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DRUGS
Narrative review

Bivalirudin in the treatment of coronary artery disease

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Abstract

Periprocedural anticoagulation continues to be a vital aspect in the management of coronary artery disease. Bivalirudin is a relatively new drug that has caught much attention in the last decade, especially in the context of percutaneous coronary intervention for acute coronary syndromes. Multiple clinical trials have shown the efficacy, safety profile and limitations of bivalirudin in contrast to previously used heparin and glycoprotein IIb/IIIa inhibitors. These trials have included patients with moderate to high-risk stable angina, unstable angina, non-ST-elevation and ST-elevation myocardial infarctions requiring PCI. The growing body of evidence on bivalirudin has also improved the understanding of its applicability and efficacy over other hirudin-based anticoagulants, however continual review of more recent evidence is important in order to integrate bivalirudin more widely across the various guidelines. This article aims to study the cross-section of the evidence base to date on the clinical use, efficacy and risks related to the use of bivalirudin and attempts to provide the clinician with a practical overview of the role of bivalirudin in the most recent guidelines.

Keywords

Bivalirudin; Direct Thrombin Inhibitors; Anticoagulants; Acute Coronary Syndromes

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Introduction

New and novel agents targeting the anticoagulation cascade are finding increasing prevalence on the world stage of late not only in clinical trials but also within recent therapeutic guidelines.

Bivalirudin is a reversible direct thrombin inhibitor that has shown rapid integration into modern management of acute coronary syndromes (ACS) due to its strong clinical data and reduced side effect profile [1]. Since their emergence, direct thrombin inhibitors have shown several pharmacological advantages over other agents such as unfractionated heparin and glycoprotein IIb/IIIa inhibitors. Bivalirudin in particular has taken a versatile role, ranging from the treatment of unstable coronary artery disease to high-risk acute coronary syndrome [2-7]. Bivalirudin was discovered by The Medicines Company and approved by the FDA in 2000 [1]. It is currently being marketed under the trade name of Angiomax® in the United States. Other international trade names include Angiox®, Bivaflo® and Bivasave® [1].

Bivalirudin binds directly to circulating and clot-bound thrombin [2]. This prevents the cleavage of fibrinogen and inhibits activation of coagulation factors V, VIII, XIII and platelet aggregation, inhibiting clot formation [8]. The primary goals of therapy with bivalirudin are to prevent thrombotic occlusion of diseased vessels, thrombus propagation and myocardial ischaemia whilst achieving an acceptable balance with complications such as bleeding [2,9].

Through bivalirudin's rapid uptake into clinical guidelines it is quickly becoming an appealing alternative to traditional anticoagulation regimes in the setting of percutaneous intervention for both ST elevation (STEMI) and non-ST elevation myocardial infarction (NSTEMI). It is also effective in the medical management of moderate to high-risk unstable angina and NSTEMI. This article aims to review the effectiveness of bivalirudin for percutaneous coronary intervention following STEMI, moderate-high risk NSTEMI and unstable angina.

Molecular mechanism: the pharmacodynamics and pharmacokinetics of bivalirudin

Bivalirudin is a semi-synthetic analogue of a protein named hirudin, which was originally discovered in the salivary gland of the medicinal leech [8]. Like other hirudin based molecules, bivalirudin's primary effect is on the anticoagulation cascade, which is vital to its utilisation in cardiovascular medicine. The coagulation process is initiated by a complex interaction between the intrinsic and extrinsic factors found in plasma. The extrinsic activation occurs when vascular injury causes tissue factor to be exposed on endothelial cells, promoting the interaction with factor VII [9]. This contributes to the serial activation of the intrinsic factors and eventually results in the activation of thrombin [9]. Thrombin is vital to the clotting cascade due to its role in fibrinogen cleavage, cross-link formation and clot stabilisation. Normally, equilibrium is achieved between the natural procoagulants and anticoagulants preventing spontaneous clot formation. However, thrombus formation is promoted by variations in flow turbulence, blood constituents and damage to the vascular endothelium [8,9].

Bivalirudin is a peptide molecule consisting of 20 amino acid residues and contains two different binding sites – the fibrin-binding site or exosite 1 (competitive inhibition) at the carboxy-terminus and the active site at the amino-terminus [9]. It acts by binding directly to the thrombin protein via both these binding sites, without the need for any cofactors. It binds to both free and fibrin-bound thrombin with an intermediate affinity between hirudin and argatroban [9,12]. Its main role is to inhibit the activation of factors V, VIII and XIII and prevents the thrombin-mediated cleavage of fibrinogen to fibrin, thus preventing thrombus formation [8,9].

Bivalirudin is preferred over other anticoagulants due to it predictability which is explained by the linear dose-dependent pharmacokinetic property [9]. It can only be administered as an intravenous bolus or infusion and has a small volume of distribution (0.2 l/kg), which suspends it predominantly in the intravascular space [9]. The peak plasma concentration is achieved within 5 minutes of bolus infusions [1] and the onset of action is immediate. Whilst active in the system, bivalirudin causes a prolongation of PT, aPTT, thrombin time (TT) and activated platelet time (ACT) in a linear dose-dependent fashion [1,15,16]. The anticoagulation effect of bivalirudin can be monitored by checking ACT following PTCA, PCI or during CABG [9,13]. But in most catheterisation laboratories ACT is not monitored routinely with the use of bivalirudin.

Renal Function (ml/min)	Initial bolus (mg/kg)	Infusion rate for PCI (mg/kg/h)	Half-life (min)
Clcr ≥ 30	0.75	1.75	25
Clcr 10-29	0.75	1.25	60
Dialysis dependent	0.75	0.25	240

Table I. Dose-adjustments in renal impairment [1]

Bivalirudin has a short half-life of approximately 25 minutes. Upon cessation, it is rapidly cleared from plasma at a rate of 4 ml/min/kg via a dual clearance system and baseline-clotting times are achieved within 1 hour in patients with normal renal function [9]. It is metabolised predominantly through proteolytic cleavage by thrombin at the active site [14], which dislodges the molecule from both sites. As a result, binding at the active site is transient and allows for easier reversibility compared to other hirudins like lepirudin and desirudin. [10,11,12] Apart from the proteolytic cleavage, which accounts for 80% of bivalirudin's metabolism [17], renal excretion contributes to the remaining 20% and hepatic involvement is virtually negligible [12,15]. For this reason, bivalirudin requires dose adjustment in renal impairment (Table I) but not hepatic dysfunction [17].

Indications

Bivalirudin was first approved by the FDA as an effective anticoagulant during PCI or PTCA for unstable angina, where its anticoagulant effect was used to prevent thrombus formation in the peri-procedural period and subsequent complications of cardiac ischaemia [1]. However, since then it has been most commonly used in ST elevation myocardial infarction and moderate to severe non-ST elevation myocardial infarction. In addition, bivalirudin has been approved for acute coronary syndromes in patients with or at risk of heparin induced thrombocytopaenia (HIT) undergoing PCI [1-4].

Although some studies have shown positive effects of bivalirudin in patients with acute or sub-acute HITS requiring urgent cardiopulmonary bypass surgery, the evidence is still minimal and FDA approval is still pending for this use [1]. The use of bivalirudin for medical management of acute coronary syndromes is also being studied currently, but once again the lack of adequate evidence limits its application in this setting [1].

Efficacy and evidence from pivotal trials

Compared to other well-known anticoagulants, bivalirudin is a relatively new agent on the market. Since its development in 2000, it has been the subject of many pivotal trials that have investigated its efficacy, applicability and limitations (Table II). Some of the earliest trials that brought direct thrombin inhibitors into the limelight also investigated the efficacy of other hirudins such as lepirudin and desirudin. Although these hirudins showed some efficacy in the management of thromboembolic disease and anticoagulation in patients with HITS, bivalirudin has shown the most effective results for acute coronary syndromes.

Aim	Bivalirudin + GP IIb/IIIa inhibitor	Heparin + GP IIb/IIIa inhibitor	Bivalirudin alone	P-value
HORIZONS-AMI [18]				
Net adverse effects		12.1%	9.2%	< 0.05
Major Bleeding		8.3%	4.9%	< 0.001
Mortality due to cardiac causes at 30 days		2.9%	1.8%	> 0.03
Acute stent thrombosis		0.3%	1.3%	< 0.001
REPLACE-2 [19,20]				
MI at 30 days	7.0%	6.2%		< 0.001
Haemorrhage	2.4%	4.1%		< 0.001
Urgent revascularisation	1.2%	1.4%		< 0.001
Overall mortality at 12 months	1.9%	2.5%		< 0.001
ACUITY [21]				
Ischemic events	6.2%	5.5%		0.47
Major bleeding	2.5%	4.9%		< 0.001
Net clinical outcomes	8.0%	9.4%		0.17
ISAR-REACT 4 [22]				
Major Bleeding		4.6%	2.6%	0.02
Severe Thrombocytopaenia		1.2%	0.0%	-
BAT-2 [23]				
Bleeding	3.5%	9.3%		0.039
Combined end point	6.2%	7.9%		< 0.001

Table II. Summary of results from pivotal trials [18-23]

HORIZONS-AMI Trial

In this trial [18], 3602 patients with ST-elevation myocardial infarction who presented within 12 hours of the onset of symptoms and were undergoing primary PCI were recruited. Patients were either given bivalirudin alone or a combination of heparin and glycoprotein IIb/IIIa inhibitor using a randomised but open-label method. The primary end point events were major bleeding and major cardiovascular events including stroke, re-infarction, revascularisation and death. This study found that the bivalirudin group, compared to the heparin and GP IIb/IIIa group, had a reduced 30-day rate of net adverse events (9.2% vs. 12.1% respectively, relative risk = 0.76, p-value < 0.005). Majority of the risk reduction was attributed to significantly lower rates of major bleeding (4.9% vs. 8.3%, relative risk = 0.60, p-value < 0.001). Bivalirudin was also responsible for a significant reduction in 30-day mortality from both cardiac causes (1.8% vs. 2.9%, relative risk = 0.62, p-value < 0.03) and all-cause mortality (2.1% vs. 3.1%, relative risk = 0.66, p-value = 0.047). One disadvantage of bivalirudin that was discovered by this trial was the increased risk of acute stent thrombosis within 24 hours of the procedure (1.3% vs. 0.3%, p-value < 0.001), however no significant increase was seen at 30 days. In conclusion, this study demonstrated that although the early stent thrombosis was the main contributor to the increased risk of cardiovascular events in the first 24 hours post-procedure, overall benefit was seen in patients treated with bivalirudin in terms of reduced risks of major and minor bleeding, need for transfusions and incidence of net adverse events at 30 days. It is therefore proposed that bivalirudin is a suitable alternative to heparin for patients with acute ST-elevation myocardial infarction undergoing primary PCI, regardless of whether they have received heparin prior to the procedure.

REPLACE-2 trial

This trial [19,20] demonstrated the efficacy of bivalirudin in 6002 patients undergoing PCI in four key categories:

- unstable angina;
- myocardial infarction 7 days prior to procedure;
- stable angina and;
- patients with a positive exercise stress test for ischaemia.

It was a double-blinded, randomised control trial where patients were either administered a combination of bivalirudin and provisional GP IIb/IIIa inhibitor (abciximab) or heparin and GP IIb/IIIa inhibitor (abciximab). Major outcomes measured were rates of death, myocardial infarction and urgent revascularisation.

At 30 days, patients were found to have higher rates of MI (7.0% vs. 6.2%, p-value < 0.001) and the combined rates of these endpoints were higher in the bivalirudin group (7.6% vs. 7.1%, p-value < 0.001). However, overall mortality rate was lower in the bivalirudin group (0.2% vs. 0.4%, p-value < 0.001) as were the rates of major haemorrhage (2.4% vs. 4.1%, p-value < 0.001) and urgent revascularisation (1.2% vs. 1.4%, p-value < 0.001). At the 12-month follow-up, patients in the bivalirudin group were again found to have lower mortality rates when compared to the heparin and GP IIb/IIIa inhibitor group (1.9% vs. 2.5%, p-value < 0.001). This study found that major bleeding was a far more powerful predictor of death than cardiovascular events. Major haemorrhage was defined as intracranial bleeding, retroperitoneal bleeding, need for transfusion of at least 2 or more units of blood products, a fall in haemoglobin by > 4 g/dl or >3g/dL with spontaneous and non-spontaneous blood loss.

Another analysis from the REPLACE-2 trial confirmed that mortality rates in patients with major haemorrhage were significantly higher than in those without at 30 days (5.1% vs. 0.2%), 6 months (6.7% vs. 1.0%) and 1 year (8.7% vs. 1.9%, p-value<0.001 for all).

Bivalirudin showed the potential to reduce the risk of haemorrhagic complications and was therefore a suitable replacement for heparin across all acute coronary syndromes.

ACUITY trial

The ACUITY [21] is another hallmark trial in bringing bivalirudin into the foreground of cardiovascular medicine. This trial was designed to be a prospective randomised controlled trial and recruited 13,819 moderate and high-risk patients with unstable angina or non-ST elevation myocardial infarction. They were then randomly allocated to one of the following groups- UFH/enoxaparin with GP IIb/IIIa inhibitor, bivalirudin with provisional GP IIb/IIIa inhibitor, bivalirudin alone and in some cases patients were switched from a pre-treatment of UFH/enoxaparin to bivalirudin. The primary end points observed were rates of ischaemic events, major bleeding and net clinical outcomes.

Compared to patients who received heparin and GP IIb/IIIa inhibitor, the patients with bivalirudin therapy had similar rates of ischaemia (bivalirudin vs. Heparin: 6.2% vs. 5.5%, p = 0.47), lesser rates of major bleeding (2.5% vs. 4.9%, p < 0.001) and similar net clinical outcomes (8.0% vs. 9.4%, p = 0.17). In addition, it was found that those patients who switched from pre-treatment with heparin to bivalirudin had similar rates of ischaemic events compared to those who continued on UFH/enoxaparin (6.9% vs. 7.4%, p = 0.52). They also had a lower rate of major bleeding (2.8% vs. 5.8%, p < 0.01) and improved clinical outcomes (9.2% vs. 11.9%, p < 0.01).

This trial provided a significant insight into more flexible applicability of bivalirudin, especially in the setting of pre-treatment with other antithrombin agents and reinforced a conclusion reflected in previous trials: bivalirudin is as effective as heparin and GPIIb/IIIa inhibitor in preventing net ischemic events and significantly superior in reducing bleeding risks and complications.

ISAR-REACT 4 trial

In this study [22] the aim has been to assess the efficacy and applicability of bivalirudin, in contrast to a combination of unfractionated heparin and GP IIB/IIIa inhibitor (abciximab), in patients with non-ST elevation MI undergoing PCI. The trial was carried out in a double-blind manner recruiting 1,721 patients with acute non-ST elevation MI who were assigned to each of the two treatment groups equally. The primary end points that were measured were death, recurrent MI, urgent target-vessel revascularisation and major bleeding within 30 days. It was found that there was no significant difference between the two groups in the occurrence of primary end points (relative risk = 0.99, p-value = 0.94). However, the incidence of major bleeding was found to be significantly lower in the bivalirudin group (2.6% vs. 4.6%, relative risk = 1.84, p-value = 0.02). This was predominantly due to an increased frequency of TIMI minor bleeding rather ($p = 0.003$) than TIMI major bleeding ($p = 0.61$). Severe thrombocytopaenia was another complication seen in the abciximab and heparin group (1.2%), which was absent in the bivalirudin group. This also highlighted that bivalirudin is a safer choice in thrombocytopaenic patients with or without HITS as opposed to abciximab and heparin, as both these agents have been found to worsen this condition. This trial concluded that bivalirudin is equally as effective in preventing cardiovascular events and death and significantly superior to unfractionated heparin and abciximab in term of major haemorrhagic risks.

BAT-2 trial

The aim of this trial [23] was to evaluate the effect of bivalirudin in patients with unstable angina who were undergoing PTCA, using a double-blinded, multicentre, randomised trial. A group of 4,312 patients with unstable angina or post-MI angina were treated with either bivalirudin or high-dose heparin in the peri-procedural period. The efficacy endpoints comprised of death, MI, urgent revascularisation and impending or abrupt target vessel closure. The safety endpoint was major haemorrhage. The results of this study showed that the combined rates of endpoint were similar between the bivalirudin group and the heparin group (6.2% vs. 7.9%, p-value = 0.039) at 7 days. This was found to be the same at 90 days ($p = 0.012$) and 180 days ($p = 0.153$). However, significant difference was seen in the bleeding risk with bivalirudin showing less risk than heparin (3.5% vs. 9.3%, $p < 0.001$). This demonstrates that although the efficacy was non-inferior to heparin, the safety profile of bivalirudin is significantly better than heparin during PTCA for patients with unstable or post-MI angina.

Complications and safety

Haemorrhagic complications

Following the administration of bivalirudin, bleeding (minor and major collectively) continues to be the most notable complication [9,18]. Major bleeding was initially defined in the developmental trials of bivalirudin as follows:

- intracranial or retroperitoneal haemorrhage;
- clinically overt bleeding causing a reduction in haemoglobin of more than 3 g/dl;
- clinically overt bleeding leading to transfusion of 2 or more units of blood.

In addition to this, some of the pivotal trials (REPLACE-2 and ACUITY) included other measures such as haemorrhage at access site, haematoma greater than 5 cm and need for haemorrhage-controlling procedures to measure the extent of this complication [18,19].

The ACUITY trial demonstrated that there was a significant rise in overall mortality at 30 days in patients who had major haemorrhage as opposed to those who did not (7.3% vs 1.2%; $p < 0.0001$) [21].

Due to these staggering results, monitoring of clotting times and regular assessment for bleeding is a vital part of patient care following bivalirudin.

Monitoring levels

The activated clotting time (ACT) has previously been used for monitoring coagulation profile of patients on bivalirudin [24]. More recent studies have experimented with Ecarin clotting time (ECT) as opposed to the ACT. Although multiple studies have showed that ECT has shown a better correlation to bivalirudin concentrations in plasma compared to ACT [25], further evidence is required before it is implemented in clinical practice. Currently, the availability of ECT at laboratories is also limited [1].

Acute stent thrombosis

The results from the HORIZONS-AMI trial revealed that the patient group that was treated with bivalirudin was at a significantly higher risk of stent thrombosis within 24 hours of the PCI procedure: bivalirudin alone 1.3% vs. heparin and GP IIb/IIIa 0.3%, $p < 0.001$ [18]. This is a feared complication by most cardiologists, and if reduced, could further promote the use of bivalirudin in patients requiring PCI. A recent multi-centre study found that continuing a 2-hour infusion of bivalirudin post-PCI reduces the risk of acute stent thrombosis whilst maintaining the low bleeding risk: 0.7% experienced acute stent thrombosis and 1.7% had major bleeding post PCI [26]. Further studies are currently being carried out to identify more strategies to reduce the rates of acute stent thrombosis in patients who have been anticoagulated using bivalirudin.

Overdose

Bivalirudin has a wide therapeutic range with single bolus doses of up to 7.5 mg/kg being tolerated without any associated bleeding or other adverse effects [1]. In the event of an overdose, bivalirudin infusions and boluses must be immediately stopped [1]. Due to the short half-life, plasma levels are cleared rapidly [9]. There are currently no effective antidotes available for bivalirudin overdose, however clearance can be promoted by haemodialysis [9]. Following an overdose it is advised that patients are monitored for signs of haemorrhage and ACT levels are checked regularly [1].

Hypersensitivity

Like all medications, bivalirudin has a possibility for anaphylactic reaction. However, the likelihood of this occurring is less than 1% in a given population [9]. This medication does not contain immunological compounds such as antibodies or any common allergenic materials (e.g. egg protein, bovine products etc.) [1,9].

In one particular study, it was found that the drug did not promote any antibody formation at 7 and 14 days in patients treated with bivalirudin [9,14]. Another trial tested bivalirudin-treated patients for anti-bivalirudin antibodies [9,14]. Out of the 11 patients who showed positive results, 9 were false positives and the remaining two could not be retested [9,14]. These patients did not have any anaphylactic reactions in response to the drug [9,14]. Caution must still be taken if the patient has previously experienced any adverse drug reactions to hirudin molecules and the drug must be ceased upon any abnormal reactions to the medication.

Other common adverse reactions

Some of the more common adverse reactions seen in patients treated with bivalirudin include hypotension, nausea, generalized pain, headaches and injection site irritation [9,18].

Safety related to CABG procedure

Since its initial popularity with PCI, bivalirudin has been the subject of many trials, which have investigated its application in the setting of on-pump cardiopulmonary bypass (CPB) and off-pump coronary artery bypass graft (OPCAB) surgeries.

EVOLUTION-OFF was an open label, multicenter study involving a population size of 157 patients, who were randomly assigned to receive either bivalirudin or heparin during their OPCAB [27]. The regime for bivalirudin was the same as what is routinely used during PCI: 0.75 mg/kg bolus, followed by 1.75 mg/kg/h infusion for the duration of the procedure. The primary end point observed was acute procedural success. This was defined as absence of death, Q-wave MI, repeat coronary revascularization and stroke at day 7 or upon discharge, and occurred in 93% of patients in both groups. There was a significantly higher number of stroke in the heparin group (5.5% vs. 0%) however, haemorrhagic risk was similar in both groups [27].

Since then multiple trials have also tested the use of bivalirudin for on-pump cardiac bypass surgery and focused on the same primary end points as the EVOLUTION-OFF trial. 101 patients were recruited and randomized to bivalirudin or heparin. It was found that no significant difference in the primary end point data across the two groups up to 7 days follow up [9]. Rate of post-operative bleeding was greater with bivalirudin at 2 hours (238 ml vs. 160 ml, $p = 0.0009$) and a higher risk of reoperation to control bleeding [9]. This was offset by lower tendency of perioperative non-Q wave MI in the bivalirudin group [9]. The results of these trials showed that bivalirudin has the potential to be a replacement for heparin during CPB [9]. This was further emphasized by the CHOOSE trials where the safety and efficacy of bivalirudin was evaluated in comparison to heparin, in patients with heparin induced thrombocytopaenia (HIT) [28]. With a procedural success of 94% receiving bivalirudin, it was concluded that bivalirudin is a preferred alternative anticoagulant for patients with HIT requiring cardiac surgery [28].

Comparison with abciximab

Abciximab is a potent intravenous glycoprotein IIb/IIIa inhibitor that became prominent in cardiovascular medicine in the early 1990s. Since then, its antiplatelet effect has been widely used in the management of acute coronary syndromes, especially in the setting of percutaneous coronary intervention. Abciximab prevents the binding of adhesive molecules such as von Willebrand factor and fibrinogen to the Gp IIb/IIIa receptor, ultimately preventing platelet cross-link formation and platelet aggregation [9].

Many pivotal trials including EPIC, EPILOG, EPISTENT have shown the superiority of abciximab over placebo and heparin in the setting of PCI or angioplasty, in terms of 30-day mortality and AMI rates. However, HORIZONS-AMI, ACUITY, ISAR REACT 4 and REPLACE-2 have compared the effect of bivalirudin and GP IIb/IIIa inhibitor (abciximab). The results from these trials are showed following.

- HORIZONS-AMI [18]:
  - significant decreases in net adverse effects (9.2% vs. 12.1%) and major bleeding (4.9% vs. 8.4%) at 30 days and up to 2 years;
  - early stent thrombosis (< 24h) was higher by 1% in the bivalirudin group but no significant difference between 30 days to 2 years.
- ACUITY & ISAR-REACT 4 [21,22]:
  - no significant rise in net adverse effects at 30 days;
  - lower rates of bleeding in the bivalirudin group.
- REPLACE-2 [19,20]:

- significant reduction in rates of major bleeding with bivalirudin (2.4% vs. 4.1%).
- reduction in mortality rates by 24% in the bivalirudin group which persisted up to 12 months.

GUSTO V and FINESSE trials also investigated the application of abciximab for thrombolysis and collectively found that there was no significant mortality benefit but the risk of major bleeding and transfusion rates was higher [29].

Abciximab also carries a risk of thrombocytopaenia in addition to the risk of heparin-induced thrombocytopaenia from co-administered heparin [30]. The mechanism for this is thought to be due to immune-mediated response to the amino acid residues of the monoclonal antibody once it has interacted with the receptor [29,30]. A pooled analysis of eight randomised trials found that abciximab increased the incidence of mild (4.2% vs. 2%) and severe thrombocytopaenia (1% vs. 0.4%) when compared to placebo [31]. Bivalirudin does not carry this risk, therefore is a suitable choice in patients with or at risk of thrombocytopaenia from any cause [9].

In contrast to the evidence supporting the use of bivalirudin prior to cardiac surgery in multiple trials, abciximab has been shown to carry a significant increase in bleeding complications and mortality, even up to 6 hours post-cessation of the drug [31]. Patients whose procedure was complicated by bleeding required up to 6 units of packed red cells, 30 units of platelets and 8 units of fresh frozen plasma peri-operatively [31-36]. These trials have had variable results and although recent abciximab infusion is not a contra-indication to emergent cardiac surgery, it contributes to a higher bleeding risk and therefore demands greater peri-operative monitoring [32-34].

Evidence from current era: the EUROMAX study

In the recently published EUROMAX study [37] that compared bivalirudin therapy with heparin and optional GP IIb/III a inhibitor initiated in the ambulance in patients presenting with STEMI who were taken for primary PCI, there was a 40% relative risk reduction and more than a 3% absolute reduction in the risk of major bleeding or death at 30 days (5.1% vs. 8.5%, RR = 0.60, 95% CI: 0.43-0.82, p = 0.001) in the bivalirudin treatment arm.

There was a 28% relative risk reduction in the secondary triple outcome measure of death, re-infarction, or non-CABG major bleeding; 6.6% versus 9.2% (RR = 0.72, 95% CI = 0.54-0.96, p = 0.02). This result that was driven by a 57% relative risk reduction in major bleeding, 2.6% versus 6.0% (RR = 0.43, 95% CI: 0.28-0.66, p < 0.001). In this study the risk of acute stent thrombosis was 1.1% vs. 0.2% (95% CI: 1.37-27.24, p = 0.007) in the bivalirudin arm.

This study replicated the observations made in the previous studies in a modern-day context characterized by the optimal use of novel P2Y12 receptor blockers, discretionary use of GPIIb/IIIa inhibitors, radial access and early initiation of treatment [37].

Current guidelines for the use of bivalirudin

ACC/AHA 2013 updated guidelines for STEMI

The focused update of the ACC/AHA guidelines for the management of STEMI from 2013 acknowledged that bivalirudin is a reasonable alternative anticoagulant for heparin in those STEMI patients who receive fibrinolysis with streptokinase, have heparin-induced thrombocytopaenia or who, in the opinion of the physician, may benefit from anticoagulation [38]. This applies to the setting of primary PCI and regardless of whether the patient received pretreatment with UFH or not (Table III) [39].

Bivalirudin is a reasonable choice for use in PCI in patients	Recommendation	Level of evidence
With or without pretreatment with UFH or clopidogrel	I	B
Who received fibrinolytic treatment with streptokinase	I	B
Who have heparin-induced thrombocytopaenia	I	B
Who have high risk of bleeding	II	B

Table III. Summary of the recommendations for the use of bivalirudin according to the ACC/AHA Guidelines for the management of STEMI [38,39]

Based on the HERO-2 trial, it is advised that the regimen of 0.25 mg/kg bolus is followed by an intravenous infusion of 0.5 mg/kg per hour for the first 12 hours and 0.25 mg/kg per hour for the subsequent 36 hours shows optimum efficacy. It is also recommended that a reduction in the infusion rate be considered if the PTT is above 75 seconds within the first 12 hours [38-40]. However, it was advised that prospective studies be reviewed in order to understand the risk of acute and subacute stent thrombosis associated with the use of bivalirudin as previous results had confounding bias posed by concurrent use of UFH or clopidogrel. Class I recommendation (Level of evidence: B) [38,39].
Bivalirudin is also considered a reasonable choice of anticoagulation for STEMI patients with high risk of bleeding undergoing PCI. Class II recommendation (Level of evidence: B) [38,39].

ESC guidelines for STEMI 2012

The European guidelines also include bivalirudin as an effective anticoagulant for acute myocardial infarctions [41]. Following the review of the hallmark and some more recent trials, the 2012 guidelines have highlighted that a combination of bivalirudin and GP IIb/IIIa inhibitors is preferred to unfractionated heparin and GP IIb/IIIa inhibitors in the setting of a ST elevation myocardial infarction [41]. It is once again advised that the dosing regimen be followed. Class I recommendation (Level of evidence: B) [41].

2011 AACF/AHA/SCAI guideline for percutaneous coronary intervention

It has been recommended that for patients undergoing PCI, bivalirudin is a useful anticoagulant with or without prior treatment with UFH (Class I recommendation, Level of evidence: B) [42]. It is also accepted for use in patients at risk of or have heparin-induced thrombocytopaenia, as a replacement for UFH (Class I recommendation, Level of evidence: B) [42]. These recommendations were based on the recent literature supporting bivalirudin lower bleeding risk in the short term, however, caution is advised for a small increase in the risk of early ischaemic events [42].

Conclusion

For patients with acute coronary syndrome, early revascularization with PCI in combination with antiplatelet and antithrombotic therapies provide the best prognosis. Several anticoagulants have been trialed over the years and whilst some have been impressively efficacious newer agents in the market warrant for frequent updates and reviews of the current guidelines. Bivalirudin is a relatively new drug that has proven beneficial in the setting of coronary intervention for STEMI, NSTEACS and moderate to high-risk stable IHD [1]. Bivalirudin is a hirudin-based anticoagulant, which works by interfering with the activation of clotting factors, and thereby, limiting the cleavage of clot based

and circulating thrombin and the subsequent coagulation process [8,9]. Compared to other anticoagulants, the side effects of bivalirudin are far less, with major bleeding being the most significant one [9].

Several hallmark trials have revealed that bivalirudin is comparable to heparin and GP IIb/IIIa inhibitors in terms of preventing cardiac ischaemia. However, the benefit of bivalirudin is predominantly in reduction of risk of major bleeding, overall mortality and HITS associated complications [18-23]. Bivalirudin is also considered a safe replacement for UFH in patients requiring CABG procedure [27,28]. The reduced risk of HITS is an additional benefit of bivalirudin that has especially promoted its use in patients with or at risk of HITS [28]. Despite its recent emergence, bivalirudin has been incorporated into the current cardiac guidelines and continues to be the subject of ongoing research and development to yield more applicability in the field of cardiology.

The review in brief	
Clinical question	This article reviews the cross-section of the evidence base to date on the clinical use; efficacy and risks related to the use of bivalirudin and attempts to provide the clinician with a practical overview of the role of bivalirudin in the most recent guidelines.
Type of review	Narrative
Conclusions	Bivalirudin is a direct thrombin inhibitor that has shown significantly superior benefits in efficacy and safety. There is a growing evidence base for the efficacy, safety profile and limitations of bivalirudin relative to the traditional agents such as heparin and glycoprotein IIb/IIIa inhibitors. The evidence base covers the full spectrum of the acute coronary syndrome requiring percutaneous intervention (PCI) that include moderate to high-risk stable angina, unstable angina, non-ST-elevation and ST-elevation myocardial infarctions requiring PCI. The predictable pharmacodynamics and pharmacokinetics, rapid onset and offset of action and significantly low bleeding risk highlight the advantages of this agent. Early stent thrombosis (within the 1st 24-hours) observed in some trials was a serious concern. Some authorities advocate the practice of continuing the infusion for 2 hours after the interventional procedure to address this issue. The growing evidence base supporting the use of this agent has resulted in its preferred recommendation in the latest guidelines published by the peak bodies for the management acute coronary syndrome. Furthermore the cost efficacy compared to the combined use of heparin with GP2b3a inhibitors makes this an economically viable alternative.
Limitations	Lack of evidence for the use of this agent in the setting of acute coronary syndrome.

Questions for further research

The evidence base at hand is convincing enough to recommend bivalirudin as an alternative to heparin together with GPIIbIIIa inhibitors in the management of acute coronary syndrome in the catheterization laboratory. However there are practical questions yet to be answered in other areas where anticoagulation and antithrombotic therapy is required. More research is required to examine the benefit of bivalirudin as an alternative to traditional anticoagulants in the setting of medical management of acute coronary syndrome. Furthermore research in the future may shed light into its use in coronary artery by pass surgery, cardiac valve surgery, and the treatment of thromboembolic conditions such as pulmonary embolism. Heparin is commonly used for bridging of anticoagulant therapy for surgery in those on long-term oral anticoagulant therapy. More research in the future may examine the use of bivalirudin for this application too.

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