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Review Article

Does Bivalirudin Improve Outcomes in Contemporary Percutaneous Coronary Intervention?

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Abstract

Adequate anticoagulation is critical for successful Percutaneous Coronary Intervention (PCI). Unfractionated heparin has long been the standard, but bivalirudin quickly became an attractive alternative when early studies suggested a bleeding benefit without an increase in ischemic outcomes. Over the last 20 years, clinical trials have evaluated the relative efficacy and safety of heparin and bivalirudin across the spectrum of coronary artery disease presentations and in the setting of concomitant glycoprotein IIb/IIIa inhibitors, pre-treatment with oral antiplatelet agents, and radial rather than femoral arterial access. There is little doubt that bivalirudin monotherapy reduces bleeding when compared to heparin with routine glycoprotein IIb/IIIa inhibitor use, but this comparison is of diminishing relevance to contemporary PCI. Whether bivalirudin monotherapy is superior to heparin monotherapy remains the subject of much debate.

Keywords: Percutaneous Coronary Intervention; Anticoagulation; Unfractionated Heparin; Bivalirudin

Abbreviations

ACUITY: Acute Catheterization and Urgent Intervention Triage Strategy; BARC: Bleeding Academic Research Consortium; BRIGHT: Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial; CAD: Coronary Artery Disease; EUROMAX: European Ambulance Acute Coronary Syndrome Angiography; GP IIb/IIIa inhibitor: Glycoprotein IIb/IIIa inhibitor; HEAT-PPCI: How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention; HORIZONS-AMI: Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ISAR-REACT 3: Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3; ISAR-REACT 4: Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4; MACE: Major Adverse Cardiac Events; MATRIX: Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; MI: Myocardial Infarction; NACE: Net Adverse Clinical Events; NAPLES: Novel Approaches for Preventing or Limiting Events; NSTEMI: Non-ST Segment Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; REPLACE-2: Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; STEMI: ST-segment Elevation Myocardial Infarction; TVR: Target Vessel Revascularization; UFH: Unfractionated Heparin

Introduction

Percutaneous Coronary Intervention (PCI) is a common treatment for the full spectrum of Coronary Artery Disease (CAD). Effective antithrombotic therapy is absolutely critical to safe, successful PCI and prevents thrombus formation on the guide catheter, on guide wires, and at the site of intracoronary endothelial disruption resulting from balloon dilation and stent implantation. Intravenous Unfractionated Heparin (UFH) has long been the standard anticoagulant during PCI, but in the last 10 to 15 years the direct thrombin inhibitor bivalirudin has become an attractive alternative. Unlike UFH, bivalirudin does not require a cofactor and is active against both free and thrombus-bound thrombin [1]. Furthermore, the unpredictable pharmacokinetics of UFH in individual patients makes precise dosing difficult and result in somewhat unpredictable anticoagulant effects. Based on trials of bivalirudin monotherapy compared to UFH with routine glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor use, bivalirudin enjoys a reputation for less bleeding. However, GP IIb/IIIa inhibitors are no longer routinely used with UFH, so the currently relevant comparison is bivalirudin monotherapy to UFH monotherapy. Despite nearly 20 years of clinical trials, the relative advantages and disadvantages of bivalirudin monotherapy over UFH monotherapy remain unclear.

Trials in Non-Primary PCI

Major randomized clinical trials of UFH and bivalirudin in PCI are summarized in **Table 1**. The first major study of bivalirudin in PCI was the Hirulog Angioplasty Study which randomized 4098 patients with unstable angina or post-infarction angina undergoing balloon angioplasty to high-dose UFH (a bolus of 175 units/kg followed by a continuous infusion) or bivalirudin and showed no difference in in-hospital death or ischemic outcomes in the per-protocol analysis [2]. However, in-hospital major hemorrhage occurred in 9.8% of patients receiving UFH but only 3.8% of patients receiving bivalirudin ($P < 0.001$). Notably, the re-analysis of this study by the intention-to-treat principle confirmed the bleeding advantage of bivalirudin up to 90 days (3.7% vs 9.3%, $P < 0.001$), and additionally suggested a benefit for the composite of death, Myocardial Infarction (MI), or revascularization at 90 days (15.7% vs 18.5%, $P = 0.012$) which was not maintained at 180 days (23.0% vs 24.7%, $P = 0.153$) [3].

Subsequently, the use of GP IIb/IIIa inhibitors with UFH became routine, and PCI progressed from balloon angioplasty to coronary stenting. Therefore, the Randomized Evaluation in PCI Linking

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Table 1: Summary of major randomized controlled trials of heparin (UFH, enoxaparin, or both) and bivalirudin to support percutaneous coronary intervention. All endpoints are assessed at the same time as the primary endpoint unless otherwise noted. ACS = Acute Coronary Syndrome; BARC = Bleeding Academic Research Consortium; CABG = Coronary Artery Bypass Grafting; GPI = Glycoprotein IIb/IIIa Inhibitor; N = Sample Size; NR = Not Reported; NS = Not Significant; PCI = Percutaneous Coronary Intervention; TLR = Target-Lesion Revascularization; TVR = Target-Vessel Revascularization. *The other primary outcomes were major bleeding at 30 days (see table) and the composite of death, MI, and unplanned revascularization for ischemia at 30 days (no difference between groups). **Definite stent thrombosis. †Reinfarction. ‡The other primary efficacy endpoint was the composite of death, MI, stroke, or BARC type 3 or 5 bleeding at 30 days (no difference between groups).

Trial	N	PCI Population	Primary Outcome Definition	Primary Outcome Result	Bleeding Outcome Definition	Bleeding Outcome Result	Myocardial Infarction	All Stent Thrombosis	All-Cause Death	Notes
Bivalirudin vs UFH + GPI										
REPLACE-2 (2003) [4]	6010	Non-primary PCI	Death, MI, urgent repeat revascularization at 30 days, in-hospital bleeding	Bivalirudin: 9.2% UFH: 10.0% P = 0.32	Major bleeding	Bivalirudin: 2.4% UFH: 4.1% P <0.001	Bivalirudin: 7.0% UFH: 6.2% P = 0.23	NR	Bivalirudin: 0.2% UFH: 0.4% P = 0.26	86% received pre-PCI with $P2Y_{12}$ inhibitor
ACUITY (PCI subgroup, 2007)) [6]	5180	Non-primary PCI	Death, MI, unplanned revascularization for ischemia, major bleeding at 30 days*	Bivalirudin: 12% UFH: 13% P = 0.057	Non-CABG major bleeding (co-primary outcome)	Bivalirudin: 4% Heparin: 7% P <0.0001	Bivalirudin: 6% Heparin: 6% P = 0.19	Bivalirudin: 1% Heparin: 1% P = 0.87	Bivalirudin: 1% Heparin: 0.9% P = 0.53	69% received pre-PCI with $P2Y_{12}$ inhibitor Excludes the bivalirudin + GPI arm Heparin includes UFH or enoxaparin
HORIZONS-AMI(2008) [10]	3602	Primary PCI	Death, reinfarction, TVR for ischemia, stroke, major bleeding at 30 days	Bivalirudin: 9.2% UFH: 12.1% P = 0.005	Non-CABG major bleeding (co-primary endpoint)	Bivalirudin: 4.9% UFH: 8.3% P =<0.001	Bivalirudin: 1.8% UFH: 1.8% P = 0.90†	Bivalirudin: 2.5% UFH: 1.9% P = 0.30	Bivalirudin: 2.1% UFH: 3.1% P = 0.047	100% received pre-PCI $P2Y_{12}$ inhibitor per protocol Acute stent thrombosis (within 24 hours) increased with bivalirudin (1.3% vs 0.3%, P <0.001)
ISAR-REACT 4 (2011) [7]	1721	Non-primary PCI	Death, large recurrent MI, urgent TVR, major bleeding at 30 days	Bivalirudin: 11.0% UFH: 10.9% P = 0.94	Major bleeding	Bivalirudin: 2.6% UFH: 4.6% P = 0.02	Bivalirudin: 11.4% UFH: 12.0% P = NS	Bivalirudin: 0.7% UFH: 0.6% P = NS**	Bivalirudin: 1.6% UFH: 1.4% P = NS	100% received pre-PCI $P2Y_{12}$ inhibitor per protocol
EUROMAX(2013) [12]	2218	Primary PCI	Death or non-CABG major bleeding at 30 days	Bivalirudin: 5.1% Heparin: 8.5% P = 0.001	Non-CABG major bleeding	Bivalirudin: 2.6% Heparin: 6.0% P =<0.001	Bivalirudin: 1.7% Heparin: 0.9% P = 0.08†	Bivalirudin: 1.6% Heparin: 0.5% P = 0.02**	Bivalirudin: 2.9% Heparin: 3.1% P = 0.86	91% received pre-PCI $P2Y_{12}$ inhibitor per protocol 47% radial arterial access Heparin includes UFH or enoxaparin Acute stent thrombosis (within 24 hours) increased with bivalirudin (1.1% vs 0.2%, P = 0.007)

Trial	N	PCI Population	Primary Outcome Definition	Primary Outcome Result	Bleeding Outcome Definition	Bleeding Outcome Result	Myocardial Infarction	All Stent Thrombosis	All-Cause Death	Notes
BRIGHT(2015) [16]	1465	Primary PCI	Death, reinfarction, ischemia-driven TVR, stroke, bleeding at 30 days	Bivalirudin: 8.8% UFH: 17.0% P = <0.001	All bleeding (BARC types 1-5) BARC 3-5 bleeding	Bivalirudin: 4.1% UFH: 12.3% P = NR (significant) Bivalirudin: 0.5% UFH: 2.1% P = NR (significant)	Bivalirudin: 1.0% UFH: 0.8% P = NS†	Bivalirudin: 0.6% UFH: 0.7% P = NS	Bivalirudin: 1.8% UFH: 2.1% P = NS	97% received pre-PCI $P2Y_{12}$ inhibitor per protocol 78% radial arterial access UFH dose was 60 units/kg Bivalirudin dose was 0.75 mg/kg bolus and 1.75 mg/kg/h infusion with post-PCI infusion
Bivalirudin vs UFH monotherapy										
Hirulog Angioplasty Study (1995) [2]	4098	Non-primary PCI	In-hospital death, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin	Bivalirudin: 11.4% UFH: 12.2% P = NS	Major bleeding	Bivalirudin: 3.8% UFH: 9.8% P =<0.001	Bivalirudin: 3.2% UFH: 3.9% P = 0.20	NR	Bivalirudin: 0.4% UFH: 0.2% P = 0.27	No pre-PCI $P2Y_{12}$ inhibitor UFH dose was 175 units/kg bolus followed by 18-24 hour infusion of 15 units/kg/hr Bivalirudin dose was 1.0 mg/kg bolus followed by2.5 mg/kg/h infusion for 4 hours and 0.2 mg/kg/hr infusion for 14-20 hours
ISAR-REACT 3(2008) [8]	4570	Non-primary PCI	Death, MI, urgent TVR for ischemia at 30 days, in-hospital major bleeding	Bivalirudin: 8.3% UFH: 8.7% P = 0.57	Major bleeding	Bivalirudin: 3.1% UFH: 4.6% P = 0.008	Bivalirudin: 5.6% UFH: 4.8% P = NR	Bivalirudin: 0.5% UFH: 0.4% P = 0.52**	Bivalirudin: 0.1% UFH: 0.2% P = NR	100% received pre-PCI $P2Y_{12}$ inhibitor per protocol UFH dose was 140 units/kg Bivalirudin dose was 0.75 mg/kg bolus and 1.75 mg/kg/h infusion

Trial	N	PCI Population	Primary Outcome Definition	Primary Outcome Result	Bleeding Outcome Definition	Bleeding Outcome Result	Myocardial Infarction	All Stent Thrombosis	All-Cause Death	Notes
HEAT-PPCI(2014) [13]	1829	Primary PCI	Death, stroke, reinfarction, TLR at 28 days	Bivalirudin: 8.7% UFH: 5.7% P = 0.01	Major bleeding (BARC type 3-5; primary safety outcome)	Bivalirudin: 3.5% UFH: 3.1% P = 0.59	Bivalirudin: 2.7% UFH: 0.9% P = 0.004	Bivalirudin: 3.4% UFH: 0.9% P = 0.001	Bivalirudin: 5.1% UFH: 4.3% P = 0.43	>99% received $P2Y_{12}$ inhibitor per protocol UFH dose was 70 units/kg Bivalirudin dose was 0.75 mg/kg bolus and 1.75 mg/kg/h infusion 81% radial arterial access 82% underwent PCI Acute stent thrombosis (within 24 hours) increased with bivalirudin (2.9% vs 0.9%, P = 0.007)
BRIGHT(2015) [16]	1464	Primary PCI	Death, reinfarction, ischemia-driven TVR, stroke, bleeding at 30 days	Bivalirudin: 8.8% UFH: 13.2% P = 0.008	All bleeding (BARC types 1-5) BARC 3-5 bleeding	Bivalirudin: 4.1% UFH: 7.5% P = NR (significant) Bivalirudin: 0.5% UFH: 1.5% P = NS	Bivalirudin: 1.0% UFH: 1.2% P = NS†	Bivalirudin: 0.6% UFH: 0.9% P =NS	Bivalirudin: 1.8% UFH: 1.8% P = NS	96% received pre-PCI $P2Y_{12}$ inhibitor per protocol UFH dose was 100 units/kg Bivalirudin dose was 0.75 mg/kg bolus and 1.75 mg/kg/h infusion with post-PCI infusion 79% radial arterial access

Trial	N	PCI Population	Primary Outcome Definition	Primary Outcome Result	Bleeding Outcome Definition	Bleeding Outcome Result	Myocardial Infarction	All Stent Thrombosis	All-Cause Death	Notes
NAPLES III (2015) [15]	837	Non-primary PCI	In-hospital major bleeding	See bleeding outcome	In-hospital major bleeding (primary outcome)	Bivalirudin: 3.3% UFH: 2.6% P = 0.54	Bivalirudin: 22.0% UFH: 21.5% P = NS	Bivalirudin: 0.5% UFH: 0.5% P = 0.99	Bivalirudin: 2.4% UFH: 1.4% P = 0.31	100% received pre-PCI $P2Y_{12}$ inhibitor per protocol UFH dose was 70 units/kg Bivalirudin dose was 0.75 mg/kg bolus and 1.75 mg/kg/h infusion No radial access Outcomes except for bleeding are assessed at 30 days
MATRIX(2015) [17]	7213	Primary and non-primary PCI	Death, MI, or stroke at 30 days‡	Bivalirudin: 10.3% UFH: 10.9% P = 0.44	Any bleeding BARC type 3 or 5	Bivalirudin: 11.0% UFH: 13.6% P = 0.001 Bivalirudin: 1.4% UFH: 2.5% P = <0.001	Bivalirudin: 8.6% UFH: 8.5% P = 0.93	Bivalirudin: 1.0% UFH: 0.6% P = 0.048**	Bivalirudin: 1.7% UFH: 2.3% P = 0.04	82% received a pre-PCI oral ant platelet agent other than aspirin 25.9% of UFH-treated patients received a GPI compared to 4.6% of bivalirudin-treated patients UFH dose was 70-100 units/kg without GPI or 50-70 units/kg with GPI Bivalirudin dose was 0.75 mg/kg bolus and 1.75 mg/kg/h infusion with or without post-PCI infusion 50% radial arterial access

Angiomax to Reduced Clinical Events (REPLACE-2) trial randomized 6010 patients undergoing urgent or elective PCI to bivalirudin with provisional GP IIb/IIIa inhibitor use (actual use in 7.2%) or UFH with routine GP IIb/IIIa inhibitor use (actual use in 96.5%) [4]. There was no difference in the primary composite outcome of 30-day death, MI, urgent revascularization, and in-hospital major bleeding (9.2% vs 10.0% for bivalirudin vs UFH, P = 0.32), but in-hospital major bleeding was reduced in favor of bivalirudin (2.4% vs 4.1%, P <0.001). The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial randomized 13,819 patients with unstable angina or

non-ST segment elevation myocardial infarction (NSTEMI) to UFH or enoxaparin with routine GP IIb/IIIa inhibitor use, bivalirudin with GP IIb/IIIa inhibitor use, or bivalirudin monotherapy [5]. All patients had coronary angiography within 72 hours of randomization, and analysis of the subgroup of 7789 patients undergoing PCI showed no difference in the composite of ischemic outcomes and major bleeding at 30 days. However, major bleeding not related to Coronary Artery Bypass Grafting (CABG) was significantly reduced with bivalirudin monotherapy compared to heparin (UFH or enoxaparin) with routine GP IIb/IIIa inhibitor use (4% vs 7%, P <0.0001) [6]. Notably, lack of pre-treatment with a thienopyridine appeared to confer a slightly elevated risk for ischemic events with bivalirudin monotherapy. Finally, the double-blind Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4 (ISAR-REACT 4) trial randomized 1721 patients with an NSTEMI to UFH with routine GP IIb/IIIa inhibitor use or bivalirudin with provisional GP IIb/IIIa use. At 30 days, there was no difference in the primary composite endpoint of death, MI, urgent Target Vessel Revascularization (TVR), or major bleeding (10.9% vs 11.0% for UFH vs bivalirudin, respectively; P = 0.94). Again, bivalirudin was superior with regard to major bleeding (2.6% vs 4.6%, P = 0.02) [7].

In the mid 2000's, pre-treatment with a clopidogrel became common practice and was thought to mitigate the benefit of concomitant GP IIb/IIIa inhibitor use during PCI. Therefore, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 3) trial randomized 4570 patients with stable or unstable angina undergoing PCI who were pre-treated with 600 mg of clopidogrel to UFH monotherapy or bivalirudin monotherapy [8]. Notably, the UFH dose was nearly double the current guideline-recommended dose (140 units/kg vs 70-100 units/kg) [9]. At 30 days, there was no difference the primary composite endpoint of 30-day ischemic outcomes or in-hospital major bleeding, but in-hospital major bleeding was significantly reduced in the bivalirudin arm (3.1% vs 4.6%, P = 0.008).

Trials in Primary PCI

A wave of trials of bivalirudin in the primary PCI population began several years after the trials in patients undergoing non-primary PCI. The first was the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial which randomized 3602 patients with STEMI undergoing primary PCI to UFH with routine GP IIb/IIIa inhibitor use or bivalirudin monotherapy [10]. Pre-treatment with clopidogrel or ticlopidine was required by protocol. The primary outcome consisted of the composite of major bleeding, death, reinfarction, TVR for ischemia, and stroke at 30 days and was reduced in the bivalirudin arm (9.2% vs 12.1%, P = 0.005). This was driven by non-CABG major bleeding (4.9% vs 8.3%, P <0.001), but bivalirudin also conferred an overall mortality benefit (2.1% vs 3.1%, P = 0.047). These benefits came at the cost of an increased risk of acute stent thrombosis (1.3% vs 0.3%, P <0.001 in favor of UFH) with no difference in stent thrombosis at 30 days. Furthermore, non-CABG bleeding (6.9% vs 10.5%, P = 0.0001), all-cause mortality (5.9% vs 7.7%, P = 0.03), and cardiac mortality (2.9% vs 5.1%, P = 0.001) favored bivalirudin at 3 years [11]. Similarly, the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) study randomized 2218 patients with STEMI to bivalirudin monotherapy or UFH with routine GP IIb/IIIa inhibitor use during transport, with nearly half of patients having radial access [12]. The primary outcome of death or non-CABG major bleeding at 30 days was reduced in the bivalirudin arm (5.1% vs 8.5%, P = 0.001), driven by non-CABG major bleeding (2.6% vs 6.0%, P <0.001), and came at the cost of increased acute stent thrombosis (1.1% vs 0.2%, P = 0.007). Notably, the mortality difference seen in HORIZONS-AMI was not replicated in EUROMAX.

Mirroring the shift in bivalirudin trials in non-primary PCI, primary PCI trials evolved with contemporary practice to compare bivalirudin monotherapy to heparin monotherapy. The first such study was the single-center How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) study that caused much controversy when it was published in 2014. Designed as a pragmatic trial utilizing delayed consent, the investigators randomized 1829 patients with STEMI (97% of patients not previously enrolled) to UFH monotherapy or bivalirudin monotherapy [13]. Bailout GP IIb/IIIa use was low in both arms (13-15%), all but 9 patients received a P2Y12 inhibitor loading dose, and 82% of patients underwent PCI. Surprisingly, the primary efficacy outcome consisting of the composite of all-cause mortality, stroke, reinfarction, and unplanned target lesion revascularization at 28 days was reduced in the UFH arm (5.7% vs 8.7%, P = 0.01). Again, acute stent thrombosis was increased with bivalirudin compared to UFH (0.9% vs 2.9%, P = 0.007). Perhaps even more surprisingly, the primary safety outcome of major bleeding (Bleeding Academic Research Consortium [BARC] [14] type 3-5) at 28 days was equal in both arms (3.1% vs 3.5% for UFH and bivalirudin, respectively; P = 0.59).

Shortly thereafter, the single-center Novel Approaches for Preventing or Limiting Events (NAPLES) III trial randomized 837 patients at increased bleeding risk and without cardiac biomarker elevation who were undergoing PCI to UFH monotherapy or bivalirudin monotherapy [15]. GP IIb/IIIa use was minimal in both arms, and there was no difference in the primary outcome of in-hospital major bleeding (2.6% vs 3.3% for UFH vs bivalirudin, respectively; P = 0.54). In addition, there was no difference in MI, stent thrombosis, or death at 30 days or one year. Although this trial was considerably smaller than most others in the same arena, it is useful in that its findings are similar to those of HEAT-PPCI.

Next, the multicenter Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial (BRIGHT) randomized 2194 patients undergoing primary PCI for STEMI (over 87%) or emergent NSTEMI to bivalirudin monotherapy with a post-PCI infusion, UFH monotherapy, or UFH with the GP IIb/IIIa inhibitor tirofiban [16]. Nearly all patients were pre-treated with a P2Y12 inhibitor and just under 80% of patients had radial access. The primary composite outcome of all-cause death, reinfarction, ischemia-driven TVR, stroke, or bleeding at 30 days occurred in 8.8% of bivalirudin-treated patients, 13.2% of UFH monotherapy-treated patients (P = 0.008), and 17.0% of UFH and tirofiban-treated patients (P = <0.001). This difference was driven by BARC type 1-5 bleeding (4.1% vs 7.5% vs 12.3% for bivalirudin, UFH, and UFH with tirofiban, P <0.001), while there was a trend towards reduced BARC type 3-5 bleeding with bivalirudin monotherapy compared to UFH monotherapy. No

difference was seen in death, reinfarction, stroke, or stent thrombosis, and findings persisted out to one year. Notably, while nearly all prior trials had used Angiomax (The Medicines Company, Parsippany, NJ), BRIGHT used a generic formulation (Salubris Pharmaceuticals Co, China).

Most recently, the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial randomized 7213 patients with an ACS (55.6% STEMI) and planned for PCI to UFH or bivalirudin monotherapy [17]. Additionally, patients receiving bivalirudin were further randomized to bivalirudin cessation at the conclusion of PCI or a post-PCI bivalirudin infusion. The primary outcomes were the composite of Major Adverse Cardiac Events (MACE) defined as death, MI, or stroke as well as the composite of MACE or major bleeding (net adverse clinical events, or NACE). There was no significant difference between UFH and bivalirudin in either primary outcome, nor did a post-PCI bivalirudin infusion impact rate of TVR or stent thrombosis. However, major bleeding (BARC type 3 or 5) was decreased with bivalirudin (1.4% vs 2.5%, P <0.001) as was any bleeding, and it was fatal bleeds that largely drove decreases in all-cause (1.7% vs 2.3%, P = 0.04) and cardiac (1.5% vs 2.2%, P = 0.03) mortality with bivalirudin. However, definite stent thrombosis was increased with bivalirudin (1.0% vs 0.6%, P = 0.048). Importantly, 25.9% of patients in the UFH arm and 4.6% of patients in the bivalirudin arm received a GP IIb/IIIa inhibitor, and 82% of patients received clopidogrel, prasugrel, or ticagrelor prior to angiography.

The Controversy Continues

So what are we to make of these seemingly similar studies with divergent outcomes? Does bivalirudin truly have a lower risk of bleeding than UFH, or is the increased bleeding risk with UFH conferred by the much higher rate of concomitant GP IIb/IIIa inhibitor use? If a bleeding benefit is present, is it obliterated by the shift to a radial-first arterial access strategy? Do bivalirudin-treated patients have an increased risk of acute stent thrombosis? And finally, is the potential mortality benefit of bivalirudin over UFH real?

The advantage of bivalirudin monotherapy over UFH with a GP IIb/IIIa inhibitor for bleeding outcomes is effectively incontrovertible. However, in contemporary practice GP IIb/IIIa inhibitors have largely been relegated to use for complications of PCI including no-reflow or a high thrombus burden. The currently relevant comparison is bivalirudin monotherapy to UFH monotherapy, and for that the evidence is less clear. The only large randomized clinical trial to address this question in the non-primary PCI population is the ISAR-REACT 3 trial which showed reduced bleeding in favor of bivalirudin [8]. However, the UFH dose was nearly twice that recommended by current PCI guidelines (140 units/kg bolus as compared to the recommended 70-100 units/kg bolus), a difference which biased the results in favor of bivalirudin. In contrast, NAPLES III was a much smaller trial in non-primary PCI but used guideline-consistent UFH and bivalirudin dosing and showed equivalent major bleeding (by the REPLACE bleeding definition) between UFH and bivalirudin [15]. In primary PCI, MATRIX showed a benefit for bleeding with bivalirudin, but GP IIb/IIIa use was more than 5 times greater in the UFH arm, again biasing results in favor of bivalirudin [17]. Additionally, the single-center HEAT-PPCI trial showed no difference in BARC type 3-5bleeding, and the multicenter BRIGHT trial, which used a generic bivalirudin different than all other trials, showed less BARC type 1-5 bleeding with bivalirudin and a trend towards less BARC type 3-5 bleeding [13,16]. Finally, two recent meta-analyses showed no difference in bleeding between bivalirudin and heparin monotherapy in patients undergoing PCI [18,19]. Therefore, whether bivalirudin truly improves bleeding outcomes over UFH monotherapy remains somewhat unclear. We are inclined to think that while there may be some reduction in bleeding risk with bivalirudin over UFH, the difference is probably small.

Interestingly, two recent observational studies have suggested a major reduction or elimination of any benefit in bleeding outcomes conferred by bivalirudin over UFH when radial arterial access is used in preference to femoral access [20,21]. However, the randomized trials noted above do not support this. MATRIX randomized patients to femoral or radial access (each arm had 50% of each), and access site did not modify the effect of anticoagulant on any of the major outcomes [17]. In addition, BRIGHT had high rates of radial access and showed a reduction in all bleeding including both access site-related and non-access site-related bleeding [16]. Therefore, although access site-related bleeding rates are reduced with radial compared to femoral arterial access, it appears that this does not eliminate the possibility of a bleeding advantage favoring bivalirudin.

The available trials are largely consistent in the conclusion that bivalirudin does not confer a significant benefit with regard to ischemic outcomes compared to either UFH or UFH with a GP IIb/IIIa inhibitor. However, HORIZONS-AMI, EUROMAX, and HEAT-PPCI all showed an increase in acute stent thrombosis while HEAT-PPCI and MATRIX showed an increase in definite stent thrombosis with bivalirudin compared to either UFH or UFH with a GP IIb/IIIa inhibitor [10,12,13,17]. Although this has generally not translated into a long-term difference in stent thrombosis and does not appear to impact mortality (indeed, mortality has occasionally been lower in the bivalirudin arm despite increased stent thrombosis!), stent thrombosis can still be a very morbid and devastating complication. Therefore, although relatively rare, the increase in stent thrombosis with bivalirudin is a major cause for concern.

Finally, both HORIZONS-AMI and MATRIX showed a mortality benefit to bivalirudin over UFH with and without GP IIb/IIIa inhibitor use [10,17] First, it is important to note that mortality was one of many secondary outcomes in both trials, and the P-values were marginally significant in both. Therefore, it remains possible that these mortality differences are simply the result of type I statistical error. Furthermore, both HORIZONS-AMI and MATRIX suggested that the mortality benefit of bivalirudin was likely driven by reductions in major or fatal bleeding. Therefore, if the finding of a mortality reduction is not the result of statistical error, it likely depends on the ability of bivalirudin to decrease bleeding. As we have argued above, this remains to be convincingly demonstrated for UFH monotherapy compared to bivalirudin monotherapy, which is the comparison most relevant to contemporary practice.

Conclusion

Within the contemporary PCI environment marked by provisional use of GP IIb/IIIa inhibitors and common pre-treatment with potent oral antiplatelet regimens, the purported bleeding benefit conferred

by bivalirudin monotherapy compared to UFH monotherapy during PCI is small at best and non-existent at worst. Furthermore, the clear signal for increased acute stent thrombosis with bivalirudin should give operators pause. These facts combined with the considerable cost savings of UFH over bivalirudin suggest that given the available evidence, UFH should be the preferred anticoagulant to support PCI. Future clinical trials should look to address the gaps in evidence noted above, with particular attention paid to the non-primary PCI setting which has a different peri-procedural risk profile and a paucity of evidence for the contemporary anticoagulation environment.

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