

Acute Kidney Injury in patients with acute coronary syndrome undergoing invasive management treated with Bivalirudin versus Unfractionated Heparin: insights from the MATRIX trial

Authors: Antonio Landi^a, MD, Mattia Branca^b, PhD, Giuseppe Andò^c, MD, PhD, Filippo Russo^d, MD, Enrico Frigoli^b, MD, Giuseppe Gargiulo^e, MD, Carlo Briguori^f, MD, PhD, Pascal Vranckx^g, MD, PhD, Sergio Leonardi^h, MD, MHS, Felice Gragnanoⁱ, MD, Paolo Calabròⁱ, MD, PhD, Gianluca Campo^j, MD, PhD, Giuseppe Ambrosio^k, MD, Andrea Santucci^k, MD, Ferdinando Varbella^l, MD, Tiziana Zaro^m, MD, Dik Heg^b, PhD, Stephan Windeckerⁿ, MD, Peter Jüni^o, MD, Giovanni Pedrazzini^a, MD, Marco Valgimigli^{a,n}, MD, PhD, *for the MATRIX Investigators*

Affiliations:

^a Division of Cardiology, Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland.

^b CTU Bern, University of Bern, Switzerland.

^c Azienda Ospedaliera Universitaria Policlinico "Gaetano Martino", University of Messina, Messina, Italy.

^d Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

^e Department of Advanced Biomedical Science, University of Naples Federico II, Naples, Italy

^f Interventional Cardiology Unit, Mediterraneo Cardiocentro, Naples, Italy.

^g Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium. Faculty of medicine and life sciences, University of Hasselt, Hasselt, Belgium.

^h University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

ⁱ Division of Cardiology, "Sant'Anna e San Sebastiano" Hospital, Caserta, Italy; Department of Translational Medicine, University of Campania "Luigi Vanvitelli," Caserta, Italy.

^j Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona (FE), Italy

^k Department of Cardiology, Azienda Ospedaliero-Universitaria "S. Maria Della Misericordia", Perugia, Italy.

^l Cardiology Unit, Ospedali Riuniti di Rivoli, ASL Torino 3, Turin, Italy. Azienda Ospedaliera Universitaria San Luigi Gonzaga Orbassano, Turin, Italy.

^m A.O. Ospedale Civile di Vimercate (MB), Vimercate, Italy.

ⁿ Department of Cardiology, University of Bern, Bern, Switzerland.

^o Department of Medicine and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Relationship with Industries and other entities

Dr. Andò reports personal fees and non-financial support from Bayer, Daiichi Sankyo, Pfizer - Bristol Myers Squibb, Boeringer Ingelheim, personal fees from Menarini, AstraZeneca, Chiesi, and Biosensors, and non-financial support from Amgen, outside the submitted work. **Prof. Vranckx** reports personal fees from Bayer, personal fees from Daiichi Sankyo, and personal fees from CLS Behring. **Prof. Campo** reports grants and personal fees from Abbott, SMT, Boston Scientific, GE, Siemens and Astrazeneca, outside the submitted work. **Prof. Windecker** reports research and educational grants to the institution from Abbott, Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo, V-Wave. Prof. Windecker serves as unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, Bayer. BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, Terumo, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. **Dr. Jüni** reports honoraria to the institution for participation in advisory boards and/or consulting from Amgen, Ava , Fresenius, a grant to the institution from Appili Therapeutics; he serves as unpaid member of the steering group of trials funded by Appili Therapeutics, Abbott Vascular and Terumo. **Prof. Valgimigli** reports grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Biosensors, personal fees from Idorsia, outside the submitted work. The other authors report no relationships relevant to the contents of this paper to disclose.

Funding

The trial was sponsored by the Società Italiana di Cardiologia Invasiva (GISE, a non-profit organisation), which received grant support from The Medicines Company and Terumo. This substudy did not receive any direct or indirect funding.

Running title: Acute Kidney Injury with Bivalirudin or Unfractionated Heparin

Word count (including text, references, tables and figure legends): 4,633

Twitter handles: @vlgmrc (Marco Valgimigli), @antoniolandii (Antonio Landi)

Corresponding author:

Prof. Marco Valgimigli, MD, PhD

Cardiocentro Ticino Institute

Ente Ospedaliero Cantonale

Via Tesserete, 48

CH-6900, Lugano, Switzerland

Phone: +41 91 805 33 47

Fax: +41 91 805 31 73

e-mail: marco.valgimigli@cardiocentro.org

ABSTRACT (239 words)

Background

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

Among 7,213 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.

Results

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 to 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 to 1.08; $p=0.50$), whereas a >0.5 mg/dl absolute sCr increase occurred in 176 patients (5.0%) with bivalirudin versus 189 patients (5.4%) with UFH (OR: 0.92; 95% CI: 0.75 to 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 to 1.07; $p=0.21$). Subgroup analyses of the primary endpoint suggested a benefit with bivalirudin in patients randomized to femoral access.

Conclusions

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

Trial Registration: [clinicaltrials.gov NCT01433627](https://clinicaltrials.gov/ct2/show/study/NCT01433627)

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 in patients presenting with 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 hemodynamic 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 versus 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 (NSTE-ACS) undergoing invasive management.

METHODS

Study design and population

MATRIX was a program of 3 independent randomized controlled, multicenter, superiority trials (NCT01433627) in patients with ACS undergoing invasive management (14). The first trial (MATRIX-Access) compared radial versus femoral access in 8,404 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 7,213 ACS patients in whom PCI was planned.

MATRIX Treatment Duration compared prolonged bivalirudin administration with a post-PCI infusion versus short-term bivalirudin administration without a post-PCI infusion in 3,610 patients assigned to receive bivalirudin.

Patients with NSTEMI-ACS 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 2 high-risk criteria among the following: 1) age of 60 years or older, elevation of cardiac biomarkers, or electrocardiographic changes compatible with ischemia; and 2) 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 ischemia 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 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 labeling, 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 2 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 to 100 U or 50 to 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 sub-study 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 t-test in case of continuous variables and the chi-square or Fisher exact test in case of categorical data. The differences at lesion level considered the nested structure of lesions within individuals and then were analysed using multilevel 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, Texas).

RESULTS

Among 7,213 patients enrolled in the MATRIX-Antithrombin trial from 78 centers 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 end-stage renal disease on dialysis treatment. Among the 7,085 patients included in the analysis, 3,550 subjects were allocated to bivalirudin and 3,535 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 randomly allocated to receive or not post-PCI bivalirudin infusion are presented in **Supplementary Table 1**.

AKI occurred in 1,213 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 anemia or diabetes) and received higher amounts of contrast volume (**Supplementary Table 2**); 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 Table 2**).

Endpoints according to antithrombotic therapy

Before randomization, sCr and 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 versus 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 in 616 patients (17.4%) in the UFH group (odds ratio [OR] 0.97; 95% confidence interval [CI]: 0.85 to 1.09; $p=0.58$) (**Figure 1, Table 3**). Both components of the AKI primary 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 to 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 to 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 to 1.07; $p=0.21$). Stage 1 or 3 AKI were not reduced but 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 Table 3**.

Subgroups analyses and multivariate modeling

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 modeling, random allocation to radial access was associated with a significantly lower risk of AKI in patients randomized to UFH (**Supplementary Table 4**), while the treatment effect of the randomized access-site on AKI was not observed in those treated with bivalirudin (**Supplementary Table 5**)

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 versus 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 AKI in favor of bivalirudin, albeit not statistically significant. The study results were also mainly consistent across the pre-defined study subgroups. However, in the sub-population 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 versus 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%) versus 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% versus 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 risk of AKI in the overall population or in 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 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 UFH (15) was greater than the one observed with RA versus FA in the MATRIX trial (9). Therefore, our results suggest that bleeding avoidance strategies do not necessarily translate into an effect on AKI prevention. The reasons why RA but not bivalirudin was associated with a lower occurrence of AKI remain speculative but lend support to the role of embolization into the renal circulation.

The observation that bivalirudin may exert a beneficial effect on AKI prevention only among patients who received FA may be a spurious finding. Yet, it may also suggest that a bleeding prevention strategy may mitigate the consequences of renal embolization in a possible two-hit hypothesis whereby renal under-perfusion may be especially detrimental if micro-embolization into the renal district has concomitantly occurred.

Study limitations

Some limitations of this analysis should be considered. Firstly, the independent clinical events committee did not adjudicate AKI events and AKI occurrence relied solely on measurements of sCr values. Since the results of the primary endpoints were negative, differential effects across subgroups of the randomized treatments should be considered hypothesis-generating. As in the AKI-MATRIX study, the intensity of peri-procedural hydration, type of used contrast media or nephrotoxic drugs discontinuation were not systematically collected in the study case report form (6). Thus, we were not able to adjust study outcomes according to these variables. In addition,

time and date of sCr peak during index hospitalization and after discharge were not collected. Finally, MATRIX Antithrombin and Treatment Duration compared two antithrombotic strategies (bivalirudin with bailout GPI versus UFH with planned use of GPI), so the different use of GPI in both treatment arms may represent a potential confounder on study outcomes.

CONCLUSIONS

This study demonstrated that the risk of post-procedural AKI was not significantly lower with bivalirudin compared with UFH and discretionary use of GPI among ACS patients undergoing invasive management.

REFERENCES

1. Tsai TT., Patel UD., Chang TL., et al. Contemporary Incidence, Predictors, and Outcomes of Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Interventions: Insights From the NCDR Cath-PCI Registry. *JACC Cardiovasc Interv* 2014;7(1):1–9. Doi: <https://doi.org/10.1016/j.jcin.2013.06.016>.
2. Valle JA, McCoy LA, Maddox TM, et al. Longitudinal Risk of Adverse Events in Patients With Acute Kidney Injury After Percutaneous Coronary Intervention. *Circ Cardiovasc Interv* 2017;10(4):e004439. Doi: 10.1161/CIRCINTERVENTIONS.116.004439.
3. Azzalini L., Kalra S. Contrast-Induced Acute Kidney Injury - Definitions, Epidemiology, and Implications. *Interv Cardiol Clin* 2020;9(3):299–309. Doi: 10.1016/j.iccl.2020.02.001.
4. Marenzi G., Cosentino N., Bartorelli AL. Acute kidney injury in patients with acute coronary syndromes. *Heart* 2015;101(22):1778 – 1785. Doi: 10.1136/heartjnl-2015-307773.
5. Steinvil A, Garcia-Garcia HM, Rogers T, et al. Comparison of Propensity Score-Matched Analysis of Acute Kidney Injury After Percutaneous Coronary Intervention With Transradial Versus Transfemoral Approaches. *Am J Cardiol* 2017;119(10):1507–11. Doi: 10.1016/j.amjcard.2017.02.032.
6. Andò G., Cortese B., Russo F., et al. Acute Kidney Injury After Radial or Femoral Access for Invasive Acute Coronary Syndrome Management: AKI-MATRIX. *J Am Coll Cardiol* 2017;69(21):2592–603. Doi: <https://doi.org/10.1016/j.jacc.2017.02.070>.
7. Andò G., Gagnano F., Calabrò P., Valgimigli M. Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2018;92(7):E518–26. Doi: <https://doi.org/10.1002/ccd.27903>.
8. Valgimigli M., Gagnor A., Calabrò P., et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015;385(9986):2465–76. Doi: 10.1016/S0140-6736(15)60292-6.

9. Valgimigli M., Frigoli E., Leonardi S., et al. 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. *Lancet* 2018;392(10150):835–48. Doi: 10.1016/S0140-6736(18)31714-8.
10. Rothenbühler M., Valgimigli M., Odutayo A., et al. Association of acute kidney injury and bleeding events with mortality after radial or femoral access in patients with acute coronary syndrome undergoing invasive management: secondary analysis of a randomized clinical trial. *Eur Heart J* 2019;40(15):1226–32. Doi: 10.1093/eurheartj/ehy860.
11. Steg PG., van 't Hof A., Hamm CW., et al. Bivalirudin Started during Emergency Transport for Primary PCI. *N Engl J Med* 2013;369(23):2207–17. Doi: 10.1056/NEJMoa1311096.
12. Zeymer U., van 't Hof A., Adgey J., et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. *Eur Heart J* 2014;35(36):2460–7. Doi: 10.1093/eurheartj/ehu214.
13. Han Y., Guo J., Zheng Y., et al. Bivalirudin vs Heparin With or Without Tirofiban During Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction: The BRIGHT Randomized Clinical Trial. *JAMA* 2015;313(13):1336–46. Doi: 10.1001/jama.2015.2323.
14. Valgimigli M. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. *Am Heart J* 2014;168(6):838-845.e6. Doi: <https://doi.org/10.1016/j.ahj.2014.08.013>.
15. Valgimigli M., Frigoli E., Leonardi S., et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. *N Engl J Med* 2015;373(11):997–1009. Doi: 10.1056/NEJMoa1507854.
16. Slocum NK., Grossman PM., Moscucci M., et al. The changing definition of contrast-induced nephropathy and its clinical implications: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *Am Heart J* 2012;163(5):829–34. Doi:

<https://doi.org/10.1016/j.ahj.2012.02.011>.

17. Andò G., Cortese B., Frigoli E., et al. Acute kidney injury after percutaneous coronary intervention: Rationale of the AKI-MATRIX (acute kidney injury-minimizing adverse hemorrhagic events by TRansradial access site and systemic implementation of angioX) sub-study. *Catheter Cardiovasc Interv* 2015;86(5):950–7. Doi: <https://doi.org/10.1002/ccd.25932>.
18. Narula A., Mehran R., Weisz G., et al. Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy. *Eur Heart J* 2014;35(23):1533–40. Doi: 10.1093/eurheartj/ehu063.
19. Chew DP., Lincoff AM., Gurm H., et al. *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(5):581–5. Doi: 10.1016/j.amjcard.2004.11.003.
20. Mehran R., Nikolsky E., Lansky AJ., et al. 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(8):748–57. Doi: <https://doi.org/10.1016/j.jcin.2009.05.018>.
21. Washam JB, Kaltenbach LA, Wojdyla DM, et al. Anticoagulant Use Among Patients With End-Stage Renal Disease Undergoing Percutaneous Coronary Intervention. *Circ Cardiovasc Interv* 2018;11(2):e005628. Doi: 10.1161/CIRCINTERVENTIONS.117.005628.
22. Marbach JA., Wells G., Santo P Di., et al. Acute kidney injury after radial or femoral artery access in ST-segment elevation myocardial infarction: AKI-SAFARI. *Am Heart J* 2021;234:12–22. Doi: <https://doi.org/10.1016/j.ahj.2020.12.019>.
23. Scolari F, Ravani P, Gaggi R, et al. The Challenge of Diagnosing Atheroembolic Renal Disease. *Circulation* 2007;116(3):298–304. Doi: 10.1161/CIRCULATIONAHA.106.680991.

FIGURE LEGENDS

Graphical abstract. Acute kidney injury in patients with acute coronary syndrome (ACS) undergoing invasive management treated with bivalirudin versus unfractionated heparin (UFH). Abbreviations: SCr, serum creatinine; OR, odds ratio.

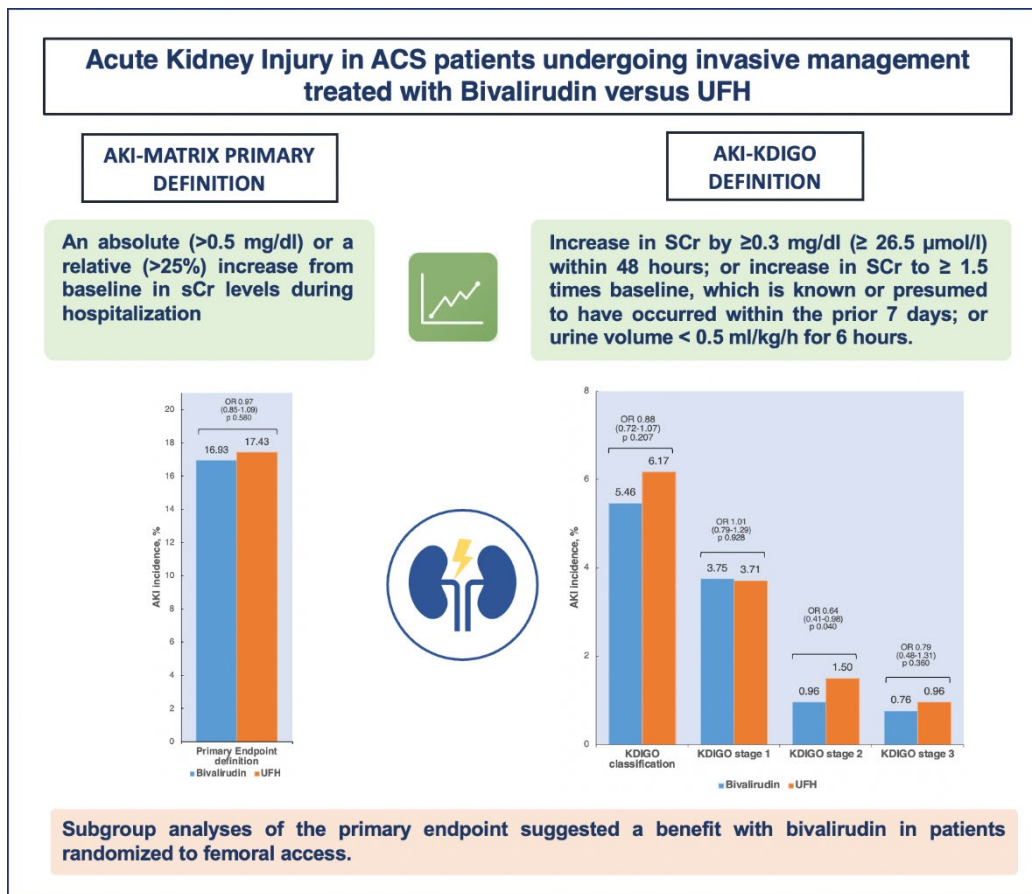


Figure 1. Incidence of AKI in patients randomized to bivalirudin versus UFH and assessed according to primary endpoint definition and KDIGO classification. Abbreviations: AKI= acute kidney injury; UFH= unfractionated heparin; OR= odds ratio; KDIGO= Kidney Disease Improving Global Outcomes.

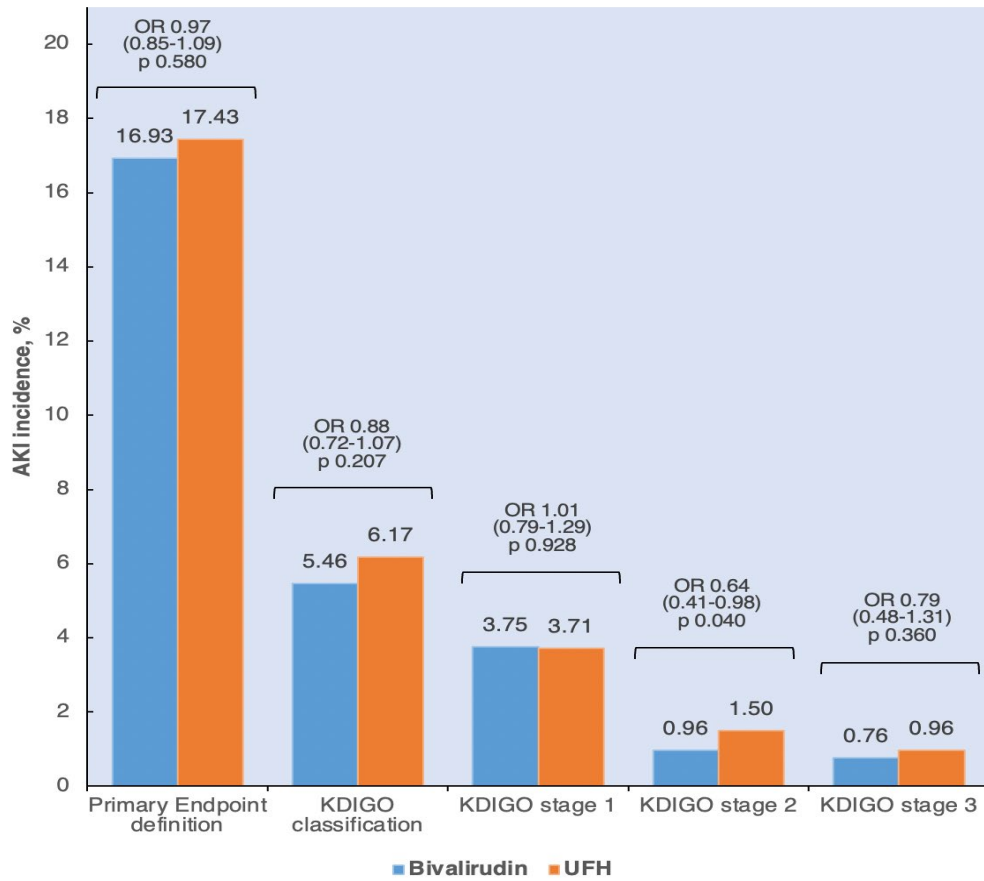


Figure 2. Subgroup analysis of the primary endpoint. Abbreviations: AKI= acute kidney injury; UFH= unfractionated heparin; CI= confidence interval; STEMI= ST-segment elevation myocardial infarction; NSTEMI= non-ST segment elevation acute coronary syndrome; LVEF= left ventricle ejection fraction. * P value for trend across ordered groups.

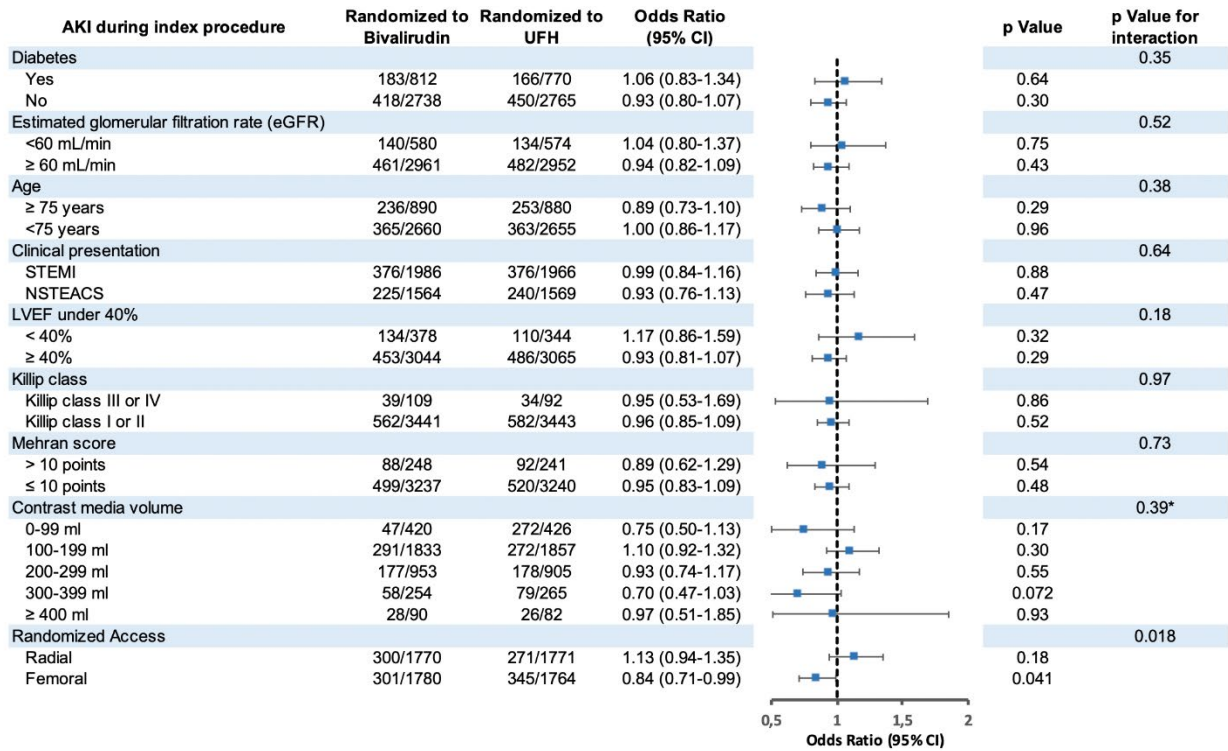


Table 1. Baseline and procedural characteristics. Values are mean \pm SD, n (%), n, or median (interquartile range) [§] systolic blood pressure <80 mmHg; * <12g/dl for women, <13g/dl for men. *Abbreviations: UFH = unfractionated heparin; ACE= Angiotensin-converting enzyme; STEMI= ST-segment elevation myocardial infarction; NSTEMI= non-ST elevation acute coronary syndrome; EF= ejection fraction; Hb= hemoglobin; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; GPI= glycoprotein IIb/IIIa inhibitors; TIMI= thrombolysis in myocardial infarction.*

	Bivalirudin (N=3550)	UFH (N=3535)	p Value
Clinical characteristics			
Age (years)	65.4 \pm 11.9	65.4 \pm 11.8	0.82
\geq 75 years	890 (25.1)	880 (24.9)	0.86
Male sex	2689 (75.7)	2715 (76.8)	0.30
Hypotension [§]	22 (0.6)	35 (1.0)	0.08
Anemia *	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
NSTEMI	1564 (44.1)	1569 (44.4)	0.78
NSTEMI, troponin negative	161 (4.5)	158 (4.5)	0.89
NSTEMI, troponin positive	1403 (39.5)	1411 (39.9)	0.73
NSTEMI with ST-segment deviation	730 (20.6)	726 (20.5)	0.98
NSTEMI with T Wave inversion	441 (12.4)	499 (14.1)	0.04
EF \leq 35%	316 (9.2)	295 (8.7)	0.40
Systolic arterial pressure (mmHg)	138.7 \pm 26.0	138.3 \pm 25.8	0.59
Hb at baseline	14.0 \pm 1.9	14.0 \pm 2.0	0.38
Glucose at baseline	140.7 \pm 65.7	138.2 \pm 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
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
Postdilation	2021 (45.9)	2021 (46.5)	0.57

Table 2. Renal function. Values are mean \pm SD. Abbreviations: eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; other abbreviations as in Table 1.

	Randomized to Bivalirudin (N=3550)	Randomized to UFH (N=3535)	p Value
Creatinine, mg/dL			
Pre-PCI	0.98 \pm 0.35	0.98 \pm 0.34	0.54
Post-PCI	1.08 \pm 0.55	1.08 \pm 0.57	0.64
At hospital discharge	1.00 \pm 0.43	1.01 \pm 0.47	0.40
Creatinine clearance / eGFR, ml/min/1.73m² (MDRD formula)			
Pre-PCI	83.61 \pm 24.98	84.61 \pm 25.69	0.10
Post-PCI	78.39 \pm 24.92	78.89 \pm 26.14	0.41
At hospital discharge	83.69 \pm 25.59	84.15 \pm 26.73	0.46

Table 3. Acute kidney injury (AKI). Abbreviations as in Table 1 and 2. *Excluding patients who underwent angiography only.

	Randomized to Bivalirudin	Randomized to UFH	Odds Ratio (95% CI)	p Value
All patients receiving an angiography and/or PCI	(N=3550)	(N=3535)		
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*	(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 n or n (%) unless otherwise indicated.