Impact of sex on comparative outcomes of bivalirudin versus unfractionated heparin in patients with acute coronary syndromes undergoing invasive management: a pre-specified analysis of the MATRIX trial

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KEYWORDS

- ACS/NSTE-ACS
- adjunctive pharmacotherapy
- STEMI

Abstract

Aims: Our aim was to assess whether bivalirudin compared with unfractionated heparin (UFH) is associated with consistent outcomes in males and females with acute coronary syndrome (ACS) undergoing invasive management.

Methods and results: In the MATRIX programme, 7,213 patients were randomised to bivalirudin or UFH. Patients in the bivalirudin group were subsequently randomly assigned to receive or not a post-PCI bivalirudin infusion. The 30-day co-primary outcomes were major adverse cardiovascular events (MACE), defined as death, myocardial infarction, or stroke, and net adverse clinical events (NACE), defined as MACE or major bleeding. The primary outcome for the comparison of a post-PCI bivalirudin infusion with no post-PCI infusion was a composite of urgent target vessel revascularisation (TVR), definite stent thrombosis (ST), or NACE. The rate of MACE was not significantly lower with bivalirudin than with heparin in male (rate ratio [RR] 0.90, 95% confidence interval [CI]: 0.75-1.07; p=0.22) and female patients (RR 1.06, 95% CI: 0.80-1.40; p=0.67) without significant interaction (p_{int}=0.31), nor was the rate of NACE (males: RR 0.85, 95% CI: 0.72-1.01; p=0.07; females: RR 0.98, 95% CI: 0.76-1.28; p=0.91; p_{int}=0.38). Post-PCI bivalirudin infusion, as compared with no infusion, did not significantly decrease the rate of urgent TVR, definite ST, or NACE (males: RR 0.84, 95% CI: 0.66-1.07; p=0.15; females: RR 1.06, 95% CI: 0.74-1.53; p=0.74; p_{int}=0.28).

Conclusions: In ACS patients, the rates of MACE and NACE were not significantly lower with bivalirudin than with UFH in both sexes. The rate of the composite of urgent TVR, definite ST, or NACE was not significantly lower with a post-PCI bivalirudin infusion than with no post-PCI infusion in both sexes.

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Abbreviations

ACS	acute coronary syndrome
GPI	glycoprotein IIb/IIIa inhibitor
MACE	major adverse cardiovascular events
MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
NACE	net adverse clinical events
PCI	percutaneous coronary intervention
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
TVR	target vessel revascularisation
UFH	unfractionated heparin

Introduction

Over the past decade, antithrombotic therapies after an acute coronary syndrome (ACS) have improved outcomes more in men than in women[1,2], raising the question as to whether there are sex-specific differences in treatment patterns and response to such therapy. However, there is contrasting evidence on the impact of sex on clinical outcomes, particularly on overall and cardiovascular mortality, in patients treated for coronary artery disease. There are also differences in presenting clinical characteristics and pathophysiologic profile, as well as disparities in treatment which may contribute considerably to this outcome discrepancy[3]. A large body of evidence suggests that female patients have increased periprocedural bleeding risk as compared to males[4,5]. Recently the radial access has been shown to be effective in reducing such risk compared to the femoral access in ACS patients managed invasively[6].

We sought to investigate whether the use of bivalirudin, either continued or discontinued after percutaneous coronary intervention (PCI), instead of unfractionated heparin (UFH), might be associated with consistent or differential efficacy and safety effects in male and female patients with ACS undergoing invasive management as part of a pre-specified analysis in the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) programme.

Methods

STUDY DESIGN, OUTCOMES AND STATISTICAL ANALYSIS

The design and main results of the MATRIX trial have been reported previously[7-9]. Details are shown in **Supplementary Appendix 1.**

Results

PATIENTS

From October 2011 to November 2014, at 78 centres in Italy, the Netherlands, Spain, and Sweden, 3,610 patients were assigned to receive bivalirudin (males: 2,731, 75.7%; females: 879, 24.3%), either with a post-PCI infusion (1,799 patients [males: 1,351, 75.1% and females: 448, 24.9%]) or without a post-PCI infusion (1,811 patients [males: 1,380, 76.2% and females: 431, 23.8%]), and 3,603 were assigned to receive UFH (males: 2,764, 76.7%; females: 839, 23.3%).

Female and male subgroups allocated to bivalirudin versus UFH and to post-PCI bivalirudin infusion versus no post-PCI infusion were generally well matched in terms of demographics, medical history, clinical presentation, procedural aspects and therapy at discharge **(Supplementary Table 1-Supplementary Table 3)**.

CLINICAL OUTCOMES ACCORDING TO ANTITHROMBIN TYPE

MACE occurred in 256 patients (9.4%) in the bivalirudin group and in 287 patients (10.5%) in the UFH group (rate ratio [RR] 0.90, 95% confidence interval [CI]: 0.75 to 1.07; p=0.22) in males and in 115 (13.1%) and 104 (12.4%) females (RR 1.06, 95% CI: 0.80 to 1.40; p=0.67) without significant interaction (p_{int}=0.31) **(Table 1, Figure 1, Figure 2)**. A total of 276 patients (10.2%) in the bivalirudin group, as compared with 323 patients (11.8%) in the UFH group, had a NACE (RR 0.85, 95% CI: 0.72 to 1.01; p=0.07) in males, and 125 (14.2%) as compared with 121 (14.4%) female patients had a NACE (RR 0.98, 95% CI: 0.76 to 1.28; p=0.91) without significant interaction (p_{int}=0.38) **(Table 1, Figure 1, Figure 2)**.

Compared with UFH, bivalirudin was apparently associated with a lower rate of all-cause death in male (1.2% vs. 1.9%; RR 0.63, 95% CI: 0.41 to 0.98; p=0.041) but not in female patients (3.1% vs. 3.8%; RR 0.80, 95% CI: 0.48 to 1.34; p=0.40); however, there was no detectable signal of heterogeneity across genders (p_{int}=0.49) **(Table 1, Figure 1, Figure 3)**. This was similarly observed for cardiovascular death (males: 1.1% vs. 1.8%; RR 0.60, 95% CI: 0.38 to 0.95; p=0.028; females: 3.0% vs. 3.6%; RR 0.82, 95% CI: 0.49 to 1.40; p=0.47; p_{int}=0.38) **(Table 1)**. There were no significant differences between bivalirudin and UFH in both male and female patients for the rates of individual endpoints of myocardial infarction (MI), stroke, target vessel revascularisation (TVR), and stent thrombosis (ST) **(Table 1, Figure 1, Figure 3)**. Bivalirudin consistently reduced rates of major bleeding (BARC 3 or 5) compared with UFH across genders (males: 1.2% vs. 2.0%; RR 0.59, 95% CI: 0.38 to 0.92; p=0.019; females: 2.0% vs. 4.1%; RR 0.47, 95% CI: 0.26 to 0.85; p=0.01; p_{int}=0.53) **(Table 1, Figure 1, Figure 3)**. This difference was mainly driven by access-related events in males and by non-access-related bleeding in females, with fatal, TIMI major and GUSTO severe bleeding being lower in female patients only **(Table 1)**.

CLINICAL OUTCOMES ACCORDING TO BIVALIRUDIN TREATMENT DURATION

The primary composite outcome was observed in 128 patients (9.6%) who received post-PCI bivalirudin and in 154 patients (11.2%) who did not receive post-PCI bivalirudin (RR 0.84, 95% CI: 0.66 to 1.07; p=0.15) in males and, respectively, in 67 (15.0%) versus 61 female patients (14.2%) (RR 1.06, 95% CI: 0.74 to 1.53; p=0.74) (p_{int}=0.28) **(Supplementary Table 4, Figure 4, Figure 5)**. No significant differences or interactions were observed in terms of MACE, NACE, or individual endpoints of death, MI, stroke, TVR or ST **(Supplementary Table 4, Figure 6)**.

Table 1. Clinical outcomes at 30 days for the antithrombin type study.

	Male				Female				*p*-value for interaction
	Bivalirudin (N=2,731)	UFH (N=2,764)	Rate ratio (95% CI)	*p*-value	Bivalirudin (N=879)	UFH (N=839)	Rate ratio (95% CI)	*p*-value	
Co-primary composite endpoint of all-cause mortality, MI or stroke	256 (9.4)	287 (10.5)	0.90 (0.75-1.07)	0.22	115 (13.1)	104 (12.4)	1.06 (0.80-1.40)	0.67	0.31
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	276 (10.2)	323 (11.8)	0.85 (0.72-1.01)	0.066	125 (14.2)	121 (14.4)	0.98 (0.76-1.28)	0.91	0.38
Composite of all-cause mortality, MI, stroke, BARC 3 or 5, urgent TVR, or definite stent thrombosis	282 (10.4)	329 (12.0)	0.86 (0.73-1.01)	0.069	128 (14.6)	121 (14.4)	1.01 (0.78-1.31)	0.94	0.30
All-cause mortality	32 (1.2)	51 (1.9)	0.63 (0.41-0.98)	0.041	27 (3.1)	32 (3.8)	0.80 (0.48-1.34)	0.40	0.49
Cardiovascular death	30 (1.1)	50 (1.8)	0.60 (0.38-0.95)	0.028	26 (3.0)	30 (3.6)	0.82 (0.49-1.40)	0.47	0.38
Myocardial infarction	220 (8.1)	233 (8.5)	0.95 (0.78-1.15)	0.59	87 (10.0)	70 (8.4)	1.19 (0.86-1.66)	0.30	0.24
Stroke	9 (0.3)	9 (0.3)	1.01 (0.40-2.54)	0.99	4 (0.5)	7 (0.9)	0.54 (0.16-1.85)	0.32	0.43
Transient ischaemic attack	1 (0.0)	2 (0.1)	0.50 (0.05-5.56)	0.57	4 (0.5)	7 (0.8)	0.54 (0.16-1.85)	0.32	0.96
Urgent target vessel revascularisation	37 (1.4)	26 (0.9)	1.44 (0.87-2.38)	0.15	15 (1.7)	9 (1.1)	1.59 (0.69-3.63)	0.27	0.84
Definite stent thrombosis	28 (1.0)	17 (0.6)	1.66 (0.91-3.05)	0.094	8 (0.9)	4 (0.5)	1.90 (0.57-6.33)	0.29	0.85
Acute definite stent thrombosis	15 (0.6)	11 (0.4)	1.38 (0.63-3.00)	0.42	5 (0.6)	2 (0.2)	2.37 (0.46-12.27)	0.29	0.55
Subacute definite stent thrombosis	13 (0.5)	6 (0.2)	2.19 (0.83-5.76)	0.10	3 (0.3)	2 (0.2)	1.42 (0.24-8.54)	0.70	0.68
Definite or probable stent thrombosis	33 (1.2)	30 (1.1)	1.11 (0.68-1.82)	0.68	12 (1.4)	5 (0.6)	2.28 (0.80-6.49)	0.11	0.22
Acute definite or probable stent thrombosis	17 (0.6)	13 (0.5)	1.32 (0.64-2.73)	0.45	5 (0.6)	3 (0.4)	1.58 (0.38-6.64)	0.53	0.83
Subacute definite or probable stent thrombosis	16 (0.6)	17 (0.7)	0.95 (0.48-1.88)	0.88	7 (0.8)	2 (0.2)	3.33 (0.69-16.07)	0.11	0.14
Bleeding	274 (10.1)	337 (12.3)	0.81 (0.69-0.95)	0.012	117 (13.6)	145 (17.6)	0.74 (0.58-0.95)	0.019	0.55
Type 1	135 (5.0)	169 (6.2)	0.80 (0.64-1.01)	0.056	55 (6.5)	68 (8.4)	0.76 (0.53-1.08)	0.13	0.79
Type 2	106 (3.9)	110 (4.0)	0.97 (0.74-1.27)	0.84	45 (5.2)	43 (5.2)	0.98 (0.64-1.50)	0.94	0.96
Type 3abc	29 (1.1)	51 (1.9)	0.57 (0.36-0.90)	0.015	15 (1.7)	21 (2.5)	0.67 (0.35-1.31)	0.24	0.69
Type 3a	14 (0.6)	25 (0.9)	0.56 (0.29-1.08)	0.081	10 (1.2)	13 (1.6)	0.73 (0.32-1.66)	0.45	0.63
Type 3b	12 (0.4)	25 (0.9)	0.48 (0.24-0.96)	0.034	4 (0.5)	8 (1.0)	0.47 (0.14-1.57)	0.21	0.97
Type 3c	3 (0.1)	1 (0.0)	3.02 (0.31-29.10)	0.31	1 (0.1)	0 (0.0)	2.86 (0.12-70.11)	1.00	0.59
Type 4	1 (0.0)	4 (0.1)	0.25 (0.03-2.25)	0.18	0 (0.0)	0 (0.0)	–	–	–
Type 5ab	3 (0.1)	3 (0.1)	1.01 (0.20-4.99)	0.99	2 (0.2)	13 (1.6)	0.15 (0.03-0.65)	0.0033	0.065
Type 5a	2 (0.1)	1 (0.0)	2.01 (0.18-22.21)	0.56	2 (0.2)	10 (1.2)	0.19 (0.04-0.87)	0.016	0.071
Type 5b	1 (0.0)	2 (0.1)	0.50 (0.05-5.56)	0.57	0 (0.0)	3 (0.4)	0.14 (0.01-2.71)	0.12	0.26
Type 3 or 5	32 (1.2)	54 (2.0)	0.59 (0.38-0.92)	0.019	17 (2.0)	34 (4.1)	0.47 (0.26-0.85)	0.010	0.53
Type 3 or 5 related to access site	9 (0.4)	20 (0.7)	0.45 (0.21-0.99)	0.043	10 (1.2)	12 (1.4)	0.79 (0.34-1.83)	0.58	0.34
Type 3 or 5 not related to access site	23 (0.8)	34 (1.3)	0.68 (0.40-1.16)	0.15	7 (0.8)	22 (2.7)	0.30 (0.13-0.70)	0.0033	0.11
Type 2, 3 or 5	138 (5.1)	164 (6.0)	0.85 (0.67-1.06)	0.15	62 (7.1)	77 (9.3)	0.75 (0.53-1.06)	0.10	0.57
Type 2, 3 or 5 related to access site	65 (2.4)	84 (3.1)	0.78 (0.56-1.08)	0.13	40 (4.6)	48 (5.8)	0.78 (0.51-1.19)	0.25	0.99
Type 2, 3 or 5 not related to access site	73 (2.7)	80 (3.0)	0.92 (0.67-1.27)	0.61	22 (2.5)	29 (3.5)	0.72 (0.41-1.26)	0.24	0.45
Major bleeding	12 (0.4)	18 (0.7)	0.67 (0.32-1.39)	0.28	4 (0.5)	15 (1.8)	0.25 (0.08-0.76)	0.0082	0.14
Minor bleeding	9 (0.4)	20 (0.8)	0.45 (0.21-0.99)	0.043	8 (0.9)	13 (1.6)	0.58 (0.24-1.41)	0.22	0.68
Major or minor bleeding	21 (0.8)	38 (1.4)	0.55 (0.33-0.95)	0.028	12 (1.4)	28 (3.4)	0.40 (0.20-0.80)	0.0067	0.47
Severe bleeding	13 (0.5)	14 (0.5)	0.94 (0.44-1.99)	0.86	3 (0.3)	12 (1.4)	0.24 (0.07-0.84)	0.015	0.059
Moderate bleeding	8 (0.3)	13 (0.5)	0.62 (0.26-1.50)	0.28	8 (0.9)	13 (1.6)	0.58 (0.24-1.41)	0.22	0.92
Mild bleeding	252 (9.3)	307 (11.2)	0.82 (0.69-0.97)	0.023	106 (12.3)	119 (14.6)	0.82 (0.63-1.08)	0.16	0.98
Severe or moderate bleeding	21 (0.8)	27 (1.0)	0.78 (0.44-1.39)	0.40	11 (1.3)	25 (3.0)	0.41 (0.20-0.85)	0.012	0.17
Composite of surgical access-site repair or blood products transfusion	18 (0.7)	38 (1.4)	0.48 (0.27-0.83)	0.0079	18 (2.1)	29 (3.5)	0.58 (0.32-1.05)	0.070	0.62
Surgical access-site repair	1 (0.0)	9 (0.3)	0.11 (0.01-0.88)	0.012	4 (0.5)	3 (0.4)	1.26 (0.28-5.64)	0.76	0.041
Blood products transfusion	17 (0.7)	34 (1.3)	0.50 (0.28-0.90)	0.018	14 (1.6)	29 (3.5)	0.45 (0.24-0.86)	0.013	0.82

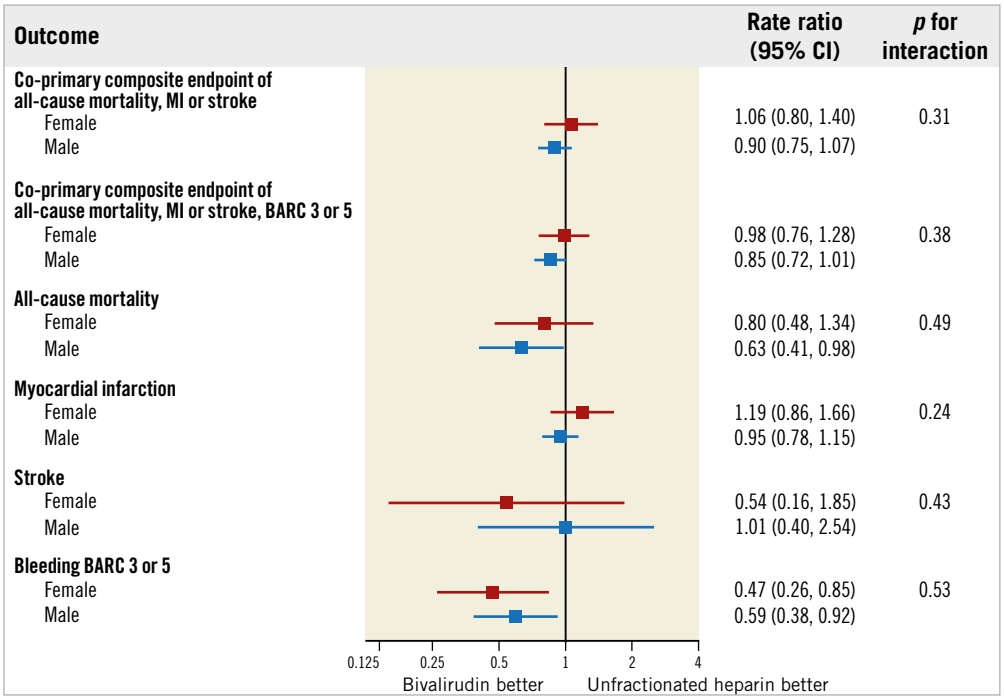


Figure 1. *Main outcomes of bivalirudin versus unfractionated heparin in male and female patients. Bivalirudin and UFH were compared on the basis of sex subgroups, with rate ratios (RR) and 95% confidence intervals (CIs), for the co-primary endpoints and their components (death, myocardial infarction, stroke, BARC 3 or 5).*

There was no significant between-group heterogeneity in the rate of bleeding, with BARC 2 events being significantly higher in male and numerically higher in female patients in the post-PCI bivalirudin arm, while BARC 3 or 5 events which were not related to the access site were lower in both sexes **(Supplementary Table 4)**.

ADDITIONAL ANALYSES

Supplementary Figure 1-Supplementary Figure 4 list the effect of randomised antithrombin type on MACE and NACE in male and female patients according to pre-specified subgroups. In male patients, the randomised treatment effect appeared consistent across most subgroups, with the exception of patients with an increased body mass index (BMI) or those with prior exposure to UFH, in whom bivalirudin, as compared to UFH, lowered MACE and NACE. The treatment effect was also largely consistent in female patients.

Supplementary Figure 5-Supplementary Figure 8 show the effect of randomised bivalirudin treatment duration on MACE and NACE in male and female patients according to pre-specified subgroups.

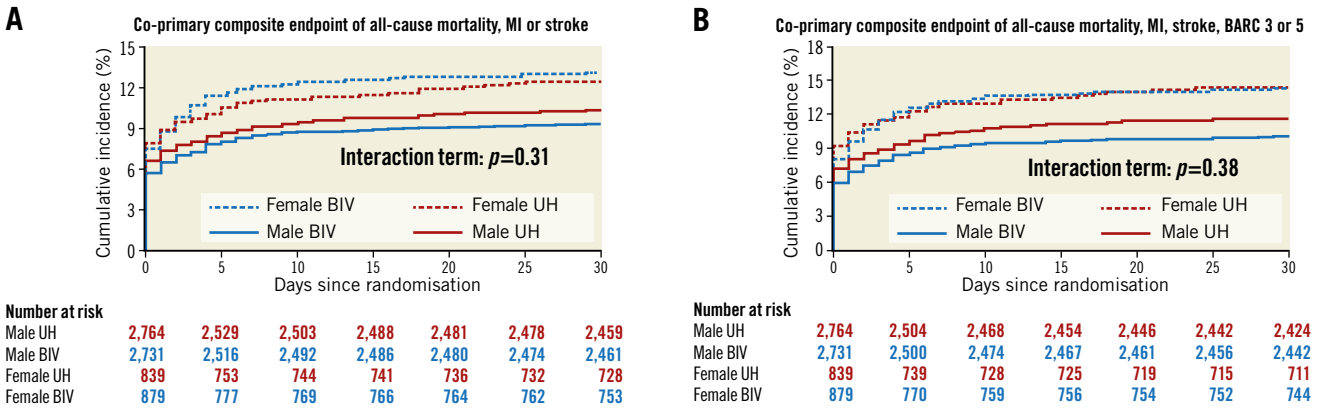


Figure 2. *Co-primary composite outcomes of bivalirudin versus unfractionated heparin at 30 days in male and female patients. A) & B) Cumulative incidence of the co-primary outcomes of MACE and NACE, respectively. Blue indicates bivalirudin, red indicates UFH, continuous line indicates male, dashed line indicates female.*

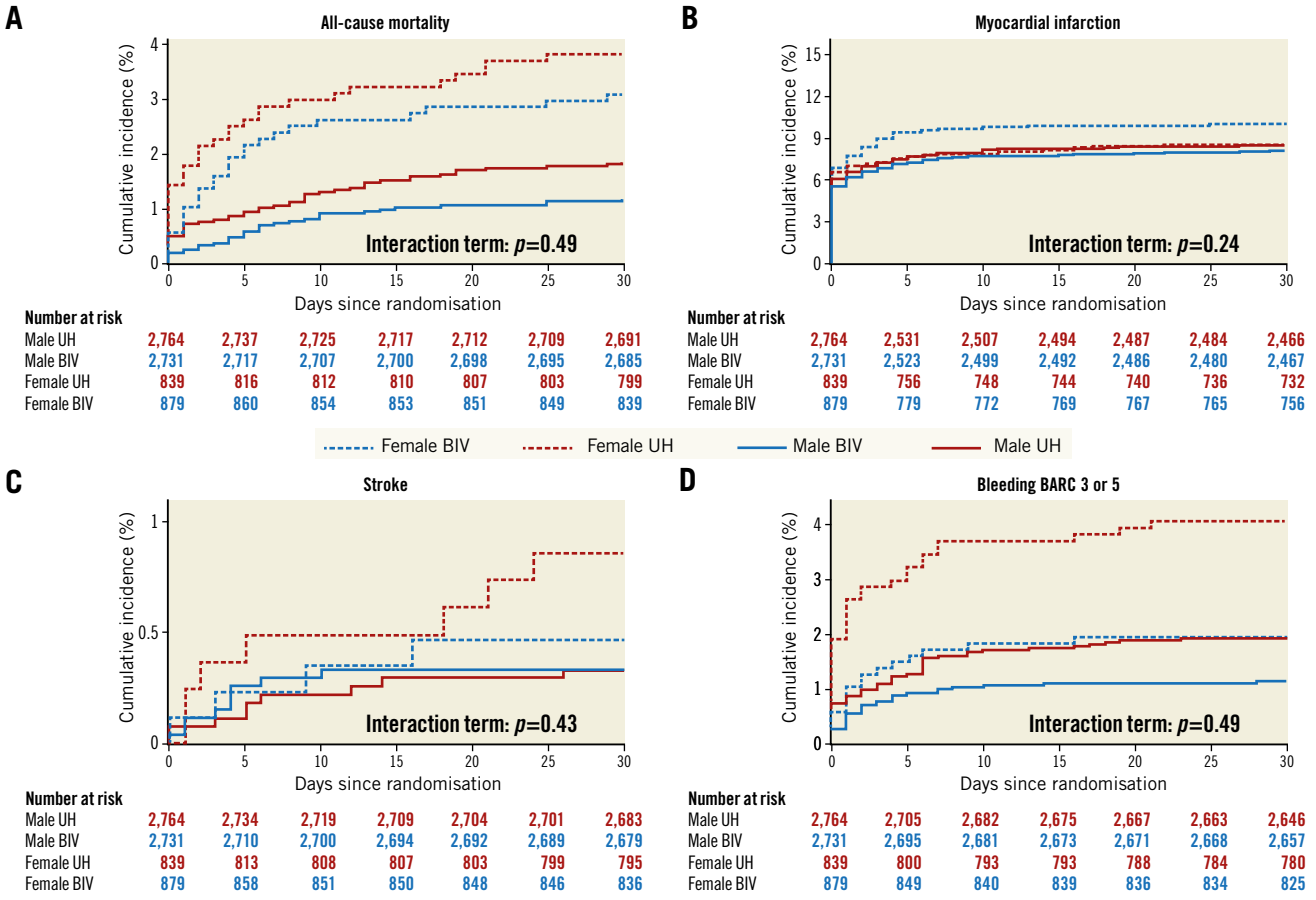


Figure 3. *Components of co-primary composite outcomes of bivalirudin versus unfractionated heparin at 30 days in male and female patients. Panels show the cumulative incidence of the co-primary outcome components of all-cause death (A), myocardial infarction (B), stroke (C), and BARC 3 or 5 bleeding (D). Blue indicates bivalirudin, red indicates UFH, continuous line indicates male, dashed line indicates female.*

Discussion

MATRIX is the largest randomised study on bivalirudin in STEMI, one of the largest in NSTE-ACS patients, and the only randomised comparison of post-PCI versus no post-PCI bivalirudin infusion. The study failed to show that bivalirudin as compared to UFH±GPI reduces MACE or NACE, and post-PCI bivalirudin infusion did not reduce the rate of the primary endpoint compared with no post-PCI infusion. In secondary endpoint analyses, bivalirudin compared to UFH±GPI decreased the rate of fatalities and the risk of major bleeding, mainly non-access-site related, in both randomly allocated access sites.

The results of the sex-based pre-specified analysis can be summarised as follows:

1) There was no signal of heterogeneity across sexes for any of the primary endpoints, including MACE and NACE for the bivalirudin versus UFH±GPI comparison and the composite of NACE, definite ST and urgent TVR for the assessment of post-PCI bivalirudin infusion.
2) In secondary stratified analyses, bivalirudin remained associated with lower risks of mortality and bleeding in both sexes, with no signal of a sex-based treatment effect on interaction testing. Mortality was numerically lower with bivalirudin in both female and male patients, albeit it reached statistical significance in the latter group only, probably reflecting a power issue. BARC 3 or 5 bleeding was significantly reduced in both sexes, interestingly owing to a reduction of access-site events in males and non-access-site-related occurrences in females.

Sex differences in cardiovascular outcomes is a topic of great interest and debate in the cardiology community, with data supporting such a discrepancy as opposed to others suggesting that women treated for coronary artery disease have different clinical, procedural and treatment profiles compared with men, which may largely explain the observed dissimilarities in prognosis. Indeed, after correcting for sex-based confounders, such disparities, particularly in mortality and major composite endpoints, seem to be no longer demonstrated[3,6]. However, female patients have been associated with higher rates of periprocedural bleeding[4,5]. This was also confirmed in a previous pre-specified analysis of MATRIX where we observed a greater risk of access-site bleeding and transfusion rates in female as compared with male patients after adjusting for confounders[6]. Additional interest in this topic is related to the fact that women represent a limited number of patients

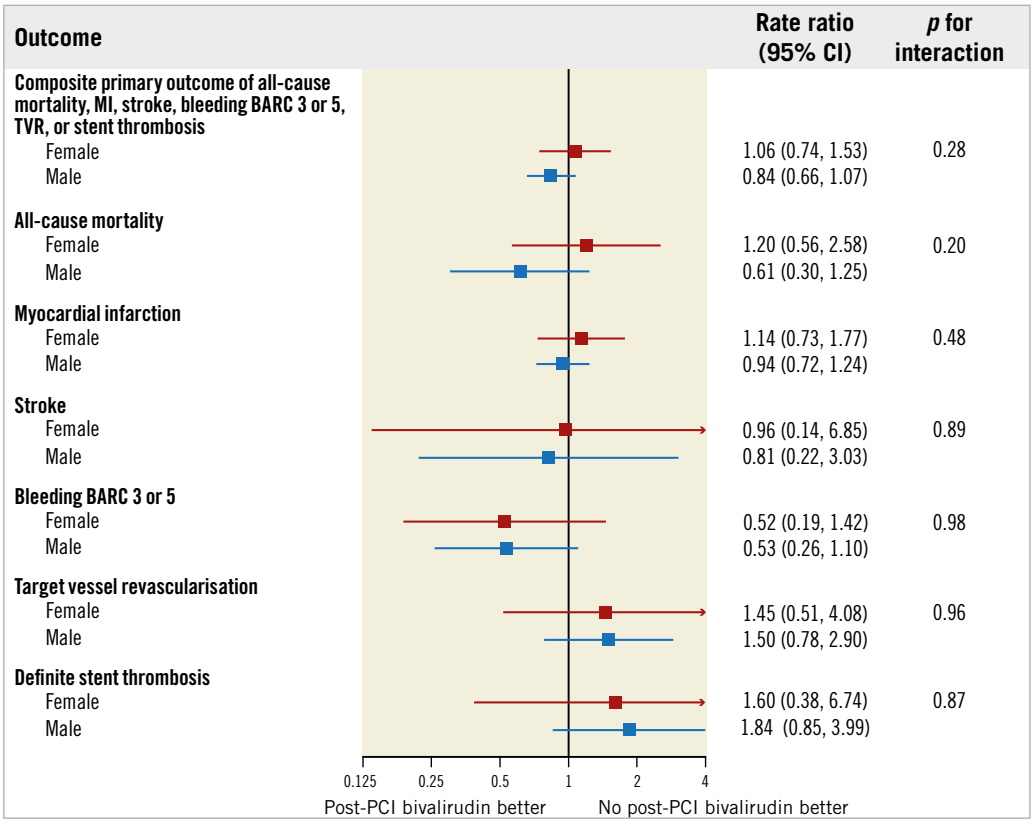
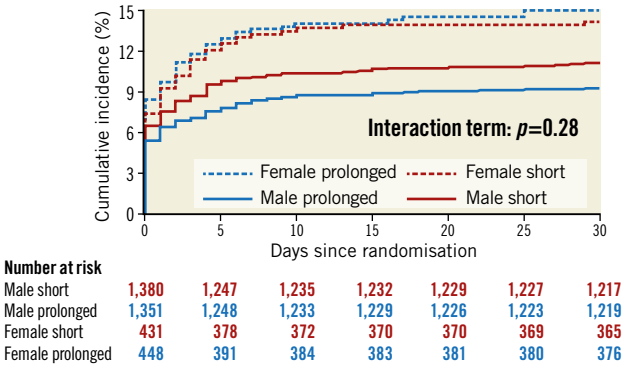


Figure 4. *Main outcomes of post-PCI bivalirudin infusion versus no post-PCI bivalirudin infusion in male and female patients. Bivalirudin infusion and no infusion post PCI were compared on the basis of sex subgroups, with rate ratios (RR) and 95% confidence intervals (CIs), for the primary endpoint and its components (death, myocardial infarction, stroke, BARC 3 or 5, urgent TVR and definite ST).*

included in the majority of cardiovascular trials. Against this background, it seems particularly relevant to explore whether there are sex-specific differences in treatment patterns and response to antithrombotic therapy.



Number at risk							
Male short	1,380	1,247	1,235	1,232	1,229	1,227	1,217
Male prolonged	1,351	1,248	1,233	1,229	1,226	1,223	1,219
Female short	431	378	372	370	370	369	365
Female prolonged	448	391	384	383	381	380	376

Figure 5. *Primary composite outcome of post-PCI bivalirudin infusion versus no post-PCI bivalirudin infusion at 30 days in male and female patients. Cumulative incidence of the primary composite outcome of urgent TVR, definite ST, or NACE. Blue indicates prolonged bivalirudin infusion, red indicates no post-PCI infusion, continuous line indicates male, dashed line indicates female.*

In a patient-level pooled analysis of three randomised controlled trials (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE-2]; Acute Catheterization and Urgent Intervention Triage strategY [ACUITY]; and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]) including 14,784 patients (25.6% were women), bivalirudin was compared with UFH plus GPI in ACS patients undergoing PCI. Compared with males, females were associated with higher 30-day bleeding events which in turn emerged as being the strongest independent predictor of one-year mortality rather than gender *per se*. Additionally, both sexes experienced similar safety benefits of bivalirudin in reducing bleeding complications, but women experienced a more pronounced benefit of bivalirudin in reducing one-year mortality than men[10]. Importantly, these results come from trials in which UFH was administered with routine use of GPI, there was no use of newer antiplatelet agents, and PCI procedures were almost exclusively performed by the femoral access. In the sex-based analysis of BRIGHT, a trial comparing bivalirudin versus heparin versus heparin plus tirofiban in acute MI patients undergoing PCI, female patients receiving bivalirudin were associated with significantly lower rates of 30-day bleeding and NACE, but no differences in terms of mortality, ST or MACE[11]. In the sex-based analysis of the ISAR-REACT 4 trial, where patients with NSTEMI (n=1,721; 399 women, 23.2%) were randomly allocated to receive

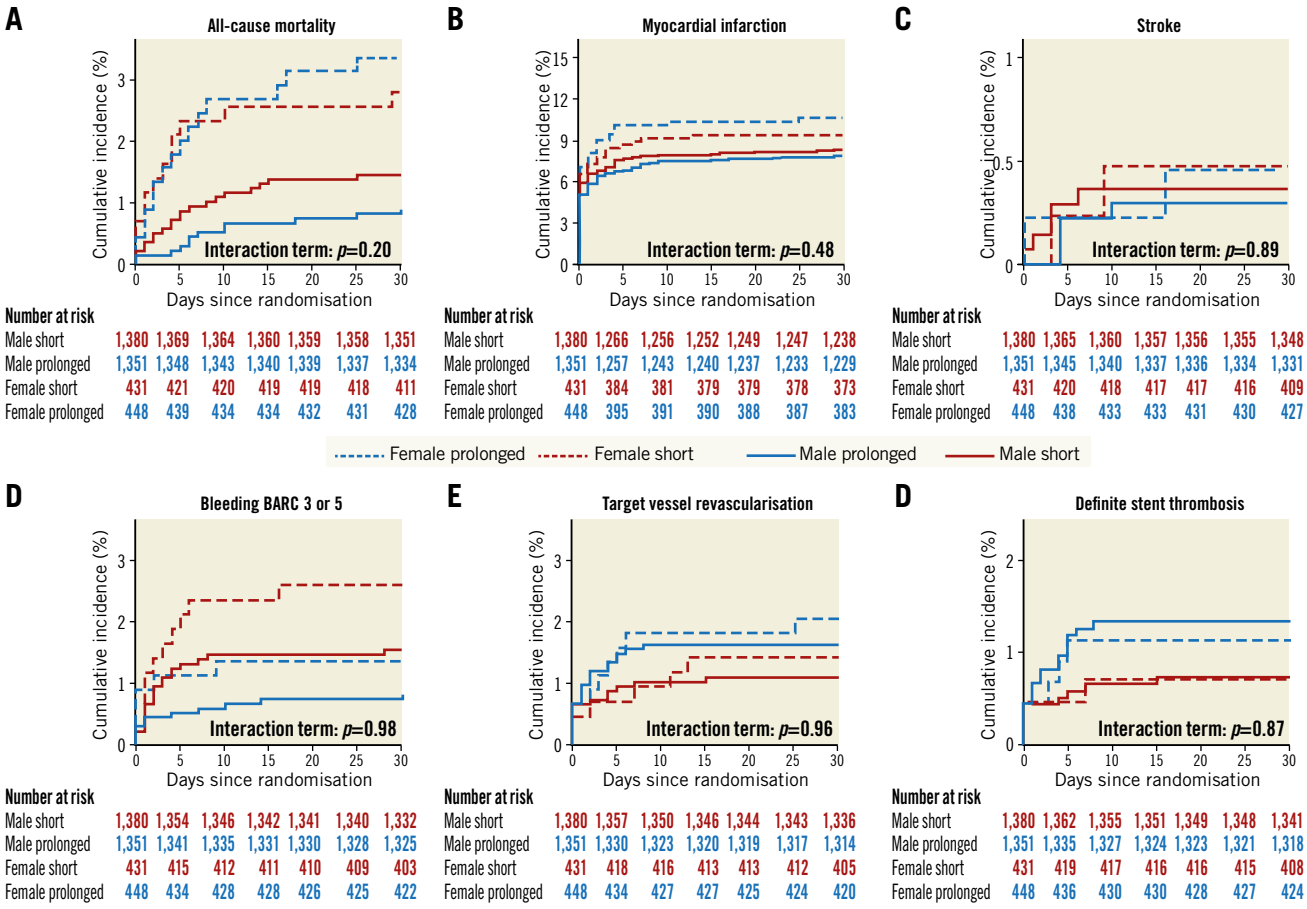


Figure 6. *Components of primary composite outcome of post-PCI bivalirudin infusion versus no post-PCI bivalirudin infusion at 30 days in male and female patients. Panels show the cumulative incidence of the primary outcome components of all-cause death (A), myocardial infarction (B), stroke (C), BARC 3 or 5 bleeding (D), urgent TVR (E) and definite ST (F). Blue indicates prolonged bivalirudin infusion, red indicates no post-PCI infusion, continuous line indicates male, dashed line indicates female.*

bivalirudin or heparin plus abciximab, there were no between-group differences in the main outcome (30-day composite of death, large recurrent MI, urgent TVR or major bleeding), but bivalirudin reduced major bleeding in both male and female patients[12].

Our current results are entirely consistent with previous evidence, indicating that bivalirudin provides a consistent effect in both sexes, resulting in lower risks of bleeding complications across many of the available RCTs. Additionally, in MATRIX, we found that reduction of bleeding, mainly the most severe episodes, was irrespective of GPI use[12]. Interestingly, however, in the context of the recently reported VALIDATE-SWEDEHEART trial, where bivalirudin did not reduce the primary composite endpoint of NACE or clinically relevant bleeding at six months after intervention as compared to UFH alone, there was a signal of heterogeneity across sexes (p_{int}=0.05), with female patients apparently deriving a greater benefit from treatment as compared to males[2]. Therefore, in summary, current evidence shows either a consistent or perhaps a slightly greater treatment effect in female patients treated with bivalirudin as compared to UFH, a finding which seems to be justifiable by prior observations that females are at increased risk for periprocedural bleeding occurrences.

The inconsistent effect of bivalirudin on the NACE endpoint probably reflects differences in study design, choice of the comparator arm, patient selection and endpoint definitions across available studies. Similarly, the effect of bivalirudin on mortality has been inconsistently observed across trials and some registry data[13], which may reflect the fact that this effect, if real, may be small, and probably confounded by the baseline risk status of patients and concomitant treatment and medications.

Prior observations that the use of bivalirudin increases the risk of acute ST have prompted investigations to mitigate that risk by prolonging bivalirudin infusion after PCI[14,15]. Overall, the MATRIX Treatment Duration study found that post-PCI infusion of bivalirudin did not result in lower rates of the primary endpoint or definite ST at 30 days than with no post-PCI infusion. This latter finding was also confirmed in the present analysis in both male and female patients.

In current practice, when deciding on the anticoagulation strategy to adopt in ACS patients undergoing PCI, it should also be borne in mind that bivalirudin remains much more expensive than UFH; however, updated cost-effectiveness analyses are warranted.

Limitations

Although this is a pre-specified subgroup analysis, the MATRIX Antithrombin and Treatment Duration trials were not powered to explore differences between sexes; randomisation was not stratified by sex. We did not adjust for multiple comparisons, increasing the risk of type I error. The protocol allowed discretionary use of GPI in the heparin group and two different infusion regimens in the post-PCI bivalirudin infusion group. Although this is consistent with clinical practice, it makes the study results more difficult to interpret.

Conclusions

Among male and female patients with ACS undergoing invasive treatment, neither the rate of MACE nor the rate of NACE was significantly lower with bivalirudin than with unfractionated heparin and discretionary use of glycoprotein IIb/IIIa inhibitors. In both sexes, the post-PCI infusion of bivalirudin for at least four hours after the intervention did not result in a lower rate of the composite outcome of ischaemic and bleeding events, including stent thrombosis, than with no post-PCI infusion. Our observations of lower risks of bleeding and especially of fatality rates in both male and female patients undergoing invasive management should be interpreted in the context of the available evidence, which suggests a rather consistent and inconsistent treatment effect of bivalirudin on bleeding and fatal endpoints, respectively, both in males and females.

Impact on daily practice

Current data show that neither male nor female patients gained significant benefit in terms of composite endpoints by receiving bivalirudin compared with heparin with discretionary use of GPI, although a lower rate of bleeding was observed. Also, the post-PCI infusion of bivalirudin was not superior to no infusion in both sexes.

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Conflict of interest statement

G. Gargiulo reports research grant support from the Cardiopath PhD programme. M. Zimarino reports personal fees from AstraZeneca, outside the submitted work. G. Casu reports personal fees from Boston Scientific and Bayer SpA, outside the submitted work. V. Guiducci reports personal fees from Bayer, outside the submitted work. F. Liistro reports personal fees from Medtronic, outside the submitted work. J.M. de la Torre Hernandez reports unrestricted grants from Boston Scientific and Abbott and being on the advisory panel for Medtronic, Boston Scientific and Abbott, outside the submitted work. A. van 't Hof reports grants and personal fees from The Medicines Company, during the conduct of the study, grants from Medtronic, grants and personal fees from AstraZeneca, and grants and personal fees from Daiichi Sankyo, outside the submitted work. E. Omerovic reports personal fees for advisory board work from Boston Scientific and Bayer, and an institutional grant from AstraZeneca, outside the submitted work. S. Windecker reports research contracts to the institution from Amgen, Abbott, Biotronik, Boston Scientific, and St. Jude Medical, outside the submitted work. M. Valgimigli reports grants from The Medicines Company and Terumo, during the study, grants from AstraZeneca, and personal fees from Abbott, Amgen, and Bayer, outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Figure 1. Subgroup analysis of MACE in male patients for the antithrombin-type study.

Supplementary Figure 2. Subgroup analysis of NACE in male patients for the antithrombin-type study.

Supplementary Figure 3. Subgroup analysis of MACE in female patients for the antithrombin-type study.

Supplementary Figure 4. Subgroup analysis of NACE in female patients for the antithrombin-type study.

Supplementary Figure 5. Subgroup analysis of MACE in male patients for the treatment duration study.

Supplementary Figure 6. Subgroup analysis of NACE in male patients for the treatment duration study.

Supplementary Figure 7. Subgroup analysis of MACE in female patients for the treatment duration study.

Supplementary Figure 8. Subgroup analysis of NACE in female patients for the treatment duration study.

Supplementary Table 1. Baseline characteristics.

Supplementary Table 2. Procedural characteristics.

Supplementary Table 3. Medications at discharge.

Supplementary Table 4. Clinical outcomes at 30 days for the bivalirudin treatment duration study.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00247

Supplementary data

Supplementary Appendix 1. Methods

Study design and patients

Briefly, MATRIX was a programme (clinicaltrials.gov: NCT01433627) of three independent randomised controlled trials in an all-comers population with ACS. The first trial, MATRIX Access Site, compared transradial access with transfemoral access in 8,404 ACS patients, 6,172 (73.4%) males and 2,232 (26.6%) females. Here we report on a pre-specified sex-related sub-analysis of the two other, nested trials, which were conducted as additional randomised comparisons in subgroups of patients. The second trial, MATRIX Antithrombin, was a randomised comparison of two antithrombotic strategies: bivalirudin with use of glycoprotein IIb/IIIa inhibitors (GPI) restricted to angiographic complications (e.g., no-reflow or giant thrombus) compared with UFH with use of GPI left to the discretion of the investigator. These strategies were compared in the overall population with STEMI (n=4,010) and in patients without ST-segment elevation for whom PCI was planned (n=3,203, 72.9% of the overall population without ST-segment elevation). The third trial, MATRIX Treatment Duration, was a randomised comparison within patients assigned to bivalirudin, comparing prolonged bivalirudin administration after PCI with short-term administration during PCI only. Detailed inclusion and exclusion criteria have been published previously. All patients gave written informed consent.

Study protocol and randomisation

Using a computer-generated random sequence, we randomised patients in a 1:1 ratio to receive bivalirudin or UFH, with a random block size stratified by type of ACS, intended or ongoing use of $P2Y_{12}$ inhibitor (clopidogrel versus ticagrelor or prasugrel), and study site. 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. All interventions were administered in an open-label fashion. Bivalirudin was given according to the product labelling, with a bolus of 0.75 mg per kilogram of body weight, followed immediately by an infusion of 1.75 mg per kilogram per hour until completion of the PCI. In those assigned to bivalirudin prolongation, the choice between two regimens (full dose for up to 4 hours or reduced dose of 0.25 mg per kilogram per hour for at least 6 hours) was made at the discretion of the treating physicians. UFH was administered at a dose of 70 to 100 units or 50 to 70 units per kilogram in patients not receiving or receiving GPI, respectively. Subsequent UFH dose adjustment on the basis of the activated clotting time was left to the discretion of the treating physicians. A GPI could be administered before PCI in all patients in the UFH group on the basis of the treating physician's judgement, but the drug was to be administered in the bivalirudin group only in patients who had periprocedural ischaemic complications after PCI. The use of other medications was allowed according to professional guidelines.

Follow-up and study outcomes

Clinical follow-up was performed at 30 days. The two co-primary 30-day composite outcomes of MATRIX Antithrombin were major adverse cardiovascular events (MACE), defined as the composite of all-cause mortality, MI, or stroke, and net adverse clinical events (NACE), defined as the composite of MACE or non-CABG-related major bleeding (BARC type 3 or 5). The primary outcome for MATRIX Treatment Duration was a composite of urgent target vessel revascularisation (TVR), definite stent thrombosis (ST), or NACE. Secondary outcomes included each component of the composite outcomes, cardiovascular mortality, and ST (defined as the definite or probable occurrence of a stent-related thrombotic event according to the Academic Research Consortium classification). Bleeding was also assessed and adjudicated on the basis of the TIMI and GUSTO scales. All outcomes were pre-specified. An independent clinical events committee blinded to treatment allocation adjudicated all suspected events.

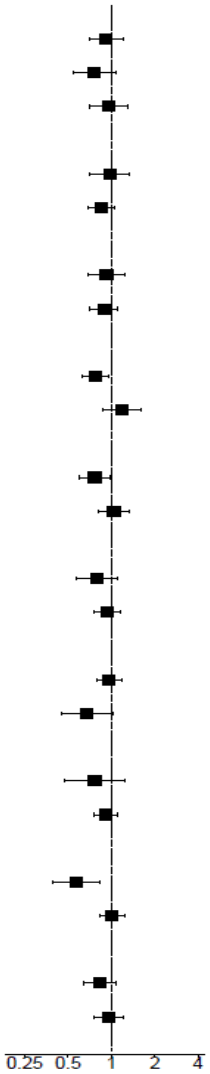
Statistical analysis

Statistical analyses were performed by an academic statistical group led by one of the authors (BRdC), who had access to the full de-identified data set. The MATRIX Antithrombin trial was designed as a superiority study on two co-primary outcomes at 30 days expecting a rate reduction of 30%, corresponding to a rate ratio of 0.70. Thus, with an alpha error set at 0.025 to correct for the two co-primary endpoints, we considered that a sample size of 6,800 randomised patients (3,400 patients in each group) would provide 85% power for MACE and 95% power for NACE. For MATRIX Treatment Duration, we determined that 1,700 patients in each study group would provide a power of 86% to detect a rate ratio (RR) of 0.70 for the primary endpoint at a two-sided alpha level of 0.05.

All analyses were performed per the intention-to-treat principle, including all patients in the analysis based on the allocated treatment. Events up to 30 days post randomisation were considered. We analysed primary and secondary outcomes separately for male and female patients as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding two-sided p-values. We did not perform any adjustments for multiple comparisons but set the alpha error at 2.5% to correct for the two co-primary outcomes. We analysed secondary outcomes with a two-sided α set at 5% to allow conventional interpretation of results. Survival curves were constructed using Kaplan-Meier estimates. We performed stratified analyses according to pre-specified subgroups (centre's annual volume of percutaneous coronary intervention, age, type of ACS, body mass index, intended start or continuation of prasugrel or ticagrelor, diabetes, estimated glomerular filtration rate, history of peripheral vascular disease, previous heparin, and randomisation to access site) and estimated possible effect modifications using interaction terms or tests for trend across ordered groups separately for the male and female study populations. All analyses were performed using the statistical package Stata 13.1.

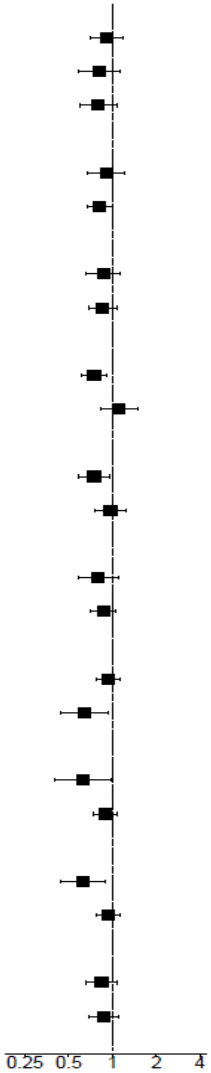
Supplementary Figure 1. Subgroup analysis of MACE in male patients for the antithrombin-type study.

Composite endpoint: death, MI or stroke	Bivalirudin	UFH	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.91
Low (247-544)	113/933	118/907	0.92 (0.70-1.21)	0.55	
Intermediate (548-991)	58/905	81/972	0.76 (0.54-1.07)	0.12	
High (1000-1950)	85/893	88/885	0.96 (0.70-1.31)	0.78	
Age					0.49
≥75	87/559	86/539	0.98 (0.71-1.33)	0.88	
<75	169/2172	201/2225	0.85 (0.69-1.05)	0.14	
Type of ACS					0.83
STEMI	84/1549	90/1544	0.93 (0.69-1.25)	0.62	
NSTE-ACS	172/1182	197/1220	0.89 (0.71-1.11)	0.31	
BMI					0.026
≥25	161/1904	204/1914	0.78 (0.63-0.97)	0.023	
<25	95/827	83/850	1.19 (0.88-1.62)	0.26	
Intended start or continuation of prasugrel or ticagrelor					0.089
Yes	115/1600	151/1636	0.77 (0.60-0.98)	0.036	
No	141/1131	136/1128	1.04 (0.81-1.33)	0.76	
Diabetes					0.40
Yes	72/594	85/565	0.79 (0.57-1.10)	0.16	
No	184/2137	202/2199	0.93 (0.76-1.15)	0.51	
Estimated glomerular filtration rate (eGFR)					0.12
≥60 mL/min	212/2359	221/2381	0.97 (0.79-1.17)	0.73	
<60 mL/min	42/359	61/364	0.68 (0.45-1.02)	0.059	
History of peripheral vascular disease					0.51
Yes	35/222	42/210	0.77 (0.48-1.24)	0.27	
No	221/2509	245/2554	0.91 (0.76-1.10)	0.34	
Previous UFH					0.0088
Yes	44/914	78/951	0.57 (0.39-0.84)	0.0034	
No	212/1817	209/1813	1.01 (0.83-1.24)	0.90	
Randomisation to access					0.45
Radial	120/1383	143/1392	0.84 (0.65-1.08)	0.16	
Femoral	136/1348	144/1372	0.96 (0.75-1.22)	0.72	



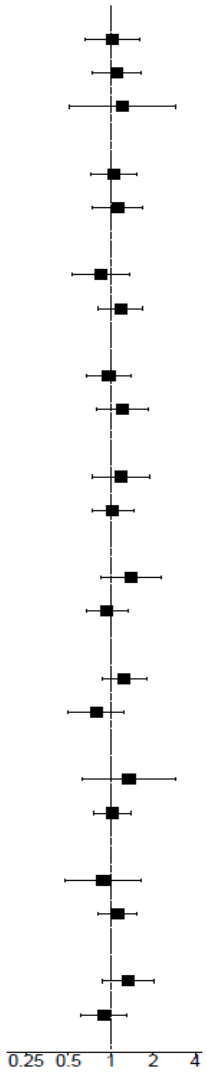
Supplementary Figure 2. Subgroup analysis of NACE in male patients for the antithrombin-type study.

Composite endpoint: death, MI, stroke or BARC 3 or 5	Bivalirudin	UFH	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.47
Low (247-544)	119/933	125/907	0.91 (0.70-1.19)	0.50	
Intermediate (548-991)	67/905	88/972	0.81 (0.58-1.12)	0.20	
High (1000-1950)	90/893	110/885	0.80 (0.60-1.07)	0.13	
Age					0.56
≥75	97/559	102/539	0.91 (0.68-1.22)	0.53	
<75	179/2172	221/2225	0.82 (0.67-1.01)	0.055	
Type of ACS					0.93
STEMI	100/1549	114/1544	0.87 (0.66-1.14)	0.30	
NSTE-ACS	176/1182	209/1220	0.85 (0.68-1.07)	0.16	
BMI					0.029
≥25	172/1904	226/1914	0.75 (0.61-0.92)	0.0060	
<25	104/827	97/850	1.11 (0.83-1.49)	0.47	
Intended start or continuation of prasugrel or ticagrelor					0.13
Yes	127/1600	170/1636	0.75 (0.59-0.95)	0.016	
No	149/1131	153/1128	0.97 (0.76-1.23)	0.81	
Diabetes					0.65
Yes	79/594	92/565	0.80 (0.58-1.10)	0.16	
No	197/2137	231/2199	0.87 (0.71-1.06)	0.16	
Estimated glomerular filtration rate (eGFR)					0.090
≥60 mL/min	225/2359	243/2381	0.93 (0.77-1.12)	0.45	
<60 mL/min	49/359	74/364	0.65 (0.44-0.94)	0.022	
History of peripheral vascular disease					0.15
Yes	38/222	54/210	0.63 (0.40-0.98)	0.038	
No	238/2509	269/2554	0.89 (0.74-1.07)	0.22	
Previous UFH					0.047
Yes	52/914	85/951	0.62 (0.44-0.89)	0.0078	
No	224/1817	238/1813	0.93 (0.77-1.13)	0.48	
Randomisation to access					0.86
Radial	131/1383	155/1392	0.84 (0.66-1.07)	0.16	
Femoral	145/1348	168/1372	0.87 (0.69-1.09)	0.23	



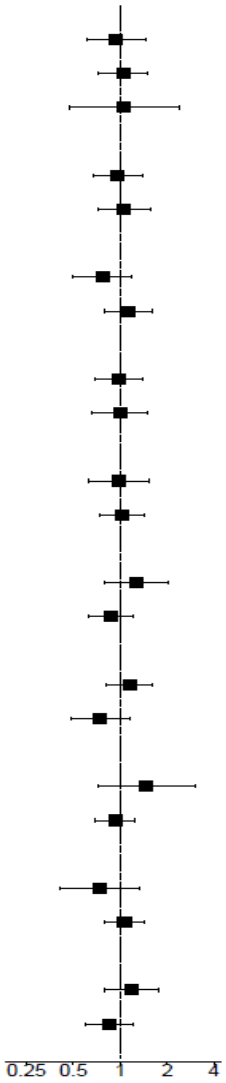
Supplementary Figure 3. Subgroup analysis of MACE in female patients for the antithrombin-type study.

Composite endpoint: death, MI or stroke	Bivalirudin	UFH	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.79
Low (247-544)	43/282	45/302	1.03 (0.65-1.61)	0.91	
Intermediate (548-991)	59/417	50/387	1.10 (0.74-1.64)	0.62	
High (1000-1950)	13/180	9/150	1.22 (0.51-2.90)	0.66	
Age					0.83
≥75	59/347	59/365	1.05 (0.72-1.55)	0.79	
<75	56/532	45/474	1.12 (0.75-1.69)	0.58	
Type of ACS					0.29
STEMI	34/463	39/454	0.85 (0.54-1.36)	0.50	
NSTE-ACS	81/416	65/385	1.17 (0.82-1.69)	0.39	
BMI					0.44
≥25	65/534	62/494	0.97 (0.67-1.40)	0.87	
<25	50/345	42/345	1.21 (0.78-1.86)	0.39	
Intended start or continuation of prasugrel or ticagrelor					0.65
Yes	43/424	32/370	1.19 (0.74-1.91)	0.48	
No	72/455	72/469	1.04 (0.73-1.46)	0.85	
Diabetes					0.19
Yes	42/230	31/228	1.39 (0.85-2.28)	0.19	
No	73/649	73/611	0.94 (0.67-1.32)	0.71	
Estimated glomerular filtration rate (eGFR)					0.12
≥60 mL/min	74/639	57/606	1.25 (0.87-1.80)	0.22	
<60 mL/min	38/230	45/224	0.79 (0.50-1.25)	0.32	
History of peripheral vascular disease					0.52
Yes	17/74	13/74	1.35 (0.62-2.91)	0.45	
No	98/805	91/765	1.03 (0.76-1.39)	0.86	
Previous UFH					0.50
Yes	21/252	22/233	0.88 (0.48-1.63)	0.69	
No	94/627	82/606	1.12 (0.82-1.53)	0.48	
Randomisation to access					0.17
Radial	53/415	40/407	1.33 (0.87-2.04)	0.19	
Femoral	62/464	64/432	0.89 (0.62-1.29)	0.55	



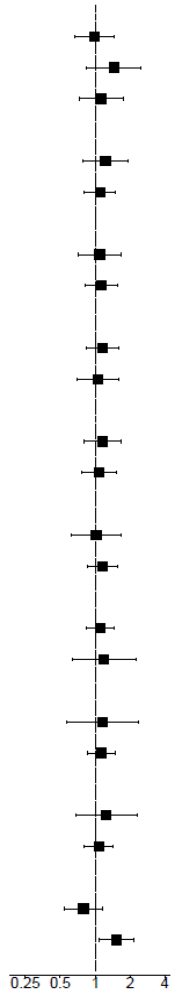
Supplementary Figure 4. Subgroup analysis of NACE in female patients for the antithrombin-type study.

Composite endpoint: death, MI, stroke or BARC 3 or 5	Bivalirudin	UFH	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.80
Low (247-544)	46/282	52/302	0.94 (0.61-1.45)	0.78	
Intermediate (548-991)	65/417	58/387	1.04 (0.72-1.51)	0.82	
High (1000-1950)	14/180	11/150	1.06 (0.47-2.40)	0.88	
Age					0.74
≥75	65/347	70/365	0.97 (0.67-1.39)	0.85	
<75	60/532	51/474	1.06 (0.72-1.56)	0.78	
Type of ACS					0.18
STEMI	39/463	49/454	0.77 (0.50-1.18)	0.23	
NSTE-ACS	86/416	72/385	1.12 (0.79-1.59)	0.53	
BMI					0.94
≥25	73/534	69/494	0.98 (0.69-1.38)	0.90	
<25	52/345	52/345	1.00 (0.66-1.50)	0.99	
Intended start or continuation of prasugrel or ticagrelor					0.89
Yes	46/424	41/370	0.98 (0.63-1.52)	0.92	
No	79/455	80/469	1.02 (0.73-1.42)	0.91	
Diabetes					0.19
Yes	46/230	37/228	1.27 (0.80-2.03)	0.30	
No	79/649	84/611	0.87 (0.63-1.21)	0.41	
Estimated glomerular filtration rate (eGFR)					0.12
≥60 mL/min	79/639	66/606	1.15 (0.82-1.62)	0.42	
<60 mL/min	43/230	53/224	0.75 (0.48-1.15)	0.18	
History of peripheral vascular disease					0.24
Yes	21/74	15/74	1.47 (0.72-3.01)	0.29	
No	104/805	106/765	0.93 (0.70-1.23)	0.60	
Previous UFH					0.28
Yes	22/252	27/233	0.74 (0.42-1.32)	0.31	
No	103/627	94/606	1.06 (0.79-1.44)	0.68	
Randomisation to access					0.23
Radial	57/415	48/407	1.18 (0.79-1.77)	0.41	
Femoral	68/464	73/432	0.85 (0.60-1.21)	0.37	



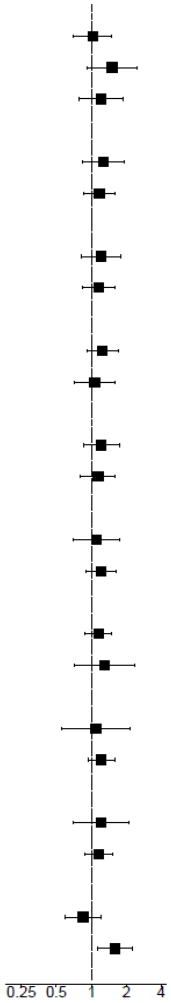
Supplementary Figure 5. Subgroup analysis of MACE in male patients for the treatment duration study.

Composite endpoint: death, MI or stroke	Post-PCI bivalirudin	No post-PCI bivalirudin	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.57
Low (247-544)	56/466	57/467	0.99 (0.67-1.46)	0.95	
Intermediate (548-991)	35/466	23/439	1.45 (0.85-2.48)	0.17	
High (1000-1950)	45/448	40/445	1.13 (0.73-1.77)	0.58	
Age					0.68
≥75	46/271	41/288	1.23 (0.79-1.91)	0.36	
<75	90/1109	79/1063	1.10 (0.80-1.50)	0.56	
Type of ACS					0.90
STEMI	44/779	40/770	1.09 (0.71-1.68)	0.68	
NSTE-ACS	92/601	80/581	1.13 (0.81-1.57)	0.47	
BMI					0.76
≥25	86/955	75/949	1.15 (0.83-1.58)	0.39	
<25	50/425	45/402	1.06 (0.70-1.62)	0.78	
Intended start or continuation of prasugrel or ticagrelor					0.79
Yes	62/805	53/795	1.16 (0.80-1.69)	0.43	
No	74/575	67/556	1.08 (0.76-1.54)	0.66	
Diabetes					0.67
Yes	37/302	35/292	1.02 (0.63-1.66)	0.93	
No	99/1078	85/1059	1.16 (0.86-1.56)	0.34	
Estimated glomerular filtration rate (eGFR)					0.82
≥60 mL/min	111/1182	101/1177	1.10 (0.83-1.46)	0.49	
<60 mL/min	24/191	18/168	1.19 (0.63-2.26)	0.59	
History of peripheral vascular disease					0.96
Yes	17/101	18/121	1.15 (0.57-2.34)	0.69	
No	119/1279	102/1230	1.13 (0.86-1.49)	0.37	
Previous UFH					0.66
Yes	24/449	20/465	1.25 (0.68-2.28)	0.47	
No	112/931	100/886	1.08 (0.81-1.43)	0.61	
Randomisation to access					0.013
Radial	54/697	66/686	0.79 (0.55-1.16)	0.23	
Femoral	82/683	54/665	1.53 (1.07-2.18)	0.019	



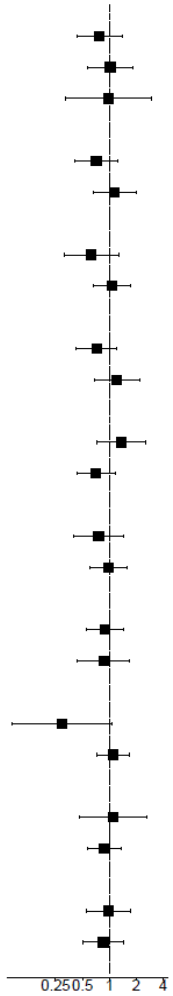
Supplementary Figure 6. Subgroup analysis of NACE in male patients for the treatment duration study.

Composite endpoint: death, MI, stroke or BARC 3 or 5	Post-PCI bivalirudin	No post-PCI bivalirudin	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.50
Low (247-544)	60/466	59/467	1.03 (0.70-1.50)	0.90	
Intermediate (548-991)	41/466	26/439	1.51 (0.91-2.49)	0.11	
High (1000-1950)	49/448	41/445	1.21 (0.78-1.86)	0.39	
Age					0.75
≥75	52/271	45/288	1.27 (0.84-1.94)	0.26	
<75	98/1109	81/1063	1.17 (0.86-1.59)	0.31	
Type of ACS					0.84
STEMI	55/779	45/770	1.22 (0.82-1.81)	0.33	
NSTE-ACS	95/601	81/581	1.16 (0.83-1.60)	0.38	
BMI					0.57
≥25	95/955	77/949	1.24 (0.91-1.70)	0.17	
<25	55/425	49/402	1.07 (0.72-1.60)	0.74	
Intended start or continuation of prasugrel or ticagrelor					0.79
Yes	70/805	57/795	1.22 (0.85-1.75)	0.27	
No	80/575	69/556	1.14 (0.81-1.61)	0.45	
Diabetes					0.74
Yes	42/302	37/292	1.10 (0.69-1.75)	0.68	
No	108/1078	89/1059	1.21 (0.90-1.62)	0.20	
Estimated glomerular filtration rate (eGFR)					0.70
≥60 mL/min	120/1182	105/1177	1.15 (0.88-1.51)	0.31	
<60 mL/min	29/191	20/168	1.31 (0.72-2.38)	0.37	
History of peripheral vascular disease					0.79
Yes	18/101	20/121	1.10 (0.56-2.16)	0.79	
No	132/1279	106/1230	1.21 (0.93-1.58)	0.15	
Previous UFH					0.87
Yes	28/449	24/465	1.21 (0.70-2.11)	0.49	
No	122/931	102/886	1.16 (0.88-1.52)	0.30	
Randomisation to access					0.012
Radial	61/697	70/686	0.85 (0.59-1.21)	0.37	
Femoral	89/683	56/665	1.60 (1.13-2.27)	0.0069	



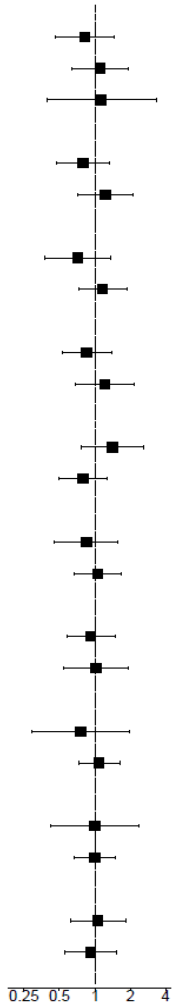
Supplementary Figure 7. Subgroup analysis of MACE in female patients for the treatment duration study.

Composite endpoint: death, MI or stroke	Post-PCI bivalirudin	No post-PCI bivalirudin	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.57
Low (247-544)	23/159	29/158	0.77 (0.43-1.39)	0.39	
Intermediate (548-991)	25/188	25/194	1.03 (0.58-1.83)	0.93	
High (1000-1950)	6/84	7/96	0.97 (0.32-2.95)	0.96	
Age					0.23
≥75	25/172	34/175	0.72 (0.41-1.24)	0.23	
<75	29/259	27/273	1.15 (0.66-1.98)	0.62	
Type of ACS					0.22
STEMI	13/227	21/236	0.63 (0.31-1.27)	0.19	
NSTE-ACS	41/204	40/212	1.07 (0.66-1.74)	0.78	
BMI					0.19
≥25	26/254	39/280	0.72 (0.43-1.21)	0.21	
<25	28/177	22/168	1.22 (0.67-2.20)	0.51	
Intended start or continuation of prasugrel or ticagrelor					0.11
Yes	24/207	19/217	1.36 (0.73-2.55)	0.33	
No	30/224	42/231	0.71 (0.43-1.16)	0.16	
Diabetes					0.52
Yes	19/118	23/112	0.76 (0.40-1.45)	0.40	
No	35/313	38/336	0.99 (0.61-1.59)	0.95	
Estimated glomerular filtration rate (eGFR)					0.92
≥60 mL/min	34/310	40/329	0.89 (0.55-1.44)	0.65	
<60 mL/min	18/116	20/114	0.86 (0.44-1.67)	0.66	
History of peripheral vascular disease					0.048
Yes	3/28	14/46	0.30 (0.08-1.08)	0.051	
No	51/403	47/402	1.09 (0.72-1.65)	0.68	
Previous UFH					0.66
Yes	11/126	10/126	1.10 (0.46-2.65)	0.83	
No	43/305	51/322	0.88 (0.57-1.35)	0.56	
Randomisation to access					0.72
Radial	26/204	27/211	0.98 (0.56-1.73)	0.96	
Femoral	28/227	34/237	0.85 (0.50-1.45)	0.56	



Supplementary Figure 8. Subgroup analysis of NACE in female patients for the treatment duration study.

Composite endpoint: death, MI, stroke or BARC 3 or 5	Post-PCI bivalirudin	No post-PCI bivalirudin	Rate Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.46
Low (247-544)	25/159	30/158	0.82 (0.46-1.45)	0.49	
Intermediate (548-991)	29/188	27/194	1.11 (0.64-1.92)	0.72	
High (1000-1950)	7/84	7/96	1.14 (0.39-3.32)	0.81	
Age					0.25
≥75	29/172	36/175	0.79 (0.47-1.33)	0.37	
<75	32/259	28/273	1.23 (0.72-2.08)	0.45	
Type of ACS					0.23
STEMI	16/227	23/236	0.71 (0.37-1.36)	0.30	
NSTE-ACS	45/204	41/212	1.16 (0.72-1.86)	0.54	
BMI					0.37
≥25	32/254	41/280	0.85 (0.53-1.38)	0.52	
<25	29/177	23/168	1.20 (0.68-2.15)	0.53	
Intended start or continuation of prasugrel or ticagrelor					0.14
Yes	26/207	20/217	1.41 (0.76-2.59)	0.27	
No	35/224	44/231	0.79 (0.50-1.26)	0.33	
Diabetes					0.59
Yes	22/118	24/112	0.85 (0.45-1.58)	0.60	
No	39/313	40/336	1.05 (0.66-1.66)	0.84	
Estimated glomerular filtration rate (eGFR)					0.81
≥60 mL/min	37/310	42/329	0.93 (0.58-1.48)	0.75	
<60 mL/min	22/116	21/114	1.02 (0.55-1.91)	0.95	
History of peripheral vascular disease					0.49
Yes	7/28	14/46	0.75 (0.29-1.96)	0.56	
No	54/403	50/402	1.09 (0.72-1.63)	0.69	
Previous UFH					1.00
Yes	11/126	11/126	1.00 (0.42-2.35)	0.99	
No	50/305	53/322	0.99 (0.66-1.50)	0.98	
Randomisation to access					0.71
Radial	29/204	28/211	1.06 (0.62-1.83)	0.82	
Femoral	32/227	36/237	0.93 (0.56-1.53)	0.77	



Supplementary Table 1. Baseline characteristics.

	ANTITHROMBIN-TYPE STUDY						TREATMENT DURATION STUDY					
	MALE			FEMALE			MALE			FEMALE		
Baseline characteristics	**Bivalirudin**	**UFH**	***p*-value**	**Bivalirudin**	**UFH**	***p*-value**	**Post-PCI bivalirudin**	**No post-PCI bivalirudin**	***p*-value**	**Post-PCI bivalirudin**	**No post-PCI bivalirudin**	***p*-value**
	(N=2,731)	(N=2,764)		(N=879)	(N=839)		(N=1,351)	(N=1,380)		(N=448)	(N=431)	
Age, yrs	63.9±11.7	63.7±11.5	0.57	70.2±11.2	70.9±11.4	0.20	63.9±11.9	64.0±11.5	0.80	70.0±11.3	70.4±11.2	0.62
>=75 yrs	559 (20.5)	539 (19.5)	0.37	347 (39.5)	365 (43.5)	0.090	288 (21.3)	271 (19.6)	0.28	175 (39.1)	172 (39.9)	0.80
STEMI	1,549 (56.7)	1,544 (55.9)	0.52	463 (52.7)	454 (54.1)	0.55	770 (57.0)	779 (56.4)	0.77	236 (52.7)	227 (52.7)	1.00
NSTE-ACS	1,182 (43.3)	1,220 (44.1)	0.52	416 (47.3)	385 (45.9)	0.55	581 (43.0)	601 (43.6)	0.77	212 (47.3)	204 (47.3)	1.00
Weight (kg)	80.5±12.6	80.1±12.8	0.27	69.1±13.4	68.4±13.2	0.28	80.8±12.8	80.2±12.4	0.22	70.2±13.8	68.0±12.9	0.016
Body mass index (kg/m^2)	27.2±3.8	27.2±3.8	0.13	26.9±5.1	26.6±4.8	0.13	27.3±3.9	27.2±3.7	0.063	27.2±5.2	26.6±5.0	0.063
Diabetes mellitus	594 (21.8)	565 (20.4)	0.49	230 (26.2)	228 (27.2)	0.72	292 (21.6)	302 (21.9)	0.11	112 (25.0)	118 (27.4)	0.17
Insulin-dependent	129 (4.7)	125 (4.5)	0.72	72 (8.2)	65 (7.7)	0.72	74 (5.5)	55 (4.0)	0.17	41 (9.2)	31 (7.2)	0.17
Current smoker	1,054 (38.6)	1,101 (39.8)	0.64	253 (28.8)	201 (24.0)	0.074	513 (38.0)	541 (39.2)	0.23	125 (27.9)	128 (29.7)	0.75
Hypercholesterolaemia	1,190 (43.6)	1,155 (41.8)	0.18	406 (46.2)	403 (48.0)	0.44	551 (40.8)	639 (46.3)	0.0036	199 (44.4)	207 (48.0)	0.28
Hypertension	1,608 (58.9)	1,610 (58.2)	0.43	656 (74.6)	612 (72.9)	0.43	803 (59.4)	805 (58.3)	0.33	328 (73.2)	328 (76.1)	0.33
Family history of coronary artery disease	765 (28.0)	769 (27.8)	0.88	226 (25.7)	223 (26.6)	0.68	372 (27.5)	393 (28.5)	0.58	116 (25.9)	110 (25.5)	0.90
Previous myocardial infarction	428 (15.7)	406 (14.7)	0.31	102 (11.6)	95 (11.3)	0.85	225 (16.7)	203 (14.7)	0.16	54 (12.1)	48 (11.1)	0.67
Previous PCI	439 (16.1)	414 (15.0)	0.26	97 (11.0)	90 (10.7)	0.84	227 (16.8)	212 (15.4)	0.31	48 (10.7)	49 (11.4)	0.76
Previous CABG	106 (3.9)	83 (3.0)	0.074	21 (2.4)	12 (1.4)	0.15	55 (4.1)	51 (3.7)	0.61	9 (2.0)	12 (2.8)	0.45
Previous TIA or stroke	122 (4.5)	120 (4.3)	0.82	59 (6.7)	65 (7.7)	0.41	70 (5.2)	52 (3.8)	0.074	34 (7.6)	25 (5.8)	0.29
Peripheral vascular disease	222 (8.1)	210 (7.6)	0.46	74 (8.4)	74 (8.8)	0.77	121 (9.0)	101 (7.3)	0.12	46 (10.3)	28 (6.5)	0.044
Chronic obstructive pulmonary disease	155 (5.7)	167 (6.0)	0.56	61 (6.9)	53 (6.3)	0.60	77 (5.7)	78 (5.7)	0.96	30 (6.7)	31 (7.2)	0.77
History of renal failure	32 (1.2)	31 (1.1)	0.86	16 (1.8)	16 (1.9)	0.89	15 (1.1)	17 (1.2)	0.77	7 (1.6)	9 (2.1)	0.56
Dialysis	3 (0.1)	2 (0.1)	0.69	2 (0.2)	0 (0.0)	0.50	0 (0.0)	3 (0.2)	0.25	0 (0.0)	2 (0.5)	0.24
Clinical presentation												
Cardiac arrest	62 (2.3)	61 (2.2)	0.87	18 (2.0)	22 (2.6)	0.43	26 (1.9)	36 (2.6)	0.23	10 (2.2)	8 (1.9)	0.69
Killip class												
I	2,497 (91.4)	2,514 (91.0)	0.53	778 (88.5)	726 (86.5)	0.21	1,243 (92.0)	1,254 (90.9)	0.29	398 (88.8)	380 (88.2)	0.75
II	160 (5.9)	183 (6.6)	0.24	64 (7.3)	81 (9.7)	0.077	81 (6.0)	79 (5.7)	0.76	34 (7.6)	30 (7.0)	0.72
III	49 (1.8)	42 (1.5)	0.43	27 (3.1)	22 (2.6)	0.58	18 (1.3)	31 (2.2)	0.072	11 (2.5)	16 (3.7)	0.28

IV	25 (0.9)	25 (0.9)	0.97	10 (1.1)	10 (1.2)	1.00	9 (0.7)	16 (1.2)	0.18	5 (1.1)	5 (1.2)	1.00
Previous lytic therapy	72 (2.6)	84 (3.0)	0.37	25 (2.8)	17 (2.0)	0.28	35 (2.6)	37 (2.7)	0.88	12 (2.7)	13 (3.0)	0.84
Systolic arterial pressure (mmHg)	138.3±25.3	137.8±25.3	0.50	139.5±27.8	139.4±27.5	0.92	138.1±25.0	138.4±25.7	0.76	139.5±28.1	139.5±27.5	0.98
Heart rate	75.8±16.7	75.2±15.9	0.16	77.5±17.4	77.8±17.9	0.79	75.6±16.9	75.9±16.5	0.61	77.0±18.4	78.1±16.4	0.36
Left ventricular ejection fraction (%)	50.5±9.5	51.1±9.4	0.019	50.5±9.7	50.3±10.1	0.69	50.3±9.3	50.7±9.6	0.22	50.5±9.8	50.5±9.6	0.97
eGFR	85.7±24.2	86.6±25.0	0.17	77.2±26.8	77.4±27.0	0.90	86.2±24.4	85.1±23.9	0.21	76.4±26.3	78.0±27.2	0.38
eGFR<60	359 (13.2)	364 (13.3)	0.95	230 (26.5)	224 (27.0)	0.81	168 (12.5)	191 (13.9)	0.27	114 (25.7)	116 (27.2)	0.62
eGFR<30	17 (0.6)	20 (0.7)	0.64	21 (2.4)	20 (2.4)	0.99	5 (0.4)	12 (0.9)	0.097	12 (2.7)	9 (2.1)	0.57
Medications before the cath lab												
Aspirin	2,597 (95.1)	2,609 (94.4)	0.24	820 (93.3)	767 (91.4)	0.14	1,292 (95.6)	1,305 (94.6)	0.20	417 (93.1)	403 (93.5)	0.80
Clopidogrel	1,243 (45.5)	1,192 (43.1)	0.075	455 (51.8)	422 (50.3)	0.54	607 (44.9)	636 (46.1)	0.54	227 (50.7)	228 (52.9)	0.51
Prasugrel	395 (14.5)	394 (14.3)	0.83	62 (7.1)	71 (8.5)	0.27	196 (14.5)	199 (14.4)	0.95	31 (6.9)	31 (7.2)	0.87
Ticagrelor	651 (23.8)	684 (24.7)	0.43	208 (23.7)	174 (20.7)	0.15	323 (23.9)	328 (23.8)	0.93	112 (25.0)	96 (22.3)	0.34
Enoxaparin	391 (14.3)	403 (14.6)	0.78	152 (17.3)	152 (18.1)	0.65	179 (13.2)	212 (15.4)	0.11	79 (17.6)	73 (16.9)	0.78
Fondaparinux	256 (9.4)	255 (9.2)	0.85	83 (9.4)	83 (9.9)	0.75	120 (8.9)	136 (9.9)	0.38	52 (11.6)	31 (7.2)	0.025
ACE inhibitors	741 (27.1)	779 (28.2)	0.38	259 (29.5)	247 (29.4)	0.99	365 (27.0)	376 (27.2)	0.89	130 (29.0)	129 (29.9)	0.77
Angiotensin II receptor antagonist	243 (8.9)	234 (8.5)	0.57	125 (14.2)	120 (14.3)	0.96	120 (8.9)	123 (8.9)	0.98	66 (14.7)	59 (13.7)	0.66
Statins	1,103 (40.4)	1,116 (40.4)	0.99	362 (41.2)	337 (40.2)	0.67	514 (38.0)	589 (42.7)	0.014	194 (43.3)	168 (39.0)	0.19
Beta-blockers	1,016 (37.2)	1,012 (36.6)	0.65	395 (44.9)	346 (41.2)	0.12	485 (35.9)	531 (38.5)	0.16	202 (45.1)	193 (44.8)	0.93
Warfarin	37 (1.4)	28 (1.0)	0.24	19 (2.2)	16 (1.9)	0.71	24 (1.8)	13 (0.9)	0.059	10 (2.2)	9 (2.1)	0.88
PPI	1,318 (48.3)	1,326 (48.0)	0.83	449 (51.1)	456 (54.4)	0.17	668 (49.4)	650 (47.1)	0.22	233 (52.0)	216 (50.1)	0.57
Previous unfractionated heparin	914 (33.5)	951 (34.4)	0.46	252 (28.7)	233 (27.8)	0.68	465 (34.4)	449 (32.5)	0.30	126 (28.1)	126 (29.2)	0.72
Bivalirudin	2 (0.1)	3 (0.1)	1.00	0 (0.0)	0 (0.0)	1.00	0 (0.0)	2 (0.1)	0.50	0 (0.0)	0 (0.0)	1.00
Glycoprotein IIb/IIIa inhibitors	4 (0.1)	4 (0.1)	1.00	1 (0.1)	2 (0.2)	0.62	1 (0.1)	3 (0.2)	0.62	1 (0.2)	0 (0.0)	1.00

Supplementary Table 2. Procedural characteristics.

	ANTITHROMBIN-TYPE STUDY						TREATMENT DURATION STUDY					
	MALE			FEMALE			MALE			FEMALE		
Procedural characteristics	**Bivalirudin**	**UFH**	***p*-value**	**Bivalirudin**	**UFH**	***p*-value**	**Post-PCI bivalirudin**	**No post-PCI bivalirudin**	***p*-value**	**Post-PCI bivalirudin**	**No post-PCI bivalirudin**	***p*-value**
Number of randomised patients	(N=2,731)	(N=2,764)		(N=879)	(N=839)		(N=1,351)	(N=1,380)		(N=448)	(N=431)	
Crossover	107 (3.9)	100 (3.6)	0.56	48 (5.5)	45 (5.4)	0.93	57 (4.2)	50 (3.6)	0.42	26 (5.8)	22 (5.1)	0.65
No PCI attempted after coronary angiography	161 (5.9)	159 (5.8)	0.82	82 (9.3)	84 (10.0)	0.63	74 (5.5)	64 (4.6)	0.32	32 (7.1)	38 (8.8)	0.36
CABG	21 (0.8)	18 (0.7)	0.60	3 (0.3)	2 (0.2)	0.69	10 (0.7)	11 (0.8)	0.86	1 (0.2)	2 (0.5)	0.54
Patient with significant lesion and medical treatment	89 (3.3)	68 (2.5)	0.076	57 (6.5)	52 (6.2)	0.81	50 (3.7)	39 (2.8)	0.20	29 (6.5)	28 (6.5)	0.99
Patient without significant lesion	51 (1.9)	73 (2.6)	0.054	22 (2.5)	30 (3.6)	0.19	14 (1.0)	14 (1.0)	0.95	2 (0.4)	8 (1.9)	0.049
PCI attempted	2,569 (94.1)	2,603 (94.2)	0.87	795 (90.4)	755 (90.0)	0.75	1,276 (94.4)	1,316 (95.4)	0.28	415 (92.6)	392 (91.0)	0.36
PCI completed	2,569 (94.1)	2,603 (94.2)	0.87	794 (90.3)	754 (89.9)	0.75	1,276 (94.4)	1,316 (95.4)	0.28	415 (92.6)	391 (90.7)	0.30
Medications administered in the cath lab												
Aspirin	169 (6.2)	185 (6.7)	0.45	63 (7.2)	63 (7.5)	0.79	80 (5.9)	89 (6.4)	0.57	34 (7.6)	29 (6.7)	0.62
Clopidogrel	179 (6.6)	200 (7.2)	0.32	60 (6.8)	83 (9.9)	0.021	99 (7.3)	81 (5.9)	0.12	36 (8.0)	25 (5.8)	0.19
Prasugrel	259 (9.5)	267 (9.7)	0.82	54 (6.1)	45 (5.4)	0.49	114 (8.4)	145 (10.5)	0.065	22 (4.9)	32 (7.4)	0.12
Ticagrelor	296 (10.8)	284 (10.3)	0.50	104 (11.8)	91 (10.8)	0.52	147 (10.9)	149 (10.8)	0.94	51 (11.4)	53 (12.3)	0.68
Glycoprotein IIb/IIIa inhibitors	124 (4.5)	770 (27.9)	<0.0001	39 (4.4)	159 (19.0)	<0.0001	42 (3.1)	82 (5.9)	0.00038	22 (4.9)	17 (3.9)	0.49
Planned GPI	0 (0.0)	659 (23.8)	<0.0001	0 (0.0)	129 (15.4)	<0.0001	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Bail-out GPI	124 (4.5)	111 (4.0)	0.34	39 (4.4)	30 (3.6)	0.36	42 (3.1)	82 (5.9)	0.00038	22 (4.9)	17 (3.9)	0.49
Unfractionated heparin	204 (7.5)	2,641 (95.5)	<0.0001	50 (5.7)	793 (94.5)	<0.0001	90 (6.7)	110 (8.0)	0.19	25 (5.6)	23 (5.3)	0.87
Unfractionated heparin (units per kilo)	38.6±27.3	76.3±27.9	<0.0001	44.9±27.5	82.7±28.4	<0.0001	38.7±30.5	39.5±24.8	0.85	42.4±25.2	47.6±30.0	0.51
Subtherapeutic regimen (<50 units per kg)	158 (5.8)	318 (11.5)	<0.0001	38 (4.3)	73 (8.7)	0.00022	70 (5.2)	81 (5.9)	0.43	20 (4.5)	16 (3.7)	0.57
Therapeutic regimen (>= 50 units per kg)	46 (1.7)	2,323 (84.0)	<0.0001	12 (1.4)	720 (85.8)	<0.0001	20 (1.5)	29 (2.1)	0.22	5 (1.1)	7 (1.6)	0.52
Bivalirudin	2,618 (95.9)	14 (0.5)	<0.0001	824 (93.7)	0 (0.0)	<0.0001	1,303 (96.4)	1,315 (95.3)	0.13	425 (94.9)	399 (92.6)	0.16
Prolonged infusion post PCI	1,316 (48.2)	3 (0.1)	<0.0001	421 (47.9)	0 (0.0)	<0.0001	1,272 (94.2)	44 (3.2)	<0.0001	408 (91.1)	13 (3.0)	<0.0001
Average duration of post-PCI bivalirudin infusion	366.1±238.4	345.0±465.3	0.88	388.2±290.0	-	-	366.4±239.4	357.6±211.3	0.81	387.3±288.5	-	-
Patients receiving full bivalirudin regimen post PCI	465 (17.0)	1 (0.0)	<0.0001	160 (18.2)	0 (0.0)	<0.0001	456 (33.8)	9 (0.7)	<0.0001	156 (34.8)	4 (0.9)	<0.0001
Average duration of full bivalirudin regimen	260.9±208.3	-	-	279.6±219.1	-	-	261.6±209.9	229.4±89.7	0.65	281.4±221.1	-	-
Patients receiving low bivalirudin regimen post PCI	851 (31.2)	2 (0.1)	<0.0001	261 (29.7)	0 (0.0)	<0.0001	816 (60.4)	35 (2.5)	<0.0001	252 (56.3)	9 (2.1)	<0.0001
Average duration of low bivalirudin regimen	423.5±234.3	500.0±537.4	0.65	454.7±307.9	-	-	424.9±234.9	390.5±221.6	0.40	452.9±305.7	-	-
Intra-aortic balloon pump	45 (1.6)	62 (2.2)	0.11	37 (4.2)	30 (3.6)	0.50	24 (1.8)	21 (1.5)	0.60	21 (4.7)	16 (3.7)	0.47

PCI completed	(N=2,569)	(N=2,603)		(N=794)	(N=754)		(N=1,276)	(N=1,316)		(N=415)	(N=391)	
TIMI 3 flow in all treated lesions	2,434 (94.7)	2,486 (95.5)	0.20	756 (95.2)	712 (94.4)	0.49	1,218 (95.5)	1,236 (94.0)	0.096	395 (95.2)	371 (94.9)	0.85
Coronary stenosis <30% in all treated lesions	2,459 (95.7)	2,486 (95.5)	0.71	758 (95.5)	717 (95.1)	0.73	1,228 (96.2)	1,253 (95.2)	0.20	396 (95.4)	372 (95.1)	0.85
Procedural success in all treated lesions	2,384 (92.8)	2,421 (93.0)	0.77	735 (92.6)	698 (92.6)	1.00	1,196 (93.7)	1,207 (91.8)	0.057	383 (92.3)	362 (92.6)	0.87
Treated vessel(s) per patient												
Left main coronary artery	100 (3.9)	94 (3.6)	0.60	43 (5.4)	33 (4.4)	0.35	46 (3.6)	61 (4.6)	0.19	29 (7.0)	21 (5.4)	0.34
Left anterior descending artery	1,295 (50.4)	1,271 (48.9)	0.27	399 (50.3)	370 (49.1)	0.66	655 (51.3)	651 (49.5)	0.35	220 (53.0)	189 (48.3)	0.18
Left circumflex artery	712 (27.7)	703 (27.0)	0.59	193 (24.3)	204 (27.1)	0.21	353 (27.7)	369 (28.1)	0.82	94 (22.7)	103 (26.3)	0.22
Right coronary artery	831 (32.4)	872 (33.6)	0.36	274 (34.5)	259 (34.4)	0.96	411 (32.2)	426 (32.4)	0.92	144 (34.7)	133 (34.0)	0.84
Bypass graft	27 (1.1)	24 (0.9)	0.64	5 (0.6)	0 (0.0)	0.029	13 (1.0)	14 (1.1)	0.91	4 (1.0)	1 (0.3)	0.20
At least two vessels treated	350 (13.6)	332 (12.8)	0.36	105 (13.2)	103 (13.7)	0.79	177 (13.9)	182 (13.8)	0.98	66 (15.9)	47 (12.0)	0.11
Lesions treated per patient (interquartile range)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.67	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.95	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.63	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.77
One lesion	2,003 (78.0)	2,054 (79.0)		633 (79.7)	600 (79.7)		984 (77.1)	1,033 (78.6)		326 (78.6)	314 (80.3)	
Two lesions	457 (17.8)	445 (17.1)		137 (17.3)	128 (17.0)		233 (18.3)	230 (17.5)		75 (18.1)	66 (16.9)	
Three or more lesions	108 (4.2)	101 (3.9)		24 (3.0)	25 (3.3)		59 (4.6)	52 (4.0)		14 (3.4)	11 (2.8)	
At least one complex lesion	1,326 (51.6)	1,371 (52.7)	0.43	391 (49.1)	382 (50.7)	0.53	652 (51.1)	690 (52.5)	0.48	220 (53.0)	181 (46.3)	0.057
Median number of stents per patient (interquartile range)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.79	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.75	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.42	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.50
Overall stent length per patient (mm)	70.5±45.2	71.3±44.3	0.55	67.0±41.2	66.6±41.4	0.85	32.1±20.2	31.8±20.6	0.65	31.8±18.5	30.2±20.0	0.24
Lesions												
Number of lesions with PCI	(N=3,264)	(N=3,269)		(N=983)	(N=936)		(N=1,639)	(N=1,660)		(N=520)	(N=481)	
Lesions stented	2,973 (91.1)	2,968 (90.8)	0.65	893 (90.8)	842 (90.0)	0.63	1,509 (92.1)	1,498 (90.2)	0.072	471 (90.6)	438 (91.1)	0.79
At least one drug-eluting stent	2,214 (67.8)	2,184 (66.8)	0.25	630 (64.1)	582 (62.2)	0.47	1,100 (67.1)	1,142 (68.8)	0.47	329 (63.3)	312 (64.9)	0.76
At least one bare metal stent	759 (23.3)	784 (24.0)	0.36	263 (26.8)	260 (27.8)	0.61	409 (25.0)	356 (21.4)	0.063	142 (27.3)	126 (26.2)	0.88
Lesions not stented	291 (8.9)	301 (9.2)	0.65	90 (9.2)	94 (10.0)	0.63	130 (7.9)	162 (9.8)	0.072	49 (9.4)	43 (8.9)	0.79
TIMI flow pre-procedure												
0 or 1	1,308 (40.1)	1,232 (37.7)	0.037	368 (37.4)	345 (36.9)	0.83	633 (38.6)	680 (41.0)	0.14	191 (36.7)	179 (37.2)	0.94
2	428 (13.1)	417 (12.8)	0.70	106 (10.8)	110 (11.8)	0.53	210 (12.8)	223 (13.4)	0.63	49 (9.4)	60 (12.5)	0.15
3	1,527 (46.8)	1,617 (49.5)	0.025	509 (51.8)	481 (51.4)	0.97	796 (48.6)	757 (45.6)	0.11	280 (53.8)	242 (50.3)	0.31
TIMI flow post-procedure												
0 or 1	56 (1.7)	53 (1.6)	0.74	14 (1.4)	25 (2.7)	0.093	25 (1.5)	32 (1.9)	0.38	6 (1.2)	9 (1.9)	0.56
2	88 (2.7)	68 (2.1)	0.17	27 (2.7)	23 (2.5)	0.64	41 (2.5)	48 (2.9)	0.23	14 (2.7)	14 (2.9)	1.00
3	3,119 (95.6)	3,145 (96.3)	0.20	942 (95.8)	888 (94.9)	0.23	1,573 (96.0)	1,580 (95.2)	0.19	500 (96.2)	458 (95.2)	0.70
Coronary stenosis <30%	3,151 (96.6)	3,142 (96.2)	0.51	940 (95.6)	889 (95.0)	0.65	1,590 (97.0)	1,596 (96.1)	0.18	497 (95.6)	458 (95.2)	0.89

Procedural success	3,067 (94.0)	3,072 (94.0)	0.99	917 (93.3)	870 (92.9)	0.80	1,550 (94.6)	1,550 (93.4)	0.18	484 (93.1)	448 (93.1)	0.97
Number of lesions stented	(N=2,973)	(N=2,968)		(N=893)	(N=842)		(N=1,509)	(N=1,498)		(N=471)	(N=438)	
Total stent length per lesion (mm)	26.0±14.3	26.2±14.2	0.46	25.4±14.2	25.6±14.9	0.72	25.9±14.5	26.3±14.4	0.55	26.0±14.1	25.2±14.7	0.36
Average stent diameter per lesion (mm)	3.1±0.5	3.1±0.5	0.32	3.0±0.4	2.9±0.4	0.053	3.1±0.5	3.1±0.5	0.75	3.0±0.4	3.0±0.4	0.55
At least one direct stenting	688 (23.1)	650 (21.9)	0.28	193 (21.6)	168 (20.0)	0.27	348 (23.1)	339 (22.6)	0.92	94 (20.0)	100 (22.8)	0.28
Post-dilatation	1,336 (44.9)	1,347 (45.4)	0.91	387 (43.3)	375 (44.5)	0.45	651 (43.1)	705 (47.1)	0.078	202 (42.9)	194 (44.3)	0.88

Supplementary Table 3. Medications at discharge.

	ANTITHROMBIN-TYPE STUDY						TREATMENT DURATION STUDY					
Medication at discharge	**MALE**			**FEMALE**			**MALE**			**FEMALE**		
	Bivalirudin (N=2,711)	**UFH (N=2,726)**	***p*-value**	**Bivalirudin (N=855)**	**UFH (N=813)**	***p*-value**	**Post-PCI bivalirudin**	**No post-PCI bivalirudin**	***p*-value**	**Post-PCI bivalirudin**	**No post-PCI bivalirudin**	***p*-value**
Aspirin	2,642 (97.5)	2,660 (97.6)	0.77	829 (97.0)	781 (96.1)	0.32	1,306 (97.2)	1,336 (97.7)	0.35	418 (96.5)	411 (97.4)	0.47
Ticlopidine*	4 (0.1)	7 (0.3)	0.55	1 (0.1)	2 (0.2)	0.53	3 (0.2)	1 (0.1)	0.37	1 (0.2)	0 (0.0)	0.32
Clopidogrel	957 (35.3)	967 (35.5)	0.89	381 (44.6)	367 (45.1)	0.81	474 (35.3)	483 (35.3)	0.97	196 (45.3)	185 (43.8)	0.67
Prasugrel*	656 (24.2)	658 (24.1)	0.96	115 (13.5)	110 (13.5)	0.96	319 (23.7)	337 (24.7)	0.58	57 (13.2)	58 (13.7)	0.80
Ticagrelor	901 (33.2)	922 (33.8)	0.65	292 (34.2)	266 (32.7)	0.54	454 (33.8)	447 (32.7)	0.55	144 (33.3)	148 (35.1)	0.58
$P2Y_{12}$ inhibition	2,518 (92.9)	2,553 (93.7)	0.26	789 (92.3)	745 (91.6)	0.63	1,250 (93.0)	1,268 (92.8)	0.80	398 (91.9)	391 (92.7)	0.69
Angiotensin II receptor antagonist or ACEI	2,222 (82.0)	2,197 (80.6)	0.20	679 (79.4)	637 (78.4)	0.59	1,104 (82.1)	1,118 (81.8)	0.81	344 (79.4)	335 (79.4)	0.98
Statins	1,999 (73.7)	1,931 (70.8)	0.017	552 (64.6)	529 (65.1)	0.83	998 (74.3)	1,001 (73.2)	0.54	274 (63.3)	278 (65.9)	0.43
Beta-blockers	2,265 (83.5)	2,252 (82.6)	0.36	699 (81.8)	684 (84.1)	0.20	1,126 (83.8)	1,139 (83.3)	0.75	346 (79.9)	353 (83.6)	0.16
Warfarin	93 (3.4)	78 (2.9)	0.23	29 (3.4)	34 (4.2)	0.40	61 (4.5)	32 (2.3)	0.0017	19 (4.4)	10 (2.4)	0.10
Diuretics	635 (23.4)	613 (22.5)	0.41	311 (36.4)	282 (34.7)	0.47	339 (25.2)	296 (21.7)	0.028	164 (37.9)	147 (34.8)	0.36
Insulin	300 (11.1)	269 (9.9)	0.15	132 (15.4)	103 (12.7)	0.10	149 (11.1)	151 (11.0)	0.97	68 (15.7)	64 (15.2)	0.83
Oral hypoglycaemic drugs	254 (9.4)	250 (9.2)	0.80	90 (10.5)	94 (11.6)	0.50	126 (9.4)	128 (9.4)	0.99	42 (9.7)	48 (11.4)	0.43
PPI	2,404 (88.7)	2,417 (88.7)	0.99	755 (88.3)	728 (89.5)	0.42	1,193 (88.8)	1,211 (88.6)	0.88	382 (88.2)	373 (88.4)	0.94
H2 blockers	106 (3.9)	103 (3.8)	0.80	36 (4.2)	31 (3.8)	0.68	52 (3.9)	54 (4.0)	0.91	15 (3.5)	21 (5.0)	0.27

Supplementary Table 4. Clinical outcomes at 30 days for the bivalirudin treatment duration study.

	TREATMENT DURATION STUDY								
	MALE				FEMALE				
Number of patients	Post-PCI bivalirudin (N=1,351)	No post-PCI bivalirudin (N=1,380)	Rate Ratio (95% CI)	*p*-value	Post-PCI bivalirudin (N=448)	No post-PCI bivalirudin (N=431)	Rate Ratio (95% CI)	*p*-value	*p*-value for interaction
At 30 days									
Composite of all-cause mortality, MI or stroke	120 (9.0)	136 (9.9)	0.89 (0.69-1.15)	0.38	61 (13.6)	54 (12.6)	1.10 (0.75-1.61)	0.64	0.38
Composite of all-cause mortality, MI, stroke, or BARC 3 or 5	126 (9.5)	150 (10.9)	0.85 (0.66-1.08)	0.19	64 (14.3)	61 (14.2)	1.01 (0.70-1.46)	0.95	0.43
Primary composite endpoint of all-cause mortality, MI, stroke, BARC 3 or 5, urgent TVR, or definite stent thrombosis	128 (9.6)	154 (11.2)	0.84 (0.66-1.07)	0.15	67 (15.0)	61 (14.2)	1.06 (0.74-1.53)	0.74	0.28
All-cause mortality	12 (1.0)	20 (1.5)	0.61 (0.30-1.25)	0.17	15 (3.4)	12 (2.8)	1.20 (0.56-2.58)	0.63	0.20
Cardiovascular death	11 (0.8)	19 (1.4)	0.59 (0.28-1.24)	0.16	14 (3.1)	12 (2.8)	1.12 (0.52-2.43)	0.77	0.24
Myocardial infarction	106 (7.9)	114 (8.3)	0.94 (0.72-1.24)	0.68	47 (10.6)	40 (9.4)	1.14 (0.73-1.77)	0.57	0.48
Stroke	4 (0.3)	5 (0.4)	0.81 (0.22-3.03)	0.76	2 (0.5)	2 (0.5)	0.96 (0.14-6.85)	0.97	0.89
Transient ischaemic attack	0 (0.0)	1 (0.1)	0.34 (0.01-8.34)	1.00	3 (0.7)	1 (0.2)	2.89 (0.30-27.95)	0.34	0.18
Urgent target vessel revascularisation	22 (1.6)	15 (1.1)	1.50 (0.78-2.90)	0.23	9 (2.0)	6 (1.4)	1.45 (0.51-4.08)	0.48	0.96
Definite stent thrombosis	18 (1.3)	10 (0.7)	1.84 (0.85-3.99)	0.12	5 (1.1)	3 (0.7)	1.60 (0.38-6.74)	0.51	0.87
Acute definite stent thrombosis	8 (0.6)	7 (0.5)	1.17 (0.42-3.23)	0.77	2 (0.4)	3 (0.7)	0.64 (0.11-3.85)	0.62	0.57
Subacute definite stent thrombosis	10 (0.7)	3 (0.2)	3.40 (0.93-12.37)	0.048	3 (0.7)	0 (0.0)	6.73 (0.35-129.91)	0.25	0.37
Definite or probable stent thrombosis	20 (1.5)	13 (0.9)	1.57 (0.78-3.17)	0.20	6 (1.4)	6 (1.4)	0.96 (0.31-2.99)	0.95	0.47
Acute definite or probable stent thrombosis	9 (0.7)	8 (0.6)	1.15 (0.44-2.99)	0.78	2 (0.4)	3 (0.7)	0.64 (0.11-3.85)	0.62	0.57
Subacute definite or probable stent thrombosis	11 (0.8)	5 (0.4)	2.24 (0.78-6.46)	0.12	4 (0.9)	3 (0.7)	1.29 (0.29-5.77)	0.74	0.55
Bleeding	138 (10.4)	136 (9.9)	1.04 (0.82-1.33)	0.75	61 (14.0)	56 (13.2)	1.06 (0.73-1.54)	0.74	0.92
Type 1	64 (4.7)	71 (5.2)	0.91 (0.65-1.29)	0.61	29 (6.8)	26 (6.1)	1.07 (0.63-1.84)	0.79	0.62
Type 2	63 (4.7)	43 (3.1)	1.51 (1.02-2.24)	0.037	26 (5.9)	19 (4.5)	1.33 (0.73-2.42)	0.34	0.73
Type 3abc	10 (0.8)	19 (1.4)	0.53 (0.25-1.15)	0.10	6 (1.4)	9 (2.1)	0.64 (0.23-1.80)	0.39	0.78
Type 3a	6 (0.5)	8 (0.6)	0.76 (0.26-2.20)	0.61	3 (0.7)	7 (1.7)	0.41 (0.11-1.59)	0.18	0.48
Type 3b	3 (0.2)	9 (0.7)	0.34 (0.09-1.25)	0.089	2 (0.4)	2 (0.5)	0.96 (0.14-6.83)	0.97	0.38
Type 3c	1 (0.1)	2 (0.1)	0.51 (0.05-5.62)	0.57	1 (0.2)	0 (0.0)	2.89 (0.12-70.75)	1.00	0.26
Type 4	0 (0.0)	1 (0.1)	0.34 (0.01-8.34)	1.00	0 (0.0)	0 (0.0)	-	-	-
Type 5ab	1 (0.1)	2 (0.1)	0.51 (0.05-5.62)	0.57	0 (0.0)	2 (0.5)	0.19 (0.01-3.95)	0.24	0.35
Type 5a	1 (0.1)	1 (0.1)	1.02 (0.06-16.28)	0.99	0 (0.0)	2 (0.5)	0.19 (0.01-3.95)	0.24	0.24
Type 5b	0 (0.0)	1 (0.1)	-	-	0 (0.0)	0 (0.0)	-	-	-

Type 3 or 5	11 (0.9)	21 (1.5)	0.53 (0.26-1.10)	0.085	6 (1.4)	11 (2.6)	0.52 (0.19-1.42)	0.20	0.98
Type 3 or 5 related to access site	6 (0.5)	3 (0.2)	2.04 (0.51-8.17)	0.30	5 (1.1)	5 (1.2)	0.96 (0.28-3.33)	0.95	0.43
Type 3 or 5 not related to access site	5 (0.4)	18 (1.3)	0.28 (0.10-0.76)	0.0074	1 (0.2)	6 (1.4)	0.16 (0.02-1.33)	0.052	0.63
Type 2, 3 or 5	74 (5.6)	64 (4.7)	1.19 (0.85-1.67)	0.31	32 (7.2)	30 (7.1)	1.04 (0.63-1.72)	0.89	0.66
Type 2, 3 or 5 related to access site	38 (2.9)	27 (2.0)	1.44 (0.88-2.37)	0.15	22 (5.0)	18 (4.2)	1.18 (0.63-2.22)	0.60	0.63
Type 2, 3 or 5 not related to access site	36 (2.7)	37 (2.7)	0.99 (0.63-1.58)	0.98	10 (2.3)	12 (2.8)	0.80 (0.35-1.86)	0.61	0.66
Major bleeding	4 (0.3)	8 (0.6)	0.51 (0.15-1.69)	0.26	1 (0.2)	3 (0.7)	0.32 (0.03-3.08)	0.30	0.72
Minor bleeding	5 (0.4)	4 (0.3)	1.27 (0.34-4.74)	0.72	3 (0.7)	5 (1.2)	0.58 (0.14-2.42)	0.45	0.42
Major or minor bleeding	9 (0.7)	12 (0.9)	0.76 (0.32-1.81)	0.54	4 (0.9)	8 (1.9)	0.48 (0.14-1.60)	0.22	0.54
Severe bleeding	3 (0.2)	10 (0.7)	0.30 (0.08-1.11)	0.056	1 (0.2)	2 (0.5)	0.48 (0.04-5.30)	0.54	0.74
Moderate bleeding	2 (0.1)	6 (0.4)	0.34 (0.07-1.68)	0.16	3 (0.7)	5 (1.2)	0.57 (0.14-2.41)	0.44	0.63
Mild bleeding	133 (10.0)	119 (8.7)	1.15 (0.89-1.48)	0.27	57 (13.1)	49 (11.5)	1.14 (0.77-1.68)	0.52	0.96
Severe or moderate bleeding	5 (0.4)	16 (1.2)	0.32 (0.12-0.86)	0.018	4 (0.9)	7 (1.6)	0.55 (0.16-1.87)	0.33	0.50
Composite of surgical access-site repair or blood products transfusion	8 (0.7)	10 (0.7)	0.81 (0.32-2.06)	0.66	12 (2.7)	6 (1.4)	1.94 (0.73-5.19)	0.18	0.20
Surgical access-site repair	0 (0.0)	1 (0.1)	0.34 (0.01-8.34)	1.00	2 (0.5)	2 (0.5)	0.96 (0.14-6.81)	0.97	0.37
Blood products transfusion	8 (0.7)	9 (0.7)	0.90 (0.35-2.34)	0.84	10 (2.3)	4 (0.9)	2.43 (0.76-7.77)	0.12	0.19