complications	49 (1.4%)	131 (3.7%)	0.37 (0.27–0.52)	<0.0001
Minor bleeding	100 (2.9%)	118 (3.4%)	0.84 (0.65–1.10)	0.21
Safety outcomes				
Non-CABG TIMI major bleeding	19 (0.5%)	19 (0.5%)	1.00 (0.53–1.89)	1.00
CABG-related bleeding	48 (1.4%)	48 (1.4%)	1.00 (0.37–1.49)	1.00
Non-CABG-related blood transfusions	39 (1.1%)	45 (1.3%)	0.87 (0.56–1.33)	0.51
All blood transfusions	99 (2.8%)	98 (2.8%)	1.01 (0.76–1.33)	0.95
Post-hoc exploratory outcomes				
ACUTY major bleeding†	66 (1.9%)	157 (4.5%)	0.43 (0.32–0.57)	<0.0001
Death, MI, or stroke, or ACUTY major bleed†	167 (4.8%)	256 (7.3%)	0.65 (0.53–0.78)	<0.0001
Non-CABG major bleeding and major vascular complications	67 (1.9%)	157 (4.5%)	0.43 (0.32–0.57)	<0.0001
Death, MI, stroke, non-CABG major bleeding, or major vascular complications	167 (4.8%)	260 (7.4%)	0.63 (0.52–0.77)	<0.0001

Data are number (%). MI=myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. ACUTY=Acute Catheterization and Urgent Intervention strategy. *As a proportion of patients who had PCI: n=2311 in the radial group and n=2349 in the femoral group. † Large haematomas diagnosed as per investigator's clinical decision.

Fig. 2 – Primary and secondary outcomes in RIVAL study.

unfractionated heparin (861 patients) or Bivalirudin (860 patients).¹⁴ Abciximab and unfractionated heparin, as compared with Bivalirudin, failed to reduce the rate of the primary end point of death, large recurrent myocardial infarction, urgent target-vessel revascularization, or major bleeding within 30 days. Major bleeding occurred in 4.6% of the patients in the abciximab group as compared with 2.6% in the Bivalirudin group.

In a recent publication in American Journal of Cardiology, Olivier Bertrand et al performed a meta-analysis to compare outcomes in patients undergoing Trans femoral PCI with UFH or Bivalirudin.¹⁵ They collected data from 16 studies involving 32,492 patients undergoing PCI [Randomized trials ($n = 3$) and observational studies ($n = 13$)]. They showed 45% relative decrease in major bleeding and a trend toward decrease of transfusions [Fig. 3], but no difference in MACE rate.

An important question that needs to be answered is whether Bivalirudin further reduces bleeding complications among patients undergoing angioplasty by radial route as well. A study by Verheugt published in JACC Cardiovascular Interventions in 2011 partially addresses this issue.¹⁶ They looked at the impact of Bivalirudin vs. Heparin + GP inhibitors on access and non-access site bleeding. They examined the pooled data of REPLACE-2, ACUTY and HORIZONS-AMI trials comprising a total of 17,393 patients.

TIMI major/minor bleeding occurred in 5.3% of patients, out of which 61.4% were non-access site bleeds. Non-access site TIMI bleeding events were associated with a 4-fold increase in one-year mortality compared to patients without any bleeding events and 2-fold increase in mortality compared to only access site bleeds. Randomization to Bivalirudin reduced chances of TIMI major/minor bleeds by 38% and TIMI major bleeds by 43% compared to Heparin plus GP inhibitors. Importantly use of Bivalirudin significantly reduced both non-access site and access site bleeding events by approximately 40%.

In this study only 7.9% of patients underwent angioplasty by radial route. Trans-radial angioplasty is expected to reduce the access site bleeds but is not expected to reduce the non-access site bleeds. Since now it is clear that Bivalirudin reduces both access site and non-access site bleeds and since non-access site bleeds contribute significantly to adverse outcomes, the policy of trans-radial angioplasty while using Bivalirudin as the anti-thrombotic therapy should produce an even lower incidence of bleeding complications.

In this issue of Indian Heart Journal Deshpande et al have presented their data of a randomized comparison of Bivalirudin + GP inhibitors versus unfractionated heparin + GP inhibitors in patients undergoing elective high risk PCI.¹⁷ Hundred and one patients randomly received UFH + GP IIb/IIIa

Fig 3 – Forest plot for incidence of major bleeding in observational studies and randomized trials in meta-analysis by Bertrand et al.¹²

inhibitor or Bivalirudin + GP IIb/IIIa inhibitor. The primary endpoint was the time to sheath removal and ambulation. The secondary endpoints were peri-procedural myocardial damage, post procedure access site bleeding and major adverse cardiac events. Bivalirudin group had significantly shorter time to sheath removal and ambulation ($P < 0.0001$) and lower peri-procedural myocardial damage ($P < 0.023$). The authors justified the use of Bivalirudin along with GP inhibitors on the premise that in India most physicians use GP inhibitors during PCI, while in most of the randomized trials it has been shown that Bivalirudin alone is as good as heparin + GP inhibitors with lesser incidence of bleeding. The number of patients is small, hence the authors used a surrogate end point namely time to sheath removal, which is understandably relevant only if PCI is done by femoral route. Another point to note is that they chose to give Bivalirudin for 4 h while most operators would stop the infusion as soon as the procedure is over. That could have resulted in an even shorter time to sheath removal. The authors should be appreciated for publishing a well conducted trial, however.

The BivaFlo registry from India which is a prospective multicenter registry studied the results of Bivalirudin in 439 moderate to high risk patients. They showed that use of Bivalirudin is associated with an extremely low rate in hospital and 30 day MACE. The minor bleeding complications were 0.9%. There were no major bleeding complications. Only 4% required bailout use of GP inhibitors.¹⁸

Bivalirudin is not in wide spread use despite its proven efficacy and strong evidence supporting it. This could be due to a variety of reasons including cost, a sentiment [especially among European cardiologists] that radial route for PCI mitigates the need for Bivalirudin and reluctance to change from existing anti-thrombotic agents used.

In conclusion Bivalirudin is an anti-coagulant of choice during PCI where risk of bleeding is high like the elderly, the underweight, patients of chronic kidney disease and patients of cerebrovascular disease and the like. There is reasonable suggestion that its use can result in reduction of mortality. With increasing use of trans-radial procedures, its role needs to be evaluated in further randomized trials.

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