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Full Length Article

Pretreatment with ticagrelor may offset additional inhibition of platelet and coagulation activation with bivalirudin compared to heparin during primary percutaneous coronary intervention

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ABSTRACT

Background: It remains unknown if bivalirudin compared to heparin confers any additional inhibition of platelet and coagulation activation during primary percutaneous coronary intervention (PPCI) after pretreatment with ticagrelor.

Methods: In this substudy of VALIDATE-SWEDEHEART trial, 103 patients pretreated with ticagrelor were randomized before PPCI to heparin or bivalirudin. Blood samples were collected before and 1 and 12 h after PPCI. We measured platelet reactivity (PR) using Multiplate, soluble P-selectin, thrombin-antithrombin complexes (TAT) and prothrombin fragments 1 + 2 (F1 + 2) as markers of platelet and coagulation activation.

Results: The median (IQR) time from ticagrelor administration to randomization was 63 (29) vs 60 (24) minutes, p = 0.28. ADP-induced PR did not significantly differ between groups over time (heparin vs bivalirudin, AUC 73 (62) vs 74 (68), p = 0.74, 32 (42) vs 43 (51), p = 0.38, 15 (15) vs 19 (15), p = 0.29, before, 1 and 12 h after PPCI). Soluble P-selectin did not significantly differ between groups. At 1 h TAT significantly increased with bivalirudin (3.0 (1.3) to 4.3 (4.2) ug/L; p < 0.01), but not with UFH (3.1 (2.1) to 3.5 (1.6) ug/L, p = 0.24). F1 + 2 increased in both groups but the rise was numerically higher with bivalirudin (170 (85) to 213 (126) pmol/L vs 168 (118) to 191 (103) pmol/L). At 12 h, a comparable significant increase in thrombin generation was observed in both groups.

Conclusion: In patients treated with ticagrelor, we found no major differences between bivalirudin and heparin in platelet aggregation or coagulation markers, which is in agreement with the neutral clinical results of the VALIDATE-SWEDEHEART study.

1. Introduction

Activated platelets, interacting with the coagulation system, play a fundamental role in the pathogenesis of ST-segment elevation myocardial infarction (STEMI) [1]. Also, the degree of platelet and coagulation inhibition during primary percutaneous coronary intervention (PPCI) is major determinants for both ischemic and bleeding complication [2,3]. Therefore, optimal antiplatelet and anticoagulant treatment during PPCI are critical in order to improve outcome [4].

Anticoagulation with unfractionated heparin (UFH) or the direct thrombin inhibitor bivalirudin, in combination with oral antiplatelet agents such as aspirin and P2Y12 inhibitors has been established as the standard pharmacotherapy during PPCI [4]. Earlier studies have shown that treatment with bivalirudin, compared to high dose UFH or UFH with additional use of glycoprotein GPIIb/IIIa inhibitors (GPI), was associated with a reduced risk for bleeding and mortality, but a higher risk for acute stent thrombosis [5,6]. However, recent studies comparing bivalirudin vs UFH monotherapy in STEMI patients have shown conflicting results [7–9].

Some evidence exist that UFH and bivalirudin exert different pharmacological properties in terms of platelet and coagulation inhibition. This underscores the importance of understanding how different drugs influence platelet function and coagulation, in order to provide mechanistic insight into clinically observed differences.

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Previous studies, including patients with stable angina, have shown that UFH may enhance platelet aggregation in therapeutic concentrations [10,11] whereas bivalirudin has been associated with an additional inhibition of platelet activation and aggregation [11–14]. Data in STEMI patients are limited despite their higher risk for both ischemic and bleeding complications. Furthermore, ticagrelor, a new potent $P2Y_{12}$ receptor inhibitor with rapid onset of action has replaced clopidogrel in the management of STEMI patients and may have offset any potential advantages of bivalirudin vs UFH [4].

The aim of this study was to compare the effects of UFH vs bivalirudin on platelet and coagulation activation in STEMI patients undergoing PPCI after pretreatment with ticagrelor. We hypothesized that treatment with bivalirudin, as compared to UFH, would confer additional inhibition of platelet activation and aggregation.

2. Methods

2.1. Study population

This was a single-center substudy of the Bivalirudin versus Heparin in ST-Segment and Non ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial (VALIDATE-SWEDEHEART trial, Clinical-TrialsRegister.eu number, 2012-005260-10; ClinicalTrials.gov number, NCT02311231) – a prospective registry-based, multicenter, randomized, controlled, open-labeled trial. The purpose of the VALIDATE-SWEDEHEART was to compare the efficacy and safety of bivalirudin vs UFH monotherapy in either STEMI or non-STEMI patients receiving novel antiplatelet therapy and undergoing PCI. A complete list of inclusion and exclusion criteria has previously been described [9].

In STEMI patients, treatment with ticagrelor, prasugrel or cangrelor before PCI was required for inclusion in the VALIDATE-SWEDEHEART trial. Intravenous administration of 5000 U UFH before arrival at the catheterization laboratory or up to 3000 U UFH intra-arterial administration before angiography at the catheterization laboratory was allowed in both groups. If PCI was planned, oral informed consent was obtained right after the coronary angiography was performed, followed by written informed consent within 24 h. Patients were randomized to receive either bivalirudin (as an intravenous bolus of 0.75 mg per kilogram of body weight followed by an infusion of 1.75 mg per kilogram per hour) or UFH (70–100 U per kilogram). Full dose post-PCI bivalirudin infusion was encouraged until completion of the last vial. Bailout-only use of GPI was allowed.

The present substudy was conducted at the University hospital of Linköping between November 7th 2014 and April 14th 2016. During this period, 149 STEMI patients were included in the VALIDATE--SWEDEHEART trial at our institute. STEMI patients, pretreated with ticagrelor before arrival at the catheterization laboratory, who were included in the main study were asked, before randomization to UFH or bivalirudin, for participation in the current substudy. Ongoing treatment with $P2Y_{12}$ inhibitors before the index event was an exclusion criteria for participation in our substudy. All patients gave oral informed consent before inclusion and written informed consent within 24 h after inclusion. The study was approved by the institutional ethical review board (Dnr 2012/796 and amendment 2014/426) and was conducted according to the declaration of Helsinki.

2.2. Blood sampling

Blood was drawn from the arterial sheath after randomization, immediately before PCI and before administration of bivalirudin or UFH (blood sample 1). Blood samples were also collected by venipuncture 1 h (60–80 min, blood sample 2) and 12 h (11–13 h, blood sample 3) after randomization. In all blood sample collections, the first 5 mL of blood was discarded and blood was gently aspirated to avoid platelet activation. Blood were drawn into blood collection tubes, Multiplate® Hirudin Blood Tubes from Roche for aggregation measurements and CTAD tubes (buffered Citrate, Theophylline, Adenosine and Dipyridamole, Becton Dickinson) for platelet and coagulation activation markers analyses. Centrifugation was performed for CTAD collected blood and platelet-poor plasma was stored in a freezer with a temperature of −70 °C.

At the time of the study design, the median time from first medical contact to PPCI was 60 min at our center. Ticagrelor was commonly administrated at the first medical contact. We assumed that 1 h after randomization, PCI would be completed and ticagrelor treatment would result in a moderate platelet inhibition. Therefore blood sampling at 1 h after randomization was considered the optimal point time to detect potential differences in platelet aggregation between treatment arms. In addition, from a clinical point of view, platelet activity at the end of the PCI procedure is an important measure.

2.3. Assessment of platelet and coagulation system activation

Residual platelet reactivity (PR) was assessed by using Multiple Electrode Aggregometry (MEA, Multiplate®, Dynabyte Medical, Munich) [15]. According to the manufacturer's instruction the blood samples were allowed to rest for 30 min to 2 h after blood collection. Platelet aggregation was stimulated with ADP (6.4 μM, with prostaglandin E1, ADP test), arachidonic acid (0.5 mM, ASPI test), collagen (3.2 μg/mL, COL test) and thrombin receptor activating peptide (30 μM, TRAP test). Aggregation measurements were expressed as area under the curve (AUC) of arbitrary aggregation units (AU) plotted against time. High residual platelet reactivity (HRPR) on ticagrelor was defined as ADP-induced AUC > 46 according to consensus statement [3]. The percent inhibition of platelet reactivity (IPR) was defined as: ((AUC baseline − AUC sample 1 or 2) / AUC baseline) × 100.

2.4. Platelet and coagulation system activation

Soluble P-selectin (sP-selectin) was measured as a surrogate marker of platelet activation and thrombin anti-thrombin complexes (TAT) and prothrombin fragments 1 + 2 (F1 + 2) as markers of ongoing thrombin generation using an enzyme-linked immunosorbent assay (ELISA) and commercial kits for each analysis (Human P-Selectin/CD62P, R&D Systems for sP-selectin, Enzygnost®TAT micro, Siemens for TAT and Enzygnost F1 + 2 (monoclonal), Siemens for F1 + 2). Values were expressed as ng/mL (reference values 18–40 ng/mL) for sP-selectin, μg/L (reference values 2.0–4.2 μg/L) for TAT and pmol/L (reference values 69–229 pmol/L) for F1 + 2.

High sensitivity troponin T (hs-TnT) as a marker of infarct size and interleukin 6 (IL-6) as a marker of systemic inflammation were measured 12 h after randomization using a standard commercial troponin T assay (Roche Troponin T hs STAT-method, on Cobas 6000 e601 analyzer) and a commercial IL-6 assay (Roche Diagnostics, Scandinavia AB, on Cobas e602), respectively. Values were expressed as ng/L for hs-TnT (reference value < 15 ng/L) and as pg/mL for IL-6 (reference value < 7 pg/mL).

2.5. Statistical analysis

Baseline characteristics are presented as counts and percentages for categorical variables and as mean and standard deviation (SD) or median and interquartile ranges (IQRs) for continuous variables. Chi-square or Fisher's exact tests and student's unpaired *t*-tests or Mann-Whitney's test were used for comparisons.

The Shapiro-Wilks test showed that platelet and coagulation variables as well as hs-TnT and IL-6 were not normally distributed, therefore the data is presented as median with IQRs. Comparisons were made with two-sided Mann-Whitney *U* test or Wilcoxon matched-pairs signed