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Bivalirudin in percutaneous coronary intervention: The EUROpean BiValIrudin UtiliSatION in Practice (EUROVISION) Registry

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ABSTRACT

Purpose: The prospective EUROVISION Registry was designed to capture patterns of use and short term outcomes in consecutive patients undergoing PCI with bivalirudin (BIV) in European centres.
Methods: A total of 2018 consecutive BIV-treated patients were included from 58 sites in 5 countries (Germany, Italy, France, Austria, United Kingdom). In-hospital and 30-day outcomes were prospectively collected and included: death, myocardial infarction (MI), stroke, urgent revascularization (URV), major and minor bleeding, stent thrombosis (ST) and thrombocytopenia (TCP).
Results: In this all-comer population, indication for PCI included STEMI (34%), NSTEMI (25%), unstable angina (16%) and stable angina (26%). Diabetes was present in 24% of patients and 30% of cases were performed via radial access. Preloading with a P2Y12 inhibitor was frequent (74%) while procedural glycoprotein inhibitor (GPI) use was low at 4.2%. Almost half (45%) of patients had received at least one additional anticoagulant prior to receiving BIV for PCI. The overall 30-day mortality was 1.0%, with low rates of MI (1.1%), URV (0.8%), ST (0.3%) and stroke (0.2%). The rate of ACUITY major bleeding was 1.6% and no TCP was reported. Dosing variations representing possible under- or over-dosing of BIV were frequent at 35%.
Conclusion: In this prospective registry of consecutive patients intended for PCI, use of BIV was associated with low rates of ischemic complications and excellent safety.

1. Introduction

Bivalirudin is a synthetic, intravenous short-acting anticoagulant that provides reversible, bivalent and direct thrombin inhibition [1]. Bivalirudin is an approved anticoagulant for all-comers percutaneous coronary intervention (PCI). Specifically bivalirudin is indicated for the treatment of acute coronary syndrome (ACS) patients intended for invasive management, including primary PCI for ST-segment elevation myocardial infarction (STEMI) and carries the highest in class recommendation (Class IB) in the updated ESC guidelines [2]. Bivalirudin should be administered as a weight-based intravenous bolus followed immediately by a weight based intravenous infusion for at least the duration of the PCI, but the infusion can be prolonged as clinically warranted. More than 5 million patients have already been treated with bivalirudin worldwide, with the majority coming from the United States, but also increasingly coming from Europe [3–5]. The EUROVISION Registry was specifically designed to capture patterns of use and short term clinical outcomes with bivalirudin in a European environment characterized by frequent preloading with

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P2Y12 inhibitors, frequent use of the radial approach and low rates of GPI use [6,7].

2. Methods

2.1. Study population

EUROVISION was conducted between May 2009 and December 2010 in a total of 58 sites from 5 European counties (Austria, France, Germany, Italy, and the United Kingdom). Consecutive patients were included in the study if they received bivalirudin for PCI and provided written informed consent for collection of their data in accordance with local data protection laws, policies and regulations. Subjects were excluded from the study if they were participating in other studies involving investigational drugs, including bivalirudin, or devices at the time of screening, or if they were not eligible for treatment with bivalirudin.

2.2. Data collection

In this prospective, non-comparative study of 2018 consecutive bivalirudin-treated patients, data were collected from the time of hospital admission up to hospital discharge and at a 30-day follow-up either by clinical visit or telephone call. At each centre, consecutive bivalirudin treated patients who provided written informed consent for the use of their data, were captured in an electronic case report form (eCRF). All events were investigator/site reported as appropriate for a post-marketing authorization registry.

2.3. Study objectives

The main objective of the prospective EUROVISION registry was to capture utilisation patterns and short term (30 days) clinical outcomes among consecutive bivalirudin-treated PCI patients. Drug utilisation data points included the time and dose of both the bolus and the infusion administration and the total duration of the infusion. In cases where the infusion was continued after the end of PCI, the total duration of the prolonged infusion was calculated as the time difference between the end of PCI and the final cessation of the bivalirudin infusion. Reference dosing was assumed to be the dosing in the approved bivalirudin label.

2.4. Outcome measurements

Efficacy outcomes collected were ischemic events occurring during the first month after PCI, including death, myocardial infarction, stroke and the need for an unplanned revascularisation. Safety outcomes collected were major and minor bleeding events, acute stent thrombosis according the ARC definition [8] and thrombocytopenia defined as a nadir platelet count lower than 100,000 cells/mm^3.

2.5. Bleeding definition

Major bleeding was defined using the ACUITY bleeding scale [9], as related or unrelated to surgery (CABG) and defined as any one of the following bleeding: intracranial, retroperitoneal, intraocular, access site haemorrhage requiring radiological or surgical intervention, reduction in haemoglobin concentration of >4 g/dL without an overt source of bleeding, or reduction in haemoglobin concentration of >3 g/dL with an overt source of bleeding and finally, a 5 centimetre (cm) diameter haematoma at puncture site, a re-operation for bleeding and the use of any blood product transfusion. All other bleeding events were considered minor bleeding.

2.6. Sample size

This study was designed to obtain descriptive information on drug dosing patterns in patients administered bivalirudin and safety information. The sample size determination was not based on statistical consideration of event estimates. The study size felt to be reasonable for this prospective evaluation of European use of bivalirudin was decided at around 2000 patients.

2.7. Statistical analysis

Descriptive statistics and/or patient data listings have been used to summarise the data. Continuous variables are summarised by means, standard deviations, medians, inter-quartile ranges, and minimum and maximum values. Categorical variables are summarised by frequencies and percentages. Multivariate analysis was used to determine independent predictors of major outcomes. A significance level of 0.15 was required to allow a variable into the model and value of 0.10 was required to stay in the model.

3. Results

3.1. Study population: demographics, medical history and procedural characteristics

Patient flow diagram is shown in Fig. 1 and baseline characteristics of the intent-to-treat study population are shown in Table 1. Overall 2018 patients were enrolled in this prospective study including 3 patients treated for patent foramen ovale who received bivalirudin (off label). As expected, the majority of the included patients were patients with an acute coronary syndrome and specifically STEMI (33.6%), NSTEMI (24.7%) or unstable angina (15.6%), while a minority of patients included had stable angina (25.9%). The mean procedural duration was 36 ± 43.6 min. Overall, a large majority of patients (74%) received a loading dose of a $P2Y_{12}$ inhibitor before the procedure (90.8% clopidogrel {65% with 600 mg and 33% with 300 mg}, and 9% prasugrel). A substantial number of patients (45%) received at least one additional antithrombin agent prior to PCI and were then switched to bivalirudin. Routine GPI use was appropriately not observed in the study population while procedural GPI use was low at 4.2% (n = 85). Activated clotting time was checked in only 2.8% suggesting operator familiarity with bivalirudin's predictable mode of action and treatment effect. Procedural data of the ITT population are summarised in Table 2. Single-vessel, two-vessel, or three-vessel disease with luminal reduction more than 50% was reported in 43.7%, 30.4% and 19.7% respectively.

3.2. Drug utilisation results

In the intent-to-treat population of 2018 patients, bolus administration was given in 100% of cases. An infusion was appropriately initiated in the vast majority of cases, while bolus only administration was given in 2.1% of the ITT population (43/2018) and in 25 patients of the 1933 PCI patients (1.29%). Among the 85 patients who were not treated with PCI, 18 received a bolus-only dosing. Notably, among STEMI

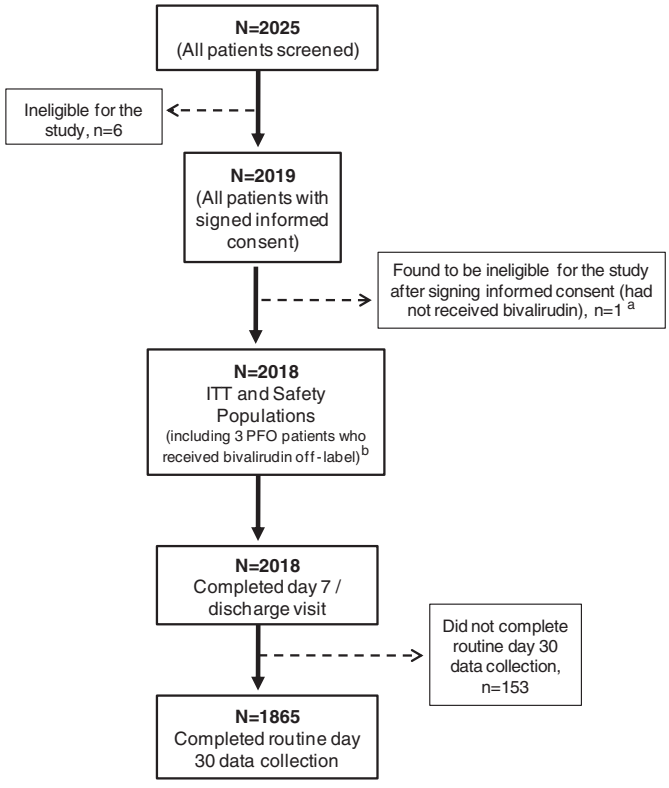

Fig. 1. Flow diagram showing patient recruitment in the registry. ITT = intent-to-treat PFO = patent foramen ovale. [a]Patient 33070050.[b]Patients 43010054, 43010055, 43010085.