








Acute kidney injury in patients with acute coronary syndrome undergoing invasive management treated with bivalirudin vs. unfractionated heparin: insights from the MATRIX trial

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Aims

Acute kidney injury (AKI) is a critical complication among patients with acute coronary syndrome (ACS) undergoing invasive management. The value of adjunctive antithrombotic strategies, such as bivalirudin or unfractionated heparin (UFH) on the risk of AKI is unclear.

Methods and results

Among 7213 patients enrolled in the MATRIX-Antithrombin and Treatment Duration study, 128 subjects were excluded due to incomplete information on serum creatinine (sCr) or end-stage renal disease on dialysis treatment. The primary endpoint was AKI defined as an absolute (>0.5 mg/dL) or a relative (>25%) increase in sCr. AKI occurred in 601 patients (16.9%) treated with bivalirudin and 616 patients (17.4%) treated with UFH [odds ratio (OR): 0.97; 95% confidence interval (CI): 0.85–1.09; $P=0.58$]. A >25% sCr increase was observed in 597 patients (16.8%) with bivalirudin and 616 patients (17.4%) with UFH (OR: 0.96; 95% CI: 0.85–1.08; $P=0.50$), whereas a >0.5 mg/dL absolute sCr increase occurred in 176 patients (5.0%) with bivalirudin vs. 189 patients (5.4%) with UFH (OR: 0.92; 95% CI: 0.75–1.14; $P=0.46$). By implementing the Kidney Disease Improving Global Outcomes (KDIGO) criteria, the risk of AKI was not significantly different between bivalirudin and UFH groups (OR: 0.88; 95% CI: 0.72–1.07; $P=0.21$). Subgroup analyses of the primary endpoint suggested a benefit with bivalirudin in patients randomized to femoral access.

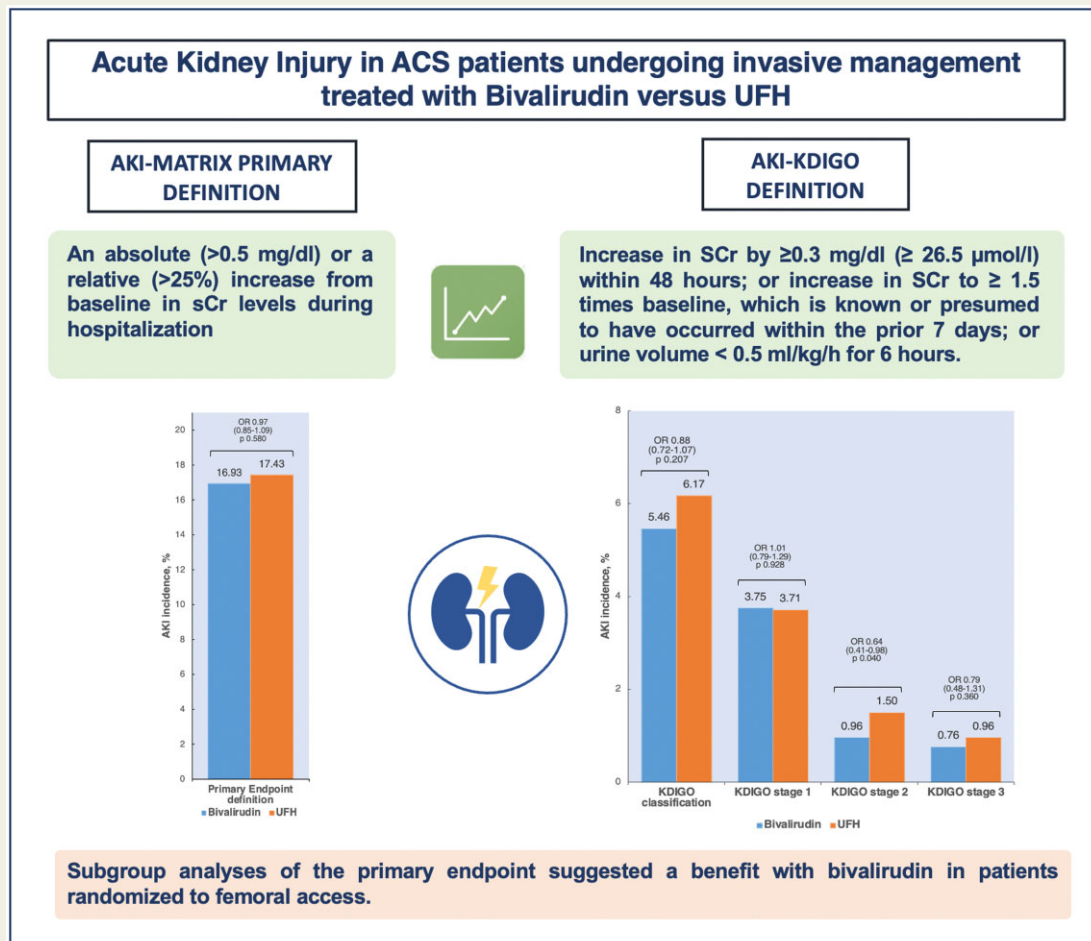
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Conclusion Among ACS patients undergoing invasive management, the risk of AKI was not significantly lower with bivalirudin compared with UFH.

Trial registration clinicaltrials.gov NCT01433627.

Graphical Abstract



Keywords Bivalirudin • Unfractionated heparin • Acute kidney injury • Acute coronary syndromes

Introduction

Among patients undergoing interventional procedures, acute kidney injury (AKI) prolongs hospital stay and is associated with worse clinical outcomes.^{1,2} The incidence of AKI ranges from 3% to 13% following percutaneous coronary intervention (PCI)³ and it is especially high in complex PCI procedures or patients presenting with the acute coronary syndrome (ACS) undergoing urgent revascularization.³ Larger volume of contrast medium or insufficient time to perform renal prophylactic measures are recognized contributing factors for AKI in patients with ACS. Alongside these, other factors, such as

haemodynamic instability, left ventricular (LV) dysfunction resulting in impaired systemic or renal perfusion and cholesterol embolization have been advocated as potential mechanisms of AKI in ACS patients undergoing invasive management.⁴ Nonetheless, effective strategies for AKI prevention and improving outcomes of ACS patients at risk for AKI are still limited in clinical practice.

There is evidence suggesting that the route of vascular access for PCI plays an important role in the risk of AKI.⁵⁻⁷ In the *Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) Access* trial, radial access (RA) was associated with lower bleeding, AKI, and all-cause mortality

compared with femoral access (FA) in patients with ACS undergoing invasive management.^{6,8,9} Whether the mortality benefit of RA is related to the lower incidence of bleeding, AKI, or both has been disentangled in a recent report, which identified AKI prevention as the major, independent determinant.¹⁰ Despite these beneficial effects, the rate of AKI in ACS patients undergoing PCI through RA remains substantial (nearly 15% in the MATRIX Access trial), emphasizing the need for further approaches for AKI prevention.

Multiple trials have shown that bivalirudin reduces the risk of major bleeding,^{9,11–13} which may in turn influence the occurrence of AKI. However, no prospective appraisal of the incidence of AKI has been carried out in randomized studies of ACS patients receiving bivalirudin vs. unfractionated heparin (UFH). We pre-specified a prospective assessment of whether bivalirudin compared with UFH reduces the incidence of AKI in subjects with ACS, including patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndrome (NSTEMI) undergoing invasive management.

Methods

Study design and population

MATRIX was a programme of three independent randomized controlled, multicentre, superiority trials (NCT01433627) in patients with ACS undergoing invasive management.¹⁴ The first trial (MATRIX-Access) compared radial vs. femoral access in 8404 patients with ACS^{8,9} and the effects of access site on AKI (AKI-MATRIX substudy) have been previously reported.⁶ MATRIX-Antithrombin compared bivalirudin with UFH [use of glycoprotein IIb/IIIa inhibitors (GPI) was left to the discretion of the investigator] in 7213 ACS patients in whom PCI was planned. MATRIX Treatment Duration compared prolonged bivalirudin administration with a post-PCI infusion vs. short-term bivalirudin administration without a post-PCI infusion in 3610 patients assigned to receive bivalirudin.

Patients with NSTEMI were eligible if they had a history consistent with new or worsening cardiac ischemia that occurred while they were at rest or with minimal activity within 7 days before randomization and met at least two high-risk criteria among the following: (i) age of 60 years or older, the elevation of cardiac biomarkers, or electrocardiographic changes compatible with ischaemia; and (ii) if they were considered to be candidates for PCI after completion of coronary angiography. 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. The main inclusion and exclusion criteria were previously reported.^{8,15}

All patients enrolled in MATRIX Antithrombin and the MATRIX Treatment Duration were eligible for this study, except those with incomplete serum creatinine (sCr) data or those who had an end-stage renal disease that required dialysis. The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent.

Study protocol and randomization

Patients were randomly assigned, in a 1:1 ratio, to receive bivalirudin or UFH, and those assigned to the bivalirudin group were subsequently randomized, in a 1:1 ratio, to receive a post-PCI bivalirudin infusion or no post-PCI infusion. The randomization sequence was computer-generated, blocked, and stratified by the type of ACS (i.e. with ST-

segment elevation vs. without ST-segment elevation), intended for or ongoing use of a P2Y12 inhibitor (clopidogrel vs. ticagrelor or prasugrel), and study site. All interventions were administered in an open-label fashion. Bivalirudin was given according to the product labelling, with a bolus of 0.75 mg/kg of body weight, followed immediately by an infusion of 1.75 mg/kg/h until completion of PCI. Receiving a post-PCI bivalirudin infusion or no post-PCI infusion was randomly determined (MATRIX treatment duration). In those assigned to bivalirudin prolongation, the choice between two regimens (full dose for up to 4 h or reduced dose of 0.25 mg/kg/h for at least 6 h) was made at the discretion of the treating physicians. UFH was administered at a dose of 70–100 U or 50–70 U/kg in patients who did not receive or received GPI, respectively. Subsequent UFH dose adjustment based on the activated clotting time was left to the discretion of the treating physicians.

Outcomes

The outcomes of the MATRIX-Antithrombin and MATRIX-Treatment Duration have been previously reported.^{9,15} The primary endpoint of this substudy was the incidence of AKI, defined as either an absolute (>0.5 mg/dL) or a relative (>25%) increase from baseline in sCr levels during hospitalization in the intention-to-treat population.^{16,17} Furthermore, the incidence of AKI was evaluated by implementing the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Sensitivity analyses were also performed in patients proceeding to PCI after diagnostic coronary angiography (i.e. excluding patients who received only an angiogram and no further PCI).

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Differences across groups were assessed using the Student's *t*-test in case of continuous variables and the χ^2 or Fisher's exact test in case of categorical data. The differences at the lesion level considered the nested structure of lesions within individuals and then were analysed using multi-level general or generalized mixed models, as appropriate. We applied multivariable logistic regression models to evaluate the association of AKI during index hospitalization with randomized access site, the individual components of the Mehran's score, bleeding, and measures of bleeding severity in the two study groups. We performed stratified logistic regressions by subgroups, including diabetes at baseline, estimated glomerular filtration rate (eGFR), age, clinical presentation, LV ejection fraction, Killip class, Mehran's score, contrast media volume, and randomized access site. The analyses were done using Stata release 16.1 (StataCorp LLC, College Station, TX, USA).

Results

Among 7213 patients enrolled in the MATRIX-Antithrombin trial from 78 centres in Italy, The Netherlands, Spain, and Sweden between October 2011 and July 2014, 128 patients (1.8%) were excluded due to incomplete sCr data or because they suffered from the end-stage renal disease on dialysis treatment. Among the 7085 patients included in the analysis, 3550 subjects were allocated to bivalirudin and 3535 to UFH.

Baseline characteristics

Baseline demographics, medical history, clinical presentation, and procedural characteristics were well matched between bivalirudin and UFH groups (Table 1). Baseline characteristics of subjects

Table 1 Baseline and procedural characteristics

	Bivalirudin (N = 3550)	UFH (N = 3535)	P-value
Clinical characteristics			
Age (years)	65.4 ± 11.9	65.4 ± 11.8	0.82
≥75 years	890 (25.1)	880 (24.9)	0.86
Male sex	2689 (75.7)	2715 (76.8)	0.30
Hypotension ^a	22 (0.6)	35 (1.0)	0.08
Anaemia ^b	671 (18.9)	679 (19.2)	0.74
Diabetes	812 (22.9)	770 (21.8)	0.27
Creatinine >1.5 mg/dL	175 (4.9)	168 (4.8)	0.73
Killip class III or IV	109 (3.1)	92 (2.6)	0.24
STEMI	1986 (55.9)	1966 (55.6)	0.78
NSTE-ACS	1564 (44.1)	1569 (44.4)	0.78
NSTE-ACS, troponin negative	161 (4.5)	158 (4.5)	0.89
NSTE-ACS, troponin positive	1403 (39.5)	1411 (39.9)	0.73
NSTE-ACS with ST-segment deviation	730 (20.6)	726 (20.5)	0.98
NSTE-ACS with T Wave inversion	441 (12.4)	499 (14.1)	0.04
EF ≤35%	316 (9.2)	295 (8.7)	0.40
Systolic arterial pressure (mmHg)	138.7 ± 26.0	138.3 ± 25.8	0.59
Hb at baseline	14.0 ± 1.9	14.0 ± 2.0	0.38
Glucose at baseline	140.7 ± 65.7	138.2 ± 61.4	0.11
Statins before cath-lab	1442 (40.6)	1428 (40.4)	0.85
ACE inhibitors before cath-lab	986 (27.8)	1007 (28.5)	0.51
Angiotensin II receptor antagonist before cath-lab	366 (10.3)	347 (9.8)	0.49
Procedural characteristics			
Radial access	1770 (49.9)	1771 (50.1)	0.84
Any cross-over during index hospitalization	262 (7.4)	258 (7.3)	0.89
Total amount of contrast used during index hospitalization—mL	199.8 ± 108.5	196.5 ± 104.8	0.20
No PCI attempted after coronary angiography during index hospitalization	195 (5.5)	178 (5.0)	0.39
CABG	21 (0.6)	19 (0.5)	0.76
Patient with significant lesion and medical treatment	143 (4.0)	118 (3.3)	0.12
Patient without significant lesion	31 (0.9)	44 (1.2)	0.13
At least one PCI attempted	3355 (94.5)	3357 (95.0)	0.39
Died during PCI	1 (0.0)	0 (0.0)	1.00
At least one PCI completed during index hospitalization	3354 (94.5)	3357 (95.0)	0.36
Medications administered in and after the catheterization laboratory			
Aspirin	236 (6.6)	265 (7.5)	0.16
Clopidogrel	242 (6.8)	284 (8.0)	0.05
Prasugrel	309 (8.7)	312 (8.8)	0.86
Ticagrelor	394 (11.1)	373 (10.6)	0.46
Bailout GPI	167 (4.7)	152 (4.3)	0.41
≥1 intra-aortic balloon pump	79 (2.2)	85 (2.4)	0.62
≥1 PCI completed	(N = 3354)	(N = 3357)	
TIMI 3 flow in all treated lesions during whole index hospitalization	3172 (94.6)	3203 (95.4)	0.12
Coronary stenosis <30% in all treated lesions	3189 (95.1)	3195 (95.2)	0.86
Procedural success in all treated lesions	3088 (92.1)	3112 (92.7)	0.33
Duration of procedure (min)	60.9 ± 36.4	60.2 ± 37.4	0.43
Amount of contrast used	205.2 ± 108.4	201.7 ± 104.1	0.19
Treated vessel(s) per patient			
Left main coronary artery	174 (5.2)	154 (4.6)	0.26
Left anterior descending artery	1848 (55.1)	1808 (53.9)	0.32
Left circumflex artery	1063 (31.7)	1033 (30.8)	0.42
Right coronary artery	1225 (36.5)	1246 (37.1)	0.60

Continued

Table 1 Continued

	Bivalirudin (N = 3550)	UFH (N = 3535)	P-value
Bypass graft	33 (1.0)	25 (0.7)	0.29
At least two vessels treated	831 (24.8)	765 (22.8)	0.06
Lesions treated per patient (interquartile range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.46
One lesion	2288 (68.2)	2333 (69.5)	
Two lesions	753 (22.5)	737 (22.0)	
Three or more lesions	313 (9.3)	285 (8.5)	
At least one complex lesion	1800 (53.7)	1842 (54.9)	0.31
Median number of stents per patient (interquartile range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.89
Overall stent length per patient—mm	66.8 ± 53.7	66.8 ± 53.6	0.97
Lesions			
Number of lesions with PCI	(N = 5030)	(N = 4947)	
Lesions stented	4407 (91.2)	4345 (91.1)	0.91
At least one drug-eluting stent	3300 (68.3)	3212 (67.4)	0.27
At least one bare-metal stent	1107 (22.9)	1133 (23.8)	0.33
Lesions not stented	427 (8.8)	422 (8.9)	0.91
TIMI flow pre-procedure			
0 or 1	1700 (35.2)	1599 (33.6)	0.09
2	571 (11.8)	553 (11.6)	0.78
3	2562 (53.0)	2612 (54.8)	0.06
TIMI flow post-procedure			
0 or 1	77 (1.6)	73 (1.5)	0.80
2	119 (2.5)	90 (1.9)	0.09
3	4637 (95.9)	4601 (96.6)	0.15
Coronary stenosis <30%	4653 (96.3)	4582 (96.2)	0.89
Procedural success	4541 (93.9)	4494 (94.3)	0.52
Number of lesions stented	(N = 4407)	(N = 4345)	
Total stent length per lesion—mm	26.2 ± 14.6	26.5 ± 15.0	0.30
Average stent diameter per lesion—mm	3.0 ± 0.5	3.0 ± 0.5	0.84
At least one direct stenting	975 (22.1)	925 (21.3)	0.31
Post-dilation	2021 (45.9)	2021 (46.5)	0.57

Values are mean ± SD, n (%), n, or median (interquartile range).

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; EF, ejection fraction; GPI, glycoprotein IIb/IIIa inhibitors; Hb, haemoglobin; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.

^aSystolic blood pressure <80 mmHg.

^b<12 g/dL for women, <13 g/dL for men.

randomly allocated to receive or not post-PCI bivalirudin infusion are presented in [Supplementary material online, Table S1](#).

AKI occurred in 1213 patients (17.1%) as defined by a relative (>25%) increase in sCr and 365 patients (5.2%) according to an absolute increase in sCr of >0.5 mg/dL. Patients who developed AKI were older, more frequently men with multiple comorbidities (including anaemia or diabetes), and received higher amounts of contrast volume ([Supplementary material online, Table S2](#)); they were more likely to present STEMI with advanced Killip class and required 4-times greater use of intra-aortic balloon pump. AKI patients presented more commonly complex coronary lesions involving the left coronary system, requiring prolonged procedural time. In addition, procedural success was lower in patients who developed AKI compared with non-AKI patients ([Supplementary material online, Table S2](#)).

Endpoints according to antithrombotic therapy

Before randomization, sCr and the estimated glomerular filtration rate (eGFR) were comparable between the two groups ([Table 2](#)). Peak sCr after intervention or at discharge did not differ in the bivalirudin vs. UFH group, as nadir eGFR during hospitalization (78.39 ± 24.92 mL/min/1.73 m² in the bivalirudin group vs. 78.89 ± 26.14 mL/min/1.73 m² in the UFH group; *P* = 0.41) or eGFR at hospital discharge (83.69 ± 25.59 mL/min/1.73 m² in the bivalirudin group vs. 84.15 ± 26.73 mL/min/1.73 m² in the UFH group, *P* = 0.46).

The primary outcome of AKI occurred in 601 patients (16.9%) in the bivalirudin group and 616 patients (17.4%) in the UFH group [odds ratio (OR) 0.97; 95% confidence interval (CI): 0.85–1.09; *P* = 0.58; [Figure 1, Table 3](#)]. Both components of the AKI primary

Table 2 Renal function

	Randomized to Bivalirudin (N = 3550)	Randomized to UFH (N = 3535)	P-value
Creatinine, mg/dL			
Pre-PCI	0.98 ± 0.35	0.98 ± 0.34	0.54
Post-PCI	1.08 ± 0.55	1.08 ± 0.57	0.64
At hospital discharge	1.00 ± 0.43	1.01 ± 0.47	0.40
Creatinine clearance/eGFR, mL/min/1.73 m ² (MDRD formula)			
Pre-PCI	83.61 ± 24.98	84.61 ± 25.69	0.10
Post-PCI	78.39 ± 24.92	78.89 ± 26.14	0.41
At hospital discharge	83.69 ± 25.59	84.15 ± 26.73	0.46

Values are expressed as mean ± SD.

eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; PCI, percutaneous coronary intervention.

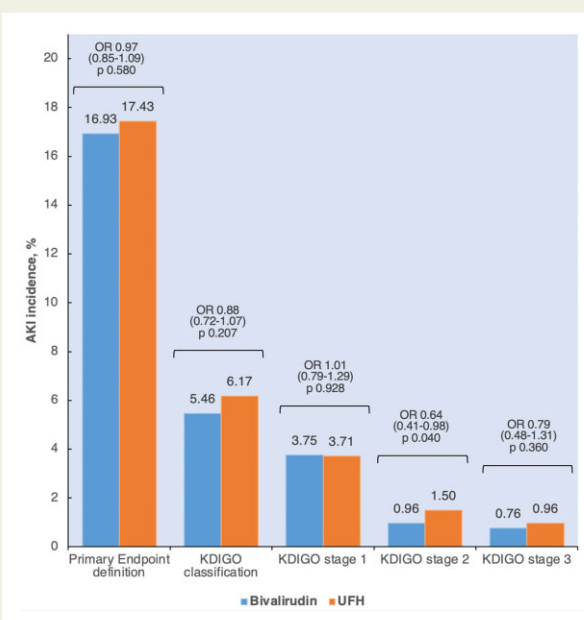


Figure 1 Incidence of AKI in patients randomized to bivalirudin vs. UFH and assessed according to primary endpoint definition and KDIGO classification. AKI, acute kidney injury; KDIGO, kidney disease improving global outcomes; OR, odds ratio; UFH, unfractionated heparin.

endpoint definition were not significantly different in patients randomized to bivalirudin. Specifically, a >25% increase in sCr was observed in 597 patients (16.8%) with bivalirudin and 616 patients (17.4%) with UFH (OR: 0.96; 95% CI: 0.85–1.08; $P=0.50$), and a >0.5 mg/dL absolute increase in sCr occurred in 176 patients (5%) with bivalirudin and 189 patients (5.4%) with UFH (OR: 0.92; 95% CI: 0.75–1.14; $P=0.46$). Among patients who underwent PCI after coronary angiography during the index hospitalization ($n=6612$), the risk of AKI did not significantly differ between the two randomized groups (Table 3).

By implementing the KDIGO criteria, AKI occurred in 194 patients (5.5%) with bivalirudin and 218 patients (6.2%) with UFH (OR: 0.88; 95% CI: 0.72–1.07; $P=0.21$). Stage 1 or 3 AKI was not reduced in the

bivalirudin group (Figure 1, Table 3), but Stage 2 was lower with bivalirudin compared with UFH (1.0 vs. 1.5%; $P=0.04$).

Study outcomes according to randomization to post-PCI bivalirudin infusion (MATRIX Treatment Duration) were not significantly different and are presented in Supplementary material online, Table S3.

Subgroups analyses and multivariate modelling

The effect of antithrombotic therapy on AKI occurrence was largely consistent across subgroups, including diabetes, eGFR, age, clinical presentation, LV dysfunction, Killip class, Mehran score, and contrast media volume (Figure 2). Positive quantitative interaction testing was noted between the randomized antithrombotic therapy and access site, suggesting a benefit with bivalirudin compared with UFH in patients allocated to FA.

At multivariate modelling, random allocation to radial access was associated with a significantly lower risk of AKI in patients randomized to UFH (Supplementary material online, Table S4), while the treatment effect of the randomized access-site on AKI was not observed in those treated with bivalirudin (Supplementary material online, Table S5).

Discussion

The MATRIX trial is one of the largest randomized studies comparing bivalirudin with UFH in ACS patients and the only randomized trial comparing post-PCI vs. no post-PCI bivalirudin infusion. The study failed to demonstrate that bivalirudin as compared to UFH with provisional use of GPI reduces major adverse cardiovascular events or net adverse clinical events, and post-PCI bivalirudin infusion did not demonstrate adjunctive benefit compared with no post-PCI infusion.⁹ However, in secondary endpoint analyses, bivalirudin consistently reduced major bleeding, including fatal and non-access site-related events as well as transfusion rates in both randomly allocated access sites.⁹

The main finding of the present analysis is that a regimen of bivalirudin monotherapy did not reduce the occurrence of AKI compared with UFH with or without GPI. These results remained consistent by implementing the KDIGO criteria, which revealed a much lower risk of AKI in the overall population and a numerically lower incidence of

Table 3 Acute kidney injury

All patients receiving an angiography and/or PCI	Randomized to Bivalirudin (N = 3550)	Randomized to UFH (N = 3535)	Odds Ratio (95% CI)	P-value
AKI according to primary endpoint definition	601 (16.9)	616 (17.4)	0.97 (0.85–1.09)	0.58
AKI 25% increase	597 (16.8)	616 (17.4)	0.96 (0.85–1.08)	0.50
AKI 0.5 increase	176 (5.0)	189 (5.4)	0.92 (0.75–1.14)	0.46
AKI related to index procedure only	566 (15.9)	582 (16.5)	0.96 (0.85–1.09)	0.55
AKI 25% increase	562 (15.8)	581 (16.4)	0.96 (0.84–1.09)	0.49
AKI 0.5 increase	171 (4.8)	184 (5.2)	0.92 (0.74–1.14)	0.45
AKI related to staged procedure only	81 (2.3)	83 (2.4)	0.97 (0.71–1.32)	0.85
AKI 25% increase	80 (2.3)	81 (2.3)	0.98 (0.72–1.34)	0.91
AKI 0.5 increase	21 (0.6)	22 (0.6)	0.95 (0.52–1.73)	0.87
KDIGO criteria	194 (5.5)	218 (6.2)	0.88 (0.72–1.07)	0.21
Stage 1	133 (3.8)	131 (3.7)	1.01 (0.79–1.29)	0.93
Stage 2	34 (1.0)	53 (1.5)	0.64 (0.41–0.98)	0.04
Stage 3	27 (0.8)	34 (1.0)	0.79 (0.48–1.31)	0.36
Dialysis during index hospitalization	1 (0.03)	0 (0.0)	1.00 (1.00–1.00)	
Only patients who underwent index PCI ^a	(N = 3315)	(N = 3297)		
AKI during hospitalization	564 (17.0)	562 (17.1)	1.00 (0.88–1.13)	0.97
AKI 25% increase	560 (16.9)	562 (17.1)	0.99 (0.87–1.12)	0.87
AKI 0.5 increase	156 (4.7)	172 (5.2)	0.90 (0.72–1.12)	0.34

Values are expressed as *n* or *n* (%) unless otherwise indicated.

PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

^aExcluding patients who underwent angiography only.

AKI in favour of bivalirudin, albeit not statistically significant. The study results were also mainly consistent across the pre-defined study subgroups. However, in the subpopulation of patients who entered the access-site randomization, we found a significant interaction with the type of allocated access site at the time of PCI. Bivalirudin reduced the incidence of AKI compared to UFH in patients randomized to FA, whereas no such effect was observed in those randomized to RA. These results are specular to what was observed for radial vs. femoral access site, in which the treatment effect for radial was mainly observed in the UFH but not in the bivalirudin group.⁸

Our overall study results are consistent with previous findings from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI),¹⁸ which did not observe a lower risk of AKI with bivalirudin (16.8%) vs. UFH plus GPI (15.5%). Yet, the results of the HORIZONS-AMI study referred solely to a selected population of STEMI patients undergoing primary PCI mainly through FA while only a minority using RA. This analysis extends these findings to a contemporary, all-comers ACS population with randomly allocated access site, including both STEMI and NSTEMI-ACS undergoing invasive management.

Previous *post-hoc* analyses of randomized studies comparing bivalirudin with UFH in ACS patients undergoing PCI do support a beneficial effect of bivalirudin on bleeding in patients with chronic kidney disease (CKD), a subset of patients at high risk for AKI.^{19,20} In the *Second Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events* (REPLACE-2) trial, bivalirudin use was associated with lower TIMI major or minor bleeding (3.2% vs. 7.1%, $P = 0.009$) compared with UFH plus a GPI in a sub-population of 886 patients with

CKD.¹⁹ The *Acute Catheterization and Urgent Intervention Triage strategy* (ACUITY) demonstrated a remarkable reduction of 30-day non-coronary artery bypass graft (CABG) major bleeding (including access site and non-access site bleeding events) in patients with CKD treated with bivalirudin compared with those treated with heparin plus a GPI (6.2% vs. 9.8%, $P = 0.008$).²⁰ A recent report from the National Cardiovascular Data Registry CathPCI Registry demonstrated a lower rate of in-hospital bleeding with bivalirudin compared with UFH (7.0% vs. 9.5%; adjusted OR: 0.82; 95% CI: 0.76–0.87) in 71 675 patients with end-stage renal disease undergoing PCI.²¹ One would expect that the more pronounced benefit of bivalirudin in reducing access site and non-access site bleeding events in patients with CKD would translate into a potential reduction of AKI compared with patients treated with UFH. We did not find an advantage of bivalirudin on the risk of AKI in the overall population or the subgroup of CKD patients.

RA has been shown to reduce the risk of AKI compared with FA, especially among patients at higher risk for AKI.⁶ However, a beneficial effect of RA for AKI prevention was not observed in another smaller and most likely underpowered randomized controlled trial comparing the two access sites.²² The advocated mechanisms through which RA may reduce AKI occurrence might include the avoidance of direct passage of catheters in the proximity of renal arteries (with potential impact on embolization into renal circulation),²³ the reduction of bleeding events,⁸ or a combination of both. The effect of bleeding prevention achieved with the use of bivalirudin as opposed to UFH¹⁵ was greater than the one observed with RA vs. FA in the MATRIX trial.⁹ Therefore, our results suggest that bleeding avoidance strategies do not necessarily translate into an effect on AKI

- coronary intervention: results from the HORIZONS-AMI substudy. *Eur Heart J* 2014;**35**:1533–1540.
19. Chew DP, Lincoff AM, Gurm H, Wolski K, Cohen DJ, Henry T, Feit F, Topol EJ. Bivalirudin versus heparin and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). *Am J Cardiol* 2005;**95**:581–585.
 20. Mehran R, Nikolsky E, Lansky AJ, Kirtane AJ, Kim Y-H, Feit F, Manoukian S, Moses JW, Ebrahimi R, Ohman EM, White HD, Pocock SJ, Dangas GD, Stone GW. Impact of chronic kidney disease on early (30-day) and late (1-year) outcomes of patients with acute coronary syndromes treated with alternative antithrombotic treatment strategies: an ACUITY (Acute Catheterization and Urgent Intervention Triage strategY). *JACC Cardiovasc Interv* 2009;**2**:748–757.
 21. Washam JB, Kaltenbach LA, Wojdyla DM, Patel MR, Klein AJ, Abbott JD, Rao SV. Anticoagulant use among patients with end-stage renal disease undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2018;**11**:e005628.
 22. Marbach JA, Wells G, Santo PD, So D, Chong A-Y, Russo J, Labinaz M, Dick A, Froeschl M, Glover C, Hibbert B, Marquis J-F, MacDougall A, Kass M, Paddock V, Quraishi AUR, Chandrasekhar J, Ghosh N, Bernick J, Le May M. Acute kidney injury after radial or femoral artery access in ST-segment elevation myocardial infarction: AKI-SAFARI. *Am Heart J* 2021;**234**:12–22.
 23. Scolari F, Ravani P, Gaggi R, Santostefano M, Rollino C, Stabellini N, Colla L, Viola BF, Maiorca P, Venturelli C, Bonardelli S, Faggiano P, Barrett BJ. The challenge of diagnosing atheroembolic renal disease. *Circulation* 2007;**116**:298–304.