Vascular access and antithrombotic therapy in patients with acute coronary syndrome

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See Articles page 835

Antithrombotic therapy plays a pivotal part in invasively managed patients with acute coronary syndrome, particularly in those who require percutaneous coronary intervention.[1] In this setting, the radial artery has become the preferred vascular access site given the reduced risk of bleeding and mortality compared with femoral access.[2] Although bivalirudin and unfractionated heparin with optional glycoprotein IIb/IIIa inhibitor use are both recommended for patients with acute coronary syndrome undergoing percutaneous coronary intervention, which of these is the most optimal treatment remains largely debated.[1,3,4] In fact, although bivalirudin has been associated with reduced bleeding, albeit of varying magnitude depending on the prevalence of glycoprotein IIb/IIIa inhibitor use and unfractionated heparin dose in the comparator arms, its effect on ischaemic events is controversial, particularly in light of the early hazard of stent thrombosis.[3–5]

MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) was a programme of three nested randomised multicentre open-label superiority trials done in invasively managed patients with acute coronary syndrome (n=8404), designed to address the comparative safety and effectiveness of radial versus femoral access (MATRIX access), bivalirudin versus unfractionated heparin with or without glycoprotein IIb/IIIa inhibitor (MATRIX antithrombin), and prolonged versus short-term bivalirudin infusion (MATRIX treatment duration).[6,7] The coprimary endpoints for MATRIX access and MATRIX antithrombin were major adverse cardiovascular events (a composite of all-cause mortality, myocardial infarction, or stroke) and net adverse clinical events (defined as the composite of non-coronary artery bypass graft-related major bleeding [Bleeding Academic Research Consortium type 3 or 5], or major adverse cardiovascular events) at 30 days. The primary outcome for MATRIX treatment duration was the composite of net adverse clinical events, target vessel revascularisation, or definite stent thrombosis at 30 days. The primary endpoints at 30 days of the three nested trials have been previously reported.[6,7] In *The Lancet*, Marco Valgimigli and colleagues report the prespecified final 1-year outcomes of the entire MATRIX programme.[8] Overall, the 1-year outcomes were confirmatory to the primary endpoint measures observed at 30 days in all three nested trials. Major adverse cardiovascular events (14·2% *vs* 15·7%; rate ratio [RR] 0·89, 95% CI 0·80–1·00; p=0·0526 did not differ between the groups but the net adverse clinical events (15·2% *vs* 17·2%; 0·87, 0·78–0·97; p=0·0128) were less frequent with radial access than with femoral access (MATRIX access). Major adverse cardiovascular events (15·8% *vs* 16·8%; 0·94, 0·83–1·05; p=0·28) and net adverse clinical events (17·0% *vs* 18·4%; 0·91, 0·81–1·02; p=0·10) did not differ with bivalirudin compared with unfractionated heparin with or without glycoprotein IIb/IIIa inhibitors (MATRIX antithrombin). The primary outcome measure was not significantly lower with post-percutaneous coronary intervention bivalirudin infusion than with no post-percutaneous coronary intervention infusion (17·4% *vs* 17·4%; 0·99, 0·84–1·16; p=0·90; MATRIX treatment duration). The treatment effects of the randomised strategies were mostly front-loaded, after which the event curves displayed a parallel course. At 1 year, complete follow-up information was available for 99·8% of patients, providing robustness to the study conclusions.

The authors should be commended for doing this large clinical trial programme. Like many trials, MATRIX is sometimes difficult to interpret because of some of its neutral findings and has already been subject to constructive criticism.[4,9] Most importantly, the data should be interpreted in the context of a study in which glycoprotein IIb/IIIa inhibitor use was left to the discretion of the operator, and thus the study design inevitably made the groups unbalanced. Moreover, in the bivalirudin arm, upstream unfractionated heparin administration, which occurred in a third of patients, was a confounder. Ultimately, the dosing regimen of patients randomly assigned to post-percutaneous coronary intervention bivalirudin infusion was at the discretion of investigator. MATRIX access is the largest trial comparing the radial versus femoral approach and is the first to my knowledge to report 1-year outcomes. The long-term benefit for net adverse clinical events, driven by a reduction in major bleeding and cardiovascular mortality, ought to change practice so that radial access

should be the default approach in invasively managed patients with acute coronary syndrome.

MATRIX antithrombin did not show superiority of bivalirudin versus unfractionated heparin with or without glycoprotein IIb/IIIa inhibitor on the composite of ischaemic and bleeding endpoints combined, irrespective of vascular access. Although it could be argued that these results still leave the controversy on the optimal antithrombotic regimen to use during percutaneous coronary intervention unresolved, the MATRIX results are among the best available data and are informative. In fact, although the trial was not powered for secondary endpoints, and thus so-called positive findings should be considered only nominally significant, the reduction in bleeding (access and non-access site) and mortality (all-cause and cardiovascular mortality) confirmed at 1 year cannot be ignored given the established link between these outcomes.[1,3,4] Thus, bivalirudin remains an acceptable treatment for patients with acute coronary syndrome undergoing percutaneous coronary intervention and a very reasonable option in high-bleeding-risk settings, where it might complement the benefits of radial access.[1,3,4] Post-percutaneous coronary intervention antithrombotic strategies aimed at reducing the risk of bleeding, such as shortening dual antiplatelet therapy duration, deescalation of $P2Y_{12}$ inhibition, and aspirin-free regimens, are part of ongoing investigations.[10–12]

Ultimately, although MATRIX treatment duration did not show a benefit of post-percutaneous coronary intervention bivalirudin infusion compared with no post-percutaneous coronary intervention infusion, when post-percutaneous coronary intervention bivalirudin was used at a full dose, as recommended in the updated product label, thrombotic complications were mitigated. However, these latter results should be interpreted with caution and remain hypothesis generating.

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BASKET-SMALL 2: advancing DCB beyond in-stent restenosis

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See Articles page 849

Drug-coated balloons (DCB) were first used as a new therapeutic option in the treatment of in-stent restenosis, with proven inhibition of restenosis in clinical studies.[1–3] DCB have received a class 1 indication in the 2014 European Society of Cardiology guidelines[4] for the treatment of both bare metal stent (BMS) and drug-eluting stent (DES) in-stent restenosis. The next question is whether DCB are effective in de-novo coronary lesions, specifically in small coronary vessels.

Percutaneous coronary intervention (PCI) in small coronary vessels (defined as <3·0 mm in diameter) is associated with an increased rate of restenosis and lesion failure[5] because PCI is less capable of accommodating neointimal growth after stenting in

Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial

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Summary

Background The Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) programme was designed to assess the comparative safety and effectiveness of radial versus femoral access and of bivalirudin versus unfractionated heparin with optional glycoprotein IIb/IIIa inhibitors in patients with the whole spectrum of acute coronary syndrome undergoing invasive management. Here we describe the prespecified final 1-year outcomes of the entire programme.

Methods MATRIX was a programme of three nested, randomised, multicentre, open-label, superiority trials in patients with acute coronary syndrome in 78 hospitals in Italy, the Netherlands, Spain, and Sweden. Patients with ST-elevation myocardial infarction were simultaneously randomly assigned (1:1) before coronary angiography to radial or femoral access and to bivalirudin, with or without post-percutaneous coronary intervention infusion or unfractionated heparin (one-step inclusion). Patients with non-ST-elevation acute coronary syndrome were randomly assigned (1:1) before coronary angiography to radial or femoral access and, only if deemed eligible to percutaneous coronary intervention after angiography (two-step inclusion), entered the antithrombin type and treatment duration programmes. Randomisation sequences were computer generated, blocked, and stratified by intended new or current use of P2Y12 inhibitor (clopidogrel *vs* ticagrelor or prasugrel), and acute coronary syndrome type (ST-elevation myocardial infarction, troponin-positive, or troponin-negative non-ST-elevation acute coronary syndrome). Bivalirudin was given as a bolus of 0·75 mg/kg, followed immediately by an infusion of 1·75 mg/kg per h until completion of percutaneous coronary intervention. Heparin was given at 70–100 units per kg in patients not receiving glycoprotein IIb/IIIa inhibitors, and at 50–70 units per kg in patients receiving glycoprotein IIb/IIIa inhibitors. Clinical follow-up was done at 30 days and 1 year. Co-primary outcomes for MATRIX access and MATRIX antithrombin type were major adverse cardiovascular events, defined as the composite of all-cause mortality, myocardial infarction, or stroke up to 30 days; and net adverse clinical events, defined as the composite of non-coronary artery bypass graft-related major bleeding, or major adverse cardiovascular events up to 30 days. The primary outcome for MATRIX treatment duration was the composite of urgent target vessel revascularisation, definite stent thrombosis, or net adverse clinical events up to 30 days. Analyses were done according to the intention-to-treat principle. This trial is registered with ClinicalTrials.gov, number NCT01433627.

Findings Between Oct 11, 2011, and Nov 7, 2014, we randomly assigned 8404 patients to receive radial (4197 patients) or femoral (4207 patients) access. Of these 8404 patients, 7213 were included in the MATRIX antithrombin type study and were randomly assigned to bivalirudin (3610 patients) or heparin (3603 patients). Patients assigned to bivalirudin were included in the MATRIX treatment duration study, and were randomly assigned to post-procedure infusion (1799 patients) or no post-procedure infusion (1811 patients). At 1 year, major adverse cardiovascular events did not differ between patients assigned to radial access compared with those assigned to femoral access (14·2% *vs* 15·7%; rate ratio 0·89, 95% CI 0·80–1·00; p=0·0526), but net adverse clinical events were fewer with radial than with femoral access (15·2% *vs* 17·2%; 0·87, 0·78–0·97; p=0·0128). Compared with heparin, bivalirudin was not associated with fewer major adverse cardiovascular (15·8% *vs* 16·8%; 0·94, 0·83–1·05; p=0·28) or net adverse clinical events (17·0% *vs* 18·4%; 0·91, 0·81–1·02; p=0·10). The composite of urgent target vessel revascularisation, stent thrombosis, or net adverse clinical events did not differ with or without post-procedure bivalirudin infusion (17·4% *vs* 17·4%; 0·99, 0·84–1·16; p=0·90).

Interpretation In patients with acute coronary syndrome, radial access was associated with lower rates of net adverse clinical events compared with femoral access, but not major adverse cardiovascular events at 1 year. Bivalirudin with

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See **Comment** page 801

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or without post-procedure infusion was not associated with lower rates of major adverse cardiovascular events or net adverse clinical events. Radial access should become the default approach in acute coronary syndrome patients undergoing invasive management.

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See Online for appendix

Introduction

The radial artery is recommended in European guidelines as the preferred vascular access site in patients with acute coronary syndrome undergoing invasive management.[1–3] In light of mounting evidence that, compared with femoral access, radial access is associated with improved outcomes[4] and quality of life, as well as lower costs,[5] use of this technique has steadily increased across the world. However, whether the short-term benefits of radial access are maintained at longer-term follow-up is unclear.

Use of bivalirudin, rather than unfractionated heparin with or without glycoprotein IIb/IIIa inhibitors, mitigates the risks of bleeding,[6] but its effects on the prevention of short-term and long-term ischaemic events remain controversial. A large study, which recruited patients with ST-segment elevation myocardial infarction, who were intervened upon almost exclusively via femoral access, showed an incremental benefit of bivalirudin on major adverse cardiovascular events over a 3-year follow-up.[7]

The Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) programme was designed to assess the comparative safety and effectiveness of radial versus femoral access and of bivalirudin versus unfractionated heparin with optional glycoprotein IIb/IIIa inhibitors in patients with the whole spectrum of acute coronary syndrome undergoing invasive management. This Article describes the prespecified final 1-year outcomes of the entire programme.

Methods

Study design and patients

MATRIX was a programme of three nested, randomised, multicentre, open-label, superiority trials in patients with acute coronary syndrome in 78 hospitals in Italy, the Netherlands, Spain, and Sweden.[8] MATRIX access compared radial versus femoral access in patients with acute coronary syndrome, including ST-elevation myocardial infarction and non-ST-elevation acute coronary syndrome, undergoing invasive management.[9] All patients with ST-elevation myocardial infarction and those with non-ST-elevation acute coronary syndrome, in whom percutaneous coronary intervention was planned after coronary angiography, were also included in the pharmacological trials. In MATRIX antithrombin type, patients with ST-elevation myocardial infarction or non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention were randomly assigned to receive bivalirudin or unfractionated heparin.[10] MATRIX treatment duration was a randomised comparison of prolonged bivalirudin administration during and after percutaneous coronary intervention versus short-term bivalirudin administration during percutaneous coronary intervention only in patients assigned to bivalirudin.[10]

Patients with non-ST-elevation acute coronary syndrome were eligible for inclusion if they had a history consistent with new or worsening cardiac ischaemia, occurring at rest or with minimal activity within 7 days before randomisation, and fulfilled at least two high-risk criteria among the following: age 60 years or older, cardiac biomarker elevation, or electrocardiographic changes compatible with ischaemia. Only those considered to be candidates for percutaneous coronary intervention after completion of coronary angiography were further considered for the antithrombin and treatment duration programmes. Patients with ST-elevation myocardial infarction were eligible if they presented within 12 h of symptom onset, or between 12 and 24 h after symptom onset if there was evidence of continuing ischaemia or previous fibrinolytic treatment. Detailed inclusion and exclusion criteria, and operators' eligibility criteria, are presented in the appendix. All patients gave written informed consent.[8]

The trial was approved by the institutional review board at each participating centre, and all patients gave written informed consent to participate.

Randomisation and masking

Patients with ST-elevation myocardial infarction were simultaneously randomly assigned (1:1) before coronary angiography to radial or femoral access and to bivalirudin, with or without post-percutaneous coronary intervention infusion or to unfractionated heparin (one-step inclusion). Patients with non-ST-elevation acute coronary syndrome were randomly assigned (1:1) before coronary angiography to radial or femoral access, and only if deemed eligible for percutaneous coronary intervention after angiography (two-step inclusion), were they entered into the antithrombin type and treatment duration programmes. Randomisation sequences were computer generated, blocked, and stratified by intended new or current use of P2Y12 inhibitor (clopidogrel *vs* ticagrelor or prasugrel), and acute coronary syndrome type (ST-elevation myocardial infarction, troponin-positive, or

Research in context

Evidence before this study

We searched PubMed from inception to July 4, 2018, for complete reports of studies written in English comparing radial versus femoral or bivalirudin versus heparin in patients with acute coronary syndrome. We used the following search terms: acute coronary syndrome, percutaneous coronary intervention, randomized controlled trial, bivalirudin, heparin, radial or transradial, femoral or transfemoral. We found no randomised trial comparing radial and femoral access outcomes for longer than 30-day follow-up, except for STEMI-RADIAL, which reported no mortality difference at 6 months, and which did not collect non-fatal ischaemic or bleeding endpoints beyond 30 days. We identified eight randomised trials with longer than 30-day outcomes for bivalirudin versus heparin in patients with acute coronary syndrome, which differed in terms of patient selection, comparator arms, bivalirudin regimen, and prespecified primary outcome measures. BAS recruited unstable angina patients who underwent transfemoral interventions and showed no difference for the composite ischaemic endpoint of death, myocardial infarction, or repeat revascularisation at 180 days, but bleeding was reduced with bivalirudin. REPLACE-2, in which around 44% of patients had acute coronary syndrome, found similar primary ischaemic endpoint event rates at 6 months and 12 months between bivalirudin and heparin plus glycoprotein IIb/IIIa inhibitors. ACUITY recruited patients with acute coronary syndrome with non-ST-segment elevation, some of whom were treated with percutaneous coronary intervention, largely via femoral access, and found no significant differences at 1 year in the rates of the primary composite ischaemic endpoint or mortality across bivalirudin, bivalirudin plus glycoprotein IIb/IIIa inhibitors, and heparin plus glycoprotein IIb/IIIa inhibitors. HORIZONS-AMI recruited patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention almost exclusively via femoral access and showed sustained benefit in terms of major adverse cardiac events for bivalirudin compared with heparin plus glycoprotein IIb/IIIa inhibitors at 3 years. ISAR-REACT 3 recruited patients with stable or unstable angina undergoing transfemoral percutaneous coronary intervention, and had similar outcomes at 1 year between bivalirudin and heparin. ISAR-REACT 4 recruited patients with non-ST-segment elevation myocardial infarction undergoing transfemoral percutaneous coronary intervention, and had similar outcomes at 1 year between bivalirudin and heparin plus abciximab. EUROMAX recruited patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with an almost even—albeit non-randomised—distribution between radial and femoral access, and showed that the reduced composite net endpoint at 30 days in the bivalirudin arm compared with heparin plus optional glycoprotein IIb/IIIa inhibitors did not translate into reduced cardiovascular or all-cause fatality rates at 1 year. Finally, BRIGHT recruited patients with myocardial infarction undergoing percutaneous coronary intervention and showed consistently lower net adverse clinical events and bleeding at 30 days and 1 year with bivalirudin compared with heparin alone or heparin plus tirofiban. To our knowledge, no study has randomised patients to receive post-percutaneous coronary intervention bivalirudin infusion versus no post-percutaneous coronary intervention bivalirudin infusion.

Added value of this study

To our knowledge, MATRIX access is the largest randomised trial to compare radial versus femoral access and the only to report 1-year follow-up data. MATRIX antithrombin type is the largest randomised trial to compare bivalirudin and heparin (plus optional glycoprotein IIb/IIIa inhibitors) across the full spectrum of patients with acute coronary syndrome undergoing invasive management and the only trial in which access site was randomised. MATRIX treatment duration is the only randomised trial available to compare prolonged post-percutaneous coronary intervention infusion with no infusion of bivalirudin.

Implications of all the available evidence

That radial access provides sustained benefits at 1 year compared with femoral access fills a knowledge gap. In conjunction with the previously reported statistically robust reduction in all-cause mortality at 30 days in meta-analyses, our findings indicate that radial access could become the default approach in patients with acute coronary syndrome undergoing invasive management. Extended follow-up at 1 year confirmed there was no superiority for bivalirudin compared with heparin with or without glycoprotein IIb/IIIa inhibitors on a composite of ischaemic or ischaemic and bleeding endpoints combined, irrespective of the allocated radial or femoral access site. However, we observed a nominally significant reduction in all-cause and cardiovascular mortality with bivalirudin at 1 year. Our programme was not powered for detecting a mortality effect of the tested interventions, which—along with the borderline statistical significance—suggests that caution should be taken in interpreting this finding. Although arising from a secondary endpoint analysis, our programme also observed a statistically robust and persistent reduction of bleeding events, including fatal occurrences with bivalirudin. Hence, bivalirudin might have a synergistic role with radial access in bleeding prevention and use of bivalirudin should be regarded as complementary more than substitutive of radial access. Post-percutaneous coronary intervention bivalirudin infusion did not mitigate the risks of stent thrombosis or other ischaemic events compared with no post-percutaneous coronary intervention infusion. The stratified analysis of the two permitted post-percutaneous coronary intervention bivalirudin regimens suggests that the full percutaneous coronary intervention, but not the reduced bivalirudin regimen, could be considered for further protection from recurrent ischaemic events when bivalirudin is used. However, the non-randomised nature of this observation makes this finding explorative and hypothesis generating.

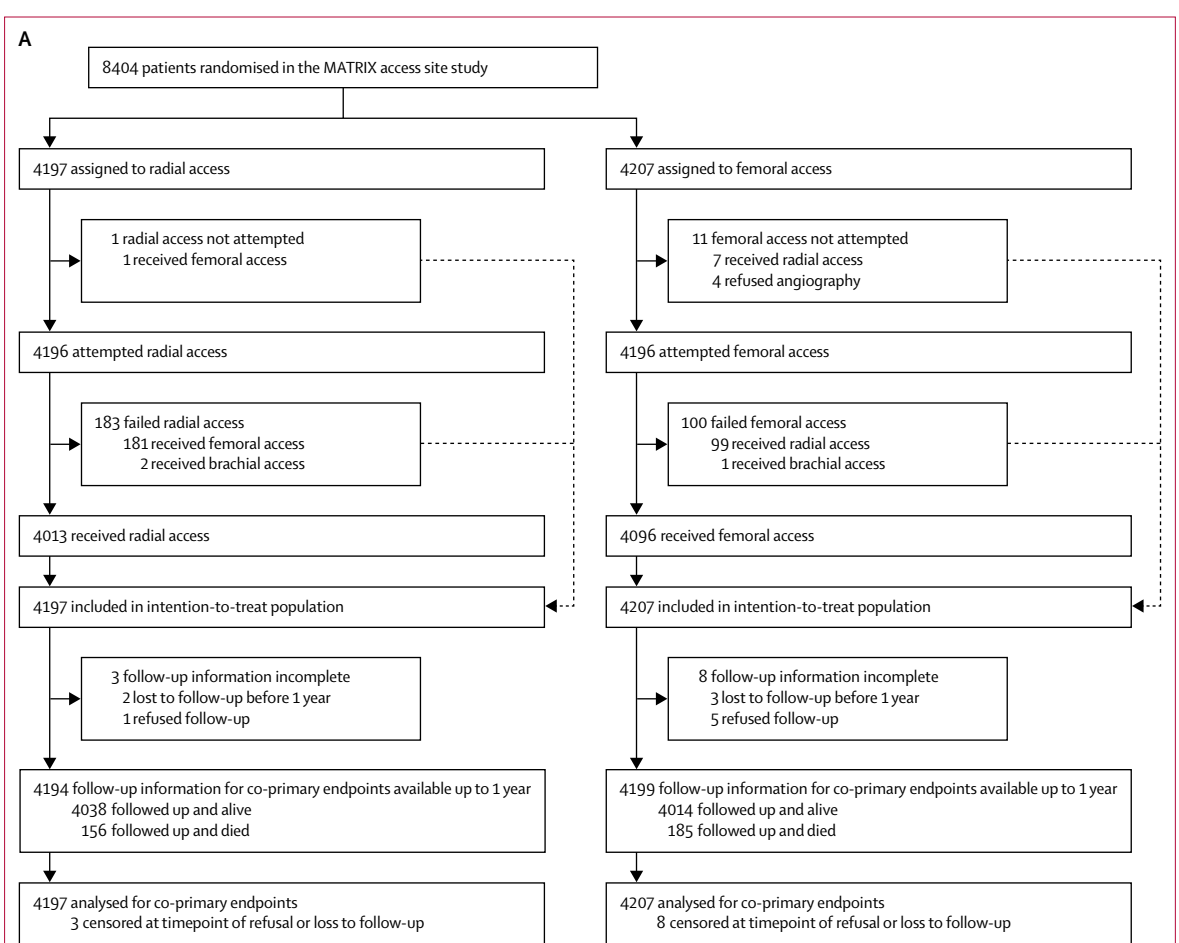
troponin-negative non-ST-elevation acute coronary syndrome). Central randomisation was concealed using a locked web-based system. The randomisation sequence was genearated by an independent statistician who was not involved in the trial. Patients were enrolled and assigned to the trial groups by investigators at each study site.

Procedures

Access site management during and after the diagnostic or therapeutic procedure was left to the discretion of the treating physician and closure devices were allowed as per local practice. Bivalirudin (Parsippany-Troy Hills, NJ, USA) was given according to the product labelling, with a bolus of 0·75 mg/kg, followed immediately by an infusion of 1·75 mg/kg per h until completion of percutaneous coronary intervention. Bivalirudin treatment was then stopped at the end of percutaneous coronary intervention or prolonged in accordance with the subsequent random assignment. In patients allocated to prolonged treatment, bivalirudin could be administered either at the full dose for up to 4 h or at a reduced dose of 0·25 mg/kg per h for at least 6 h, at the discretion of the treating physician.[8] Heparin was given at 70–100 units per kg in patients not receiving glycoprotein IIb/IIIa inhibitors and at 50–70 units per kg in patients receiving glycoprotein IIb/IIIa inhibitors. Subsequent heparin titration based on activated clotting time was left to the discretion of the treating physician.

A glycoprotein IIb/IIIa inhibitor could be administered before percutaneous coronary intervention in all patients in the heparin group on the basis of the treating physician's judgment, but could be administered in the bivalirudin group only in patients with periprocedural ischaemic complications after percutaneous coronary intervention. Use of other medications was allowed as per guidelines.[1–3] Specific protocol guidance regarding staged procedures and post-procedure use of unfractionated heparin is provided in the appendix.

Clinical follow-up was done at 30 days and 1 year. During follow-up visits, patients were assessed for adverse events and 12-lead ECG recordings, and they were questioned on their compliance with secondary prevention medications. Patency of the radial artery was



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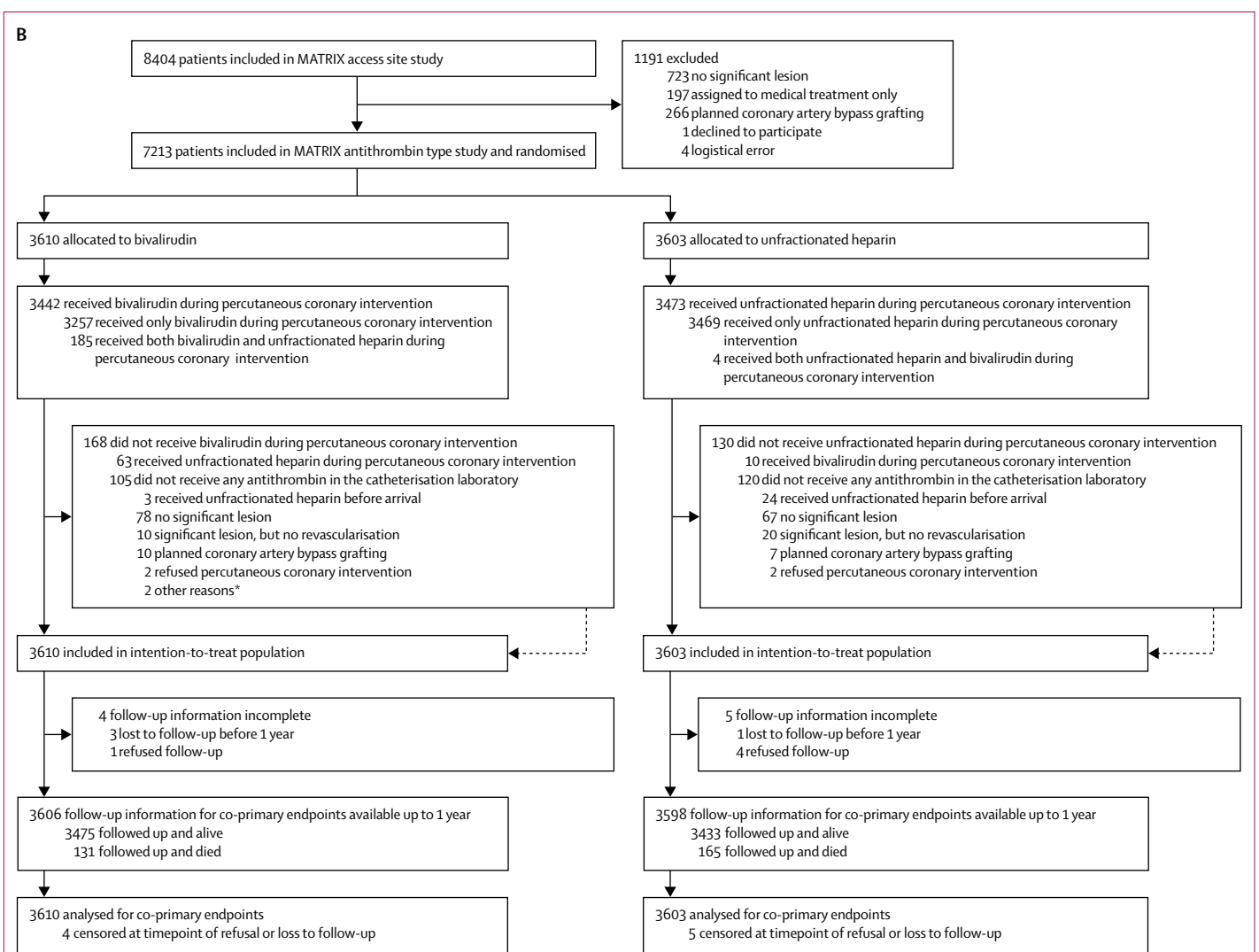
to be assessed by the presence of radial pulse as well as by the use of the reverted Barbeau's test.

Outcomes

Co-primary outcomes for MATRIX access and MATRIX antithrombin were major adverse cardiovascular events, defined as the composite of all-cause mortality, myocardial infarction, or stroke up to 30 days; and net adverse clinical events, defined as the composite of non-coronary artery bypass graft-related major bleeding (Bleeding Academic Research Consortium [BARC] type 3 or 5), or major adverse cardiovascular events up to 30 days. The primary outcome for MATRIX treatment duration was the composite of urgent target vessel revascularisation, definite stent thrombosis,[11] or net adverse clinical events up to 30 days.[8] Secondary outcomes included all (co-)primary endpoints within 1 year and each component of the composite outcomes.[8] All outcomes were prespecified. An independent clinical events committee masked to treatment allocation adjudicated all suspected events. Detailed outcome definitions and clinical events committee procedures are provided in the appendix.

Statistical analysis

The MATRIX access trial was powered for superiority on the two co-primary composite outcomes at 30 days (major adverse cardiovascular events, defined as the composite of all-cause mortality, myocardial infarction, or stroke up to 30 days; and net adverse clinical events, defined as the composite of non-coronary artery bypass graft-related major bleeding [BARC type 3 or 5], or major adverse cardiovascular events up to 30 days). For major adverse cardiovascular events, we expected rates of 6·0% in the femoral group and 4·2% in the radial group, corresponding to a rate ratio (RR) of 0·70. For net adverse



(Figure 1 continues on next page)

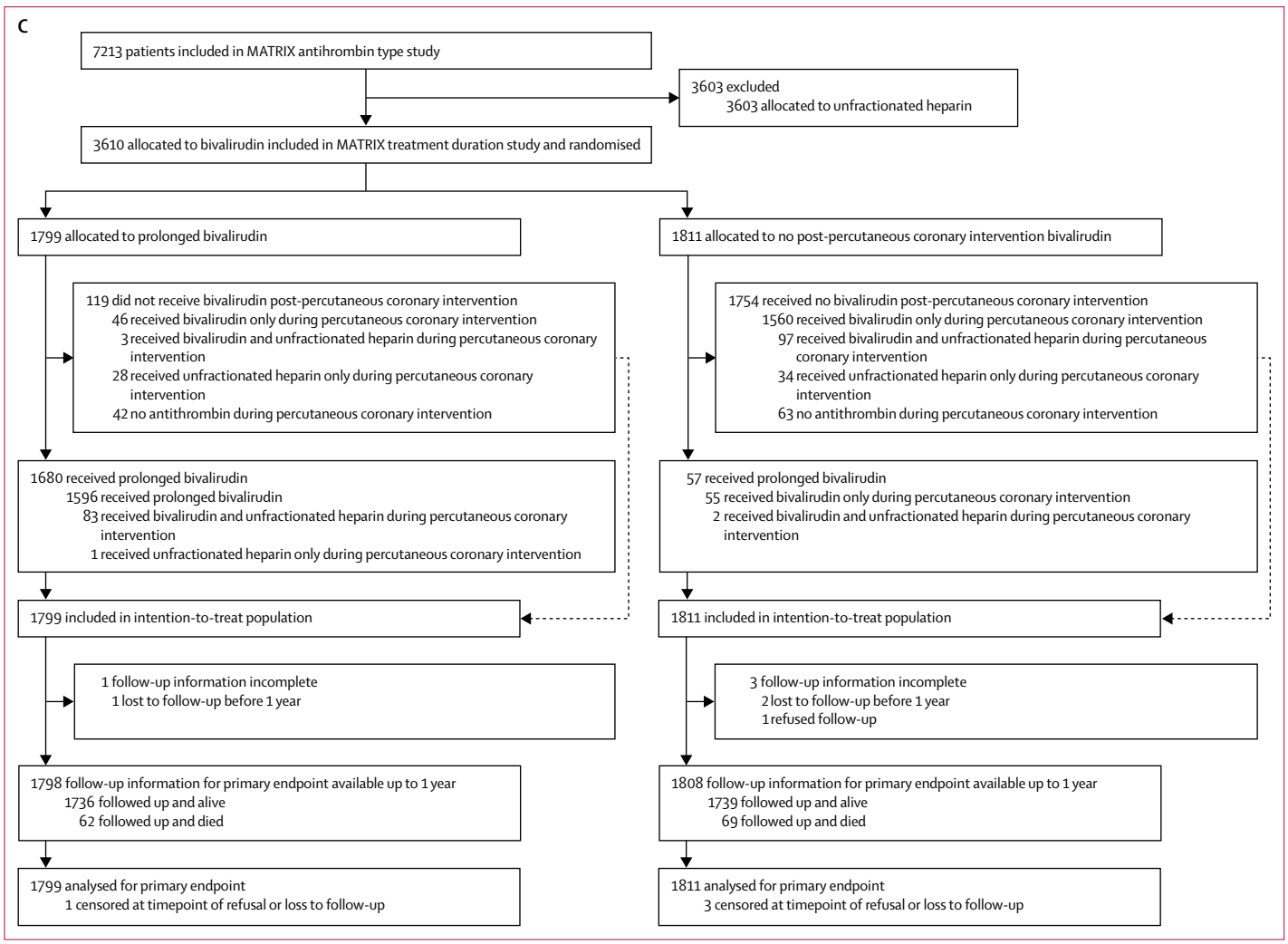


Figure 1: **Study flowcharts**
*Refused angiography after successful access site (one patient); angiography aborted because of a cerebrovascular event (one patient).

clinical events, we expected rates of 9·0% in the femoral group and 6·3% in the radial group, again corresponding to an RR of 0·70. 4100 patients per group would provide more than 90% power for these differences to be detected for the first co-primary outcome and more than 99% power for the second co-primary outcome, with a two-sided α of 2·5%.

The MATRIX antithrombin type trial was powered for superiority on its two co-primary composite outcomes at 30 days. For major adverse cardiovascular events, we expected rates of 6·0% in the heparin group and 4·2% in the bivalirudin group. For net adverse clinical events, we expected rates of 9·0% in the heparin group and 6·3% in the bivalirudin group. Both between-group differences correspond to a RR of 0·70. 3400 patients per group would provide 85% power to detect the first co-primary endpoint and 95% power to detect the second co-primary endpoint, with a two-sided α of 2·5%.

The MATRIX treatment duration trial prespecified a single superiority endpoint at 30 days, with a two-sided α of 5%. We assumed an incidence of the composite of death, myocardial infarction, stroke, urgent target vessel revascularisation, stent thrombosis, or type 3 and 5 BARC bleeding at 30 days of 10·0% with short-term bivalirudin and 7·0% with prolonged bivalirudin, corresponding to an RR of 0·70. 1700 patients per group would provide 86% power to detect this difference.

The final sample size of the whole programme was driven by the power analysis for the MATRIX antithrombin trial, taking into consideration the fact that patients with non-ST-elevation acute coronary syndrome were eligible only if proceeding to percutaneous coronary intervention. All primary outcomes at 1 year were prespecified secondary endpoints. All secondary outcomes were analysed with a two-sided α set at 5% to allow conventional interpretation of results.

	Access programme		Antithrombin type programme		Treatment duration programme	
	Radial (n=4197)	Femoral (n=4207)	Bivalirudin (n=3610)	Unfractionated heparin (n=3603)	Prolonged bivalirudin infusion (n=1799)	No post-percutaneous coronary intervention bivalirudin infusion (n=1811)
Age (years)	65·6 (11·8)	65·9 (11·8)	65·4 (11·9)	65·4 (11·9)	65·4 (12·1)	65·5 (11·7)
<75	3124 (74·4%)	3098 (73·6%)	2702 (74·8%)	2692 (74·7%)	1335 (74·2%)	1367 (75%)
≥75	1073 (25·6%)	1109 (26·4%)	908 (25·2%)	911 (25·3%)	464 (25·8%)	444 (25%)
Sex						
Men	3126 (74·5%)	3046 (72·4%)	2731 (75·7%)	2764 (76·7%)	1351 (75·1%)	1380 (76·2%)
Women	1071 (25·5%)	1161 (27·6%)	879 (24·3%)	839 (23·3%)	448 (24·9%)	431 (23·8%)
Body-mass index (kg/m²)	27·1 (4·2)	27·1 (4·2)	27·2 (4·2)	27·0 (4·1)	27·3 (4·3)	27·0 (4·0)
Diabetes mellitus	959 (22·8%)	944 (22·4%)	824 (22·8%)	793 (22·0%)	404 (22·5%)	420 (23·2%)
Insulin-dependent	209 (5·0%)	257 (6·1%)	201 (5·6%)	190 (5·3%)	115 (6·4%)	86 (4·7%)
Non-insulin-dependent	3988 (95·0%)	3950 (93·9%)	3409 (94·4%)	3413 (94·7%)	1684 (93·6%)	1725 (95·3%)
Current smoker	1459 (34·8%)	1428 (33·9%)	1307 (36·2%)	1302 (36·1%)	638 (35·5%)	669 (36·9%)
Hypercholesterolaemia	1799 (42·9%)	1892 (45·0%)	1596 (44·2%)	1558 (43·2%)	750 (41·7%)	846 (46·7%)
Hypertension	2625 (62·5%)	2686 (63·8%)	2264 (62·7%)	2222 (61·7%)	1131 (62·9%)	1133 (62·6%)
Previous myocardial infarction	585 (13·9%)	618 (14·7%)	530 (14·7%)	501 (13·9%)	279 (15·5%)	251 (13·9%)
Previous percutaneous coronary intervention	610 (14·5%)	585 (13·9%)	536 (14·8%)	504 (14·0%)	275 (15·3%)	261 (14·4%)
Previous coronary artery bypass graft	111 (2·6%)	146 (3·5%)	127 (3·5%)	95 (2·6%)	64 (3·6%)	63 (3·5%)
Previous transient ischaemic attack or stroke	195 (4·6%)	230 (5·5%)	181 (5·0%)	185 (5·1%)	104 (5·8%)	77 (4·3%)
Peripheral vascular disease	341 (8·1%)	372 (8·8%)	296 (8·2%)	284 (7·9%)	167 (9·3%)	129 (7·1%)
Renal failure	46 (1·1%)	59 (1·4%)	48 (1·3%)	47 (1·3%)	22 (1·2%)	26 (1·4%)
Dialysis	4 (0·1%)	4 (0·1%)	5 (0·1%)	2 (0·1%)	0 (0·0%)*	5 (0·3%)*
ST-segment elevation myocardial infarction	2001 (47·7%)	2009 (47·8%)	2012 (55·7%)	1998 (55·5%)	1006 (55·9)	1006 (55·5%)
Non-ST-elevation acute coronary syndrome	2196 (52·3%)	2198 (52·2%)	1598 (44·3%)	1605 (44·5%)	793 (44·1%)	805 (44·5%)
Non-ST-elevation acute coronary syndrome, troponin positive	1954 (46·6%)	1932 (45·9%)	1434 (39·7%)	1443 (40·0%)	721 (40·1%)	713 (39·4%)
ST-elevation acute coronary syndrome	2243 (53·4%)	2275 (54·1%)	2176 (60·3%)	2160 (60·0%)	1078 (59·9%)	1098 (60·6%)
Killip class >1	401 (9·6%)	407 (9·7%)	335 (9·3%)	363 (10·1%)	158 (8·8%)	177 (9·8%)
Cardiac arrest	85 (2·0%)	83 (2·0%)	80 (2·2%)	83 (2·3%)	36 (2·0%)	44 (2·4%)
Left ventricular ejection fraction (%)	51·3 (9·6)	50·8 (9·8)	50·5 (9·5)	50·9 (9·5)	50·3 (9·5)	50·7 (9·6)

Data are mean (SD) or n (%). *p<0·05 for within each MATRIX programme comparison.

Table 1: **Baseline characteristics**

Analyses were done according to the intention-to-treat principle, including all patients in the analysis according to allocated antithrombin type. No interim analysis was prespecified or done. We analysed primary and secondary outcomes as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding two-sided p values. We constructed survival curves using Kaplan-Meier estimates. We did subgroup analyses according to prespecified characteristics, including age, sex, body-mass index, presenting syndrome, type of P2Y12 inhibitor, overall or transradial percutaneous coronary intervention volume by centre, renal function, diabetes mellitus, and peripheral vascular disease, and accompanied by formal tests for subgroup by treatment interaction or tests for trend across ordered groups. We did time to first-event analyses for primary endpoints separately for the periods from randomisation to 30 days and from 31 days to 1 year. For these analyses, patients who had a primary endpoint event between randomisation and day 30 but survived until day 31 were included in a time to first event analysis of the second period, until they had a second primary endpoint event or reached 1 year, whichever came first. We did not adjust for multiple testing of secondary outcomes, therefore p values and 95% CIs from analyses of secondary outcomes should not be used for inference about treatment effects.

All analyses were done in Stata 14.2.

This trial is registered with ClinicalTrials.gov, number NCT01433627.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MV, MR, DH, and PJ had full access to all the data in the study, and MV and PJ had final responsibility for the decision to submit for publication.

	Access programme		Antithrombin type programme		Treatment duration programme	
	Radial (n=4197)	Femoral (n=4207)	Bivalirudin (n=3610)	Unfractionated heparin (n=3603)	Prolonged bivalirudin infusion (n=1799)	No post-percutaneous coronary intervention bivalirudin infusion (n=1811)
Only radial access	4013 (95·6%)	7 (0·2%)*	1676 (46·4%)	1688 (46·8%)	837 (46·5%)	839 (46·3%)
Only femoral access	1 (<0·1%)	4096 (97·4%)*	1765 (48·9%)	1748 (48·5%)	872 (48·5%)	893 (49·3%)
Both radial and femoral access	181 (4·3%)	99 (2·4%)*	167 (4·6%)	163 (4·5%)	90 (5·0%)	77 (4·3%)
Other access sites	2 (<0·1%)†	5 (<0·1%)‡	2 (<0·1%)§	4 (<0·1%)¶	0 (0·0%)	2 (<0·1%)‖
Coronary angiography completed	4195 (>99·9%)	4200 (99·8%)	3607 (99·9%)	3600 (99·9%)	1797 (99·9%)	1810 (99·9%)
Medications in the catheterisation laboratory						
Clopidogrel	269 (6·4%)	254 (6·0%)	241 (6·7%)	289 (8·0%)*	135 (7·5%)	106 (5·9%)*
Prasugrel	335 (8·0%)	291 (6·9%)	313 (8·7%)	313 (8·7%)	136 (7·6%)	177 (9·8%)*
Ticagrelor	381 (9·1%)	395 (9·4%)	400 (11·1%)	377 (10·5%)	198 (11·0%)	202 (11·2%)
Unfractionated heparin	2032 (48·4%)	1864 (44·3%)*	247 (6·8%)	3473 (96·4%)*	114 (6·3%)	133 (7·3%)
Glycoprotein IIb/IIIa inhibitors	573 (13·7%)	522 (12·4%)	163 (4·5%)	934 (25·9%)*	64 (3·6%)	99 (5·5%)*
Bivalirudin	1703 (40·6%)	1724 (41·0%)	3443 (95·4%)	14 (0·4%)*	1729 (96·1%)	1714 (94·6%)*
Post-percutaneous coronary intervention bivalirudin	861 (20·5%)	864 (20·5%)	1737 (48·1%)	3 (0·1%)*	1680 (93·4%)	57 (3·1%)*
Coronary artery bypass graft after coronary angiography	155 (3·7%)	155 (3·7%)	24 (0·7%)	17 (0·5%)	11 (0·6%)	13 (0·7%)
Percutaneous coronary intervention after coronary angiography	3367 (80·2%)	3357 (79·8%)	3399 (94·2%)	3409 (94·6%)	1691 (94·0%)	1708 (94·3%)
Planned staged percutaneous coronary intervention	767 (18·3%)	741 (17·6%)	732 (20·3%)	685 (19·0%)	356 (19·8%)	376 (20·8%)
Treated vessel(s)						
Left main coronary artery	151 (4·5%)	118 (3·5%)*	143 (4·3%)	125 (3·7%)	68 (4·1%)	75 (4·4%)
Left anterior descending artery	1676 (49·8%)	1638 (48·8%)	1686 (50·1%)	1628 (48·5%)	859 (51·4%)	827 (48·9%)
Left circumflex artery	897 (26·6%)	903 (26·9%)	898 (26·7%)	901 (26·8%)	437 (26·2%)	461 (27·2%)
Right coronary artery	1106 (32·8%)	1109 (33·0%)	1097 (32·6%)	1116 (33·2%)	547 (32·7%)	550 (32·5%)
Bypass graft	20 (0·6%)	35 (1·0%)*	32 (1·0%)	23 (0·7%)	17 (1·0%)	15 (0·9%)
Two or more vessels treated	449 (13·3%)	437 (13·0%)	454 (13·5%)	431 (12·8%)	234 (14·0%)	220 (13·0%)
Overall stent length (mm)	31·8 (19·4)	31·4 (19·6)	31·5 (19·9)	31·7 (19·1)	31·8 (19·5)	31·2 (20·2)

Data are n (%) or mean (SD). *p<0·05 for each MATRIX programme comparison. †Both radial and brachial access. ‡One patient received both femoral and brachial access, and four patients declined angiography or study participation. §One patient received both radial and femoral access, and one patient declined angiography or study participation. ¶One patient received both femoral and brachial access, one patient received both radial and brachial access, and two patients declined angiography or study participation. ‖One patient received both radial and brachial access, and one patient declined angiography or study participation.

Table 2: **Procedural characteristics of the index procedure**

Results

Between Oct 11, 2011, and Nov 7, 2014, we randomly assigned 8404 patients to radial (4197 patients) or femoral (4207 patients) access. Of these 8404 patients, 7213 were included in the MATRIX antithrombin type study and were randomly assigned to bivalirudin (3610 patients) or heparin (3603 patients). The 3610 patients assigned to bivalirudin were included in the MATRIX treatment duration study, and were randomly assigned to post-procedure infusion (1799 patients) or no post-procedure infusion (1811 patients; figure 1). Baseline characteristics and procedural features are shown in tables 1 and 2 (for details on staged intervention and medications during follow-up see appendix). 3951 (94·1%) of 4197 patients assigned to radial access and 4098 (97·4%) of 4207 patients assigned to femoral access received the allocated arterial access. 3442 (95·3%) of 3610 patients in the bivalirudin group, 3473 (96·4%) of 3603 patients in the unfractionated heparin group, 1680 (93·3%) of 1799 patients in the post-percutaneous coronary intervention bivalirudin group, and 1754 (96·9%) of 1811 patients in the no post-procedure bivalirudin group received the allocated treatment strategy.

At 1 year, complete follow-up information was available for 8391 (99·8%) of 8404 patients in the MATRIX access trial, 7204 (99·9%) of 7213 patients in the MATRIX antithrombin-type trial, and 3606 (99·9%) of 3610 patients in the MATRIX treatment duration trial, and one or more planned staged interventions were done in 1508 (17·9%), 1417 (19·6%), and 732 (20·3%) patients in the same trials.

The first co-primary outcome of major adverse cardiovascular events occurred in 595 (14·2%) of 4197 patients with radial access and 659 (15·7%) of 4207 patients with femoral access, with an RR of 0·89 (95% CI 0·80–1·00) and two-sided p=0·0526 (table 3, figure 1). The second co-primary outcome of net adverse clinical events

	Access programme			Antithrombin type programme			Treatment duration programme		
	Radial (n=4197)	Femoral (n=4207)	RR (95% CI)	Bivalirudin (n=3610)	Unfractionated heparin (n=3603)	RR (95% CI)	Prolonged bivalirudin infusion (n=1799)	No post-percutaneous coronary intervention bivalirudin infusion (n=1811)	RR (95% CI)
Co-primary composite endpoint of all-cause mortality, myocardial infarction, or stroke*	595 (14·2%)	659 (15·7%)	0·89 (0·80–1·00)	570 (15·8%)	604 (16·8%)	0·94 (0·83–1·05)	288 (16·0%)	282 (15·6%)	1·03 (0·87–1·21)
Co-primary composite endpoint of all-cause mortality, myocardial infarction, stroke, or BARC 3 or 5†	639 (15·2%)	724 (17·2%)	0·87 (0·78–0·97)	612 (17·0%)	664 (18·4%)	0·91 (0·81–1·02)	304 (16·9%)	308 (17·0%)	0·99 (0·84–1·16)
Primary composite of all-cause mortality, myocardial infarction, stroke, urgent target vessel revascularisation, definite stent thrombosis, or BARC 3 or 5	653 (15·6%)	741 (17·6%)	0·87 (0·78–0·97)	627 (17·4%)	679 (18·9%)	0·91 (0·82–1·02)	312 (17·4%)	315 (17·4%)	0·99 (0·84–1·16)
All-cause mortality	156 (3·7%)	185 (4·4%)	0·84 (0·68–1·04)	131 (3·6%)	165 (4·6%)	0·79 (0·63–0·99)	62 (3·5%)	69 (3·8%)	0·90 (0·64–1·27)
Cardiovascular death	89 (2·1%)	125 (3·0%)	0·71 (0·54–0·93)	79 (2·2%)	106 (3·0%)	0·74 (0·55–0·99)	39 (2·2%)	40 (2·2%)	0·98 (0·63–1·52)
Myocardial infarction	445 (10·7%)	480 (11·6%)	0·92 (0·81–1·05)	443 (12·4%)	449 (12·6%)	0·98 (0·86–1·12)	229 (12·9%)	214 (12·0%)	1·08 (0·89–1·30)
Stroke	25 (0·6%)	25 (0·6%)	1·00 (0·57–1·74)	20 (0·6%)	25 (0·7%)	0·79 (0·44–1·43)	9 (0·5%)	11 (0·6%)	0·82 (0·34–1·98)
Ischaemic	17 (0·4%)	20 (0·5%)	0·85 (0·44–1·62)	13 (0·4%)	19 (0·5%)	0·68 (0·34–1·37)	6 (0·3%)	7 (0·4%)	0·86 (0·29–2·56)
Haemorrhagic	7 (0·2%)	5 (0·1%)	1·40 (0·44–4·40)	6 (0·2%)	6 (0·2%)	0·99 (0·32–3·08)	3 (0·2%)	3 (0·2%)	1·00 (0·20–4·96)
Uncertain origin	1 (<0·1%)	0 (0·0%)	3·01 (0·12–73·9)	1 (<0·1%)	0 (0·0%)	2·99 (0·12–73·4)	0 (0·0%)	1 (<0·1%)	0·34 (0·01–8·34)
Transient ischaemic attack	10 (0·2%)	17 (0·4%)	0·59 (0·27–1·28)	9 (0·3%)	13 (0·4%)	0·69 (0·29–1·61)	6 (0·3%)	3 (0·2%)	2·01 (0·50–8·03)
Urgent target vessel revascularisation	112 (2·7%)	99 (2·4%)	1·13 (0·86–1·48)	111 (3·1%)	91 (2·6%)	1·22 (0·92–1·60)	67 (3·8%)	44 (2·5%)	1·53 (1·05–2·25)
Definite stent thrombosis	32 (0·8%)	28 (0·7%)	1·14 (0·69–1·90)	38 (1·1%)	22 (0·6%)	1·72 (1·02–2·91)	24 (1·3%)	14 (0·8%)	1·73 (0·89–3·34)
Definite or probable stent thrombosis	52 (1·3%)	43 (1·0%)	1·21 (0·81–1·81)	51 (1·4%)	44 (1·2%)	1·16 (0·77–1·73)	30 (1·7%)	20 (1·1%)	1·51 (0·86–2·66)
Bleeding	438 (10·5%)	705 (17·0%)	0·59 (0·53–0·67)	484 (13·6%)	565 (15·9%)	0·84 (0·74–0·95)	250 (14·0%)	234 (13·1%)	1·08 (0·90–1·30)
BARC type 3 or 5	87 (2·1%)	122 (2·9%)	0·71 (0·54–0·93)	80 (2·2%)	116 (3·3%)	0·68 (0·51–0·91)	32 (1·8%)	48 (2·7%)	0·67 (0·43–1·04)
Related to access site	18 (0·4%)	47 (1·1%)	0·38 (0·22–0·66)	24 (0·7%)	38 (1·1%)	0·63 (0·38–1·05)	14 (0·8%)	10 (0·6%)	1·41 (0·62–3·17)
Not related to access site	69 (1·7%)	76 (1·8%)	0·91 (0·65–1·25)	57 (1·6%)	78 (2·2%)	0·72 (0·51–1·02)	19 (1·1%)	38 (2·1%)	0·50 (0·29–0·87)
BARC type 3	70 (1·7%)	105 (2·5%)	0·66 (0·49–0·90)	71 (2·0%)	93 (2·6%)	0·76 (0·55–1·03)	30 (1·7%)	41 (2·3%)	0·73 (0·46–1·17)
BARC type 5	20 (0·5%)	17 (0·4%)	1·17 (0·61–2·24)	10 (0·3%)	25 (0·7%)	0·40 (0·19–0·83)	2 (0·1%)	8 (0·4%)	0·25 (0·05–1·18)
BARC type 2, 3, or 5	261 (6·3%)	384 (9·3%)	0·67 (0·57–0·78)	282 (7·9%)	310 (8·7%)	0·90 (0·76–1·06)	149 (8·4%)	133 (7·5%)	1·14 (0·90–1·44)
Related to access site	80 (1·9%)	212 (5·1%)	0·37 (0·29–0·48)	119 (3·3%)	148 (4·1%)	0·79 (0·62–1·01)	66 (3·7%)	53 (3·0%)	1·26 (0·87–1·81)
Not related to access site	186 (4·5%)	180 (4·4%)	1·03 (0·84–1·27)	168 (4·8%)	170 (4·8%)	0·98 (0·79–1·22)	86 (4·8%)	82 (4·7%)	1·06 (0·78–1·43)
Surgical access site repair or blood transfusion	56 (1·4%)	88 (2·1%)	0·63 (0·45–0·88)	50 (1·4%)	80 (2·3%)	0·62 (0·43–0·88)	28 (1·6%)	22 (1·2%)	1·28 (0·73–2·23)
Blood transfusion	51 (1·2%)	78 (1·9%)	0·65 (0·46–0·93)	44 (1·2%)	74 (2·1%)	0·59 (0·40–0·85)	26 (1·5%)	18 (1·0%)	1·45 (0·80–2·65)

Data are n (%) unless otherwise indicated. Percentages are cumulative incidence estimates. RR=rate ratio. BARC=Bleeding Academic Research Consortium. *This co-primary endpoint was designated as major adverse cardiovascular events. †This co-primary endpoint was designated as net adverse clinical events.

Table 3: **Clinical outcomes at 1 year**

occurred in 639 (15·2%) of 4197 patients with radial access and 724 (17·2%) of 4207 patients with femoral access, with an RR of 0·87 (0·78–0·97; p=0·0128; table 3, figure 2). All-cause mortality was 3·7% in the radial access group versus 4·4% in the femoral access group (RR 0·84, 0·68–1·04) and cardiovascular mortality was 2·1% in the radial access group versus 3·0% in the femoral access group (RR 0·71, 0·54–0·93; p=0·0131) at 1 year (table 3). Myocardial infarction, stent thrombosis, and stroke did not differ significantly between patients in the radial access group and patients in the femoral access group. Major BARC type 3 or 5 bleeding was reduced in the radial group (2·1% *vs* 2·9%; RR 0·71, 0·54–0·93, p=0·0137) owing to a reduction of access-site bleeding (table 3).

Major adverse cardiac events occurred in 570 (15·8%) of 3610 patients assigned to bivalirudin and 604 (16·8%) of 3603 patients assigned to heparin (RR 0·94, 95% CI 0·83–1·05; p=0·28; table 3, figure 3). 612 (17·0%) patients assigned to bivalirudin had a net adverse clinical event

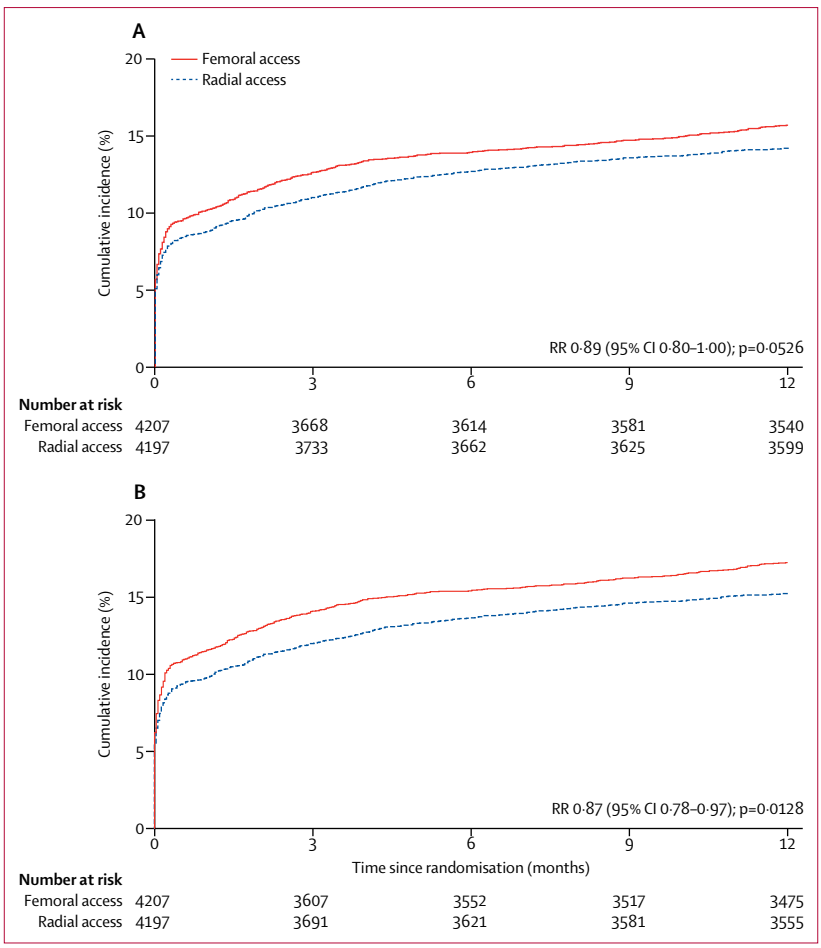


Figure 2: **Co-primary composite outcomes at 1 year in patients randomised to radial versus femoral access**
(A) All-cause mortality, myocardial infarction, or stroke. (B) All-cause mortality, myocardial infarction, stroke, or Bleeding Academic Research Consortium type 3 or 5 bleeding. RR=rate ratio.

compared with 664 (18·4%) patients assigned to heparin (RR 0·91, 0·81–1·02; p=0·10; table 3, figure 3). Bivalirudin was associated with lower risk of all-cause (3·6% *vs* 4·6%; RR 0·79, 0·63–0·99; p=0·0416) and cardiovascular mortality (2·3% *vs* 3·0%; RR 0·74, 0·55–0·99; p=0·0428; table 3). The rates of myocardial infarction or stroke were similar between those assigned to bivalirudin and heparin. The rate of definite stent thrombosis (1·1% *vs* 0·6%; RR 1·72, 1·02–2·91; p=0·0401) was slightly increased with bivalirudin, whereas the rate of major bleeding (BARC 3 or 5) was reduced in the bivalirudin group (2·2% *vs* 3·3%; RR 0·68, 0·51–0·91; p=0·0083; table 3), owing to a lower risk of access site and non-access site bleeding events.

A total of 312 (17·4%) of 1799 patients assigned to post-procedure bivalirudin had a primary composite outcome versus 315 (17·4%) of 1811 patients assigned to no post-procedure bivalirudin (RR 0·99, 95% CI 0·84–1·16; p=0·90; table 3, figure 3). None of the individual components of the primary composite endpoint differed significantly between patients with post-procedure bivalirudin and patients with no post-procedure bivalirudin (table 3).

Analyses by periods up to 30 days and thereafter up to 1 year for all primary outcomes are shown in table 4 and the appendix. Per-protocol analyses are shown in the appendix and provided consistent results. The effect of radial versus femoral access appeared consistent across major patient subgroups, including randomly allocated antithrombin type, with the exception of a positive test for trend across tertiles of the centres' proportion of radial intervention for both co-primary outcomes (appendix). The effect of bivalirudin versus heparin or bivalirudin treatment duration on the primary outcomes was consistent across subgroups, including in subgroup analyses defined by access site (appendix). Stratified analysis based on the implemented post-percutaneous coronary intervention bivalirudin regimen is shown in the appendix.

Discussion

Among patients with acute coronary syndrome undergoing invasive management, with or without ST-segment elevation, we found that use of radial access for coronary angiography, followed by percutaneous coronary intervention if indicated, was associated with reduced net adverse clinical events at 1 year. Major adverse cardiovascular events were not significantly reduced with radial access compared with femoral access. Differences between groups were driven by reductions in non-coronary artery bypass graft BARC major bleeding and cardiovascular, but not all-cause mortality with radial access.

Major adverse cardiovascular and net adverse clinical events at 1 year were not lower with bivalirudin compared with unfractionated heparin with optional glycoprotein IIb/IIIa inhibitors. At secondary endpoints analysis, bleeding risk was markedly reduced and stent thrombosis rate was increased with bivalirudin compared with heparin. Post-percutaneous coronary intervention bivalirudin infusion after intervention was not associated with lower combined 1-year ischaemic risk and bleeding risk.

Radial access has been shown, although inconsistently across studies, to be associated with improved short-term outcomes within 30 days compared with femoral access.[4] It was unclear if the benefits of radial compared with femoral access site would persist after 30 days as no large randomised study had reported the outcomes of radial versus femoral access at mid-term or long-term follow-up.

We observed a persistently lower risk of net adverse clinical events with radial access at 1 year. Period analyses did not suggest further benefits of radial access beyond 30 days, nor a loss of the treatment effect observed shortly after intervention. This latter observation has notable implications, as radial access did not expose patients to a rebound of ischaemic or bleeding events after the periprocedural phase, which might have occurred had the

revascularisation procedure undertaken via the radial approach been less effective than femoral access.

The clinical equipoise, or lack thereof, between radial and femoral access sites in patients undergoing coronary angiography or percutaneous intervention remains a subject of debate. Substantial evidence shows advantages with radial access in terms of access site-related bleeding, overall mortality, and major adverse cardiovascular events.[4] However, the absence of standardised use of antithrombotics, restricted study power, and the paucity of medium-term and long-term data for studies assessing radial versus femoral access has generated uncertainties regarding the advantages of radial access. The use of antithrombin drugs during intervention was standardised by study design and other antithrombotics, including type of oral P2Y12 inhibitor and glycoprotein IIb/IIIa inhibitor, were well matched between radial and femoral access. Therefore, our study offers novel long-term data in the largest population investigated so far, suggesting that the benefits of radial access are not affected by parenteral or oral antithrombotic medications used during or after coronary intervention.

Our 1-year analysis confirms previous findings at 30 days[9] indicating the existence of a gradient of benefits with radial access according to the operator's experience, with the greatest reduction of events observed in centres with the greatest proportion of radial procedures and no sign of harm in those at low or intermediate proportion of radial procedures. In our trial, in contrast to a previous study,[12] operators qualified for participation on the basis of the number of transradial interventions done, not just the number of catheterisations done, with a cutoff of 75 or more transradial interventions required in the year preceding study initiation. Moreover, all operators participating in the programme had performed transfemoral intervention as a senior cardiologist for at least 2 years.[8,9] Number of events in both radial and femoral access groups tended to be higher in centres with higher proportions of radial procedures. Therefore, despite consistency with previous observations[13], our results might indicate a selection bias with centres with a low or intermediate proportion of radial procedures recruiting patients at somewhat lower risk, in whom the benefits of radial access might be lower.

Extended follow-up up to 1 year confirmed the findings observed at 30 days and showed that bivalirudin was not superior to unfractionated heparin with or without glycoprotein IIb/IIIa inhibitors for purely ischaemic or ischaemic and safety combined endpoints.[10] However, bivalirudin was associated with a robust decrease in bleeding events at 1 year, due to a consistent reduction in both access site and non-access site related events. Therefore, bivalirudin had a complementary role in reducing bleeding risk with respect to access site selection. Bivalirudin was also associated with lower mortality rates. These findings, which are consistent with a previous study,[7] should be interpreted with caution considering that

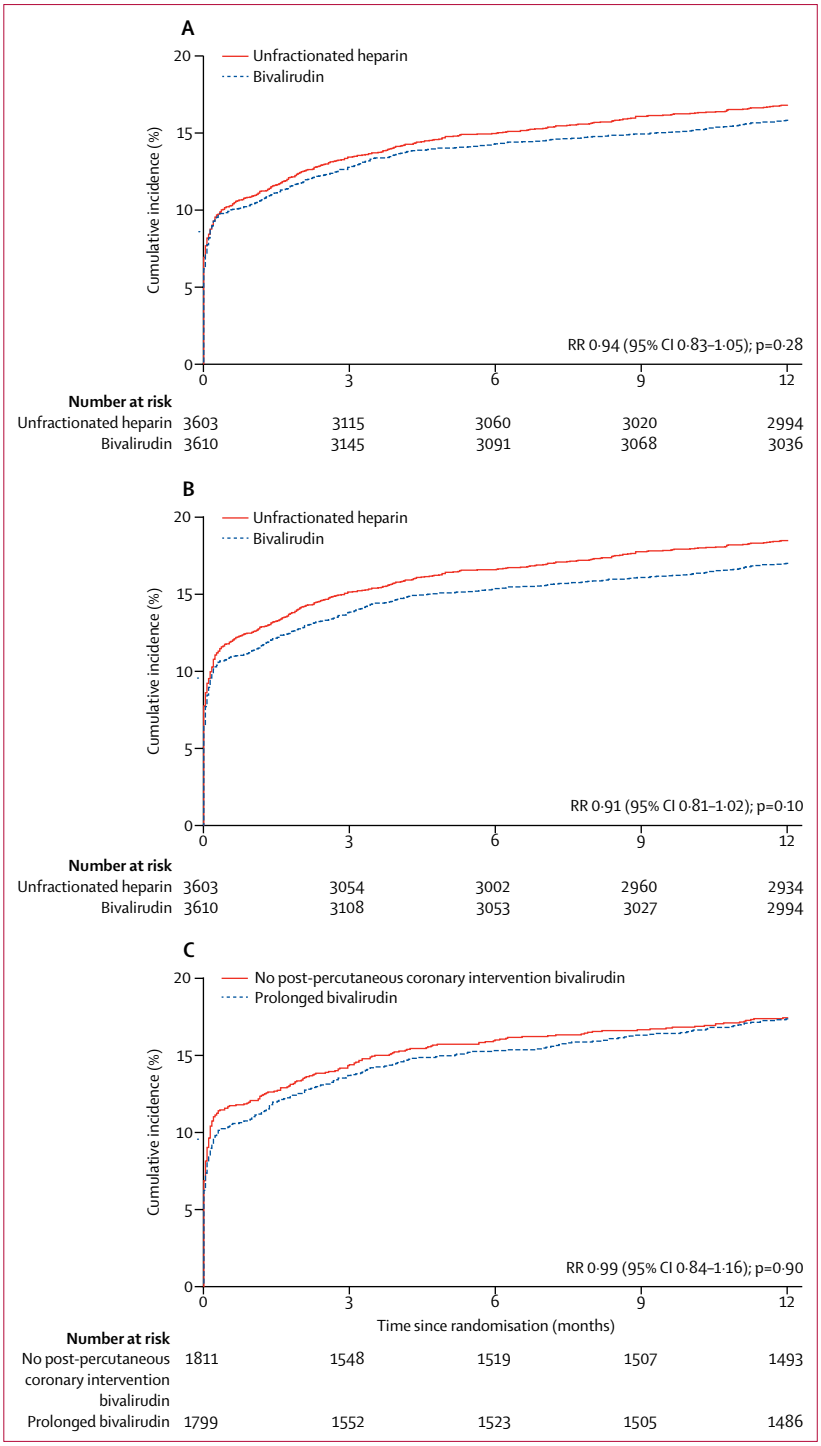


Figure 3: **Co-primary composite outcomes at 1 year in patients randomised to bivalirudin, with or without post-percutaneous coronary intervention and in patients randomised to unfractionated heparin**
(A) All-cause mortality, myocardial infarction, or stroke. (B) All-cause mortality, myocardial infarction, stroke, or BARC type 3 or 5 bleeding. (C) All-cause mortality, myocardial infarction, stroke, definite stent thrombosis, urgent target vessel revascularisation or BARC type 2, 3, or 5 bleeding. BARC=Bleeding Academic Research Consortium. RR=rate ratio.

	Access programme				Antithrombin type programme				Treatment duration programme			
	Radial (n=4197)	Femoral (n=4207)	RR (95% CI)	p value*	Bivalirudin (n=3610)	Unfractionated heparin (n=3603)	RR (95% CI)	p value*	Prolonged bivalirudin infusion (n=1799)	No post-percutaneous coronary intervention bivalirudin infusion (n=1811)	RR (95% CI)	p value*
Co-primary composite endpoint of all-cause mortality, myocardial infarction, or stroke within 30 days†	369 (8·8%)	429 (10·2%)	0·85 (0·74–0·99)	0·21	374 (10·4%)	392 (10·9%)	0·95 (0·82–1·10)	0·73	183 (10·2%)	191 (10·5%)	0·96 (0·78–1·18)	0·39
Co-primary composite endpoint of all-cause mortality, myocardial infarction, or stroke after 30 days†	200 (4·8%)	199 (4·8%)	1·00 (0·82–1·22)	..	170 (4·8%)	185 (5·3%)	0·91 (0·74–1·12)	..	90 (5·1%)	80 (4·5%)	1·13 (0·84–1·53)	..
Co-primary composite endpoint of all-cause mortality, myocardial infarction, stroke, or BARC 3 or 5 within 30 days‡	410 (9·8%)	486 (11·6%)	0·83 (0·73–0·96)	0·21	408 (11·3%)	450 (12·5%)	0·90 (0·78–1·03)	0·81	194 (10·8%)	214 (11·8%)	0·90 (0·74–1·11)	0·21
Co-primary composite endpoint of all-cause mortality, myocardial infarction, stroke, or BARC 3 or 5 after 30 days‡	209 (5·1%)	214 (5·2%)	0·97 (0·80–1·18)	..	183 (5·2%)	195 (5·5%)	0·93 (0·76–1·14)	..	97 (5·5%)	86 (4·8%)	1·14 (0·85–1·52)	..
Primary composite of all-cause mortality, myocardial infarction, stroke, urgent target vessel revascularisation, definite stent thrombosis, or BARC 3 or 5 within 30 days	419 (10·0%)	491 (11·7%)	0·84 (0·74–0·97)	0·23	415 (11·5%)	456 (12·7%)	0·90 (0·78–1·04)	0·77	197 (11·0%)	218 (12·0%)	0·90 (0·74–1·10)	0·098
Primary composite of all-cause mortality, myocardial infarction, stroke, urgent target vessel revascularisation, definite stent thrombosis, or BARC 3 or 5 after 30 days	234 (5·7%)	240 (5·8%)	0·97 (0·81–1·16)	..	208 (5·9%)	220 (6·3%)	0·94 (0·77–1·13)	..	113 (6·4%)	95 (5·3%)	1·20 (0·91–1·58)	..
All-cause mortality within 30 days	66 (1·6%)	91 (2·2%)	0·72 (0·53–0·99)	0·21	59 (1·6%)	83 (2·3%)	0·71 (0·51–0·99)	0·38	27 (1·5%)	32 (1·8%)	0·85 (0·51–1·41)	0·74
All-cause mortality after 30 days	90 (2·2%)	94 (2·3%)	0·95 (0·71–1·27)	..	72 (2·0%)	82 (2·3%)	0·87 (0·63–1·19)	..	35 (2·0%)	37 (2·1%)	0·95 (0·60–1·51)	..
Cardiovascular death within 30 days	60 (1·4%)	83 (2·0%)	0·72 (0·52–1·01)	0·87	53 (1·5%)	77 (2·1%)	0·68 (0·48–0·97)	0·42	25 (1·4%)	28 (1·5%)	0·90 (0·52–1·54)	0·58
Cardiovascular death after 30 days	29 (0·7%)	42 (1·0%)	0·69 (0·43–1·10)	..	26 (0·7%)	29 (0·8%)	0·89 (0·52–1·51)	..	14 (0·8%)	12 (0·7%)	1·17 (0·54–2·53)	..
Myocardial infarction within 30 days	299 (7·1%)	330 (7·8%)	0·90 (0·77–1·06)	0·40	310 (8·6%)	305 (8·5%)	1·01 (0·86–1·19)	0·71	155 (8·6%)	155 (8·6%)	1·00 (0·79–1·26)	0·29
Myocardial infarction after 30 days	107 (2·6%)	103 (2·5%)	1·03 (0·79–1·36)	..	96 (2·7%)	100 (2·8%)	0·95 (0·72–1·26)	..	54 (3·0%)	42 (2·4%)	1·29 (0·86–1·93)	..
Stroke within 30 days	16 (0·4%)	16 (0·4%)	1·00 (0·50–2·00)	1·00	13 (0·4%)	16 (0·4%)	0·81 (0·39–1·68)	0·94	6 (0·3%)	7 (0·4%)	0·86 (0·29–2·56)	0·89
Stroke after 30 days	9 (0·2%)	9 (0·2%)	0·99 (0·39–2·50)	..	7 (0·2%)	9 (0·3%)	0·77 (0·29–2·07)	..	3 (0·2%)	4 (0·2%)	0·75 (0·17–3·36)	..
Urgent target vessel revascularisation within 30 days	49 (1·2%)	40 (1·0%)	1·23 (0·81–1·86)	0·78	52 (1·4%)	35 (1·0%)	1·48 (0·97–2·28)	0·15	31 (1·7%)	21 (1·2%)	1·49 (0·85–2·59)	0·99
Urgent target vessel revascularisation after 30 days	59 (1·4%)	52 (1·3%)	1·13 (0·78–1·64)	..	52 (1·5%)	53 (1·5%)	0·97 (0·66–1·42)	..	31 (1·7%)	21 (1·2%)	1·48 (0·85–2·58)	..
Definite stent thrombosis within 30 days	30 (0·7%)	27 (0·6%)	1·11 (0·66–1·87)	0·64	36 (1·0%)	21 (0·6%)	1·71 (1·00–2·93)	0·91	23 (1·3%)	13 (0·7%)	1·78 (0·90–3·52)	0·70
Definite stent thrombosis after 30 days	2 (0·0%)	1 (0·0%)	1·99 (0·18–21·92)	..	2 (0·1%)	1 (0·0%)	1·98 (0·18–21·89)	..	1 (0·1%)	1 (0·1%)	1·01 (0·06–16·06)	..

(Table 4 continues on next page)

	Access programme				Antithrombin type programme				Treatment duration programme			
	Radial (n=4197)	Femoral (n=4207)	RR (95% CI)	p value*	Bivalirudin (n=3610)	Unfractionated heparin (n=3603)	RR (95% CI)	p value*	Prolonged bivalirudin infusion (n=1799)	No post-percutaneous coronary intervention bivalirudin infusion (n=1811)	RR (95%CI)	p value*
(Continued from previous page)												
BARC type 3 or 5 within 30 days	65 (1·5%)	99 (2·4%)	0·65 (0·48–0·89)	0·20	55 (1·5%)	98 (2·7%)	0·56 (0·40–0·77)	0·0331	19 (1·1%)	36 (2·0%)	0·53 (0·30–0·92)	0·41
BARC type 3 or 5 after 30 days	19 (0·5%)	18 (0·4%)	1·05 (0·55–2·00)	..	20 (0·6%)	16 (0·5%)	1·24 (0·64–2·39)	..	9 (0·5%)	11 (0·6%)	0·82 (0·34–1·98)	..

RR=rate ratio. BARC=Bleeding Academic Research Consortium. *Interaction p value between the within 30 days result and after 30 days result. †This co-primary endpoint was designated as major adverse cardiovascular events. ‡This co-primary endpoint was designated as net adverse clinical events.

Table 4: **Analyses by period up to 30 days and from 31 days to 1 year for ischaemic and bleeding endpoints**

our study was not powered for mortality and that statistical significance was borderline at the conventional 5% for both all-cause and cardiovascular fatalities. Myocardial infarction rates did not differ between groups; however, stent thrombosis continued to be higher with bivalirudin, which has been previously observed.[7,14,15] Our findings for the co-primary endpoints were consistent with a recent trial,[16] which observed no difference in terms of a composite of ischaemic and bleeding endpoints at 180 days. We found no evidence of a better effect of bivalirudin compared with heparin in women, observed previously.[16] However, there were trends for both co-primary endpoints favouring the use of bivalirudin instead of unfractionated heparin in patients with impaired renal function, which warrants further investigation.

Post-percutaneous coronary intervention bivalirudin infusion was not associated with a decrease in the composite ischaemic and bleeding endpoint. Stent thrombosis rates were higher with post-percutaneous coronary intervention bivalirudin infusion as compared with no post-percutaneous coronary intervention bivalirudin administration. However, in the small number of patients who received the full 1·75 mg/kg per h dose of bivalirudin, as suggested in the updated product label for continued use after percutaneous coronary intervention, the risk of ischaemic events including stent thrombosis and bleeding was lower compared with no post-percutaneous coronary intervention infusion. This observation, which should be interpreted with caution because of the non-randomised nature of our analysis, might help to reconcile previous findings on stent thrombosis when bivalirudin was used with or without full regimen post-percutaneous coronary intervention infusion.[6,7,14–16] Given these findings and in keeping with the European Society of Cardiology guidelines,[1] bivalirudin—administered with a full post-percutaneous coronary intervention regimen—appears to be an appealing treatment, especially in patients with high bleeding risk.[17]

In conclusion, in patients with acute coronary syndrome, radial access was associated with lower rates of net adverse clinical events, but not major adverse cardiovascular events, compared with femoral access at 1 year. The composites of major adverse cardiovascular or net adverse clinical events at 1 year were not lower with bivalirudin compared with unfractionated heparin. Post-procedure bivalirudin, when administered at low or full regimen, was not associated with a lower composite of urgent target vessel revascularisation, definite stent thrombosis, or net adverse clinical events at 1 year compared with no post-percutaneous coronary intervention infusion.

Contributors

MV was responsible for study conception and design and obtained study funding. MV, MR, DH, and PJ did the analysis and interpreted the results in collaboration with all remaining authors. MV, EF, SL, PV, MT, FV, PC, SG, PR, CB, GA, MF, UL, RG, PS, FR, MN, AL, BC, AA, SI, GE, GF, AS, GS, NdC, PT, AvH, EO, and SB were responsible for data acquisition. MV wrote the manuscript and together with PJ had full access to the final data. All authors critically revised the paper for important intellectual content and approved the final version.

Declaration of interests

MV reports grants from The Medicines Company and Terumo during the conduct of the study; and grants and personal fees from AstraZeneca, personal fees and non-financial support from The Medicines Company, and personal fees from Terumo, St Jude Vascular, Alvimedica, Abbott Vascular, and Correvio outside the submitted work. SL reports grants and personal fees from AstraZeneca and personal fees from Chiesi, outside the submitted work. PV reports personal fees from Bayer Health Care, Daiichi Sankyo, AstraZeneca, and Terumo, outside the submitted work. FV reports grants, personal fees and other fees from AstraZeneca, Daiichi Sankyo, Bayer, Pfizer BMS, Boehringer, Servier, CID Alvimedica, Teleflex, Stentys, and Chiesi, and other fees from Sanitex, Abbott St Jude, and Boston SC, outside the submitted work. GA reports non-financial support from Terumo, during the conduct of the study; personal fees and non-financial support from Bayer, non-financial support from Boehringer Ingelheim and Philips, and personal fees from Daiichi Sankyo, AstraZeneca, Menarini, and Pfizer, outside the submitted work. UL reports grants from GISE during the conduct of the study; personal fees from Bayer, Boehringer, MSD, and Servier, outside the submitted work. BC reports grants, personal fees and non-financial support from Abbott Vascular St Jude, personal fees from AB Medica, Daiichi-Sankyo, and Amgen, grants from AstraZeneca, and grants and personal fees from Sanofi and Stentys, outside the submitted work. SW reports grants from Abbott, Bayer, Amgen, Biotronik, Boston Scientific, Edwards Lifescience, Medtronic, St Jude, and Terumo, outside the submitted work. PJ serves as an

unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company. All other authors declare no competing interests.

Data sharing

The study protocol and statistical analysis plan underlying this manuscript are available upon request. MATRIX is an investigator-initiated programme. Multiple substudies are predefined and have been already assigned to investigators as compensation for their unpaid participation. MATRIX investigators who provide a methodologically sound study proposal will be granted priority access to the study data for a period of 48 months. Beginning 48 months and ending 120 months after publication of this study, individual patient data underlying the results of this Article, after deidentification and including data dictionary and analytic code, will be made available for subanalyses after approval of the submitted protocol by the executive committee. After 48 months, the data will be available at the data warehouse based in the Clinical Trials Unit, University of Bern (Bern, Switzerland), but without investigator support other than deposited metadata.

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