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SYSTEMATIC REVIEWS

Safety, efficiency and cost effectiveness of Bivalirudin: A systematic review

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Abstract

AIM

To review the early and more recent studies of Bivalirudin, to assess the safety, effectiveness, and cost benefits of this drug.

METHODS

Literature search of MEDLINE and PubMed databases from 1990 to 2017 using keywords as "bivalirubin" and "angiomax", combined with the words "safety", "effectiveness", "efficiency", "side effects", "toxicity", "adverse effect", and "adverse drug reaction".

RESULTS

A total of 66 publications were reviewed. The changes in clinical practice and differences in clinical protocols make it difficult to do direct comparisons of studies among each other. However, most trials showed decreased bleeding complications with bivalirudin, although ischemic complications and mortality were mostly comparable, with some favor towards bivalirudin.

CONCLUSION

Bivalirudin and heparin are both acceptable options according to current ACA/AHA guidelines. Authors conclude however, that that due to bivalirudin safer bleeding profile, it should be the preferred medication for anticoagulation.

Key words: Efficiency; Cost effectiveness; Bivalirudin; Safety

Core tip: Bivalirudin is a direct thrombin inhibitor used in clinical practice since 1990's. It was initially introduced as an alternative medication to heparin during percutaneous coronary intervention. Early studies showed advantages of bivalirudin over heparin. We did a systematic review of the literature since 1990 and summarized all relevant trials. The majority showed better outcomes with bivalirudin. However, some trials are difficult to compare directly as protocols and patient populations differ. Bivalirudin and heparin are both acceptable options according to current

ACA/AHA guidelines. Authors conclude however, that that due to bivalirudin safer bleeding profile, it should be the preferred medication for anticoagulation.

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INTRODUCTION

To prevent peri-procedural thrombotic complications, anticoagulation is required during percutaneous coronary intervention (PCI) and other percutaneous transluminal coronary angioplasty. The most common anticoagulant regimens are unfractionated heparin (UFH) and low molecular weight heparins (LMWHs)[1]. Bivalirudin (Angiomax) is a specific and reversible direct thrombin inhibitor, used for anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty, patients undergoing PCI, or in patients with, or at risk of heparin-induced thrombocytopenia (HIT), undergoing PCI[2]. Evidence from early trials has pointed unique advantages with this drug with predictable pharmacokinetics, avoidance of HIT, and perhaps most importantly, a reduction in bleeding complications. The purpose of this study is to review the early and more recent studies of Bivalirudin, to assess the safety, effectiveness, and cost benefits of this drug.

MATERIALS AND METHODS

A literature search was performed of the MEDLINE and PubMed database from 1990-2017, using keywords as "Bivalirudin" or "angiomax", combined with the words "safety", "effectiveness", "efficiency", "side effects", "toxicity", "adverse effect", and "adverse drug reaction".

RESULTS

Drug information

Drug information was showed in Table 1.

Early trials comparing bivalirudin to other anticoagulant drugs

In 1993, bivalirudin was introduced in a multicenter dose escalation study to overcome the theoretical limitations of heparin. The appropriate dose was set to 1.8-2.2 mg/kg per hour, and was suggested as a feasible sole anticoagulant drug in patients with stable or unstable patients undergoing elective coronary angioplasty. They documented that it was associated with rapid onset of action, dose dependent anticoagulant effect and minimal bleeding complications[3].

In 1995, Bittl *et al*[4] performed a randomized, double blind, multicenter study comparing bivalirudin with high dose [UFH (initial bolus of 175 U/kg)] in patients undergoing urgent coronary angioplasty for unstable angina, or post-infarction (< 2 wk after myocardial infarction) angina. The results showed that the overall safety profile of bivalirudin was found to be superior[5]. This study was also reproduced in 2001, with an intention to treat principle, using contemporary and more clinically accepted endpoints and reducing the proportion of the missing data. The results of this reanalysis showed, again, that bivalirudin reduced ischemic complications, defined as death, myocardial infarction (MI) or repeat revascularization, at 7 d (6.2% *vs* 7.9%, $P = 0.039$), 90 d (17.5% *vs* 24.3%, $P < 0.001$) and 180 d (24.5% *vs* 30.3%, $P < 0.001$) follow-ups. This benefit was more apparent and persistent in the post-infarction angina patient group at 7 d (4.9% *vs* 9.9%, $P < 0.009$), 90 d (13.3% *vs* 27.2%, $P < 0.001$) and 180 d (20.3% *vs* 32.0%, $P < 0.001$) follow-ups. This reanalysis also documented significantly lesser major hemorrhagic events with bivalirudin at 7-d, 90-d and 180-d follow-ups (3.5% *vs* 3.7% *vs* 9.3%, $P < 0.001$). Thus, this study determined bivalirudin's unique and unexpected uncoupling of outcomes for an anticoagulant, *i.e.,* lesser ischemic events as well as lesser bleeding complications[6]. However, this study used a high dose UFH that might have exaggerated the benefits seen in major bleeding rates with bivalirudin.

The results of a double-blind, randomized HERO study in 1997 showed that bivalirudin can be used as an adjunct to improve the early patency achieved with streptokinase in STEMI patients presenting within 12 h. This effect of bivalirudin was found to be more effective than using UFH as an adjunct, and was achieved at a lower aPTT levels. Furthermore, it was not associated with increased bleeding risk[7]. The bolus dose of UFH in this study was 5000 U, which is approximately 71 U/kg in a 70 kg patient.

A meta-analysis was done, analyzing 11 studies with a total number of 35970 patients, comparing different direct thrombin inhibitors with UFH in patients with acute coronary syndrome (ACS) (including patients who underwent PCI). In this analysis, it was found that bivalirudin reduced the composite of death and MI and also reduced the major bleeding events[8]. But none of these eleven studies used glycoprotein Ⅱb/Ⅲa inhibitor.

Before Thienopyridine introduction, in 2001, Kleiman *et al*[9] performed a study on 42 patients who underwent elective PCI and they found that combining bivalirudin with eptifibatide is a feasible drug combination of choice. There were no major bleeding events, and only a single non-Q-wave MI occurred in a patient treated with bivalirudin. The CACHET study in 2001 was an open label, randomized trial performed on patients who underwent PCI for elective coronary balloon angioplasty or stenting. Patients with acute MI (< 12 h) were excluded. It showed that bivalirudin with planned or provisional abciximab was at least as

Table 1 Dose information

Dose	0.75 mg/kg IV bolus then 1.75 mg/kg per hour if no prior antithrombotic therapy is administered
	For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV bolus, then 1.75 mg/kg per hour IV infusion
Half life	Healthy patients: 25 min. The half-life is Increased in patients with CKD, and is estimated to 3.5 h in dialysis-dependent patients
Mechanism of action	Reversible direct thrombin inhibitor. Thus, inhibits thrombin by directly binding to it
Theoretical advantages over heparin-	Directly inhibits thrombin
	Binds to clot-bound thrombin also
	Lab monitoring of efficacy is not required
	Does not cause HIT
	Short half life
	Almost nil thrombin induced platelet aggregation
Antidote and toxicity	No known antidote
	Should be discontinued 3 h before CABG
	In cases of toxicity, hemodialysis should be considered
CKD	Dose is reduced in patients with renal failure
Recommendations from the American College of Cardiology/ American Heart Association and European Society of Cardiology for the use of bivalirudin in patients undergoing PCI	Class of recommendation - I, level of Evidence-B
	For patients undergoing PCI: Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH
	Class of recommendation - I, level of Evidence-C
	With HIT: It is recommended that bivalirudin or argatroban be used to replace UFH
	Class of recommendation - I, level of Evidence-B
	Either discontinue bivalirudin or continue at 0.25 mg/kg per hour for up to 72 h at the physician's discretion if given before diagnostic angiography and no PCI or CABG

PCI: Percutaneous coronary intervention; CKD: Chronic kidney disease; HIT: Heparin-induced thrombocytopenia; UFH: Unfractionated heparin.

safe and effective as UFH (initial bolus of 70 U/kg), plus planned abciximab in reducing the composite clinical endpoint of death, MI, repeat revascularization or major bleeding. However, this was a pilot study with a small sample size of only 268 patients[10]. The REPLACE-2 trial from 2003 was a randomized, double blind, active-controlled trial conducted among 6010 patients undergoing urgent or elective PCI. Patients presenting with acute MI were excluded. Study patients received either bivalirudin or UFH (65 U/kg initial bolus) plus glycoprotein Ⅱb/Ⅲa inhibitors (GPI). GPI were used provisionally in the bivalirudin group. This study showed that bivalirudin was not inferior to UFH plus GPI in reducing the incidence of ischemic events (death, MI and repeat revascularization) at 30-d (7.6% *vs* 7.1%, *P* = 0.40) and 6 mo (18.8% *vs* 17.5%, *P* = 0.21) follow-ups. The mortality in the bivalirudin group at 30-d (0.2% *vs* 0.4%, *P* = 0.26), 6 mo (1.0% *vs* 1.4%, *P* = 0.15) and 1 year (1.89% *vs* 2.46%, *P* = 0.16) follow-ups is non-inferior to UFH plus GPI. However, the results were not statistically significant. The 30-d major bleeding episodes were statistically significantly lower in bivalirudin group (2.4% *vs* 4.1%, *P* < 0.001)[11].

The, PROTECT-TIMI 30 from 2005, evaluated glycoprotein Ⅱb/Ⅲa inhibition role with eptifibatide when administered with indirect thrombin inhibition as compared with monotherapy with bivalirudin among patients with non-ST-segment elevation. 857 moderate to high risk patients with at least one or more of the following risk factors: Diabetes, a positive cardiac biomarker either CK-MB or troponin T/I, ST-segment deviation > 0.5 mm, or TIMI risk score ⩾ 3, was evaluated when presenting with chest pain or an anginal equivalent symptom at rest ⩾ 10 min in the setting of a non ST elevation acute coronary syndrome, which were anticipated to undergo PCI of a native coronary artery. This study compared the combination of eptifibatide and heparin (UFH/enoxaparin) with bivalirudin. Results showed that the primary end point of post-PCI coronary flow reserve was significantly higher with bivalirudin (1.43 *vs* 1.33, *P* = 0.036). The myocardial perfusion (post-PCI TMPG) was found to be better in eptifibatide group (57.9% *vs* 50.9%, *P* = 0.048) and the 48 h post-PCI composite of death and MI was lower in eptifibatide group (8.8% *vs* 6.6%, *P* = 0.246). Duration of post-PCI ischemia was also lower in eptifibatide group (36 min *vs* 169 min, *P* = 0.013). In the UFH plus eptifibatide group, there were increased bleeding episodes, more notably TIMI minor bleeding episodes, (2.5% *vs* 0.4%, *P* = 0.027) and bleeding episodes that required transfusion (4.4% *vs* 0.4%, *P* < 0.001). This study showed that, moderate- to high-risk patients with ACS undergoing PCI, bivalirudin therapy lowers bleeding and the need for blood transfusion and is thus safer than heparin plus eptifibatide therapy[12].

The ACUITY trial evaluated the role of bivalirudin in patients with moderate or high-risk ACS patients. Patients with acute ST elevation or shock were the important exclusion criteria in this study. The anti-thrombotic regimens used in this study were heparin (UFH or enoxaparin) plus GPI, bivalirudin plus GPI, and bivalirudin monotherapy. This trial was a 13819 patient, open label study in which the patients were randomized

to receive one of the above three antithrombotic regimens. Bivalirudin had comparable clinical outcomes in patients with moderate and high-risk acute coronary syndromes treated with glycoprotein Ⅱb/Ⅲa inhibitors in whom percutaneous coronary intervention is done as unfractionated heparin or enoxaparin. Moreover, anticoagulation with bivalirudin alone suppressed adverse ischemic events to a similar extent as does glycoprotein Ⅱb/Ⅲa inhibitors plus heparin, while also significantly lowering the risk of major hemorrhagic complications[13].

The ARMYDA-7 BIVALVE study compared bivalirudin with UFH in 401 high-risk patients undergoing PCI. The inclusion criteria in this study was the following: Age > 75 years, diabetes mellitus (definitions according to the American Diabetes Association criteria), chronic renal failure (CrCl between 30 and 60 mL/min). Clopidogrel 600 mg was preloaded in all patients in this study. At 30-d follow-up, it was found that bivalirudin caused similar rates of MACE, *i.e.,* cardiac death, MI, stent thrombosis, or target vessel revascularization (11.1% *vs* 8.9% $P = 0.56$) with significantly lower rates of bleeding (1.5% *vs* 9.9%, $P = 0.0001$)[14]. One of the important exclusion criteria was to exclude patients who were undergoing primary PCI for acute MI.

The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) was, open-label, randomized trial done on 3602 patients who were undergoing primary PCI for STEMI (presentation from onset of symptoms < 12 h). Patients were randomized to receive bivalirudin or UFH (initial bolus of 60 U/kg) plus GPI (control). Patients then underwent randomization to bare metal or paclitaxel-eluting stents. Ninety-two point seven percent of patients underwent primary PCI and the rest were treated either medically or by primary CABG. A very small portion of patients were deferred PCI (0.2%). Ninety-four point five percent of patients received GPI in patients who were assigned to UFH plus GPI. Seven point two percent of patients in the patients assigned to bivalirudin group required GPI (mainly because of absence of reflow or giant thrombus after PCI). At 30 d, the MACE rates were significantly lower in bivalirudin group (9.2% *vs* 12.1%, $P = 0.005$). Bivalirudin group patients also had lower rates of non-CABG-related major bleeding (NCRMB 4.9% *vs* 8.3%, $P < 0.005$) and all-cause mortality (2.1% *vs* 3.1%, $P = 0.047$). The significant benefit in the NACE rates was mainly due to the lower major bleeding rates in the bivalirudin group[15]. At one year, reductions in MACE (15.6% *vs* 18.3%, $P = 0.022$), NCRMB (5.8% *vs* 9.2%, $P < 0.0001$) and all-cause mortality (3.5% *vs* 4.8%, $P = 0.037$) rates were noted with bivalirudin. MACE rates were similar between the two groups (11.9% *vs* 11.9%, $P = 0.98$)[16]. Reduction in one-year mortality (8.4% *vs* 15.9%, $P = 0.01$) and MI recurrence (3.6% *vs* 7.9%, $P = 0.042$) was also found in high risk patients[17]. In patients with diabetes mellitus, significant benefit was seen in terms of reduction in cardiac death at 30 d with bivalirudin compared with the control group (2.1% *vs* 5.5%, $P = 0.01$). At one year, similar benefit in reduction of cardiac death was noted which was more evident in insulin dependent-DM patients (1.4% *vs* 9.4%, $P = 0.04$). However, no benefit was seen in NCRMB rates (8.7% *vs* 10.7%, $P = 0.42$)[18].

Studies on bleeding profile and other outcomes

A subanalysis of the REPLACE-2 study showed that pretreatment with antithrombin therapy before randomization did not affect the bleeding outcomes in patients treated with bivalirudin[19]. Even in the subanalysis of patients with renal impairment (creatinine clearance < 60 mL/min), lower bleeding incidence and efficacy that was non-inferior to UFH plus GPI, showed in another subanalysis of the REPLACE-2 trial[20]. However, it should be noted that none of the individual subgroup in this trial was sufficiently powered to support definitive conclusions. This study documented that using bivalirudin with provisional GPI was easy to administer, as well as simple because only 7.2% ($P = 0.001$) patients in this group required provisional GPI inhibitors compared with 5.2% ($P = 0.001$) of provisional use and 96.5% (P value not significant) of planned use of GPI inhibitors in patients of the UFH group[11]. However, this study did not include patients with acute MI or unstable ischemic syndromes who often require empiric GPI. This study determined with certainty that using bivalirudin with provisional GPI is appropriate in the subgroup of patients with low to moderate risk characteristics for periprocedural or long-term ischemic complications of PCI, especially if these patients have more risk factors for bleeding. This approach was cost effective with savings from $375 to $400 per patient in the 4651 United States patients studied[21]. Since almost one fourth of the patients undergoing PCI are diabetic patients, a post hoc analysis of REPLACE-2 was done only on patients with diabetes mellitus and found that no difference in both short and long term ischemic events in the bivalirudin and UFH plus GPI groups[22]. Moreover, in patients with diabetes mellitus who underwent PCI, bivalirudin as a monotherapy resulted in similar 30 d composite ischemia (8.5% *vs* 9.7%, $P = 0.63$-1.22) and lower major bleeding rates (4.6% *vs* 8.5%, $P = 0.36$-0.81) when compared with heparin plus GPI group[23]. Furthermore, a study analyzed the outcomes in NSTEACS patients of this trial who were pretreated with heparin and then switched to bivalirudin. Though the composite ischemia was similar in these patients when compared with patients on consistent heparin plus GPI (9.0% *vs* 8.2%, $P = 0.47$), these patients had lesser rates of 30 d major bleeding episodes (3.5% *vs* 6.7%, $P < 0.01$)[24].

The NAPLES trial from 2009 was done on 355 diabetic patients undergoing elective PCI for asymptomatic/stable/unstable angina. It compared bivalirudin monotherapy with the combination of UFH and tirofiban in these patients. After 30-d follow up, the composite endpoint (death, MI, revascularization and all bleeding) was found to be lower in the bivalirudin group (18.0% *vs* 31.5%, $P = 0.004$)[25]. At that time, evidence was

increasing that pretreatment with 300 mg or 600 mg clopidogrel improves outcomes[13,15,26-28]. The ISAR-REACT 3 and 4 trials, studied the efficacy and safety of bivalirudin compared with that of UFH in patients with stable or unstable angina (cardiac biomarker negative), pretreated with 600 mg clopidogrel, undergoing PCI. Overall, the rates of major bleeding were significantly lower with bivalirudin (3.1% *vs* 4.6%, $P = 0.008$).

The 30-d primary outcome (composite of death, MI, urgent target-vessel revascularization and major bleeding) with bivalirudin was similar to that of UFH (8.3% *vs* 8.7%, $P = 0.57$), showed in a study with 4570 enrolled patients with stable or unstable angina. The rates of major bleeding were significantly lower with bivalirudin (3.1% *vs* 4.6%, $P = 0.008$)[29]. No significant differences in the primary outcome was found between the two groups even after one year of follow up (17.1% *vs* 17.5%, $P = 0.816$)[30]. In the subgroup of unstable angina patients (836 patients) of this study, the 30-d primary outcome with bivalirudin was similar to that of UFH (10.0% *vs* 10.8%, $P = 0.88$)[29]. No significant differences in the primary outcome was found in this subgroup of patients between the two groups even after one year of follow up (21.5% *vs* 20.1%, $P = 0.458$)[30]. In this study the dose of heparin was high (140U/kg initial bolus). This might have made the benefit with bivalirudin in reducing major bleeding rates more apparent. ISAR-REACT 3A study compared the reduced dose of UFH (initial bolus of 100 U/kg) with bivalirudin in 2505 stable (cardiac biomarker negative) patients undergoing PCI. UFH at 100 U/kg showed net clinical benefit in these patients when compared with bivalirudin[31].

ISAR-REACT 4, a randomized, double blind study done in 2011, on 1721 patients compared the combination of abciximab plus UFH (70 U/kg initial bolus) with bivalirudin in patients with NSTEMI undergoing PCI. All patients received pretreatment with 600 mg clopidogrel. The primary end point of net clinical outcome (death, large recurrent MI, urgent target-vessel revascularization and major bleeding) was similar in both the groups at 30 d (10.9% *vs* 11.0%, $P = 0.94$). The relative risk of major bleeding was lower with bivalirudin (approximately 0.55)[32].

ISAR-REACT 3 and 4 trials showed that bivalirudin was non-inferior in reducing ischemic complications, and safer than UFH in clopidogrel pretreated patients. A pooled analysis from the ACUITY and ISAR-REACT 4 NSTEMI patients who underwent PCI after clopidogrel pretreatment found that bivalirudin monotherapy was as efficient as heparin (UFH/enoxaparin) plus GPI in reducing net adverse clinical events (13.4% *vs* 14.7%, $P = 0.21$) and superior to heparin plus GPI in reducing major bleeding events (3.4% *vs* 6.3%, $P = 0.21$)[31]. However, a recent meta-analysis did not support that pretreatment with clopidogrel, improved outcomes[33].

The Naples Ⅲ was a double blind, randomized trial that included 837 patients with increased risk of to receive either bivalirudin or heparin infusion for transfemoral elective coronary stenting. Patients had to be cardiac biomarkers negative without any EKG changes, suggesting ongoing acute or recent MI. The primary endpoint was the rate of in-hospital major bleed, which occurred in 2.6% (11 patients) in the heparin group *vs* 3.3% (14 patients) in the bivalirudin group. The authors concluded that there was no difference between these two groups in the rate of major bleeding[34].

Safety with combination drug use

The REPLACE-1 study was done to evaluate whether bivalirudin in combination with planned GPI was an effective and safe approach or not. The patients were randomized in an open-label fashion to receive bivalirudin or UFH during the procedure. Seventy-six percent of patients received GPI blockade in this study in which 71.7% of patients received it in a planned fashion (almost identical percentage of patients in bivalirudin and UFH groups). Overall, the composite efficacy endpoint of death, MI and revascularization occurred in 5.6% of patients in the bivalirudin group compared with 6.9% of patients in the UFH group. The major bleeding rates with bivalirudin were non-inferior to that of UFH (2.1% *vs* 2.7%, $P = 0.52$). In patients who received GPI, 7.2% of patients in the bivalirudin group experienced the composite of death, MI and revascularization compared with 6.1% of patients in the UFH group and the major bleeding episodes were the same (2.9% *vs* 2.9%) in both the groups. Thus, this study showed that, regardless of whether patients received GPI or not, bivalirudin reduces the ischemic events. Furthermore, this trial represented the largest prospective dataset of bivalirudin administered concomitantly with planned GP Ⅱb/Ⅲa blockade and provided evidence of the safety and efficacy of this combined antithrombotic approach[35]. These end points were recorded during the hospital stay or within 48 h, whichever came first, which was different from a set time duration used in CACHET trial (7 d). Also, this was a blinded study unlike CACHET trial. REPLACE-2 supported the findings in CACHET trial.

The PROTECT-TIMI 30 trial was a randomized, open label, parallel group study on 857 moderate to high risk patients (having at least one or more of these risk features, *i.e.,* diabetes, a positive cardiac biomarker either CK-MB or troponin T/I, ST-segment deviation > 0.5 mm, or TIMI risk score ⩾ 3) with non ST elevation acute coronary syndromes presenting with chest discomfort or an anginal equivalent at rest ⩾ 10 min and were anticipated to undergo PCI of a native coronary artery. This study compared the combination of eptifibatide and heparin (UFH/enoxaparin) with bivalirudin. Results showed that the primary end point of post-PCI coronary flow reserve was significantly higher with bivalirudin (1.43 *vs* 1.33, $P = 0.036$). The myocardial perfusion (post-PCI TMPG) was found to be better in eptifibatide group (57.9% *vs* 50.9%, $P = 0.048$) and the 48 h post-PCI composite of death and MI was lower in eptifibatide

group (8.8% *vs* 6.6%, *P* = 0.246). Duration of post-PCI ischemia was also lower in eptifibatide group (36 min *vs* 169 min, *P* = 0.013). In the UFH plus eptifibatide group, there were increased bleeding episodes more notably TIMI minor bleeding episodes (2.5% *vs* 0.4%, *P* = 0.027) and bleeding episodes that required transfusion (4.4% *vs* 0.4%, *P* < 0.001). This study showed that bivalirudin therapy lowers bleeding and the need for blood transfusion and thus safer than heparin plus eptifibatide therapy[12].

Mortality rates

When bivalirudin plus GPI was compared with heparin plus GPI in the ACUITY trial in a subgroup analysis of 7780 patients undergoing urgent PCI that there were no significant difference in 30 d rates of composite ischemia, *i.e.,* death, MI or revascularization (9% *vs* 8%, *P* = 0.16) and major bleeding (8% *vs* 7%, *P* = 0.32). In this subgroup analysis, when bivalirudin monotherapy group was compared with heparin plus GPI, the proportion of individuals with composite ischemia was found to be very much the same (8.8% *vs* 8.2%, *P* = 0.45) but the major bleeding events were significantly lower in the bivalirudin monotherapy patients (4.5% *vs* 7.8% *P* < 0.0001)[13]. In naive patients who were administered heparin plus GPI (*n* = 1462), similar rates of composite ischemia (5.5% *vs* 6.2%, *P* = 0.47) and more major bleeding rates (4.9% *vs* 2.5%, *P* = 0.28 to 0.75), were noted at 30 d when compared with patients naive to antithrombin therapy who were administered bivalirudin monotherapy (*n* = 1427). The one-year follow up of PCI subgroup patients showed similar rates of composite ischemia and mortality in all the 3 regimen groups[24]. In a major review, although the study demonstrated that using bivalirudin had several advantages such as being more cost effective, and lesser major bleeding events, it received criticism from researchers due to the open-label design, not including patients with acute STEMI, stating that using such definitions of bleeding endpoints made comparison between studies tough, considering hematoma > 5 cm at the puncture site as a major bleeding event among other factors[36]. Dangas *et al*[37] showed that patients who received UFH as early treatment and were switched to bivalirudin, 30 d (7.6% *vs* 12.3%, *P* = 0.0001) and 2 years (8.4% *vs* 13.0%, *P* = 0.0003), major bleeding rates were found to be lower than that of the control group. These patients also had lower 30-d (1.6% *vs* 2.9%, *P* = 0.04) and 2 year (2.3% *vs* 3.8%, *P* = 0.04) rates of cardiac mortality. MI recurrence rate (4.0% *vs* 7.1%, *P* = 0.0002) was also found to be lower at 2-year follow-up[37]. At 3 years, lower rates of all-cause mortality (5.9% *vs* 7.7%, *P* = 0.03) and NCRMB (6.9% *vs* 10.5%, *P* = 0.0001) were found with bivalirudin. For every 1000 patients treated with bivalirudin, 18 lives were saved. MACE (21.9% *vs* 21.8%, *P* = 0.95) and NACE (25.5% *vs* 27.6%) rates were similar between the two groups[38]. A pooled analysis of the patients who underwent PCI in REPLACE-2, ACUITY and HORIZONS-AMI trials showed that there is a strong positive association between NCRMB within 30 d and the 1 year mortality risk, post PCI[2]. This study supported the conclusions derived by the researchers in other similar analysis[39]. In the integer based risk score for NCRMB (TIMI) developed by this pooled analysis researchers, bivalirudin monotherapy was the only variable that received a negative score (-6) among all the 28 variables[2].

Timing studies

A *post-hoc* analysis was done to assess whether the timing of clopidogrel administration had any influence on safety and efficacy. They found that, in patients who received clopidogrel before or within 30 min after PCI, treatment with bivalirudin monotherapy resulted in significantly less bleeding rates (3.5% *vs* 6.6%, *P* < 0.0001) and similar 30-d composite ischemia (8.2% *vs* 8.3%, risk ratio: 0.98, 95% confidence interval: 0.81 to 1.20) when compared with heparin plus GPI treatment. They also found that, in the patients who receive clopidogrel > 30 min or not at all after PCI, bivalirudin monotherapy might be associated with worst ischemic outcomes (14.1% *vs* 8.5%, risk ratio: 1.66, 95%CI: 1.05 to 2.63)[40]. This might have been dueto the short half-life of bivalirudin. A subset of high risk patients undergoing PCI of the left anterior descending artery (LAD), was studied separately. Among 1445 patients who underwent PCI to the LAD, in the HORIZONS-AMI trial, the use of bivalirudin was associated with significantly lower rates of cardiac death (3.8% *vs* 6.8%, *P* = 0.01), reinfarction (5.3% *vs* 9.5%, *P* < 0.004), and major bleeding events (7.3% *vs* 11.8%, *P* = 0.004) compared to UFH plus GPI[41].

Ideally, the treatment for STEMI should be started when patients are on their way to the hospital. The EUROMAX study addressed this question by comparing the use of bivalirudin *vs* heparin plus optional GPI (control group) during emergency transport to the hospital for primary PCI. A total 2218 patients were enrolled. The primary outcome of death and non-CABG major bleeding occurred in 5.1% in bivalirudin group *vs* 8.5% in control group (*P* = 0.001). The study specified that bivalirudin had to be continued for at least 4 h after PCI. One of the limitations of the study was that GPI administration was not randomized and 11.5% of patients in bivalirudin group received it comparing to 69.1% in heparin group[42].

In contrast, the HEAT-PPCI study showed that bivalirudin was not beneficial over heparin in PCI. This was an open-label, single center, randomized trial where 1829 patients were randomized to either receive bivalirudin or heparin. The primary outcome of MACE occurred in 8.7% of patients in bivalirudin group and 5.7% in heparin group (95%CI: 1.09-2.13, *P* = 0.01). The superiority of heparin was primarily due to decreased rate of reinfarction. Both groups were given GPIs at same rate. Patients were given a bolus of bivalirudin at the end of the procedure if activated clotting time was less than

225 s but the drip was not continued after procedure[43].

The Bright trial was conducted at 82 centers in China. In this trial, 2194 patients with MI, both STEMI and NSTEMI, were randomized into three groups: The first group received bivalirudin alone, the second group heparin alone and the third group received heparin plus tirofiban infusion. In the bivalirudin group the medication had to be given for at least 30 min and no more than 4 h post PCI, and reduced dose of infusion (0.2 mg/kg per hour comparing to mandatory rate 1.75 mg/kg per hour right after PCI) could be administered for up to 20 h post PCI at physician discretion (15.6% patients of bivalirudin group). In the third group tirofiban infusion was given for 18 to 36 h total. The primary outcome of the study was net clinical adverse events (NACE) at 30 d consisting of major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) and bleeding. NACE occurred in 65 patients (8.8%) in bivalirudin group compared to 96 patients (13.2%) in heparin alone group (P = 0.008). The 30-d bleeding rate was also less frequent in bivalirudin group at 4.1% comparing to 7.5% in heparin alone group and 12.3% in bivalirudin plus tirofiban group (P < 0.001)[44].

The Matrix trial studied patients with ACS undergoing PCI and compared heparin infusion to bivalirudin with or without post-PCI continuation of bivalirudin. The primary outcomes of the study were MACE and NACE. There was no significant difference in MACE in bivalirudin group and heparin group (10.3% *vs* 10.9%, P = 0.44), or in NACE (11.2% *vs* 12.4%, respectively, P = 0.12). Bivalirudin was associated with a lower rate of death from any cause than was heparin (1.7% *vs* 2.3%, P = 0.04), as well as lower rate of death from cardiac causes (1.5% *vs* 2.2%, P = 0.03). Post-PCI infusion of bivalirudin did not significantly change the outcome in comparison to stopping the infusion after completing procedure. In this study the use of transfusion without overt bleeding did not satisfy the criteria for major bleeding[45].

Bivalirudin was compared to heparin not only during PCI but also during transcatheter valve replacement (TAVR). In this Bravo-3 trial, 802 patients with aortic stenosis were randomized to receive bivalirudin or UFH during the procedure. Although bivalirudin group showed slightly better results in the number of major bleedings at 48 h (6.9% *vs* 9.0%, P = 0.27) and net adverse cardiovascular events at 30 d (14.4% *vs* 16.1%, P = 0.35), these results were not statistically significant. Authors concluded that UFH should be used during the procedure because of the lower cost[46].

Stent thrombosis comparison trials

Within the first 24 h post-PCI stent thrombosis rates were more in patients assigned to bivalirudin compared with the control group (1.4% *vs* 0.3%, P < 0.001). The stent thrombosis rates after 24 h were more in the control group than with bivalirudin (4.4% *vs* 2.8%; P = 0.02). Stent thrombosis occurred at a higher rate in patients who received higher loading dose (600 mg) of clopidogrel[47]. Stent thrombosis rates were similar in both the groups at 30 d, one year and 3-year follow ups. When compared to bare metal stents, stent thrombosis rates were lesser with paclitaxel-eluting stents.at 3 years (9.4% *vs* 15.1%, P < 0.0001)[38].

Bivalirudin in fondaparinux pre-treated patients undergoing PCI

Fondaparinux is a factor Xa inhibitor, given subcutaneously. Today, this drug is approved in patients undergoing orthopedic surgery and as initial therapy for venous thromboembolisms. The clinical value of fondaparinux in patients with ACS has also been investigated[48]. The PENTUA (Pentasaccharide in Unstable Angina) study on NSTEMI patients compared different doses of fondaparinux against enoxaparin in patients with non-ST elevation ACS. In PCI patients, there were no significant differences between the groups in the primary endpoint of death, MI, or recurrent ischemia at the end of 9 d[49]. A study done on 20078 patients with ACS were randomly assigned to receive either Fondaparinux (2.5 mg daily) or enoxaparin (1 mg per kilogram of body weight twice daily) for a mean of six days and evaluated death, myocardial infarction, or refractory ischemia at nine days (the primary outcome); major bleeding; and their combination. Patients were followed for up to 6 mo. Fondaparinux was found to be similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduced major bleeding complications and improved long term mortality and morbidity[50].

The OASIS-5 study compared 2.5 mg daily fondaparinux with enoxaparin 1 mg/kg twice daily for a mean of 6 d in over 20000 patients with ACS. The primary endpoint of death, MI, or refractory ischemia at 9 d was similar between the groups and there was a non-significant trend toward lower event rates with fondaparinux at 30 d. Furthermore, Fondaparinux markedly lowered the rates of bleeding (2.2 % *vs* 4.1%). The mortality rates with fondaparinux were lower at both 30 and 180 d follow-up[51]. However, OASIS-6 (Sixth Organization to Assess Strategies in Acute Ischemic Syndromes) was a randomized, double-blind study performed on STEMI patients. Two point five milligram dose fondaparinux was compared to UFH. It showed that the patients in the fondaparinux group had excess PCI complications and catheter thrombosis rates. In this study, no benefit was seen in death and reinfarction rates with fondaparinux in patients undergoing primary PCI[52].

SWITCH Ⅲ was an open-label, randomized, multicenter pilot study done on 100 patients with non-ST-segment elevation ACS initially treated with fondaparinux and undergoing early invasive strategy. It compared treatment with bivalirudin *vs* UFH in these patients. Results in this study suggest that bivalirudin when compared to standard-dose UFH, had a similar safety profile in terms of thrombotic events and peri-PCI

Table 2 Major studies comparing bivalirudin and heparin

Trial name	Type of trial	Number of patients	Bleeding risk	Thrombosis risk	Mortality benefit	Comments
REPLACE-2	Randomized, double blind	6010	Favors bivalirudin	Bivalirudin noninferior	Bivalirudin noninferior	
ACUITY	Randomized, open-label	13819	Favors bivalirudin	Comparable	Comparable	
ARMYDA-7 BIVALVE	Randomized, open-label	401	Favors bivalirudin	Comparable	Comparable	Primarily decrease in access site bleeding in bivalirudin group
HORIZONS-AMI	Randomized, open-label, multicenter	3602	Favors bivalirudin	Comparable	Favors bivalirudin	Heparin group was given glycoprotein Ⅱb/Ⅲa inhibitors
NAPLES	Randomized, open-label	355	Favors bivalirudin	Comparable	No deaths in study period	All patients with diabetes mellitus. Heparin group was given tirofiban
ISAR-REACT 4	Randomized, double-blind	1721	Favors bivalirudin	Comparable	Comparable	Heparin group was given abciximab
NAPLES III	Randomized, double-blind	837	Comparable	Not studied	Not studied	Femoral approach access in PCI
EUROMAX	Randomized, open-label	2218	Favors bivalirudin	Favors heparin	Comparable	GP Ⅱb/Ⅲa inhibitor was optional in heparin group
HEAT-PPCI	Randomized, open-label	1829	Comparable	Favors heparin	Favors heparin	Use of GP Ⅱb/Ⅲa was option in both groups
BRIGHT	Randomized, open-label	2194	Favors bivalirudin	Comparable	Comparable	
MATRIX	Randomized, open-label	7213	Favors bivalirudin	Favors heparin	Favors bivalirudin	Post-PCI infusion of bivalirudin didn't affect the outcome

PCI: Percutaneous coronary intervention.

bleeding. Thus, in NSTEACS patients initially treated with upstream fondaparinux who undergo PCI, bivalirudin can be used[53].

Trials on newer antiplatelet drugs with bivalirudin

Prasugrel and ticagrelor are the novel antiplatelet drugs. In patients undergoing PCI for ACS, dual antiplatelelet therapy with aspirin and prasugrel reduced the ischemic events in TRITON-TIMI 38 study[54]. Another study showed that prasugrel was found to be as safe and effective as clopidogrel in ACS patients undergoing PCI with bivalirudin anticoagulation[55]. The benefit of reduction in ischemic events was more in STEMI patients. BRAVE-4 trial on patients undergoing urgent PCI for STEMI demonstrated a more pronounced inhibition of platelet aggregation as well as platelet adhesion and aggregate formation to collagen under flow in prasugrel plus bivalirudin treated patients[56].

DISCUSSION

In conclusion, bivalirudin is now the most commonly used anticoagulant for transradial PCI in the United States, while weight adjusted unfractionated heparin remains the most common choice outside the United States[57]. Table 2 outlines the biggest studies comparing bivalirudin to heparin. Bivalirudin reduced both ischemic and bleeding events in femoral-treated patients, even though no such clinical benefit was observed in the radial-treated patients[58]. Except in stable (cardiac biomarker negative) patients where heparin could be used, bivalirudin should be considered for anticoagulation in patients undergoing PCI especially if a patient has increased risk of bleeding. Switching from UFH or enoxaparin or fondaparinux to bivalirudin is also an option. Furthermore bivalirudin is safe to use in patients with HIT. The combination of newer antiplatelet drugs with bivalirudin in PCI patients has shown promising results. The cost of bivalirudin is high. However, this therapy reduces the overall costs since it lowers complications, hospital stays, and all over mortality[59,60]. Moreover, the combination of bivalirudin and drug eluting stents has resulted in better outcomes. Peri-procedural PCI bleeding avoidance strategies have become paramount to optimize the clinical benefit, and the interaction between bivalirudin and radial approach deserves additional investigations. There are numerous studies comparing heparin against bivalirudin. Unfortunately, many of them are difficult to compare because of difference in protocols and definitions. Some of the studies, like HORIZONS AMI, were conducted in the era when administration of GPIs was routine and newer P2Y12 inhibitors like ticagrelor and prasugrel were not yet available. The HEAT-PPCI trial showed the heparin to be superior over bivalirudin in preventing major adverse ischemic events. Heparin's longer half-life may partially explain the decreased rate of ischemic events in HEAT-PPCI trial. Many trials defined the requirement for the transfusion as a major bleeding but this was not the case in MATRIX trial unless there was overt bleeding. Recent ACC/AHA guidelines do not specify the preference of one medication over another during PCI for NSTEMI or STEMI, and both heparin and bivalirudin are acceptable

options in these guidelines. Each individual patient's ischemic and bleeding risks should be taken into account. However, in spite of some minor conflicting data, we conclude that bivalirudin should be used as preferred method of anticoagulation during PCI for ACS as the majority of randomized trials showed more superior long-term advantages over heparin, including safety, efficiency and cost-effectiveness. This will likely bring higher value to patients, defined as better outcomes for less cost, which is the ultimate goal in healthcare.

COMMENTS

Background

Anticoagulation is required during (PCI) and other percutaneous transluminal coronary angioplasty. Historically, heparin was used for this purpose until 1990's when bivalirudin was introduced to clinical practice. There is still ongoing debate about the drug of choice for peri-PCI anticoagulation.

Research frontiers

Bivalirudin is a direct thrombin inhibitor with a short half-life and this quality may decrease bleeding complications during PCI. There is extensive amount of literature comparing bivalirudin to heparin.

Innovations and breakthroughs

In this article the authors reviewed the literature comparing bivalirudin to heparin.

Applications

The article will help to understand the literature comparing bivalirudin to heparin and to make conscious and medical decision making between these medication.

Terminology

Bivalirudin is a direct thrombin inhibitor widely used to prevent thrombotic complication during PCI.

Peer-review

This is an excellent review about the safety, effectiveness, and cost benefits of bivalirudin. This manuscript is nicely structured and well written.

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