International Journal of Cardiology 211 (2016) 119–123

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Frequency and prognostic significance of access site and non-access site bleeding and impact of choice of antithrombin therapy in patients undergoing primary percutaneous coronary intervention. The EUROMAX trial

Sinem Kilic [a,1], Arnoud W.J. van't Hof [a,*,1], Jurrien ten Berg [b,1], Ana Ayesta Lopez [c,1], Uwe Zeymer [d,1], Martial Hamon [e,1], Louis Soulat [f,1], Debra Bernstein [g,1], Efthymios N. Deliargyris [g,1], Phillippe Gabriel Steg [h,i,1]

[a] Isala, Department of Cardiology, Zwolle, The Netherlands
[b] St. Antonius Hospital, Department of Cardiology, Nieuwegein, The Netherlands
[c] Cardiology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain
[d] Klinikum Ludwigshafen, Ludwigshafen, Germany
[e] Clinical Research Department, University of Caen, Caen, France
[f] Services d'Aide Médicale Urgente, Service Mobile d'Urgence et de Réanimation Urgences, Centre Hospitalier, Chateauroux, France
[g] The Medicines Company, Parsippany, NJ, United States
[h] Université Paris-Diderot, Sorbonne Paris Cité, INSERM Unité-1148, Département Hospitalo-Universitaire Fibrosis Inflammation Remodeling, and Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France
[i] NHLI, Royal Brompton Hospital, Imperial College, London, UK

ARTICLE INFO

Article history:
Received 14 September 2015
Received in revised form 16 February 2016
Accepted 28 February 2016
Available online 3 March 2016

Keywords:
Access site
Bivalirudin
Bleeding
Percutaneous coronary intervention
Thrombolysis in myocardial infarction (TIMI)

ABSTRACT

Background: The overall impact of post percutaneous coronary intervention (PCI) bleeding on long term prognosis after acute coronary syndromes (ACS) has been established, but it may differ between access and non-access related bleeding events. The impact of antithrombin choice on bleeding may also differ according to the origin of the bleed. We sought to determine the origin of bleeding relative to the access site, its prognostic significance and the respective impact of antithrombin therapy in the EUROMAX trial.
Methods: We performed a blinded review of the case records of all TIMI major or minor bleeds in the EUROMAX trial and assigned them in one of 2 categories: access site bleeds (ASB), or rest of bleeds (ROB). Incidence of bleeding for each category was assessed according to randomization to antithrombotic treatment.
Results: A total of 231 out of 2198 patients suffered a TIMI major/minor bleed (10.5%) and ASB accounted for 48.5%, while ROB for 51.5% of the bleeds. Thirty day mortality was 2.5% (50/1967) for patients without a bleed, 2.7% (3/112, $p = 0.76$ vs. no bleed) for patients with ASB, and 10.9% (13/119, $p < 0.0001$ vs. no bleed) for ROB patients. The use of bivalirudin reduced both ASB and ROB with relative risk reductions of 34% and 46% respectively.
Conclusions: In contemporary primary PCI, bleeding originates with equal frequency either at or away from the access site. Access site bleeds were not associated with an excess in 30 day mortality, but the rest of the bleeds were. Bivalirudin is associated with a lower risk of bleeding irrespective of origin.
Clinical trial registration: ClinicalTrials.gov identifier NCT01087723.

1. Introduction

In patients with acute coronary syndromes (ACS) an early invasive strategy with percutaneous coronary intervention (PCI), whenever appropriate, in combination with antithrombotic treatment is the preferred approach and is recommended by both the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association ST-segment elevation myocardial infarction (STEMI) guidelines [1–4]. The most common complications in contemporary ACS management are recurrent myocardial infarction (MI) and bleeding both of which have been associated with excess early and late mortality [5–7].

Previous reports have suggested a differential impact on mortality according to whether bleeding originates from the arterial access site or from a more systemic source [5]. The radial approach can dramatically reduce the risk for access related bleeding complications, however,

* Corresponding author at: Isala Hospital, Department of Cardiology, Dr. Van Heesweg 2, 8025 AB Zwolle, The Netherlands. Tel.: +31 38 424 50 00; fax: +31 38 424 76 76.
E-mail address: v.r.c.derks@isala.nl (A.W.J. van't Hof).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.02.131
0167-5273/

without the ability to reduce non-access related bleeding [8]. In contrast, bivalirudin has consistently reduced all types of bleeding in multiple multicenter trials when compared to heparin with or without glycoprotein IIb/IIIa inhibitors (GPI). Recently, however, two single center trials have challenged the ability of bivalirudin to reduce bleeding, possibly because of broader use of radial arterial access, and lower heparin dosing with limited GPI use [9,10].

The current analysis sought to determine the frequency and prognostic significance of bleeds originating from the access site compared with the rest of the bleeds, and the impact of antithrombin choice in the contemporary, international, multicenter European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial, in which radial arterial access was left at the discretion of the operator, and in which GPI use was not mandated and heparin dosing was low in the control arm.

2. Methods

2.1. Study population

The EUROMAX study design has been previously described in detail [1]. The study enrolled men and non-pregnant women of 18 years of age or older, presenting within 12 h from symptom onset with a presumed diagnosis of STEMI. All patients had to be scheduled for angiography with the intention of performing primary PCI within 2 h after first medical contact. The main exclusion criteria were treatment with any anticoagulant before randomization, recent surgery, and a history of bleeding. Patients were identified, initial consent was obtained, randomization was performed, and study drug administration was initiated in the ambulance or in a non-PCI hospital. Patients were transported urgently to the primary PCI hospital, where treatment was continued and outcomes data collected. All patients provided written, informed consent and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Study treatments

Patients randomized to bivalirudin received a bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h. The protocol specified the continuation of the infusion for at least 4 h after the end of the PCI at a dose of 0.25 mg/kg/h; however, continuation at the full dose (1.75 mg/kg/h) was also permitted according to investigator's discretion. The use of GPI in the bivalirudin arm was limited to bailout in cases of high thrombus burden or microvascular obstruction (no reflow).

Patients in the control group received either unfractionated heparin (median dose of 61 U/kg [Q1–Q3: 56–71 U/kg] for patients given GPI, and 60 U/kg [Q1–Q3: 53–77 U/kg] for those not given GPI or an intravenous bolus of enoxaparin (0.5 mg/kg). The use of GPI was left to investigator's discretion and was categorized as routine when treatment commenced before angiography or bailout when it was initiated after angiography. All patients received aspirin and an approved P2Y 12 inhibitor as early as possible after first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference.

2.3. Study outcomes

All ischemic and bleeding events within 30 days were adjudicated by an independent and blinded clinical events committee. Bleeding was adjudicated using the protocol bleeding definition as well as the standardized thrombolysis in myocardial infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) scales. For this analysis we opted for the more popular TIMI scale to allow comparisons with previous reports and across other trials. The TIMI major bleeding was defined as a reduction of hemoglobin of ≥5 g/dl (or >15% in hematocrit), with or without overt bleeding, or any intracranial bleeding. A TIMI minor bleeding was defined as a 3 to 5 g/dl decrease in hemoglobin (or 9% to 15% in hematocrit) with an observed source of bleeding or a hemoglobin drop of 4 to 5 g/dl (or 12% to 15% hematocrit) without an observed source.

Every adjudicated TIMI major/minor bleed underwent a blinded medical review (performed by AAL) and was assigned in one of two categories: access site bleeds (ASB) or rest of bleeds (ROB). The intent of this categorization was to ensure an accurate assessment of the frequency and impact of bleeding originating solely from the access site. Accordingly, ASB were bleeds arising only from the access site or any retroperitoneal bleeds and ROB were all other bleeds not limited to the access site. Based on available information from case records, ROB were further classified according to organ system or to no location (occult). The incidence of bleeding for each category was also assessed according to randomized treatment.

2.4. Statistical analysis

Continuous variables were summarized by medians and interquartile ranges. Categorical variables were summarized by frequencies and percentage. A p-value of <0.05 was considered statistically significant. The rates of 30-day mortality as a function of ASB or ROB were determined. To evaluate the adjusted association between bleeding site and 30-day mortality, we constructed a Cox proportional hazards regression model that adjusted for baseline imbalances. Covariates were selected with a forward stepwise procedure from a large number of candidate variables with $p < 0.20$ as the criterion for entry into the model. Adjusted odds ratios (OR) of the risk for mortality with 95% confidence intervals (CI) were presented. The chi-square test was used for comparisons of event rates or, in the case of sparse data, Fisher's exact test was used. Log-rank test was used to compute the significance of time-to-event data. Analyses were performed with the use of SAS software, version 9.2.

3. Results

A total of 2198 patients being transported for primary PCI were randomized in the EUROMAX trial. A TIMI major or minor bleed within 30 days occurred in 231 patients (10.5%), comprising a major bleed in 37 (1.7%) and a minor bleed in 195 (8.9%).

3.1. Sites of bleeding

The breakdown for all 231 bleeding events is shown in Table 1. The frequencies of ASB (112/231, 48.5%) and ROB (119/231, 51.5%) were comparable. The ROB group comprised mostly non-access site bleeds, but also included cases with both access and non-access bleeding and cases where a location was not listed. Based on the case records, ROB were further classified according to organ system, other (when they did not qualify for any of the named categories), or no location (Fig. 1).

Table 1
Classification according to the origin of the bleeds.

All patients	N = 2198 n/N (%)
No bleeding	1967 (89.5)
All TIMI major/minor	231/1967 (10.5)
Access site bleed (ASB)	112/231 (48.5)
Rest of bleeds (ROB)	119/231 (51.5)
Non-access site only	72/119 (60.5)
Both access and non-access site	18/119 (15.1)
No location	29/119 (24.4)