Cardiovascular Revascularization Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Bivalirudin versus heparin in women undergoing percutaneous coronary intervention: A systematic review and meta-analysis of randomized clinical trials☆,☆☆

Marwan Saad [a], Ramez Nairooz [a], Ahmed Rashed [b], Hesham K. Abdelaziz [c], Amgad Mentias [d], J. Dawn Abbott [e,*]

[a] Department of Medicine, Division of Cardiovascular Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[b] Department of Medicine, Division of Cardiovascular Medicine, Wayne State University/Detroit Medical Center, Detroit, MI, USA
[c] Department of Cardiovascular Medicine, Blackpool Teaching Hospital NHS Foundation Trust, Lancashire Cardiac Centre, Blackpool, UK
[d] Department of Medicine, Division of Cardiovascular Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA
[e] Division of Cardiovascular Medicine, Rhode Island Hospital, Brown Medical School, Providence, RI, USA

ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 18 February 2017
Accepted 23 February 2017
Available online xxxx

Keywords:
Bivalirudin
heparin
women
PCI

ABSTRACT

Background: The anticoagulant of choice during percutaneous coronary intervention (PCI) in women is not well established.
Methods: An electronic search was conducted for trials that randomized patients undergoing PCI to bivalirudin versus heparin, and reported outcomes of interest in women. Random effects DerSimonian–Laird risk ratios (RR) were calculated. Main outcome was net adverse clinical events (NACE) at 30-days. Other outcomes included major adverse cardiac events (MACE), all-cause mortality, myocardial infarction (MI), target vessel revascularization (TVR), and major bleeding at 30-days. 1-year all-cause mortality and MACE were also examined.
Results: Nine trials that randomized women undergoing PCI to bivalirudin ($n = 3960$) versus heparin ($n = 4050$) were included. At 30-days, bivalirudin was associated with reduced risk of NACE (RR = 0.85; 95% CI 0.73–0.98; $p = 0.03$), mainly driven by reduction in major bleeding (RR = 0.59; 95% CI 0.49–0.71; $p < 0.001$) compared with heparin. No difference in MACE ($p = 0.92$), all-cause mortality ($p = 0.23$), MI ($p = 0.86$); or TVR ($p = 0.53$) was demonstrated between both groups. At 1-year, the risk of MACE and all-cause mortality was similar in both groups. On a subgroup analysis, the benefit associated with bivalirudin appeared to be less evident when Glycoprotein IIb/IIIa inhibitors (GPI) was used as bailout therapy with heparin, however without significant interaction. Furthermore, in STEMI population, no difference in NACE, MACE, or major bleeding was observed between both groups.
Conclusion: In women undergoing PCI, bivalirudin is associated with reduced risk of major bleeding and NACE compared with heparin especially when GPI is routinely used.

1. Introduction

Anticoagulation during percutaneous coronary intervention (PCI) prevents ischemic events by reducing thrombus formation on intravascular equipment, as well as at the site of coronary endothelial disruption resulting from balloon dilation and stent implantation [1]. Heparin with or without glycoprotein IIb/IIIa inhibitors (GPI) has long been the standard anticoagulant during PCI. The direct thrombin inhibitor bivalirudin (Angiomax®, The Medicines Company) became an attractive alternative after studies showed a possible reduction in the risk of major bleeding and net adverse clinical events (NACE) with bivalirudin compared to heparin [2–4]. This was however challenged by meta-analyses suggesting that the benefit of bivalirudin over heparin is largely related to routine administration of GPI with heparin, as well as the high doses of heparin used [5–7].

Women undergoing PCI are at higher risk of bleeding complications and mortality compared with men, thus the weighted risk versus benefit of the type of anticoagulation used is of utmost importance [8,9]. Unfortunately, only a few studies were designed to assess the anticoagulant of choice during PCI in women [10–12]. While favorable bleeding outcomes with bivalirudin compared to heparin have been observed in women, the impact of routine versus bailout use of GPI, and clinical presentation on such outcomes has not been investigated. Furthermore, a recent pooled analysis showed a reduced risk of 1-year mortality with bivalirudin compared to heparin in women undergoing PCI, however that analysis was limited to 3 studies [13]. We aim to conduct a more comprehensive meta-analysis including all randomized clinical trials to date, with the objective to assess short and long-term clinical outcomes of bivalirudin versus heparin in women undergoing

☆ Funding: None.
☆☆ Conflicts of interest: The authors have no conflicts of interest to declare.
* Corresponding author at: Division of Cardiology, Rhode Island Hospital, Brown Medical School, 593 Eddy St, 814 APC, Providence, RI, USA. Tel.: +1 401 444 8540.
E-mail address: jabbott@lifespan.org (J.D. Abbott).

http://dx.doi.org/10.1016/j.carrev.2017.02.019
1553-8389/

Table 1
Characteristics of included studies.

Study	Year	Patient population	Patients, n[a]	Treatment strategies	GPI use in heparin arm, %	Primary outcome
BRIGHT	2015	STEMI	127/265	Bivalirudin vs UFH alone or plus tirofiban	50	Death/MI/TVR, stroke or bleeding
MATRIX	2015	STEMI, NSTEMI and UA	879/839	Bivalirudin vs UFH	0.2	Death/MI or stroke and net adverse events (MACE + major bleeding)
BRAVE-4	2014	STEMI	65/58	Bivalirudin plus prasugrel vs. UFH plus clopidogrel	6.1	Death/MI/unplanned TVR/definite in stent thrombosis, stroke or major bleeding
EUROMAX	2013	STEMI	275/248	Bivalirudin vs UFH or LMWH plus optional GPI	69.1	Death and non-CABG related major bleeding
ISAR-REACT 4	2011	NSTEMI	199/200	Bivalirudin vs. UFH (70 μ/kg bolus) plus abciximab	99.6	Death/MI/urgent TVR, and major bleeding
HORIZONS-AMI	2008	STEMI	412/430	Bivalirudin vs UFH plus GPI	97.7	Major bleeding and combined adverse events (death/MI/TVR/stroke and major bleeding)
ISAR-REACT 3	2008	Elective PCI or UA	545/530	Bivalirudin vs UFH 140 μ/kg bolus	0.2	Death/MI/urgent TVR, and in-hospital bleeding
ACUITY	2006	NSTEMI or UA	700/701	Bivalirudin vs UFH or LMWH plus GPI	96.6	Death/MI/unplanned TVR, and major bleeding
REPLACE-2	2003	Elective PCI, UA or MI >7 days old	758/779	Bivalirudin vs UFH (bolus 65 IU/kg) and GPI	96.5	Death/MI/urgent TVR and in-hospital bleeding

GP = glycoprotein inhibitor; PCI = percutaneous coronary intervention; UA = unstable angina; MI = myocardial infarction; UFH = unfractionated heparin; TVR = target vessel revascularization; STEMI = ST segment elevation myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; LMWH = low molecular weight heparin; CABG = coronary artery bypass grafting; MACE = major adverse cardiac events.
[a] Numbers are representative of women in bivalirudin/heparin groups respectively.

PCI, and to explore whether routine use of GPI and clinical presentation affect these outcomes.

2. Methods

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [14]. A systematic electronic search of PubMed, Cochrane Library, Web of Science and EMBASE databases was conducted from inception until January 2017, without language restriction, using the key words "bivalirudin", "angiomax", "heparin", "percutaneous coronary intervention", "women", "female", "sex" and "gender" both separately and in combination. Supplemental Fig. 1 illustrates the search strategy. We also searched the reference lists of all the retrieved

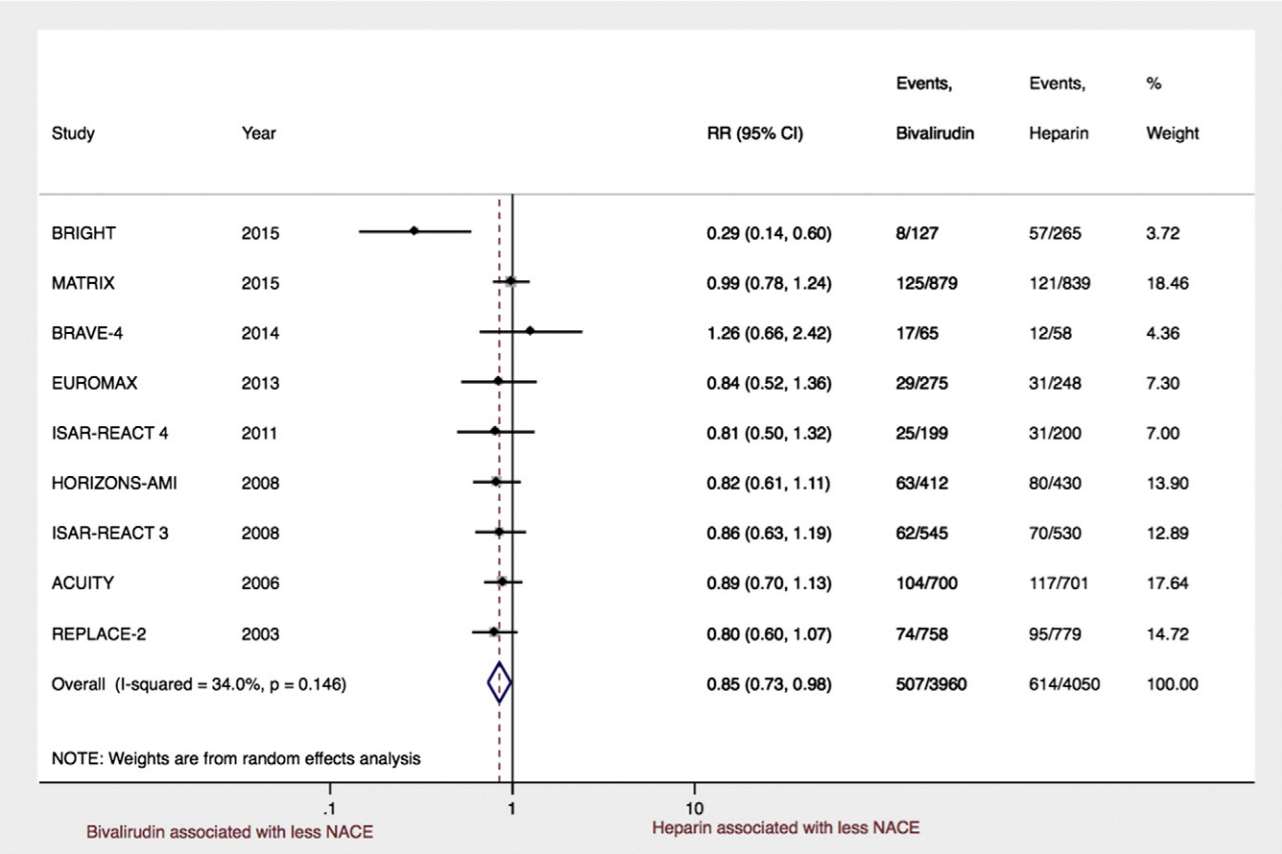

Fig. 1. Summary forest plot of NACE at 30-days. The relative size of the data markers indicates the weight of the sample size from each study. NACE = net adverse clinical events; CI = confidence interval; RR = risk ratio.

Please cite this article as: Saad M, et al, Bivalirudin versus heparin in women undergoing percutaneous coronary intervention: A systematic review and meta-analysis of random..., Cardiovasc Revasc Med (2017), http://dx.doi.org/10.1016/j.carrev.2017.02.019