Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Efficacy and safety of bivalirudin in coronary artery disease patients with mild to moderate chronic kidney disease: Meta-analysis

Xiaofang Zeng (MD)[a], A. Michael Lincoff (MD)[b], Stefanie Schulz-Schüpke (MD)[c], Philippe Gabriel Steg (MD)[d], Yedid Elbez (MSc)[d], Roxana Mehran (MD)[e], Gregg W. Stone (MD)[f], Thomas McAndrew (PhD)[g], Jianhui Lin (MSc)[h], Xindan Zhang (MD)[a], Wenhai Shi (MD)[a], Han Lei (MD)[a], Zhicheng Jing (MD, PhD)[i], Wei Huang (MD, PhD)[a,*]

[a] *Department of Cardiology, The First Affiliated Hospital, Chongqing Medical University, Chongqing, China*
[b] *Cleveland Clinic Foundation, Cleveland, OH, USA*
[c] *ISA Research Center, Deutsches Herzzentrum, Technische Universität, Munich, Germany and German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance*
[d] *French Alliance for Cardiovascular Clinical Trials (FACT), DHU-FIRE, Hôpital Bichat (Assistance Publique-Hôpitaux de Paris), Université Paris-Diderot, Sorbonne-Paris Cité and INSERM U-1148, Paris, France*
[e] *Department of Cardiology, Icahn School of Medicine at Mount Sinai, New York, USA*
[f] *Department of Cardiology, New York-Presbyterian Hospital/Columbia University Medical Center, New York, USA*
[g] *Clinical Trials Center, Cardiovascular Research Foundation, New York, USA*
[h] *Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield Medical School, Sheffield, UK*
[i] *State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China*

ARTICLE INFO

Article history:
Received 8 July 2017
Received in revised form 28 September 2017
Accepted 14 October 2017
Available online xxx

Keywords:
Bivalirudin
Chronic kidney disease
Coronary artery disease
Efficacy
Safety

ABSTRACT

Background: Patients with chronic kidney disease (CKD) have elevated bleeding and ischemic outcomes. We aim to assess the short- and long-term efficacy and safety of bivalirudin compared to heparin plus glycoprotein IIb/IIIa inhibitors (GPIs) in coronary artery disease (CAD) patients with CKD.
Methods: Randomized trials were searched in PubMed, Cochrane, and Embase databases up to January 2017. Among the trials retrieved, efficacy endpoints were defined as mortality, myocardial infarction (MI), repeat revascularization, stent thrombosis, and major adverse cardiac events (MACEs). Safety endpoints were reported as non-coronary artery bypass grafting (CABG) related major bleeding and thrombolysis in myocardial infarction (TIMI) major bleeding. Risk ratio (RR) and 95% confidence interval (CI) were calculated for each outcome using a fixed effect model.
Results: Five studies with a total of 3796 patients were included. In short-term follow up (30 days), bivalirudin significantly reduced non-CABG related major bleeding ($p = 0.0004$) and TIMI major bleeding ($p = 0.007$) compared to heparin plus GPIs. No significant differences were observed in rates of mortality, MI, repeat revascularization, stent thrombosis, and MACEs between the two groups in short- and long-term follow up (6 months to 3 years). In patients with ST elevated myocardial infarction (STEMI) with concurrent CKD, the decreased non-CABG related major bleeding ($p = 0.04$) without increasing ischemic events was also observed after short-term follow up.
Conclusions: (1) Bivalirudin is safer than and as effective as heparin plus GPIs in CAD patients with CKD. (2) Impaired renal function does not affect the safety benefits of bivalirudin. (3) Similar efficacy profiles were identified between the two groups after both short- and long-term follow up in the CAD patients with CKD.

* Corresponding author at: 1 Youyi Road, Yuzhong District, Chongqing, 400016, China.
E-mail address: weihuangcq@gmail.com (W. Huang).

https://doi.org/10.1016/j.jjcc.2017.10.018
0914-5087/

Introduction

Chronic kidney disease (CKD) is prevalent in patients with cardiovascular disease [1]. Approximately 31% of ST-segment-elevated myocardial infarction (STEMI) patients and 43% of non-ST-segment-elevated myocardial infarction (NSTEMI) patients present with renal dysfunction [2]. CKD is an independent risk factor associated with ischemic and bleeding complications for patients with cardiovascular disease [3,4]. Patients suffering from coronary artery disease (CAD) with concurrent CKD are associated with increased clinical severity and poor prognosis, including severe bleeding, myocardial infarction (MI), and poor survival compared to patients with normal renal function [1–3]. Due to CKD therapy-related side effects, these patients are frequently excluded from many randomized trials. Thus, CKD patients are less likely to receive evidence-based therapy making it difficult to draw conclusions regarding this subgroup [4–7].

Bivalirudin, a direct thrombin inhibitor with a short-term biological half-life (25 min under normal renal function), offers a predictable and dose-dependent anticoagulation degree [8,9]. Bivalirudin has become an alternative drug for CKD patients compared with heparin plus glycoprotein IIb/IIIa inhibitors (GPIs) and was prescribed more frequently in patients with progressive, more advanced CKD, including CKD stage 5 compared to patients without CKD [6]. However, whether bivalirudin is truly beneficial, in terms of both short- and long-term efficacy and safety profiles, remains unclear in CAD patients with concurrent CKD.

We conducted this meta-analysis to investigate and assess: (1) whether renal dysfunction has an impact on the reduced bleeding complications (safety profile) when anticoagulated with bivalirudin in CAD patients; (2) the short- and long-term efficacy of bivalirudin compared to heparin plus GPIs in CAD patients, as well as in STEMI patients, with renal dysfunction.

Methods

Data sources and search strategy

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines [10]. Three reviewers independently conducted a systematic review of randomized controlled trials (RCTs) in the PubMed, Embase, and Cochrane databases up to January 2017. We searched these databases with the following keywords: “bivalirudin”, “heparin”, “CAD”, and “CKD”. Details on the search strategy are listed in the supplementary material. The references of all included articles were also reviewed to identify other studies that may satisfy the inclusion criteria of this analysis. No language restriction was applied.

Study selection and data extraction

Works satisfying the following criteria were included: (1) RCTs, (2) studies that involved patients with CAD and impaired renal function confirmed by available laboratory data on creatinine clearance (CrCl), (3) studies that compared bivalirudin plus the provisional use of GPIs with heparin (unfractionated heparin or enoxaparin) plus GPIs, (4) pre-specified subgroups of randomized studies for patients with CAD in the setting of CKD, and (5) studies with supplied data on efficacy and safety outcomes of bivalirudin. Studies with ineligible study design, populations, and outcomes were excluded.

A two-step process was conducted to recognize the eligible studies for inclusion. First, the title and abstract of all the citations were screened, and the citations that did not meet the inclusion criteria were discarded. Afterward, we obtained the full text of the remaining citations for further selection according to the inclusion criteria. We also contacted the study authors to collect the unpublished baseline characteristics and outcomes of included trials. Data were extracted and conflicting opinions were resolved by consensus. The information obtained included sample size, intervention components, length of follow up, etc. Quality assessment was conducted according to the Cochrane Collaboration Assessment for risk of bias with Review Manager 5.1.0 [11].

Endpoints and definitions

Efficacy endpoints reported were mortality, MI, repeat revascularization, stent thrombosis and major adverse cardiac events (MACEs, reported as a composite of mortality, MI, repeat revascularization, or stroke). Safety endpoints were reported as non-coronary artery bypass grafting (CABG)-related major bleeding and thrombolysis in myocardial infarction (TIMI) major bleeding. Short- and long-term follow up were defined as the results reported 30 days and 6 months to 3 years after percutaneous intervention (PCI), respectively.

Revascularization was performed in accordance with either clinical indications or study protocol. Stent thrombosis was referred to the criteria of the Academic Research Consortium [12] which regarded any MI on the evidence from angiographic confirmation of in-stent thrombus or any unexplained death after the procedure. The safety outcomes were reported as non-CABG-[13] and TIMI-related [14] major bleeding including life-threatening bleeding such as intracranial, retroperitoneal, or intraocular bleeding. CKD was reported as renal impairment with a CrCl of less than 60 ml/min on the basis of the admission laboratory data (prior to any contrast media exposure) calculated using the Cockcroft–Gault equation.

Statistical analysis

Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated as summary statistics. Heterogeneity was assessed using the I^2 statistic with values <25% considered as low and >75% as high. I^2 was defined as the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance) [15]. Random-effects models were used when high heterogeneity was detected ($I^2 > 50\%$); otherwise, fixed-effects models were adopted. Type I error was held at 5%

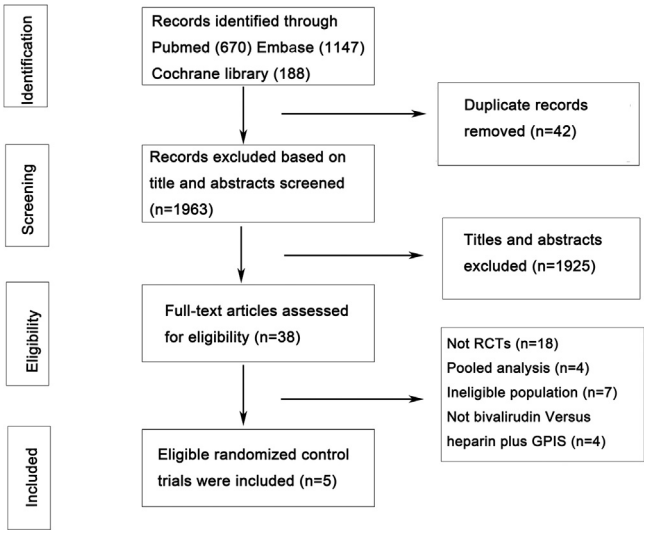

Fig. 1. Flow chart of study selection. GPIs, glycoprotein IIb/IIIa inhibitors; RCTs, randomized controlled trials.

Please cite this article in press as: Zeng X, et al. Efficacy and safety of bivalirudin in coronary artery disease patients with mild to moderate chronic kidney disease: Meta-analysis. J Cardiol (2017), https://doi.org/10.1016/j.jjcc.2017.10.018