Post-Procedural Bivalirudin Infusion at Full or Low Regimen in Patients With Acute Coronary Syndrome

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Effect of Post-procedural Bivalirudin Infusion at Full or Low Regimen in Patients with Acute Coronary Syndrome with or without ST-segment Elevation: An Analysis of the MATRIX trial.

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Running title: Optimal regimen of bivalirudin in ACS

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ABSTRACT

Background: The value of prolonged bivalirudin infusion after percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS) patients with or without ST-segment elevation remains unclear.

Objectives: To assess efficacy and safety of a full or low post-PCI bivalirudin regimen in ACS patients with or without ST-segment elevation.

Methods: The MATRIX program assigned bivalirudin to patients without or with a post-PCI infusion at either a full (1.75 mg/kg/h) for up to 4 hours, or reduced (0.25 mg/kg/h) for up to 6 hours, regimen at the operator's discretion. The primary endpoint was the 30-day composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events (composite of all-cause death, myocardial infarction, or stroke [MACE] or major bleeding).

Results: Among 3610 patients assigned to bivalirudin, 1799 were randomized to receive and 1811 not to receive a post-PCI bivalirudin infusion. Post-PCI full bivalirudin was administered in 612 (STEMI=399; NSTE-ACS=213) whereas 1068 (STEMI=519; NSTE-ACS=549) patients received the low regimen. The primary outcome did not differ in STEMI or NSTE-ACS patients who received or did not receive post-PCI bivalirudin. However, full as compared to low bivalirudin regimen remained associated with a significant reduction of the primary endpoint after multivariable (rate ratio 0.21, 95% CI 0.12-0.35; $p<0.001$) or propensity-score (rate ratio 0.16, 95% CI 0.09-0.26; $p<0.001$) adjustment. Full post-PCI bivalrudin was associated with improved outcomes consistently across ACS types and in comparison with the no post-PCI infusion or heparin groups.

Conclusion: In ACS patients with or without ST-segment elevation, the primary endpoint did not differ with or without post-PCI bivalirudin infusion but a post-PCI full dose was associated with improved outcomes when compared with no or low-dose post-PCI infusion or heparin (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX [MATRIX]; NCT01433627).

Keywords: MATRIX, bivalirudin duration, bivalirudin dose, acute coronary syndrome, STEMI, NSTE-ACS.

CONDENSED ABSTRACT

The optimal regimen of bivalirudin after percutaneous coronary intervention (PCI) and whether this differs across acute coronary syndrome (ACS) with or without ST-segment elevation is unknown. This analysis found no differences between post-PCI bivalirudin infusion vs no infusion for the primary endpoint or other outcomes in STEMI and NSTE-ACS. Yet after adjustment, the full post-PCI bivalirudin dose was associated to improved efficacy and safety outcomes when compared to the low post-PCI bivalirudin regimen, no post-PCI infusion or unfractionated heparin groups.

ABBREVIATIONS

ACS=acute coronary syndrome

BARC=Bleeding Academic Research Consortium

CABG=coronary artery bypass grafting

GPI=glycoprotein IIb/IIIa inhibitor

GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries

MACE=major adverse cardiovascular events

MI=myocardial infarction

NACE=net adverse clinical events

NSTE-ACS=non-ST-segment elevation ACS

PCI=percutaneous coronary intervention

ST=stent thrombosis

STEMI=ST-segment elevation myocardial infarction

TIMI=thrombolysis in myocardial infarction

UFH=unfractionated heparin

INTRODUCTION

Percutaneous coronary intervention (PCI) in conjunction with periprocedural anticoagulant and antiplatelet therapy improves clinical outcomes in patients suffering from either ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndromes (NSTE-ACS). Yet, invasively managed ACS patients have an increased risk of bleeding, which in turn could be associated with higher mortality (1). Bivalirudin administration at the time of PCI has been repeatedly shown to mitigate bleeding complications compared to unfractionated heparin (UFH) with or without glycoprotein IIb/IIIa inhibitors (GPI) (2-8). Moreover, while major adverse cardiovascular events (MACE) did not differ at 30 days, bivalirudin administration was associated to higher acute stent thrombosis (ST) in STEMI (but not NSTE-ACS) and trends towards higher peri-procedural MI in NSTE-ACS patients, especially in those in whom administration of oral P2Y12 inhibitors was delayed (5,8-10).

The prolongation of bivalirudin infusion after PCI has been empirically employed as a potentially safe measure to mitigate the ischemic hazards associated to the use of bivalirudin. However, evidence remains limited.

Data comparing post-PCI versus no post-PCI bivalirudin infusion is largely indirect considering that HORIZONS-AMI (2) and HEAT-PPCI (11) studies investigated only a no-post-PCI infusion strategy, BRIGHT (4) and EUROMAX (3) mandated the use of a full and a full or low post-PCI bivalirudin dose, respectively, and no other large study prior to MATRIX had so far investigated the value of a post-PCI bivalirudin regimen in NSTE-ACS patients.

Therefore, the aim of this analysis was to assess the role of post-PCI bivalirudin in patients with STEMI and NSTE-ACS enrolled in the MATRIX Treatment Duration trial, with a focus on the comparative effectiveness of the full versus the low post-PCI regimen.

METHODS

Study Design

The main results of the MATRIX program including three randomized, multicenter, open-label superiority trials in patients with an ACS had been reported previously (6,12,13).

Here, we report the outcomes stratified by the type of ACS (STEMI and NSTE-ACS) from the MATRIX Treatment Duration, whereby 3610 patients were assigned to receive bivalirudin with or without a prolonged post-PCI bivalirudin infusion.

Patients

Detailed inclusion and exclusion criteria were previously reported (6,12,14). Briefly, patients with NSTE-ACS were eligible if they had a history consistent with new or worsening cardiac ischemia, occurring while they were at rest or with minimal activity within 7 days before randomization, and met at least two high-risk criteria among the following: aged 60 years or older, elevated cardiac biomarkers, or electrocardiographic changes compatible with ischemia and if they were considered to be candidates for PCI after completion of coronary angiography. Patients with STEMI were eligible if presenting within 12 hours after the onset of symptoms or between 12 and 24 hours after symptom onset if there was evidence of continuing ischemia or previous fibrinolytic treatment. All patients provided written informed consent.

Study Protocol and Randomization

Patients were randomly assigned, in a 1:1 ratio, to receive bivalirudin or UFH. Patients who were assigned to the bivalirudin group were subsequently randomly assigned, in a 1:1 ratio, to receive a post-PCI bivalirudin infusion or no post-PCI infusion. Central randomization was concealed with the use of a Web-based system. Randomization sequences were computer generated, blocked, and stratified according to type of ACS (STEMI vs troponin positive vs troponin-negative NSTE-ACS) and intended new or ongoing use of a $P2Y_{12}$ inhibitor (clopidogrel vs ticagrelor or prasugrel).

Randomization was performed before coronary angiography for STEMI patients and immediately after completion of angiography but before the start of PCI for patients with NSTE-ACS.
All interventions were administered in an open label fashion. Bivalirudin was given according to the product labeling, with a bolus of 0.75 mg per kilogram of body weight, immediately followed by an infusion of 1.75 mg per kilogram per hour until completion of the PCI. Bivalirudin was then stopped at the end of PCI or prolonged in accordance with the subsequent random assignment. Among patients assigned to receive prolonged treatment, bivalirudin could be administered either at the full dose for up to 4 hours or at a reduced dose of 0.25 mg per kilogram per hour for at least 6 hours. The choice between the two regimens was at the the treating physician's discretion . A GPI was allowed in the bivalirudin group only in patients who had periprocedural ischemic complications (i.e., no reflow or giant thrombus) after PCI (bailout therapy). Other medications were allowed according to professional guidelines. The protocol mandated a consistent use of the randomly allocated antithrombin regimen in cases of staged procedures.

Follow-up and Outcomes

Clinical follow-up was performed at 30-day. The primary outcome for MATRIX Treatment Duration was a composite of urgent target-vessel revascularization, definite ST, or net adverse clinical events (NACE) up to 30 days. Coprimary outcomes for MATRIX Antithrombin and Access site were MACE, defined as a composite of death from any cause, myocardial infarction, or stroke, and NACE, defined as a composite of major bleeding that was not related to coronary-artery bypass grafting (CABG) (Bleeding Academic Research Consortium [BARC] type 3 or 5) or MACE. Secondary outcomes included each component of the composite outcomes, death from cardiovascular causes, and ST. Bleeding was also assessed and adjudicated on the basis of the Thrombolysis in Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scales. All outcomes were prespecified.

An independent clinical-events committee whose members were unaware of the study-group assignments adjudicated all suspected events. Detailed definitions of outcomes and procedures of the clinical-events committee were previously provided (6,12,14).

Statistical analysis

Details regarding the statistical analysis have been reported previously (6,12,14). Briefly, MATRIX Treatment Duration was powered assuming that the incidence of the primary endpoint at 30 days would be 10.0% with short-term bivalirudin and 7.0% with prolonged bivalirudin (rate ratio of 0.70), therefore, the enrollment of 1700 patients in each study group provided a power of 86% to detect this difference at a two-sided alpha level of 0.05. Analyses were performed according to the intention-to-treat principle, including all patients in the analysis according to the allocated post-PCI regimen of bivalirudin. Primary and secondary outcomes were analyzed as time-to-first event using the Mantel–Cox method, accompanied by log–rank tests to calculate corresponding two-sided p-values. Survival curves were constructed using Kaplan–Meier estimates and percentages reported for outcomes are Kaplan–Meier estimates of cumulative incidence.

To compare the two different bivalirudin dosages (full vs low, irrespective of the final treatment duration) in the group receiving post-PCI infusion, multivariable and propensity score adjustment models were performed. The multivariable model included the following variables: year of randomization, center, access site randomized, diabetes, type of ACS, hypertension, previous PCI, previous stroke or TIA, peripheral vascular disease, eGFR, hemoglobin at baseline, TIMI flow 0-1 before PCI, P2Y12 inhibitor at discharge, and procedure duration. A propensity score that indicated the likelihood of receiving a full or low post-PCI bivalirudin infusion was calculated by using a nonparsimonious multivariable logistic regression including the following variables: year of randomization, center, access-site randomized, age, sex, body mass index, diabetes, type of ACS, smoking, hypertension, hypercholesterolemia, previous MI, previous PCI, previous CABG, previous stroke or TIA, peripheral vascular disease, eGFR, left ventricular ejection fraction,

hemoglobin at baseline, medications pre-PCI (clopidogrel, fondaparinux, ACE-inhibitors, statins, beta blockers, proton pump inhibitors, unfractionated heparin), PCI completed, GPI intraprocedural, ticagrelor intraprocedural, ≥2 vessels treated, ≥3 lesions treated, total SYNTAX score, ≥1 BMS, TIMI flow 0-1 before PCI, procedural success in all lesions, large and/or small vessel caliber, proximal location of the lesion, presence of thrombus in the treated lesion. This score had a very good predictive ability (ROC 0.92; **Supplementary Figure 1**). The individual propensity score was incorporated into the adjustment model to compare outcomes.

All analyses in the overall study population were stratified by type of ACS and accompanied by $\chi 2$ tests for interaction. Secondary analyses were also performed separately in STEMI and NSTE-ACS subgroups and were stratified according to age, sex, body mass index, type of P2Y12 inhibitor, overall or transradial PCI volume by center, renal function, diabetes mellitus, peripheral vascular disease and access site randomization, and accompanied by $\chi 2$ tests for interaction or tests for trend across ordered groups".

Secondary outcomes were analyzed with a two-sided alpha set at 5% to allow conventional interpretation of results. All analyses were performed using the STATA version 14.1 (StataCorp, College Station, Texas) and R (R Foundation, Vienna, Austria) statistical packages.

RESULTS

Patients

From October 11, 2011, to November 7, 2014, at 78 centers in Italy, the Netherlands, Spain, and Sweden, 3610 patients were assigned to receive bivalirudin as part of the MATRIX program. Of these, 1799 (STEMI=1006; NSTE-ACS=793) patients were randomized to receive and 1811 (STEMI=1006; NSTE-ACS=805) to not receive a post-PCI bivalirudin infusion. Post-PCI bivalirudin infusion was administered at full or low dose in 612 (STEMI=399; NSTE-ACS=213) and 1068 (STEMI=519; NSTE-ACS=549) patients respectively, whereas 119 patients did not receive post-PCI infusion. The distribution of patients receiving a full or low dose during time is shown in **Figure 1**.

Baseline and procedural characteristics, stratified by ACS type, of patients randomized to receive or not to receive post-PCI bivalirudin infusion were generally well-balanced (**Supplementary Tables 1-3**). Baseline and procedural characteristics stratified by actual post-PCI bivalirudin regimen in those assigned to post-PCI bivalirudin are shown in **Supplementary Tables 4-6**. Compared with patients receiving a low bivalirudin regimen, those treated with a full post-PCI bivalirudin dose were slightly younger, less frequently affected by cardiovascular risk factors, had a history of MI or coronary revascularization or were treated with anti-hypertensive/lipid-lowering agents. Yet, they were more frequently smokers or exposed to ticagrelor (as opposed to clopidogrel) or UFH before angiography, more frequently presenting TIMI flow 0-1 before PCI, and more frequently treated with ticagrelor or DES implantation (**Supplementary Tables 4-6**).

Clinical outcomes of post-PCI prolonged vs no infusion of bivalirudin

The primary composite outcome was similar in patients who either did or did not receive post-PCI bivalirudin in the entire population (rate ratio, 0.91, 95% CI 0.74-1.11; p=0.34). When separately appraised in STEMI and NSTEACS patients, the results remained consistent in indicating no benefit from post-PCI bivalirudin (**Supplementary Results**).

Clinical outcomes of Full vs Low dose of post-PCI prolonged bivalirudin infusion

At univariate analysis, post-PCI full dose bivalirudin was associated with a significant reduction of the primary endpoint consisting of urgent target-vessel revascularization, definite ST, or NACE as compared to low dose bivalirudin infusion (rate ratio 0.29, 95% CI 0.19-0.44; p<0.001). After multivariable adjustment, this composite endpoint remained lower in the full versus low post-PCI bivalirudin arm (rate ratio 0.21, 95% CI 0.12-0.35; p<0.001). The propensity-score adjustment provided consistent results (rate ratio 0.16, 95% CI 0.09-0.26; p<0.001) (**Table 1; Central illustration and Figure 2**).

Similar findings were observed for the MACE (unadjusted rate ratio 0.31, 95% CI 0.2-0.47; p<0.001; multivariable adjusted rate ratio 0.23, 95% CI 0.13-0.39; p<0.001; propensity-score adjusted rate ratio 0.17, 95% CI 0.1-0.29; p<0.001) or NACE (unadjusted rate ratio 0.30, 95% CI 0.2-0.45; p<0.001; multivariable adjusted rate ratio 0.22, 95% CI 0.13-0.36; p<0.001; propensity-score adjusted rate ratio 0.16, 95% CI 0.09-0.27; p<0.001) endpoints favoring the full as compared to the low post-PCI bivalirudin regimens (**Table 1**). The benefit of post-PCI full bivalirudin dose was driven by a reduction of MI, ST, TVR and BARC 3 or 5, whereas the rates of all-cause death, cardiovascular mortality or stroke did not differ (**Table 1; Central illustration and Figures 3-4**). Overall, these findings remained consistent across the ACS subtypes (**Supplementary Tables 8 and 9**).

Clinical outcomes of post-PCI Full dose bivalirudin vs no post-PCI infusion or vs heparin

Compared with the no post-PCI bivalirudin infusion group, full dose post-PCI bivalirudin was associated with a significantly lower rate of the primary endpoint, as well as MACE or NACE, and this effect was mainly driven by lower rates of MI and BARC 3 or 5 bleeding events (**Table 2, Supplementary Tables 10 and 11**). When compared with the heparin plus provisional GPI group, full dose post-PCI bivalirudin regimen was associated with a significantly lower rate of the primary endpoint, as well as MACE or NACE, and this effect was driven by lower rates of all-cause and

cardiovascular death as well as of MI or BARC 3 or 5 bleeding events (**Table 3, Supplementary Tables 12 and 13**).

DISCUSSION

MATRIX was the first trial to explore, in a randomized manner, the differences among post-PCI bivalirudin infusion versus no bivalirudin infusion in invasively managed ACS patients. The present analysis sought to further investigate the stratified outcomes of post-PCI bivalirudin infusion versus no infusion in STEMI versus NSTE-ACS patients across the full spectrum of all pre-defined endpoints as well as the impact of post-PCI bivalirudin dose on outcomes. The main findings of this analysis can be summarized as follows: a) there were no differences between post-PCI bivalirudin infusion vs no infusion for the primary or other secondary efficacy and safety endpoints in patients either presenting STEMI or NSTE-ACS. This observation further reinforces the notion that the type of ACS was not a treatment modifier in our study; b) the post-PCI full dose of bivalirudin remained associated after both multivariable or propensity score adjusted analyses to beneficial effects in terms of ischemic non-fatal endpoints, including ST and MI as well as bleeding events when compared to the low post-PCI bivalirudin dose; c) after multivariable or propensity-score adjustment, patients receiving full dose bivalirudin after PCI showed improved outcomes as compared to patients receiving only intra-procedural bivalirudin or UFH with provisional GPI. The improved outcome with full dose post-PCI bivalirudin was driven by lower MI and bleeding rates when the group was compared with bivalirudin without post-PCI bivalirudin infusion, whereas all-cause and cardiovascular mortality endpoints also favored the full dose post-PCI bivalirudin group when it was compared with UFH±GPI.

STEMI and NSTE-ACS patients differ with respect to multiple baseline and procedural characteristics as well as with post-procedural risks. Yet, they share the same underlying coronary

artery disease characterized by plaque rupture and show similar independent association with adverse outcome (15).

STEMI patients, who are intervened upon as early as possible after symptoms onset, are characterized by having an evolving MI with rising cardiac biomarkers, which prevents in many instances the ascertainment of periprocedural necrotic injury after coronary intervention. This is at variance with NSTE-ACS patients in whom an invasive management is typically performed hours or days after symptoms onset when cardiac biomarkers are declining; a setting which allows peri-procedural MI ascertainment. On the other hand, the risk of acute and subacute ST is higher in STEMI as compared to NSTE-ACS patients, which is at least in part explained by a slow onset of action from oral P2Y12 inhibitors (16). Prolonging bivalirudin infusion after primary PCI completion has therefore been proposed as a therapeutic measure to mitigate that risk. At variance with STEMI patients undergoing coronary intervention, no study has so far observed a higher risk of acute or subacute ST in patients receiving bivalirduin as compared to UFH with or without GPI. This observation may speak against the need to prolong bivalirudin infusion to further optimize outcomes. Yet, a small randomized study in 178 patients with stable (58%) or unstable (42%) angina and complex coronary anatomy, found that prolonged post-PCI infusion significantly reduced the incidence of periprocedural myocardial damage (defined as creatine kinase-MB increase ≥3 times upper limit of normal) compared with no infusion without differences in death and other clinical outcomes at 1- and 6-month follow-up (17).

In the HORIZONS-AMI, bivalirudin administration was limited, as per protocol, to the procedural period with interruption of the infusion at the end of PCI (2). The study showed a significant increase in the acute ST (absolute 1% excess that was not extended in ST rates at 30 days) in the bivaluridin arm compared with UFH plus GPI. Subsequently, the EUROMAX trial was designed to test whether bivalirudin, initiated during transport for primary PCI in STEMI, was superior to UFH in a more contemporary practice of the STEMI patients' management (3). As opposed to HORIZONS-AMI, bivalirudin in the EUROMAX trial was prolonged as per protocol for at least 4

hours after PCI. Moreover, the protocol specified that the dosage after PCI had to be 0.25 mg/kg/h, but the full dose (1.75 mg/kg/h) was also permitted. In accordance with the HORIZONS-AMI, the EUROMAX confirmed the same 1% absolute increase in acute ST as compared with UFH with optional GPI, despite extending bivalirudin infusion for up to 4 hours after PCI, but major bleeding was reduced. A specific subanalysis of this trial showed that a high-dose of post-PCI bivalirudin was associated to similar rates of acute ST compared with UFH+GPI, while low-dose was independently associated to higher rates of acute ST (18). In the BRIGHT trial, bivalirudin was administered during and after the procedure at 1.75 mg/kg/h (4). The post-procedure infusion was at least 30 minutes and up to 4 hours. At the operator's discretion, a supplementary infusion at low dose (0.2 mg/kg/h) was allowed for up to 20 hours. All patients received a postprocedure infusion of the 1.75mg/kg/h bivalirudin PCI dose for a median duration of 180 minutes, and 115 patients (15.6%) thereafter received the optional 0.2mg/kg/h dose for a median duration of 400 minutes. Any ST and acute ST were not increased, while bleeding and NACE were reduced in the bivalirudin-treated patients. In the HEAT-PPCI, bivalirudin was administered without post-PCI prolonged infusion (a re-bolus of 0.3 mg/kg was provided in case of activated clotting time <225s at the end of PCI), and was associated with increased ST and MACE rates whereas bleeding did not differ (11). ST was observed at a high rate of incidence, at approximately 3.4% at variance with the 1.0% rate in the MATRIX Trial (6).

Most of the evidence in NSTE-ACS patients is outdated and almost exclusively based on bivalirudin administration during PCI only (19). Thus, before MATRIX, limited data existed on the value of bivalirudin used at the currently suggested regimen versus UFH alone in contemporary practice. Our study explored the benefit of bivalirudin compared with UFH across the whole spectrum of ACS patients receiving a concomitant bleeding-avoidance strategy, such as trans-radial access and/or UFH alone. An aggregate data network meta-analysis suggested that post-PCI bivalirudin given at full regimen decreases the rate of ST and ischemic events (19,20). This analysis was largely based on MATRIX study results, but the existence of bias in the analysis was not

assessed. The recent VALIDATE-SWEEDHEART trial contributed to new evidence on bivalirudin versus UFH alone, showing no differences between groups (including ST) across ACS types (21). In this study, the protocol mandated the use of post-PCI bivalirudin at full regimen. So the MATRIX trial remains today the only study in which STEMI and NSTE-ACS patients treated with bivalirudin were randomized to either receive or not to receive post-PCI bivalirudin infusion. Our findings altogether lend support to the use of a post-PCI full bivalirudin infusion regimen to further optimize outcomes in bivalirudin-treated ACS patients (which is in keeping with the updated FDA label of the product), owing to the reduction of ischemic risk without compromising safety, and extend the previous evidence that came from the EUROMAX substudy, which focused on ST only (18). Full post-PCI bivalirudin infusion provided consistent protection in both STEMI and NSTE-ACS towards ST and periprocedural MI risks. While as expected, the risk of ST was in absolute terms greater in STEMI as compared to NSTE-ACS patients, full post-PCI bivalirudin infusion decreased that risk consistently across both types of ACS. In addition, full post-PCI bivalirudin decreased the risks of MI, mainly periprocedural MI. Interestingly, benefits largely came from a mitigation of the risk during index intervention in NSTE-ACS, whereas full post-PCI bivalirudin was associated to lower periprocedural MI risk which was mainly during planned staged interventions in STEMI patients. This observation is explained by the difficulties in ascertaining additional necrotic injury in patients already suffering from an evolving MI.

The rates of BARC 3 or 5 bleeding also remained lower after adjustment in the group that received post-PCI full bivalirudin regimen as compared to who received a low post-PCI bivalirudin regimen or those who did not receive a post-PCI drug infusion. The bleeding risk remained lower in patients treated with the full post-PCI bivalirudin infusion also as compared to those assigned to UFH±GPI, owing to lower risks of access-site and non-access site related bleeding.

Study limitations

This study is affected by the protocol limitation which allowed for two different regimens of post-PCI bivalirudin infusion. Therefore, even if we had conducted multiple adjustments to account for differences between the groups, all these secondary findings should be considered explorative and interpreted with caution.

This analysis provides important knowledge regarding the role of the bivalirudin regimens during the periprocedural period. However, as in previous studies, it is not powered for ST as a primary outcome, and therefore these findings should be considered as hypothesis-generating.

The higher risk of bleeding in patients who received the low post-PCI bivalirudin regimen might have arisen by the protocol mandated longer duration of post-PCI bivalirudin infusion in such patients. Conversely, the lower risk of bleeding in patients receiving the full post-PCI bivalirudin regimen, when compared to those who did not receive infusion -largely attributable to an excess of pericardial bleeding- is counterintuitive. This may reflect a spurious finding or be explained by residual confounding not totally corrected by adjustment. Only a large randomized trial of bivalirudin with a prolonged post-PCI infusion at full dose versus UFH alone would provide conclusive evidence.

CONCLUSION

In patients with ACS, with or without ST-segment elevation undergoing invasive management, the composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events, as well as other explored endpoints, were not significantly lower with a post-PCI bivalirudin infusion compared with no post-PCI infusion. However, a post-PCI bivalirudin infusion at full dose was associated with improved outcomes and was safe when compared with other investigated anti-thrombin strategies, including low post-PCI bivalirudin infusion, no infusion or unfractionated heparin±GPI. Further studies are needed to confirm these observations.

CLINICAL PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE. Multiple data shows that bivalirudin was associated to higher risk of acute stent thrombosis (ST) in STEMI (but not NSTE-ACS) patients, suggesting that a prolonged post-PCI infusion might reduce such risk. However, the optimal regimen of bivalirudin after percutaneous coronary intervention (PCI), and whether this differs across acute coronary syndrome (ACS) with or without ST-segment elevation, is unknown.

COMPETENCY IN PATIENT CARE. In the MATRIX trial, there were no differences between post-PCI bivalirudin infusion vs no infusion for the primary endpoint or other outcomes in STEMI and NSTE-ACS. Additionally, the full post-PCI bivalirudin dose was associated to improved efficacy and safety outcomes after an adjustment was made/applied, when compared to the low post-PCI bivalirudin regimen, no post-PCI infusion or unfractionated heparin groups.

TRANSLATIONAL OUTLOOK. Additional investigation is needed to assess the effects of bivalirudin at full dose post-PCI versus UFH alone in contemporary practice and to assess the cost-effectiveness of these strategies.

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Conflicts of interest:

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FIGURE LEGENDS

Central Illustration. Full or Low post-PCI bivalirudin regimen: Forest Plot of Main Clinical Outcomes. Propensity score adjusted rate ratios (RR) of main outcomes at 30 days for Full versus Low post-PCI bivalirudin regimen in the overall population and stratified by STEMI and NSTE-ACS.

BARC=Bleeding Academic Research Consortium; CI=confidence interval; MI=myocardial infarction; ST=stent thrombosis; TVR=Target Vessel Revascularization.

Figure 1. Distribution of patients receiving a Full or a Low post-PCI bivalirudin infusion during time. Bars report the proportion per week of Full and Low dose of post-PCI bivalirudin infusion during each month of trial enrollment. Vertical dashed lines indicate the publication time of relevant scientific evidence that might have influenced operators' decision. Circles indicate the proportion per week of myocardial infarction (red) and definite stent thrombosis (orange) and continuous lines (red and orange) indicate the corresponding regressions.

Figure 2. Kaplan-Meier curve for the primary endpoint according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type. The cumulative incidence of the primary outcome (composite of all-cause death, myocardial infarction, stroke, bleeding BARC 3 or 5, target vessel revascularization or definite stent thrombosis) up to 30 days, among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose.

Figure 3. Kaplan-Meier curve for individual components of the primary endpoint according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type. The cumulative incidence of the primary outcome components including all-cause death (A), myocardial infarction (B), stroke (C), bleeding BARC 3 or 5 (D), target vessel revascularization (E) and definite stent thrombosis (F) up to 30 days, among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose.

Figure 4. Kaplan-Meier curve for myocardial infarction according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type. The cumulative incidence of myocardial infarction

up to 30 days and stratified by time (<24h, 2-7 days and 8-30 days) among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose.

Table 1. Clinical outcomes at 30 days in post-PCI bivalirudin prolonged infusion at full versus low dose.

OUTCOME	Post-PCI prolonged bivalirudin Full dose (n=612)	Post-PCI prolonged bivalirudin Low dose (n=1068)	Unadjusted Rate Ratio (95% CI)	P-value*	Multivariable Adjusted Rate Ratio (95% CI)	P-value	Propensity Score Adjusted Rate Ratio (95% CI)	P-value
Death, MI, Stroke, BARC 3 or 5, TVR, ST	27 (4.4%)	154 (14.4%)	0.29 (0.19-0.44)	<0.001	0.21 (0.12-0.35)	<0.001	0.16 (0.09-0.26)	<0.001
Death, MI, Stroke	26 (4.2%)	141 (13.2%)	0.31 (0.2-0.47)	<0.001	0.23 (0.13-0.39)	<0.001	0.17 (0.1-0.29)	<0.001
Death, MI, Stroke, BARC 3 or 5	27 (4.4%)	149 (14%)	0.3 (0.2-0.45)	<0.001	0.22 (0.13-0.36)	<0.001	0.16 (0.09-0.27)	<0.001
Death	5 (0.8%)	18 (1.7%)	0.48 (0.18-1.3)	0.141	---	---	0.37 (0.1-1.42)	0.15
Cardiovascular death	5 (0.8%)	16 (1.5%)	0.54 (0.2-1.48)	0.227	---	---	0.46 (0.11-1.82)	0.27
MI	21 (3.4%)	123 (11.5%)	0.29 (0.18-0.45)	<0.001	0.24 (0.14-0.41)	<0.001	0.16 (0.09-0.29)	<0.001
MI <24h	17 (2.8%)	91 (8.5%)	0.32 (0.19-0.53)	<0.001	0.31 (0.17-0.56)	<0.001	0.18 (0.04-0.36)	<0.001
MI 2-7days	3 (0.5%)	24 (2.2%)	0.2 (0.06-0.68)	0.004	0.22 (0.05-0.90)	0.035	0.16 (0.04-0.72)	0.017
MI 8-30 days	1 (0.2%)	8 (0.7%)	0.2 (0.03-1.61)	0.093	0.02 (0.0-0.24)	0.002	0.04 (0.0-0.39)	0.005
Stroke	1 (0.2%)	4 (0.4%)	0.44 (0.05-3.9)	0.444	---	---	0.17 (0.01-2.67)	0.21
TIA	1 (0.2%)	2 (0.2%)	0.87 (0.08-9.63)	0.911	---	---	1.07 (0.03-35.82)	0.97
TVR	3 (0.5%)	28 (2.6%)	0.19 (0.06-0.61)	0.002	0.15 (0.04-0.6)	0.007	0.11 (0.03-0.47)	0.003
ST definite	1 (0.2%)	22 (2.1%)	0.08 (0.01-0.58)	0.001	0.05 (0.01-0.47)	0.008	0.05 (0.01-0.45)	0.008
Acute	1 (0.2%)	9 (0.8%)	0.19 (0.02-1.53)	0.082	0.11 (0.01-1.09)	0.059	0.08 (0.01-0.88)	0.038
Subacute	0 (0%)	13 (1.2%)	---	---	---	---	---	---
ST definite <24h	1 (0.2%)	10 (0.9%)	0.17 (0.02-1.36)	0.059	0.10 (0.01-1.00)	0.05	0.09 (0.01-0.93)	0.044
ST definite 2-7days	0 (0%)	11 (1.1%)	---	---	---	---	---	---
ST definite 8-30 days	0 (0%)	1 (0.1%)	---	---	---	---	---	---
ST definite/probable	1 (0.2%)	25 (2.3%)	0.07 (0.01-0.51)	0.001	0.04 (0.01-0.36)	0.004	0.04 (0-0.34)	0.003
Acute	1 (0.2%)	10 (0.9%)	0.17 (0.02-1.36)	0.059	0.06 (0.01-0.63)	0.018	0.05 (0.01-0.52)	0.012
Subacute	0 (0%)	15 (1.4%)	---	---	---	---	---	---
Bleeding	30 (4.9%)	147 (13.8%)	0.34 (0.23-0.5)	<0.001	0.17 (0.11-0.28)	<0.001	0.16 (0.1-0.27)	<0.001
BARC 1	16 (2.6%)	71 (6.6%)	0.39 (0.22-0.66)	<0.001	0.23 (0.12-0.45)	<0.001	0.22 (0.11-0.45)	<0.001
BARC 2	12 (2%)	62 (5.8%)	0.33 (0.18-0.61)	<0.001	0.18 (0.09-0.39)	<0.001	0.15 (0.07-0.34)	<0.001
BARC 3	2 (0.3%)	13 (1.2%)	0.27 (0.06-1.19)	0.062	0.11 (0.02-0.59)	0.011	0.1 (0.02-0.59)	0.011
BARC 3a	0 (0%)	8 (0.7%)	---	---	---	---	---	---
BARC 3b	2 (0.3%)	3 (0.3%)	1.16 (0.19-6.96)	0.868	0.49 (0.06-4.09)	0.51	0.31 (0.03-3.15)	0.32
BARC 3c	0 (0%)	2 (0.2%)	---	---	---	---	---	---
BARC 4	0 (0%)	0 (0%)	---	---	---	---	---	---
BARC 5	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 5a	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 5b	0 (0%)	0 (0%)	---	---	---	---	---	---
BARC 3 or 5	2 (0.3%)	14 (1.3%)	0.25 (0.06-1.09)	0.046	0.12 (0.02-0.64)	0.013	0.1 (0.02-0.55)	0.008
BARC 3 or 5 access site	2 (0.3%)	8 (0.7%)	0.44 (0.09-2.05)	0.279	0.21 (0.03-1.34)	0.1	0.18 (0.03-1.26)	0.084

BARC 3 or 5 non-access site	0 (0%)	6 (0.6%)	---	---	---	---	---	---
BARC 2, 3 or 5	14 (2.3%)	76 (7.1%)	0.31 (0.18-0.55)	<0.001	0.16 (0.08-0.32)	<0.001	0.13 (0.06-0.28)	<0.001
BARC 2, 3 or 5 access site	10 (1.6%)	41 (3.8%)	0.42 (0.21-0.84)	0.011	0.29 (0.12-0.69)	0.006	0.29 (0.11-0.76)	0.011
BARC 2, 3 or 5 non-access site	4 (0.7%)	35 (3.3%)	0.2 (0.07-0.55)	0.001	0.08 (0.03-0.26)	<0.001	0.05 (0.01-0.18)	<0.001
TIMI major	0 (0%)	5 (0.5%)	---	---	---	---	---	---
TIMI minor	0 (0%)	7 (0.7%)	---	---	---	---	---	---
TIMI major/minor	0 (0%)	12 (1.1%)	---	---	---	---	---	---
GUSTO severe	0 (0%)	4 (0.4%)	---	---	---	---	---	---
GUSTO moderate	1 (0.2%)	4 (0.4%)	0.44 (0.05-3.9)	0.445	0.5 (0.03-8.27)	0.63	0.57 (0.03-11.61)	0.71
GUSTO mild	29 (4.7%)	139 (13%)	0.35 (0.23-0.52)	<0.001	0.18 (0.11-0.3)	<0.001	0.17 (0.1-0.28)	<0.001
GUSTO moderate/severe	1 (0.2%)	8 (0.7%)	0.22 (0.03-1.74)	0.114	0.2 (0.02-2.2)	0.19	0.11 (0.01-1.32)	0.083
Composite of surgical access site repair and blood transfusion	3 (0.5%)	15 (1.4%)	0.35 (0.1-1.2)	0.079	0.29 (0.05-1.68)	0.17	0.37 (0.07-1.91)	0.23
Surgical access site repair	1 (0.2%)	1 (0.1%)	1.75 (0.11-27.92)	0.69	---	---	0.84 (0.02-45.33)	0.93
Blood transfusion	2 (0.3%)	14 (1.3%)	0.25 (0.06-1.09)	0.046	0.17 (0.02-1.68)	0.13	0.3 (0.04-1.98)	0.21
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0%)	3 (0.3%)	---	---	---	---	---	---
Pericardial bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Gastrointestinal bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Genito-urinary bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Access site bleeding	2 (0.3%)	8 (0.7%)	0.43 (0.09-2.05)	0.278	0.21 (0.03-1.33)	0.097	0.18 (0.03-1.25)	0.083
Other bleeding	0 (0%)	0 (0%)	---	---	---	---	---	---

* Log-rank test

Table 2. Clinical outcomes at 30 days in post-PCI bivalirudin prolonged infusion at full dose versus no post-PCI infusion.

OUTCOME	Post-PCI prolonged bivalirudin Full dose (n=612)	No infusion (n=1811)	Unadjusted Rate Ratio (95% CI)	P-value*	Multivariable Adjusted Rate Ratio (95% CI)	P-value	Propensity Score Adjusted Rate Ratio (95% CI)	P-value
Death, MI, Stroke, BARC 3 or 5, TVR, ST	27 (4.4%)	215 (11.9%)	0.36 (0.24-0.53)	<0.001	0.36 (0.22-0.56)	<0.001	0.4 (0.26-0.62)	<0.001
Death, MI, Stroke	26 (4.2%)	190 (10.5%)	0.39 (0.26-0.59)	<0.001	0.4 (0.25-0.65)	<0.001	0.45 (0.29-0.7)	<0.001
Death, MI, Stroke, BARC 3 or 5	27 (4.4%)	211 (11.7%)	0.36 (0.24-0.54)	<0.001	0.37 (0.23-0.58)	<0.001	0.42 (0.27-0.64)	<0.001
Death	5 (0.8%)	32 (1.8%)	0.46 (0.18-1.18)	0.098	---	---	0.5 (0.18-1.36)	0.17
Cardiovascular death	5 (0.8%)	31 (1.7%)	0.47 (0.18-1.22)	0.114	---	---	0.54 (0.2-1.49)	0.23
MI	21 (3.4%)	154 (8.5%)	0.39 (0.25-0.62)	<0.001	0.43 (0.27-0.7)	0.001	0.46 (0.28-0.76)	0.002
MI <24h	17 (2.8%)	121 (6.7%)	0.41 (0.25-0.68)	<0.001	0.51 (0.30-0.88)	0.015	0.50 (0.29-0.88)	0.016
MI 2-7days	3 (0.5%)	26 (1.4%)	0.33 (0.1-1.08)	0.053	0.22 (0.06-0.76)	0.017	0.32 (0.09-1.10)	0.070
MI 8-30 days	1 (0.2%)	7 (0.4%)	0.4 (0.05-3.26)	0.377	0.36 (0.04-3.10)	0.36	0.45 (0.05-4.07)	0.48
Stroke	1 (0.2%)	7 (0.4%)	0.42 (0.05-3.43)	0.405	---	---	0.39 (0.04-3.41)	0.39
TIA	1 (0.2%)	2 (0.1%)	1.48 (0.13-16.33)	0.747	0.44 (0.01-14.5)	0.64	0.73 (0.07-8.29)	0.8
TVR	3 (0.5%)	21 (1.2%)	0.42 (0.13-1.41)	0.149	0.44 (0.12-1.53)	0.2	0.45 (0.13-1.62)	0.22
ST definite	1 (0.2%)	13 (0.7%)	0.23 (0.03-1.74)	0.118	0.25 (0.03-2.02)	0.19	0.34 (0.04-2.88)	0.32
Acute	1 (0.2%)	10 (0.6%)	0.3 (0.04-2.31)	0.216	0.35 (0.04-2.96)	0.33	0.52 (0.06-4.76)	0.57
Subacute	0 (0%)	3 (0.2%)	---	---	---	---	---	---
ST definite <24h	1 (0.2%)	8 (0.4%)	0.37 (0.05-2.95)	0.328	0.50 (0.06-4.36)	0.53	0.57 (0.06-5.24)	0.62
ST definite 2-7days	0 (0%)	4 (0.2%)	---	---	---	---	---	---
ST definite 8-30 days	0 (0%)	1 (0.1%)	---	---	---	---	---	---
ST definite/probable	1 (0.2%)	19 (1%)	0.16 (0.02-1.16)	0.037	0.24 (0.03-1.88)	0.17	0.23 (0.03-1.81)	0.16
Acute	1 (0.2%)	11 (0.6%)	0.27 (0.03-2.08)	0.176	0.35 (0.04-2.96)	0.33	0.52 (0.06-4.76)	0.57
Subacute	0 (0%)	8 (0.4%)	---	---	---	---	---	---
Bleeding	30 (4.9%)	192 (10.6%)	0.45 (0.31-0.66)	<0.001	0.46 (0.3-0.7)	<0.001	0.5 (0.33-0.77)	0.002
BARC 1	16 (2.6%)	97 (5.4%)	0.48 (0.28-0.82)	0.006	0.5 (0.27-0.92)	0.025	0.66 (0.37-1.19)	0.17
BARC 2	12 (2%)	62 (3.4%)	0.57 (0.31-1.06)	0.07	0.56 (0.28-1.11)	0.095	0.5 (0.25-1.02)	0.058
BARC 3	2 (0.3%)	28 (1.5%)	0.21 (0.05-0.88)	0.019	0.21 (0.05-0.92)	0.038	0.23 (0.05-1)	0.05
BARC 3a	0 (0%)	15 (0.8%)	---	---	---	---	---	---
BARC 3b	2 (0.3%)	11 (0.6%)	0.54 (0.12-2.43)	0.412	0.67 (0.13-3.34)	0.62	0.69 (0.14-3.54)	0.66
BARC 3c	0 (0%)	2 (0.1%)	---	---	---	---	---	---
BARC 4	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 5	0 (0%)	4 (0.2%)	---	---	---	---	---	---
BARC 5a	0 (0%)	3 (0.2%)	---	---	---	---	---	---
BARC 5b	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 3 or 5	2 (0.3%)	32 (1.8%)	0.18 (0.04-0.77)	0.009	0.21 (0.05-0.92)	0.038	0.19 (0.04-0.81)	0.025
BARC 3 or 5 access site	2 (0.3%)	8 (0.4%)	0.74 (0.16-3.49)	0.702	1.13 (0.21-6.14)	0.88	0.91 (0.16-4.99)	0.91

BARC 3 or 5 non-access site	0 (0%)	24 (1.3%)	---	---	---	---	---	---
BARC 2, 3 or 5	14 (2.3%)	94 (5.2%)	0.44 (0.25-0.76)	0.003	0.44 (0.24-0.8)	0.008	0.39 (0.21-0.74)	0.004
BARC 2, 3 or 5 access site	10 (1.6%)	45 (2.5%)	0.66 (0.33-1.3)	0.224	0.69 (0.32-1.48)	0.34	0.69 (0.32-1.5)	0.35
BARC 2, 3 or 5 non-access site	4 (0.7%)	49 (2.7%)	0.24 (0.09-0.66)	0.003	0.25 (0.09-0.72)	0.01	0.17 (0.05-0.56)	0.004
TIMI major	0 (0%)	11 (0.6%)	---	---	---	---	---	---
TIMI minor	0 (0%)	9 (0.5%)	---	---	---	---	---	---
TIMI major/minor	0 (0%)	20 (1.1%)	---	---	---	---	---	---
GUSTO severe	0 (0%)	12 (0.7%)	---	---	---	---	---	---
GUSTO moderate	1 (0.2%)	11 (0.6%)	0.27 (0.03-2.08)	0.177	0.33 (0.04-2.7)	0.3	0.24 (0.03-1.93)	0.18
GUSTO mild	29 (4.7%)	168 (9.3%)	0.5 (0.34-0.74)	<0.001	0.49 (0.32-0.77)	0.002	0.58 (0.37-0.9)	0.015
GUSTO moderate/severe	1 (0.2%)	23 (1.3%)	0.13 (0.02-0.95)	0.017	0.18 (0.02-1.36)	0.096	0.12 (0.02-0.92)	0.041
Composite of surgical access site repair and blood transfusion	3 (0.5%)	16 (0.9%)	0.55 (0.16-1.9)	0.339	0.36 (0.08-1.76)	0.21	0.48 (0.13-1.75)	0.27
Surgical access site repair	1 (0.2%)	3 (0.2%)	0.99 (0.1-9.48)	0.99	---	---	2.28 (0.16-31.8)	0.54
Blood transfusion	2 (0.3%)	13 (0.7%)	0.45 (0.1-2.01)	0.286	0.11 (0.01-1.4)	0.088	0.34 (0.07-1.57)	0.17
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Pericardial bleeding	0 (0%)	10 (0.6%)	---	---	---	---	---	---
Gastrointestinal bleeding	0 (0%)	5 (0.3%)	---	---	---	---	---	---
Genito-urinary bleeding	0 (0%)	4 (0.2%)	---	---	---	---	---	---
Access site bleeding	2 (0.3%)	8 (0.4%)	0.74 (0.16-3.47)	0.698	1.13 (0.21-6.12)	0.89	0.9 (0.16-4.97)	0.91
Other bleeding	0 (0%)	3 (0.2%)	---	---	---	---	---	---

* Log-rank test

Table 3. Clinical outcomes at 30 days in post-PCI bivalirudin prolonged infusion at full dose versus unfractionated heparin.

OUTCOME	Post-PCI prolonged bivalirudin Full dose (n=612)	Unfractionated heparin (n=3603)	Unadjusted Rate Ratio (95% CI)	P-value*	Multivariable Adjusted Rate Ratio (95% CI)	P-value	Propensity Score Adjusted Rate Ratio (95% CI)	P-value
Death, MI, Stroke, BARC 3 or 5, TVR, ST	27 (4.4%)	450 (12.5%)	0.34 (0.23-0.5)	<0.001	0.38 (0.24-0.59)	<0.001	0.41 (0.27-0.61)	<0.001
Death, MI, Stroke	26 (4.2%)	391 (10.9%)	0.38 (0.25-0.56)	<0.001	0.44 (0.28-0.69)	<0.001	0.47 (0.31-0.72)	<0.001
Death, MI, Stroke, BARC 3 or 5	27 (4.4%)	444 (12.3%)	0.34 (0.23-0.51)	<0.001	0.38 (0.25-0.6)	<0.001	0.41 (0.27-0.62)	<0.001
Death	5 (0.8%)	83 (2.3%)	0.35 (0.14-0.87)	0.018	---	---	0.39 (0.15-0.98)	0.046
Cardiovascular death	5 (0.8%)	80 (2.2%)	0.37 (0.15-0.9)	0.023	---	---	0.41 (0.16-1.03)	0.059
MI	21 (3.4%)	303 (8.4%)	0.4 (0.26-0.62)	<0.001	0.47 (0.3-0.75)	0.001	0.51 (0.32-0.81)	0.005
MI <24h	17 (2.8%)	239 (6.6%)	0.41 (0.25-0.67)	<0.001	0.49 (0.29-0.83)	0.007	0.54 (0.32-0.92)	0..023
MI 2-7days	3 (0.5%)	44 (1.2%)	0.38 (0.12-1.24)	0.096	0.41 (0.12-1.32)	0.13	0.37 (0.11-1.25)	0.11
MI 8-30 days	1 (0.2%)	20 (0.6%)	0.28 (0.04-2.09)	0.184	0.39 (0.05-3.04)	0.37	0.52 (0.06-4.19)	0.54
Stroke	1 (0.2%)	16 (0.4%)	0.37 (0.05-2.77)	0.311	---	---	0.53 (0.06-4.35)	0.55
TIA	1 (0.2%)	9 (0.2%)	0.65 (0.08-5.16)	0.685	0.99 (0.1-9.51)	0.99	0.86 (0.09-7.84)	0.89
TVR	3 (0.5%)	35 (1%)	0.5 (0.16-1.64)	0.246	0.79 (0.23-2.66)	0.7	0.84 (0.24-2.95)	0.79
ST definite	1 (0.2%)	21 (0.6%)	0.28 (0.04-2.08)	0.183	0.51 (0.07-3.96)	0.52	0.41 (0.05-3.27)	0.4
Acute	1 (0.2%)	13 (0.4%)	0.45 (0.06-3.46)	0.433	0.88 (0.11-7.25)	0.91	0.66 (0.08-5.57)	0.7
Subacute	0 (0%)	8 (0.2%)	---	---	---	---	---	---
ST definite <24h	1 (0.2%)	11 (0.3%)	0.53 (0.07-4.14)	0.543	1.03 (0.12-8.61)	0.98	0.67 (0.08-5.78)	0.72
ST definite 2-7days	0 (0%)	7 (0.2%)	---	---	---	---	---	---
ST definite 8-30 days	0 (0%)	3 (0.1%)	---	---	---	---	---	---
ST definite/probable	1 (0.2%)	35 (1%)	0.17 (0.02-1.22)	0.045	0.33 (0.04-2.54)	0.29	0.27 (0.03-2.06)	0.21
Acute	1 (0.2%)	16 (0.4%)	0.37 (0.05-2.77)	0.311	0.88 (0.11-7.25)	0.91	0.63 (0.08-5.29)	0.67
Subacute	0 (0%)	19 (0.5%)	---	---	---	---	---	---
Bleeding	30 (4.9%)	482 (13.4%)	0.35 (0.24-0.51)	<0.001	0.35 (0.23-0.52)	<0.001	0.35 (0.24-0.52)	<0.001
BARC 1	16 (2.6%)	237 (6.6%)	0.39 (0.23-0.65)	<0.001	0.38 (0.22-0.66)	0.001	0.43 (0.25-0.74)	0.002
BARC 2	12 (2%)	153 (4.2%)	0.46 (0.25-0.82)	0.007	0.44 (0.24-0.83)	0.011	0.42 (0.22-0.81)	0.009
BARC 3	2 (0.3%)	72 (2%)	0.16 (0.04-0.66)	0.004	0.18 (0.04-0.74)	0.018	0.16 (0.04-0.67)	0.012
BARC 3a	0 (0%)	38 (1.1%)	---	---	---	---	---	---
BARC 3b	2 (0.3%)	33 (0.9%)	0.36 (0.09-1.48)	0.138	0.36 (0.08-1.57)	0.17	0.35 (0.08-1.51)	0.16
BARC 3c	0 (0%)	1 (0%)	---	---	---	---	---	---
BARC 4	0 (0%)	4 (0.1%)	---	---	---	---	---	---
BARC 5	0 (0%)	16 (0.4%)	---	---	---	---	---	---
BARC 5a	0 (0%)	11 (0.3%)	---	---	---	---	---	---
BARC 5b	0 (0%)	5 (0.1%)	---	---	---	---	---	---
BARC 3 or 5	2 (0.3%)	88 (2.4%)	0.13 (0.03-0.54)	0.001	0.17 (0.04-0.72)	0.015	0.13 (0.03-0.52)	0.004
BARC 3 or 5 access site	2 (0.3%)	32 (0.9%)	0.37 (0.09-1.53)	0.152	0.38 (0.09-1.65)	0.2	0.34 (0.08-1.47)	0.15

BARC 3 or 5 non-access site	0 (0%)	56 (1.6%)	---	---	---	---	---	---
BARC 2, 3 or 5	14 (2.3%)	241 (6.7%)	0.33 (0.2-0.57)	<0.001	0.35 (0.2-0.62)	<0.001	0.3 (0.16-0.54)	<0.001
BARC 2, 3 or 5 access site	10 (1.6%)	132 (3.7%)	0.44 (0.23-0.84)	0.01	0.4 (0.2-0.8)	0.01	0.39 (0.2-0.79)	0.008
BARC 2, 3 or 5 non-access site	4 (0.7%)	109 (3%)	0.21 (0.08-0.58)	0.001	0.29 (0.1-0.81)	0.017	0.18 (0.06-0.57)	0.004
TIMI major	0 (0%)	33 (0.9%)	---	---	---	---	---	---
TIMI minor	0 (0%)	33 (0.9%)	---	---	---	---	---	---
TIMI major/minor	0 (0%)	66 (1.8%)	---	---	---	---	---	---
GUSTO severe	0 (0%)	26 (0.7%)	---	---	---	---	---	---
GUSTO moderate	1 (0.2%)	26 (0.7%)	0.23 (0.03-1.67)	0.11	0.26 (0.03-1.97)	0.19	0.18 (0.02-1.34)	0.093
GUSTO mild	29 (4.7%)	426 (11.8%)	0.39 (0.27-0.56)	<0.001	0.38 (0.25-0.57)	<0.001	0.4 (0.27-0.6)	<0.001
GUSTO moderate/severe	1 (0.2%)	52 (1.4%)	0.11 (0.02-0.81)	0.009	0.15 (0.02-1.14)	0.067	0.09 (0.01-0.69)	0.02
Composite of surgical access site repair and blood transfusion	3 (0.5%)	67 (1.9%)	0.26 (0.08-0.83)	0.014	0.25 (0.06-1.07)	0.061	0.26 (0.08-0.85)	0.026
Surgical access site repair	1 (0.2%)	12 (0.3%)	0.49 (0.06-3.77)	0.484	0.56 (0.07-4.65)	0.59	0.47 (0.06-3.85)	0.48
Blood transfusion	2 (0.3%)	63 (1.7%)	0.19 (0.05-0.76)	0.008	0.13 (0.02-0.99)	0.048	0.18 (0.04-0.76)	0.02
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0%)	3 (0.1%)	---	---	---	---	---	---
Pericardial bleeding	0 (0%)	17 (0.5%)	---	---	---	---	---	---
Gastrointestinal bleeding	0 (0%)	21 (0.6%)	---	---	---	---	---	---
Genito-urinary bleeding	0 (0%)	7 (0.2%)	---	---	---	---	---	---
Access site bleeding	2 (0.3%)	30 (0.8%)	0.39 (0.09-1.63)	0.181	0.4 (0.09-1.73)	0.22	0.35 (0.08-1.54)	0.17
Other bleeding	0 (0%)	7 (0.2%)	---	---	---	---	---	---

* Log-rank test