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Radial versus femoral access in patients with acute coronary syndromes with or without ST-segment elevation

A pre-specified analysis from the randomized minimizing adverse haemorrhagic events by transradial access site and systemic implementation of angioX (MATRIX access)

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Aims To assess whether radial compared with femoral access is associated with consistent outcomes in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Methods and results In the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) programme patients were randomized to radial or femoral access, stratified by STEMI (2001 radial, 2009 femoral) and NSTE-ACS (2196 radial, 2198 femoral). 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 In the overall study population, radial access reduced the NACE but not MACE endpoint at the prespecified 0.025 alpha. MACE occurred in 121 (6.1%) STEMI patients with

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radial access vs. 126 (6.3%) patients with femoral access [rate ratio (RR) = 0.96, 95% CI = 0.75–1.24; P = 0.76] and in 248 (11.3%) NSTE-ACS patients with radial access vs. 303 (13.9%) with femoral access (RR = 0.80, 95% CI = 0.67–0.96; P = 0.016) (Pint = 0.25). NACE occurred in 142 (7.2%) STEMI patients with radial access and in 165 (8.3%) patients with femoral access (RR = 0.86, 95% CI = 0.68–1.08; P = 0.18) and in 268 (12.2%) NSTE-ACS patients with radial access compared with 321 (14.7%) with femoral access (RR = 0.82, 95% CI = 0.69–0.97; P = 0.023) (Pint = 0.76). All-cause mortality and access site-actionable bleeding favoured radial access irrespective of ACS type (Pint = 0.11 and Pint = 0.36, respectively).

Conclusion Radial as compared with femoral access provided consistent benefit across the whole spectrum of patients with ACS, without evidence that type of presenting syndrome affected the results of the random access allocation.

Keywords MATRIX • Radial • Femoral • STEMI • NSTE-ACS

Introduction

Advances in antithrombotic therapy in patients with acute coronary syndrome (ACS), along with an early invasive strategy in high-risk patients, have reduced the incidence of recurrent ischaemic events but also increased bleeding complications.[1] Bleeding is associated with short-term and long-term hazards for mortality, albeit the exact nature of this relationship remains speculative.[1–3]

The Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial is the largest randomized trial to compare radial and femoral access in largely unselected patients with ACS with or without ST-segment elevation myocardial infarction (STEMI) undergoing coronary angiography and percutaneous coronary intervention (PCI). MATRIX-Access observed a numerical reduction of major adverse cardiovascular events (MACE) in favour of radial access, which did not reach the prespecified 0.025 alpha thresholds for statistical significance. However, the use of radial access significantly reduced the rate of net adverse clinical events (NACE), defined as the composite of MACE or major bleeding.

The RIVAL (A Trial of Trans-radial Versus Trans-femoral PCI Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy) study reported inconsistent results in terms of the primary endpoint as well for mortality depending on presentation syndrome, namely non-ST-segment elevation ACS (NSTE-ACS) or STEMI.[4] Therefore, it remains unclear whether radial access should be preferred over femoral access across the entire spectrum of ACS patients.

We had prespecified to analyse the consistency of risks and benefits of each access site in patients with NSTE-ACS and STEMI undergoing invasive management.

Methods

Study design

The MATRIX-Access was conceived as a randomized, multicentre, superiority trial-comparing radial with femoral access in patients with ACS with or without STE who were about to undergo coronary angiography and PCI, if indicated.[5,6] This was the first of three trials of the MATRIX programme (registered with clinicaltrials.gov; Unique identifier: NCT01433627) and was performed in all patients with an ACS consenting to participate in the programme. The trial was approved by the institutional review board at each participating centre, and all patients gave written informed consent to participate.

Study patients

Patients were eligible if they had an ACS with or without ST-segment elevation (STE), were scheduled to undergo an invasive approach, and the interventional cardiologist was willing to proceed with either radial or femoral access with expertise for both, including at least 75 coronary interventions performed and at least 50% of interventions in ACS via the radial route during the previous year. Patients presenting with NSTE-ACS were eligible if they had a history consistent with new or worsening ischaemia, occurring at rest or with minimal activity within 7 days before randomization, and fulfilled at least two high-risk criteria (detailed in the web extra material). Patients with STEMI were eligible if they presented within 12 h of the onset of symptoms or between 12 and 24 h after symptom onset if there was evidence of continued ischaemia or previous fibrinolytic treatment and if they had STE of at least 1 mm in two or more contiguous leads, new left bundle-branch block, or true posterior MI. The main inclusion and exclusion criteria were previously reported.[5,6]

Study protocol and randomization

Before the start of angiography, patients were randomly assigned 1:1 to radial or femoral access for diagnostic angiography and PCI, if indicated, using a web-based system to ensure adequate concealment of allocation. The randomization sequence was computer generated, blocked, and stratified by site, intended new or ongoing use of ticagrelor or prasugrel, type of ACS (STEMI or troponin-positive or -negative NSTE-ACS), and anticipated use of immediate PCI. 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. The use of anticoagulants outside the protocol of the MATRIX programme was not allowed. Bivalirudin administration was consistent with the approved product labeling, whereas unfractionated heparin was dosed at 70–100 U/kg in patients not receiving glycoprotein IIb/IIIa inhibitors and at 50–70 U/kg in patients receiving glycoprotein IIb/IIIa inhibitors. Use of all other antithrombotic medications, including oral antiplatelet agents and non-antithrombotic medications, such as beta-blockers, angiotensin-converting enzyme inhibitors, and other antihypertensive agents, were allowed as per guidelines.[7]

Study outcomes

Two co-primary 30-day composite outcomes were pre-specified: MACE, defined as the composite of all-cause mortality, MI, or stroke; and NACE, defined as the composite of non-coronary artery bypass grafting (CABG)-related major bleeding (Bleeding Academic Research Consortium, BARC type 3 or 5) or MACE.[8] Secondary outcomes included each component of the composite outcomes, cardiovascular mortality, and stent thrombosis. Bleeding was also assessed and adjudicated on the basis of the TIMI and GUSTO scales.[9,10] Stent thrombosis

Table 1 Baseline characteristics of the intention-to-treat population according to initial clinical presentation (STEMI, NSTE-ACS) and access site

Baseline characteristics	STEMI			NSTE-ACS		
	Radial access (*n* = 2001)	Femoral access (*n* = 2009)	*P*-value	Radial access (*n* = 2196)	Femoral access (*n* = 2198)	*P*-value
Age—years	63.7 ± 12.1	64.0 ± 12.1	0.43	67.2 ± 11.3	67.5 ± 11.3	0.33
≥75 years	424 (21.2)	444 (22.1)	0.48	644 (29.3)	658 (29.9)	0.66
Male sex	1552 (77.6)	1541 (76.7)	0.52	1574 (71.7)	1505 (68.5)	0.020
Weight (kg)	77.4 ± 13.9	77.7 ± 13.4	0.52	77.4 ± 14.4	76.4 ± 13.7	0.024
Body mass index (kg/m≤)	26.9 ± 4.0	27.1 ± 4.1	0.22	27.2 ± 4.3	27.1 ± 4.3	0.22
Diabetes mellitus	371 (18.5)	352 (17.5)	0.013	588 (26.8)	592 (26.9)	0.42
Insulin-dependent	64 (3.2)	91 (4.5)	0.42	145 (6.6)	166 (7.6)	0.42
Current smoker	821 (41.0)	814 (40.5)	0.90	638 (29.1)	614 (27.9)	0.64
Hypercholesterolemia	754 (37.7)	814 (40.5)	0.066	1045 (47.6)	1078 (49.0)	0.33
Hypertension	1093 (54.6)	1141 (56.8)	0.70	1532 (69.8)	1545 (70.3)	0.70
Family history of coronary artery disease	557 (27.8)	567 (28.2)	0.79	589 (26.8)	580 (26.4)	0.74
Previous myocardial infarction	198 (9.9)	186 (9.3)	0.49	387 (17.6)	432 (19.7)	0.084
Previous PCI	215 (10.7)	171 (8.5)	0.017	395 (18.0)	414 (18.8)	0.47
Radial access	38 (1.9)	18 (0.9)	0.0068	81 (3.7)	66 (3.0)	0.21
Femoral access	94 (4.7)	83 (4.1)	0.38	182 (8.3)	203 (9.2)	0.27
Both radial and femoral access	8 (0.4)	5 (0.2)	0.40	28 (1.3)	30 (1.4)	0.79
Access site unknown	75 (3.7)	65 (3.2)	0.38	104 (4.7)	115 (5.2)	0.45
Previous CABG	27 (1.3)	25 (1.2)	0.77	84 (3.8)	121 (5.5)	0.0083
Previous TIA or stroke	78 (3.9)	94 (4.7)	0.22	117 (5.3)	136 (6.2)	0.22
Peripheral Vascular Disease	106 (5.3)	123 (6.1)	0.26	235 (10.7)	249 (11.3)	0.51
Chronic Obstructive Pulmonary Disease	91 (4.5)	94 (4.7)	0.84	159 (7.2)	189 (8.6)	0.096
History of renal failure	14 (0.7)	31 (1.5)	0.011	32 (1.5)	28 (1.3)	0.60
Dialysis	1 (0.0)	2 (0.1)	1.00	3 (0.1)	2 (0.1)	0.69
Clinical presentation						
Cardiac arrest	71 (3.5)	68 (3.4)	0.78	14 (0.6)	15 (0.7)	0.85
Killip class						
I	1775 (88.7)	1817 (90.4)	0.072	2021 (92.0)	1983 (90.2)	0.035
II	142 (7.1)	144 (7.2)	0.93	126 (5.7)	157 (7.1)	0.058
III	45 (2.2)	22 (1.1)	0.0044	43 (2.0)	57 (2.6)	0.16
IV	39 (1.9)	26 (1.3)	0.10	6 (0.3)	1 (0.0)	0.070
Previous lyctic therapy	94 (4.7)	103 (5.1)	0.53	0 (0.0)	1 (0.0)	1.00
Systolic arterial pressure (mmHg)	136.0 ± 27.0	136.2 ± 26.9	0.76	140.8 ± 23.9	141.2 ± 24.2	0.58
Heart rate (min^{-1})	77.2 ± 17.3	77.0 ± 17.1	0.78	75.6 ± 15.8	75.1 ± 16.5	0.38
Left ventricular ejection fraction (%)	49.2 ± 9.5	48.6 ± 9.5	0.030	53.2 ± 9.2	52.9 ± 9.6	0.44
eGFR	85.2 ± 25.7	84.5 ± 25.6	0.36	83.2 ± 25.2	82.3 ± 25.4	0.21
eGFR < 60	310 (15.7)	298 (15.0)	0.55	390 (17.8)	417 (19.1)	0.29
eGFR < 30	18 (0.9)	27 (1.4)	0.18	17 (0.8)	22 (1.0)	0.42
Medications administered before the cath-Lab						
Aspirin	1865 (93.2)	1881 (93.6)	0.59	2091 (95.2)	2073 (94.3)	0.18
Clopidogrel	734 (36.7)	738 (36.7)	0.97	1281 (58.3)	1259 (57.3)	0.48
Prasugrel	402 (20.1)	395 (19.7)	0.73	83 (3.8)	73 (3.3)	0.41
Ticagelor	378 (18.9)	394 (19.6)	0.56	600 (27.3)	635 (28.9)	0.25
Enoxaparin	57 (2.8)	91 (4.5)	0.0048	630 (28.7)	651 (29.6)	0.50
Fondaparinux	55 (2.7)	68 (3.4)	0.24	373 (17.0)	400 (18.2)	0.29
ACE inhibitors	273 (13.6)	278 (13.8)	0.86	980 (44.6)	1023 (46.5)	0.20
Angiotensin II receptor antagonist	135 (6.7)	141 (7.0)	0.73	315 (14.3)	321 (14.6)	0.81
Statins	403 (20.1)	410 (20.4)	0.83	1409 (64.2)	1453 (66.1)	0.18
Beta blockers	412 (20.6)	432 (21.5)	0.48	1282 (58.4)	1343 (61.1)	0.066
Warfarin	20 (1.0)	16 (0.8)	0.50	52 (2.4)	48 (2.2)	0.68

Continued

Table 1 *Continued*

Baseline characteristics	STEMI			NSTE-ACS		
	Radial access (*n* = 2001)	Femoral access (*n* = 2009)	*P*-value	Radial access (*n* = 2196)	Femoral access (*n* = 2198)	*P*-value
PPI	640 (32.0)	652 (32.5)	0.75	1518 (69.1)	1540 (70.1)	0.50
Previous unfractionated heparin	952 (47.6)	949 (47.2)	0.83	287 (13.1)	288 (13.1)	0.97
Bivalirudin	2 (0.1)	1 (0.0)	0.62	2 (0.1)	1 (0.0)	0.62
Glycoprotein IIb/IIIa inhibitors	2 (0.1)	1 (0.0)	0.62	6 (0.3)	5 (0.2)	0.77

Depicted are frequencies n (%) or means (SD), *P*-values come from *t*-test and χ^2 or Fisher's exact test.
STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation acute coronary syndrome; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor; TIA, transient ischaemic attack.

was defined as the definite or probable occurrence of a stent-related thrombotic event according to the Academic Research Consortium classification.[11] All outcomes were pre-specified.[5] An independent clinical events committee blinded to treatment allocation adjudicated all suspected outcome events by reviewing relevant medical records after site monitoring by Trial Form Support (Lund, Sweden) in Italy and the Netherlands, FLS-Research Support (Barcelona, Spain) in Spain, and Gothia Forum (Västra Götaland) in Sweden.

Statistical analysis

Statistical analyses were performed by an academic statistical group led by two of the authors, who had access to the full de-identified data set.

All analyses were performed according to the intention-to-treat principle, including all patients in the analysis according to the allocated access. Events up to 30 days post-randomization were considered. We analysed primary and secondary outcomes separately for STEMI and NSTE-ACS 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. Survival curves were constructed using Kaplan–Meier estimates. We performed stratified analyses according to pre-specified subgroups including age, sex, body mass index (BMI), type of P2Y12 inhibitor used, both overall and radial PCI volume by centre, renal function, diabetes, and peripheral vascular disease, and estimated possible interaction terms or trends across ordered groups separately for the STEMI and NSTE-ACS study populations. Although included in the statistical analysis plan, neither the STE-ACS analysis nor its subsets were separately powered to detect effects on clinical outcomes by the access strategy. All analyses were performed using the statistical package Stata 14.1 and R 3.3.0

Results

The MATRIX trial enrolled 8404 patients with ACS from 78 centres in Italy, the Netherlands, Spain, and Sweden between October 2011 and July 2014. Of these patients, 4010 (47.8%) fulfilled the definition for STEMI (radial: 2001, 23.8%; femoral: 2009, 23.9%) (see Supplementary material online, *eFigure S1 and S2*), and 4394 (52.2%) patients presented with NSTE-ACS (radial 2196, 26.1%; femoral 2198, 26.1%). Complete follow-up throughout 30 days was available in 4191 radial and 4196 femoral patients. Baseline characteristics were generally well balanced between randomization groups according to access site, considering the initial clinical presentation (STEMI and NSTE-ACS) (*Table 1*).

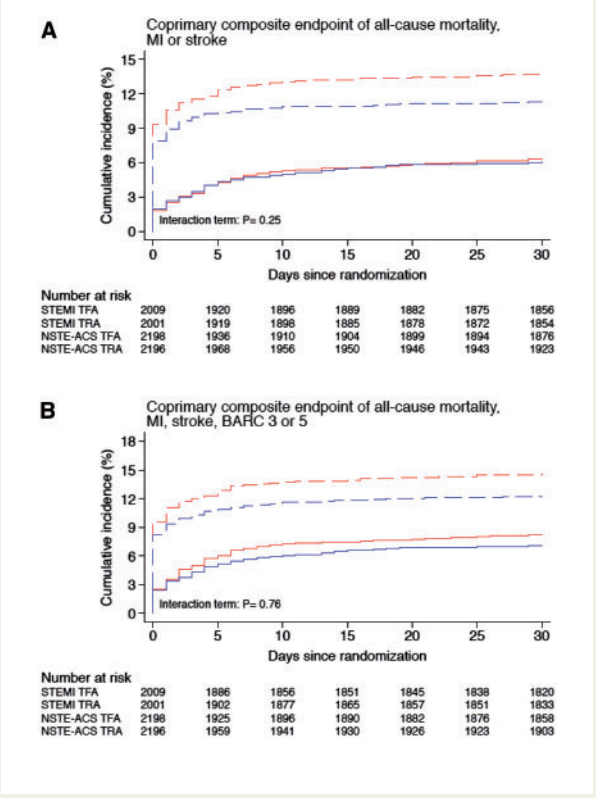

Figure 1 (*A*) All-cause mortality, myocardial infarction, or stroke, and (*B*) all-cause mortality, myocardial infarction, stroke, or Bleeding Academic Research Consortium 3 or 5 bleeding. Red lines illustrate patients randomized to femoral access and blue lines correspond to the patients randomized to radial access. Thick lines correspond to the NSTE-ACS patients and thin lines stand for the STEMI population. MI, myocardial infarction; TFA, trans femoral access; TRA, trans radial access; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

Procedural results according to clinical presentation and access site are presented in Supplementary material online, *eTable S1*. PCI

Table 2 Adjudicated and non-adjudicated clinical outcome at 30 days

Clinical outcomes	STEMI				NSTE-ACS				
	Radial access (n = 2001)	Femoral access (n = 009)	Risk ratio (95% CI)	P-value	Radial access (n = 2196)	Femoral access (n = 2198)	Risk ratio (95% CI)	P-value	P-value for interaction
Co-primary composite endpoint of all-cause mortality, MI, or stroke	121 (6.1)	126 (6.3)	0.96 (0.75–1.24)	0.76	248 (11.3)	303 (13.9)	0.80 (0.67–0.96)	0.016	0.25
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	142 (7.2)	165 (8.3)	0.86 (0.68–1.08)	0.18	268 (12.2)	321 (14.7)	0.82 (0.69–0.97)	0.023	0.76
Composite of all-cause mortality, MI, stroke, urgent TVR, definite stent thrombosis or BARC 3 or 5	148 (7.5)	170 (8.5)	0.87 (0.69–1.08)	0.21	271 (12.3)	321 (14.7)	0.83 (0.70–0.98)	0.033	0.75
All-cause mortality	48 (2.4)	55 (2.7)	0.87 (0.59–1.29)	0.49	18 (0.8)	36 (1.7)	0.50 (0.28–0.88)	0.014	0.11
Cardiovascular death	46 (2.3)	53 (2.6)	0.87 (0.58–1.29)	0.48	18 (0.8)	32 (1.5)	0.56 (0.31–1.00)	0.046	0.22
Myocardial infarction	66 (3.4)	65 (3.3)	1.02 (0.72–1.43)	0.92	233 (10.6)	265 (12.1)	0.87 (0.72–1.05)	0.13	0.42
Stroke	10 (0.5)	9 (0.5)	1.11 (0.45–2.73)	0.82	6 (0.3)	7 (0.3)	0.85 (0.29–2.54)	0.78	0.72
Transient ischaemic attack	3 (0.2)	6 (0.3)	0.50 (0.12–2.00)	0.32	2 (0.1)	7 (0.3)	0.28 (0.06–1.37)	0.095	0.60
Urgent target vessel revascularization	34 (1.7)	31 (1.6)	1.10 (0.67–1.79)	0.71	15 (0.7)	9 (0.4)	1.67 (0.73–3.81)	0.22	0.39
Definite stent thrombosis	22 (1.1)	18 (0.9)	1.22 (0.66–2.28)	0.53	8 (0.4)	9 (0.4)	0.89 (0.34–2.30)	0.80	0.58
Acute definite stent thrombosis	17 (0.9)	9 (0.5)	1.90 (0.84–4.27)	0.12	4 (0.2)	3 (0.1)	1.33 (0.30–5.96)	0.71	0.68
Subacute definite stent thrombosis	6 (0.3)	9 (0.5)	0.66 (0.24–1.87)	0.44	4 (0.2)	6 (0.3)	0.66 (0.19–2.36)	0.52	1.00
Definite or probable stent thrombosis	30 (1.5)	22 (1.1)	1.37 (0.79–2.37)	0.27	12 (0.5)	16 (0.8)	0.75 (0.35–1.58)	0.45	0.20
Acute definite or probable stent thrombosis	19 (1.0)	10 (0.5)	1.91 (0.88–4.11)	0.094	5 (0.2)	4 (0.2)	1.25 (0.33–4.66)	0.74	0.59
Subacute definite or probable stent thrombosis	12 (0.6)	12 (0.6)	1.00 (0.45–2.22)	0.99	8 (0.4)	12 (0.6)	0.66 (0.27–1.62)	0.37	0.51
Bleeding	186 (9.4)	321 (16.3)	0.56 (0.46–0.67)	<0.0001	164 (7.5)	285 (13.1)	0.55 (0.46–0.68)	<0.0001	1.00
BARC									
Type 1	90 (4.5)	159 (8.1)	0.55 (0.43–0.72)	<0.0001	78 (3.6)	147 (6.8)	0.52 (0.39–0.69)	<0.0001	0.75
Type 2	66 (3.3)	109 (5.5)	0.60 (0.44–0.81)	0.0009	61 (2.8)	106 (4.9)	0.57 (0.41–0.78)	0.0004	0.82
Type 3abc	28 (1.5)	50 (2.6)	0.56 (0.35–0.89)	0.012	26 (1.2)	34 (1.6)	0.76 (0.46–1.27)	0.29	0.38
Type 3a	13 (0.7)	26 (1.4)	0.50 (0.26–0.97)	0.036	16 (0.7)	18 (0.8)	0.89 (0.45–1.74)	0.72	0.23
Type 3b	13 (0.7)	22 (1.1)	0.59 (0.30–1.17)	0.13	10 (0.5)	15 (0.7)	0.66 (0.30–1.48)	0.31	0.83
Type 3c	2 (0.1)	3 (0.2)	0.67 (0.11–3.98)	0.65	0 (0.0)	1 (0.0)	0.33 (0.01–8.10)	1.00	0.44

Continued

Table 2 *Continued*

Clinical outcomes	STEMI				NSTE-ACS				
	Radial access (n = 2001)	Femoral access (n = 009)	Risk ratio (95% CI)	*P*-value	Radial access (n = 2196)	Femoral access (n = 2198)	Risk ratio (95% CI)	*P*-value	*P*-value for interaction
Type 4	2 (0.1)	3 (0.2)	0.67 (0.11–3.98)	0.65	4 (0.2)	3 (0.1)	1.33 (0.30–5.94)	0.71	0.56
Type 5ab	8 (0.4)	8 (0.4)	1.00 (0.37–2.66)	1.00	2 (0.1)	3 (0.1)	0.66 (0.11–3.98)	0.65	0.70
Type 5a	4 (0.2)	7 (0.4)	0.57 (0.17–1.95)	0.36	2 (0.1)	2 (0.1)	1.00 (0.14–7.08)	1.00	0.63
Type 5b	4 (0.2)	1 (0.1)	4.00 (0.45–35.85)	0.18	0 (0.0)	1 (0.0)	0.33 (0.01–8.10)	1.00	0.12
Type 3 or 5	36 (1.9)	58 (3.0)	0.62 (0.41–0.94)	0.022	28 (1.3)	37 (1.7)	0.75 (0.46–1.23)	0.26	0.54
Type 3 or 5 related to access site	8 (0.4)	29 (1.5)	0.27 (0.13–0.60)	0.0005	8 (0.4)	14 (0.6)	0.57 (0.24–1.36)	0.20	0.22
Type 3 or 5 not related to access site	28 (1.5)	29 (1.5)	0.96 (0.57–1.62)	0.89	20 (0.9)	23 (1.1)	0.87 (0.48–1.58)	0.64	0.79
Type 2, 3, or 5	100 (5.1)	166 (8.4)	0.59 (0.46–0.76)	<0.0001	89 (4.1)	141 (6.5)	0.62 (0.47–0.81)	0.0004	0.79
Type 2, 3, or 5 related to access site	32 (1.6)	104 (5.3)	0.30 (0.20–0.45)	<0.0001	37 (1.7)	93 (4.3)	0.39 (0.27–0.57)	<0.0001	0.36
Type 2, 3, or 5 not related to access site	69 (3.5)	66 (3.3)	1.05 (0.74–1.47)	0.80	52 (2.4)	49 (2.3)	1.06 (0.72–1.57)	0.77	0.96
TIMI									
Major bleeding	19 (1.0)	24 (1.2)	0.79 (0.43–1.44)	0.44	7 (0.3)	13 (0.6)	0.54 (0.21–1.34)	0.18	0.49
Minor bleeding	11 (0.6)	19 (1.0)	0.58 (0.27–1.21)	0.14	13 (0.6)	13 (0.6)	1.00 (0.46–2.15)	0.99	0.32
Major or minor bleeding	30 (1.6)	43 (2.2)	0.69 (0.44–1.11)	0.13	20 (0.9)	26 (1.2)	0.77 (0.43–1.37)	0.37	0.80
GUSTO									
Severe bleeding	16 (0.8)	17 (0.9)	0.94 (0.47–1.86)	0.86	7 (0.3)	10 (0.5)	0.70 (0.27–1.83)	0.46	0.62
Moderate bleeding	7 (0.4)	19 (1.0)	0.37 (0.15–0.87)	0.018	16 (0.7)	13 (0.6)	1.23 (0.59–2.55)	0.58	0.034
Mild bleeding	163 (8.2)	285 (14.5)	0.55 (0.45–0.67)	<0.0001	143 (6.5)	264 (12.2)	0.52 (0.42–0.64)	<0.0001	0.72
Severe or moderate bleeding	23 (1.2)	36 (1.8)	0.64 (0.38–1.07)	0.087	23 (1.1)	23 (1.1)	1.00 (0.56–1.78)	0.99	0.26
Composite of surgical access site repair or blood products transfusion	17 (0.9)	28 (1.4)	0.60 (0.33–1.10)	0.097	15 (0.7)	20 (0.9)	0.75 (0.38–1.46)	0.39	0.64
Surgical access site repair	4 (0.2)	11 (0.6)	0.36 (0.12–1.14)	0.070	7 (0.3)	5 (0.2)	1.40 (0.44–4.40)	0.57	0.096
Blood products transfusion	14 (0.7)	19 (1.0)	0.73 (0.37–1.46)	0.38	8 (0.4)	16 (0.7)	0.50 (0.21–1.16)	0.10	0.49

Percentages are cumulative incidence estimates. BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

Composite endpoint: death, MI or stroke	Radial access	Femoral access	Risk Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.82*
Low (247-544)	108/769	132/716	0.73 (0.55-0.97)	0.030	
Intermediate (548-991)	116/956	135/994	0.88 (0.68-1.15)	0.35	
High (1000-1950)	24/471	36/488	0.68 (0.40-1.15)	0.15	
Centre's proportion of radial PCI					0.22*
Low (14.9-64.4%)	65/730	83/760	0.80 (0.57-1.13)	0.20	
Intermediate (65.4-79.0%)	89/758	80/727	1.07 (0.78-1.47)	0.65	
High (80.0-98.0%)	94/708	140/711	0.64 (0.48-0.85)	0.0019	
Age					0.89
≥75 yr	94/644	115/658	0.82 (0.61-1.10)	0.18	
<75 yr	154/1552	188/1540	0.80 (0.64-1.00)	0.049	
Gender					0.45
Women	66/622	99/693	0.72 (0.52-1.00)	0.051	
Men	182/1574	204/1505	0.84 (0.68-1.04)	0.11	
BMI					0.75
≥25 kg/m^2	160/1485	190/1475	0.82 (0.66-1.03)	0.084	
<25 kg/m^2	88/711	113/723	0.77 (0.57-1.04)	0.088	
Intended start or continuation of prasugrel or ticagrelor					0.61
Yes	90/882	115/875	0.76 (0.56-1.02)	0.062	
No	158/1314	188/1323	0.83 (0.66-1.04)	0.11	
Diabetes					0.46
Yes	81/588	91/592	0.89 (0.65-1.22)	0.47	
No	167/1608	212/1606	0.77 (0.62-0.95)	0.016	
Estimated glomerular filtration rate (eGFR)					0.24
≥60 ml/min	196/1797	223/1769	0.85 (0.70-1.05)	0.13	
<60 ml/min	52/390	80/417	0.66 (0.46-0.96)	0.028	
History of peripheral vascular disease					0.79
Yes	34/235	46/249	0.76 (0.47-1.21)	0.25	
No	214/1961	257/1949	0.81 (0.67-0.99)	0.035	
Previous UFH					0.92
Yes	36/287	43/288	0.82 (0.51-1.33)	0.42	
No	212/1909	260/1910	0.80 (0.66-0.97)	0.023	
Planned GPI					0.41
Yes	17/91	15/87	1.10 (0.50-2.40)	0.81	
No	231/2105	288/2111	0.79 (0.65-0.95)	0.011	
Randomization to anti-thrombin type					0.85
Bivalirudin	116/796	140/802	0.82 (0.62-1.07)	0.14	
UFH	123/800	143/805	0.85 (0.65-1.10)	0.21	

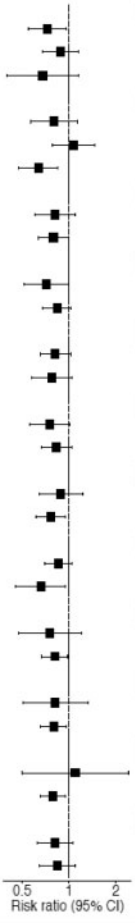

Figure 2 Non-ST-segment elevation acute coronary syndrome. ST, segment elevation myocardial infarction. *P-values are for trend across ordered groups. ACS, acute coronary syndrome; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. *P-values are for trend across ordered groups.

was attempted in more than 90% in STEMI and in ~70% of NSTE-ACS patients in both access groups. There was a highly significant qualitative interaction between crossover rates and clinical presentation [*P*-value for interaction (Pint) < 0.0001], with 4.5% of the NSTE-ACS patients and 7.2% of the STEMI patients who received intervention via femoral access against the original random allocation to radial as compared with 2.9% of the NSTE-ACS patients and 1.6% of the STEMI patients who received intervention via radial access in the femoral group (see Supplementary material online, *eTable S1*).

There were significant interactions noted for left main coronary artery lesion location, which underwent slightly more frequent treatment in the radial arm of STEMI patients (Pint = 0.024), and for TIMI 2 flow post procedure (Pint = 0.033) being more frequently observed in STEMI as compared with NSTE-ACS patients irrespective of the allocated access group.

Medications at presentation (*Table 1*), during intervention (see Supplementary material online, *eTable S1*), or at discharge (see Supplementary material online, *eTable S2*) were well matched with the only exception for sub-therapeutic dosing of unfractionated heparin (<50 U/kg), which was more often implemented in NSTE-ACS patients in both access site groups as compared with STEMI (Pint < 0.0001).

Clinical outcomes

For the co-primary outcomes of major adverse cardiac events and NACE, there were no significant interactions between the access site and type of ACS (STEMI or NSTE-ACS patients) (Pint = 0.25 and 0.76, respectively) (*Figure 1*, see Supplementary material online, *eFigure S3*).

In particular, the first co-primary outcome MACE occurred in 121 (6.1%) STEMI patients with radial access and in 126 (6.3%) patients

Composite endpoint: death, MI or stroke	Radial access	Femoral access	Risk Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.066*
Low (247-544)	36/677	53/685	0.68 (0.44-1.04)	0.074	
Intermediate (548-991)	42/723	36/718	1.16 (0.74-1.82)	0.51	
High (1000-1950)	43/601	37/606	1.18 (0.75-1.83)	0.47	
Centre's proportion of radial PCI					0.0029*
Low (14.9-64.4%)	44/686	28/740	1.73 (1.07-2.78)	0.023	
Intermediate (65.4-79.0%)	37/719	44/725	0.84 (0.54-1.30)	0.44	
High (80.0-98.0%)	40/596	54/544	0.66 (0.44-1.00)	0.050	
Age					0.53
≥75 yr	52/424	51/444	1.07 (0.72-1.59)	0.73	
<75 yr	69/1577	75/1565	0.91 (0.65-1.27)	0.58	
Gender					0.22
Women	31/449	42/468	0.75 (0.47-1.20)	0.23	
Men	90/1552	84/1541	1.07 (0.79-1.44)	0.67	
BMI					0.32
≥25 kg/m²	81/1317	78/1341	1.06 (0.77-1.45)	0.73	
<25 kg/m²	40/684	48/668	0.81 (0.53-1.24)	0.33	
Intended start or continuation of prasugrel or ticagrelor					0.40
Yes	75/1358	71/1353	1.05 (0.76-1.46)	0.75	
No	46/643	55/656	0.85 (0.57-1.26)	0.41	
Diabetes					0.36
Yes	39/371	32/352	1.15 (0.72-1.85)	0.56	
No	82/1630	94/1657	0.89 (0.66-1.19)	0.42	
Estimated glomerular filtration rate (eGFR)					0.98
≥60 ml/min	77/1670	84/1692	0.93 (0.68-1.27)	0.65	
<60 ml/min	37/310	37/298	0.94 (0.59-1.49)	0.78	
History of peripheral vascular disease					0.59
Yes	16/106	16/123	1.17 (0.58-2.37)	0.66	
No	105/1895	110/1886	0.95 (0.72-1.24)	0.70	
Previous UFH					0.26
Yes	41/952	51/949	0.80 (0.53-1.21)	0.28	
No	80/1049	75/1060	1.08 (0.78-1.48)	0.64	
Planned GPI					0.67
Yes	19/328	15/285	1.11 (0.56-2.19)	0.77	
No	102/1673	111/1724	0.94 (0.72-1.24)	0.68	
Randomization to anti-thrombin type					0.92
Bivalirudin	58/1002	60/1010	0.97 (0.68-1.40)	0.89	
UFH	63/999	66/999	0.95 (0.67-1.35)	0.77	

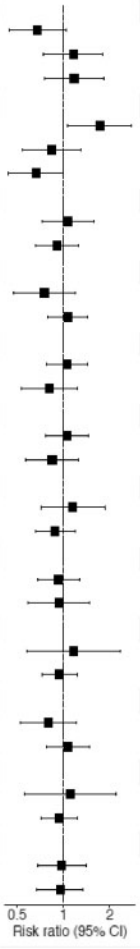

Figure 2 Continued.

with femoral access [rate ratio (RR) = 0.96, 95% CI = 0.75–1.24]. Among NSTE-ACS patients, MACE events occurred in 248 (11.3%) patients randomly assigned to radial access, compared with 303 (13.9%) patients assigned to femoral access (RR = 0.80, 95% CI = 0.67–0.96) (*Table 2*). The second co-primary outcome NACE was observed in 142 (7.2%) patients with radial access vs. in 165 (8.3%) patients with femoral access (RR = 0.86, 95% CI = 0.68–1.08) among the STEMI group, and in 268 (12.2%) patients with radial access vs. 321 (14.7%) patients with femoral access (RR = 0.82, 95% CI = 0.69–0.97) in the NSTE-ACS population (see Supplementary material online, *eFigure S4* and *Table 2*).

There was no significant interaction between access site and clinical presentation with respect to any other ischaemic secondary endpoint. All-cause and cardiovascular mortality, which numerically favoured the radial access, were significantly reduced in in the NSTE-ACS group undergoing radial access (RR = 0.50, 95% CI = 0.28–0.88; $P = 0.014$ and RR = 0.56, 95% CI = 0.31–1.00; $P = 0.046$, respectively) but not in STEMI patients (RR = 0.87, 95% CI = 0.59–1.29; $P = 0.49$ and RR = 0.87, 95% CI = 0.58–1.29; $P = 0.48$), with negative interaction testing (*Table 2*). The risks of stroke, MI, stent thrombosis, or urgent target vessel revascularization were not affected by access site, with no signal of heterogeneity with respect to the initial clinical presentation (*Table 2* and see Supplementary material online, *eFigure S4*).

Similarly, there was no significant interaction between access and type of ACS with respect to bleeding endpoints, with the only exception for GUSTO moderate (Pint = 0.034) but neither GUSTO severe nor the composite of moderate-to-severe GUSTO bleeding. Radial access reduced BARC 2–5 and BARC 3–5 bleeding, owing to a significant reduction of access site haemorrhagic complications (*Table 2*). Fatal bleeding was rare, and it did not differ across access groups within type of ACS.

Composite endpoint: death, MI, stroke or BARC 3 or 5	Radial access	Femoral access	Risk Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.95*
Low (247-544)	115/769	134/716	0.77 (0.58-1.02)	0.066	
Intermediate (548-991)	125/956	147/994	0.87 (0.68-1.12)	0.28	
High (1000-1950)	28/471	40/488	0.71 (0.43-1.17)	0.18	
Centre's proportion of radial PCI					0.26*
Low (14.9-64.4%)	72/730	88/760	0.84 (0.60-1.17)	0.30	
Intermediate (65.4-79.0%)	93/758	88/727	1.02 (0.75-1.38)	0.91	
High (80.0-98.0%)	103/708	145/711	0.68 (0.51-0.89)	0.0054	
Age					0.77
≥75 yr	106/644	125/658	0.85 (0.64-1.12)	0.25	
<75 yr	162/1552	196/1540	0.80 (0.64-1.00)	0.053	
Gender					0.30
Women	73/622	110/693	0.71 (0.52-0.98)	0.035	
Men	195/1574	211/1505	0.87 (0.71-1.07)	0.19	
BMI					0.96
≥25 kg/m²	173/1485	205/1475	0.82 (0.66-1.02)	0.075	
<25 kg/m²	95/711	116/723	0.82 (0.61-1.09)	0.17	
Intended start or continuation of prasugrel or ticagrelor					0.46
Yes	96/882	123/875	0.75 (0.57-1.00)	0.050	
No	172/1314	198/1323	0.86 (0.69-1.07)	0.18	
Diabetes					0.40
Yes	88/588	96/592	0.92 (0.67-1.25)	0.58	
No	180/1608	225/1606	0.78 (0.63-0.96)	0.019	
Estimated glomerular filtration rate (eGFR)					0.56
≥60 ml/min	204/1797	234/1769	0.85 (0.69-1.03)	0.10	
<60 ml/min	64/390	87/417	0.75 (0.53-1.06)	0.10	
History of peripheral vascular disease					0.99
Yes	40/235	50/249	0.82 (0.53-1.28)	0.39	
No	228/1961	271/1949	0.82 (0.68-0.99)	0.039	
Previous UFH					0.69
Yes	121/796	145/802	0.82 (0.63-1.07)	0.14	
No	136/800	152/805	0.88 (0.69-1.14)	0.34	
Planned GPI					0.41
Yes	17/91	15/87	1.10 (0.50-2.40)	0.81	
No	231/2105	288/2111	0.79 (0.65-0.95)	0.011	
Randomization to anti-thrombin type					0.85
Bivalirudin	116/796	140/802	0.82 (0.62-1.07)	0.14	
UFH	123/800	143/805	0.85 (0.65-1.10)	0.21	

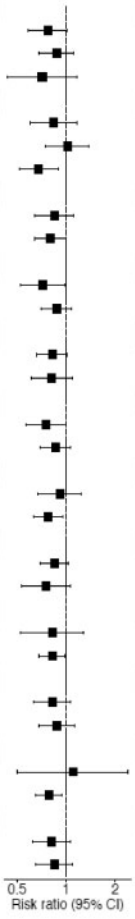

Figure 3 ST-segment elevation myocardial infarction. *P-values are for trend across ordered groups. ACS, acute coronary syndrome; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. *P-values are for trend across ordered groups.

Subgroup and sensitivity analyses

Figures 2 and *3* demonstrate the consistency of the two co-primary outcomes in patients with NSTE-ACS and STEMI across predefined subgroups. The effect of radial vs. femoral access appeared consistent across age, sex, BMI, planned or actual use of prasugrel or ticagrelor vs. clopidogrel, diabetes, renal function, history of peripheral vascular disease, and tertiles of the centres' annual volume of PCI.

Among STEMI but not NSTE-ACS patients, there was a signal for heterogeneity for both co-primary outcomes across tertiles of the centres' percentage of radial PCI (see Supplementary material online, *eTable S3*, overall volume of PCI and radial PCI per centre and tertiles boundaries). Similar findings were noted for all-cause mortality (see Supplementary material online, *eFigure S5*) but not for bleeding (see Supplementary material online, *eFigure S6*). Finally, no interaction was noted between prior administration of UFH and the occurrence of ST in the study groups, both in STEMI or NST-EACS populations.

Discussion

The results of this prespecified sub-analysis of the MATRIX-Access suggest that the overall trial results remain largely consistent in patients with NSTE-ACS and STEMI at presentation.[6] There was no significant interaction for any of the explored outcomes between the access strategy (radial or femoral artery access) and initial clinical presentation in terms of type of ACS (NSTE-ACS, STEMI). In patients with NSTE-ACS, the use of radial access significantly reduced both co-primary outcomes of MACE and NACE, as well as all-cause mortality and cardiac mortality. In patients presenting with STEMI, the use of radial access did not formally reduce all-cause or cardiac mortality,

Composite endpoint: death, MI, stroke or BARC 3 or 5	Radial access	Femoral access	Risk Ratio (95% CI)	p Value	p Value for trend or interaction
Centre's annual volume of PCI					0.28*
Low (247-544)	42/677	64/685	0.65 (0.44-0.97)	0.032	
Intermediate (548-991)	50/723	44/718	1.13 (0.75-1.71)	0.55	
High (1000-1950)	50/601	57/606	0.87 (0.59-1.29)	0.49	
Centre's proportion of radial PCI					0.0022*
Low (14.9-64.4%)	55/686	45/740	1.34 (0.90-1.99)	0.15	
Intermediate (65.4-79.0%)	42/719	51/725	0.82 (0.54-1.24)	0.35	
High (80.0-98.0%)	45/596	69/544	0.58 (0.39-0.84)	0.0042	
Age					0.70
≥75 yr	61/424	69/444	0.91 (0.64-1.30)	0.61	
<75 yr	81/1577	96/1565	0.83 (0.62-1.12)	0.23	
Gender					0.49
Women	38/449	51/468	0.76 (0.49-1.16)	0.20	
Men	104/1552	114/1541	0.90 (0.69-1.18)	0.46	
BMI					0.34
≥25 kg/m²	92/1317	100/1341	0.93 (0.70-1.24)	0.63	
<25 kg/m²	50/684	65/668	0.74 (0.51-1.08)	0.11	
Intended start or continuation of prasugrel or ticagrelor					0.46
Yes	89/1358	96/1353	0.92 (0.69-1.23)	0.58	
No	53/643	69/656	0.77 (0.54-1.11)	0.16	
Diabetes					0.61
Yes	42/371	42/352	0.94 (0.61-1.45)	0.77	
No	100/1630	123/1657	0.82 (0.63-1.07)	0.14	
Estimated glomerular filtration rate (eGFR)					0.91
≥60 ml/min	90/1670	110/1692	0.83 (0.62-1.09)	0.18	
<60 ml/min	45/310	49/298	0.85 (0.56-1.29)	0.44	
History of peripheral vascular disease					0.39
Yes	21/106	22/123	1.12 (0.60-2.07)	0.73	
No	121/1895	143/1886	0.84 (0.65-1.07)	0.15	
Previous UFH					0.91
Yes	51/952	60/949	0.84 (0.58-1.23)	0.37	
No	91/1049	105/1060	0.87 (0.65-1.15)	0.32	
Planned GPI					0.21
Yes	22/328	30/285	0.62 (0.35-1.08)	0.088	
No	120/1673	135/1724	0.91 (0.71-1.17)	0.47	
Randomization to anti-thrombin type					0.39
Bivalirudin	69/1002	73/1010	0.95 (0.68-1.33)	0.78	
UFH	73/999	92/999	0.78 (0.57-1.07)	0.12	

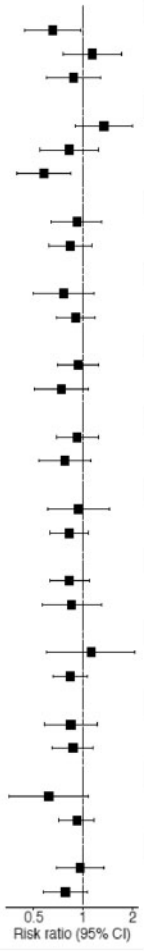

Figure 3 Continued.

albeit each endpoint numerically consistently favoured the radial access, and no signal of heterogeneity was observed. As expected, the overall event frequencies differ between NSTE-ACS and STEMI patients (for radial and femoral group combined). That is STEMI patients have more deaths, fewer MIs, more stent thrombosis and more bleeds. The use of radial access for coronary angiography followed by PCI significantly reduced the rate of BARC-actionable (BARC 2–5) bleeding events across the entire spectrum of ACS irrespective of NSTE-ACS or STEMI at the time of presentation.

MATRIX-access is the largest ($n = 8404$) randomized trial to compare radial and femoral access, including unselected patients at high baseline and procedural risk. Our study results differ from those observed in the RadIal Vs femorAL access for coronary intervention (RIVAL) study, that reported a possible mortality benefit in STEMI but not in NSTE-ACS patients with radial access, with positive interaction testing.[4] This observation triggered concern within the interventional cardiology community, given the relatively scarce comparative outcome data on radial vs. femoral access among patients with NSTE-ACS before the landmark RIVAL trial was published, particularly as mortality even trended to be higher in patients undergoing invasive management for NSTE-ACS via radial access. In MATRIX-Access, a prerandomization stratification by type of ACS (STEMI ($n = 4010$ patients) and NSTE-ACS ($n = 4394$ patients) resulted in two study groups largely balanced for clinical and angiographic characteristics. At variance with RIVAL, MATRIX-Access did not provide any signal that NSTE-ACS patients may derive less benefit than STEMI patients with radial as compared with femoral access. Hence, the finding of a more favourable effect with radial access in STEMI patients in RIVAL may be explained by random variation. An alternative hypothesis is that operators who recruited patients with NSTE-ACS in RIVAL had lower proficiency towards radial intervention than those who recruited patients with STEMI.

The proportion of PCIs undertaken via radial access emerged as a potential effect modifier in the overall MATRIX population for both

co-primary endpoints of MACE and NACE and overall mortality. However, no such treatment modification effect was observed in our current stratified analysis when NSTE-ACS patients were considered separately. In addition, although the total volume of radial PCI-procedures was higher for operators who recruited NSTE-ACS as opposed to STEMI patients in RIVAL, the interaction between pre-randomization diagnosis (STEMI vs. NSTE-ACS) and access site allocation (radial vs. femoral access) remained highly significant ($P = 0.0001$) in a multivariable model of predictors of mortality, even after adjustment for baseline variables, operator, and centre experience, suggesting that it was independent of operator and centre radial access experience. Unlike for patients with NSTE-ACS, the present analysis confirmed that for patients with STEMI the proportion of PCIs undertaken via radial access emerged as a treatment modifier with respect to both co-primary endpoints and mortality. This suggests that superiority in efficacy of radial over femoral access in STEMI patients requires considerable expertise that can be met only by high-volume radial operators.

Our present observations lend support to findings from previous position articles, expert opinion papers from Europe and North America, which endorse the preferential use of radial over femoral access but caution against the unrestricted use of radial for STEMI among inexperienced operators.[7,12–16] The available data strongly suggest that more efforts should be directed at increasing the adoption of radial vascular access and training operators to acquire the necessary skills. As any procedure or interventions, there is a learning curve with radial interventions, although several studies suggest that the curve is not steep.[17,18] Since radial access is beneficial across the entire spectrum of ACS, operators may acquire experience in elective cases before engaging in more complex and acute cases.

Limitations of our analysis need to be considered. Although reported subgroups were prespecified in the protocol and statistical analysis plan, we did not adjust for multiple comparisons, increasing the risk of type I error. Bleeding is an outcome that is dependent according to various definitions. Using the BARC consensus definitions for major bleeding, there were substantial reductions in bleeding in both the STEMI and NSTE-ACS cohorts in MATRIX. Moreover, these results were consistent when the GUSTO bleeding definitions were applied. In addition, most centres participating in the MATRIX trial were highly experienced in the radial technique; similar outcomes may not apply in centres performing lower volumes of radial access.

In conclusion, our results show that in unselected patients undergoing invasive management for treatment of ACS, the use of radial compared with femoral access provided consistent benefit across the whole spectrum of ACS without evidence that type of presenting syndrome affected the results of the random access allocation. Adequate operator experience emerged as treatment modifier in STEMI but not NSTE-ACS patients, suggesting that operators willing to transition from a default femoral to a default radial access should first accrue enough transradial volume in elective cases.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest: Pascal Vranckx reports receiving speaking or consulting fees from AstraZeneca, Bayer Health Care, Boehringer-Ingelheim, Daiichi-Sankyo, and The Medicines Co. outside the submitted work. Guiseppe Ando reports receiving speaking or consulting fees from AstraZeneca, Bayer Health Care, Menarini, Daiichi-Sankyo, Abbott Vascular and Biotronik outside the submitted work. Francesco Tomassini reports receiving speaking or consulting fees from Bayer Health Care and Daiichi-Sankyo outside the submitted work. Peter Jüni has received research grants to the institution from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, and serves as unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St Jude Medical and The Medicines Company. Stephan Windecker reports receiving has received research grants to the institution from Astra Zeneca and speaking or consulting fees from AstraZeneca outside the submitted work. Marco Valgimigli reports grants from The Medicines Company, grants from Terumo, during the study; grants from AstraZeneca, and personal fees from Terumo, St Jude Vascular, and Abbott Vascular, outside the submitted work.

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