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Transient or Persistent Acute Kidney Injury in Patients with Acute Coronary Syndrome

Authors: Antonio Landi[a], MD, Mattia Branca[b], PhD, Sergio Leonardi[c], MD, MHS, Enrico Frigoli[a,b], MD, Pascal Vranckx[d], MD, PhD, Matteo Tebaldi[e], MD, Ferdinando Varbella[f], MD, Paolo Calabro'[g], MD, PhD, Giovanni Esposito[h], MD, PhD, Gennaro Sardella[i], MD, Stefano Garducci[j], MD, Giuseppe Ando'[k], MD, PhD, Ugo Limbruno[l], MD, Paolo Sganzerla[m], MD, Andrea Santarelli[n], MD, Carlo Briguori[o], MD, PhD, Salvatore Colangelo[p], MD, Salvatore Brugaletta[q], MD, Marianna Adamo[r], MD, Elmir Omerovic[s], MD, Dik Heg[b], PhD, Stephan Windecker[t], MD, Marco Valgimigli[a,u], 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] University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
[d] Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium. Faculty of medicine and life sciences, University of Hasselt, Hasselt, Belgium.
[e] Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Cona (FE), Italy.
[f] Cardiology Unit, Ospedali Riuniti di Rivoli, ASL Torino 3, Turin, Italy; Cardiology Unit, Azienda Ospedaliera Universitaria San Luigi Gonzaga Orbassano, Turin, Italy.
[g] Division of Cardiology, "Sant'Anna e San Sebastiano" Hospital, Caserta, Italy; Department of Translational Medicine, University of Campania "Luigi Vanvitelli," Caserta, Italy.
[h] Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy.
[i] Department of Cardiovascular Sciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy.
[j] Unità Operativa Complessa di Cardiologia, ASST della Brianza (MB), Vimercate Hospital, Italy.
[k] Azienda Ospedaliera Universitaria Policlinico "Gaetano Martino", University of Messina, Messina, Italy.
[l] Cardiology Department, Misericordia Hospital, Grosseto, Italy.
[m] IRCCS Istituto Auxologico Italiano, Ospedale San Luca, Milano.
[n] Cardiovascular Department, Infermi Hospital, Rimini, Italy.
[o] Interventional Cardiology Unit, Mediterranea Cardiocentro, Naples, Italy.
[p] Division of Cardiology, San Giovanni Bosco Hospital, ASL Città di Torino, Turin, Italy.
[q] Hospital Clínic, Cardiovascular Clinic Institute, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain.
[r] Cardiology and Cardiac Catheterization Laboratory, Cardio-Thoracic Department, Civil Hospitals, University of Brescia, Brescia, Italy.
[s] Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
[t] Department of Cardiology, Inselspital, University of Bern, Bern, Switzerland
[u] Department of Biomedical Sciences, University of Italian Switzerland, Lugano, Switzerland.

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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 53 47
Fax: +41 91 805 31 73
e-mail: marco.valgimigli@eoc.ch

Abbreviation list

ACS, acute coronary syndrome

AKI, acute kidney injury

MATRIX, Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX

OR, odds ratio

HR, hazard ratio

PCI, percutaneous coronary intervention

STEMI, ST-Elevation myocardial infarction

NSTEMI, non-ST segment elevation myocardial infarction

ABSTRACT (250 words)

Background The occurrence of acute kidney injury (AKI) among acute coronary syndrome (ACS) patients undergoing invasive management is associated with worse outcomes. However, the prognostic implications of transient or persistent AKI at discharge may differ.
Objectives To evaluate the prognostic implications of transient or persistent AKI in ACS patients.
Methods. In the MATRIX trial, 203 subjects were excluded due to incomplete information or end-stage renal disease, with a study population of 8,201 patients. Transient and persistent AKI were defined as renal dysfunction no longer or still fulfilling the AKI criteria (>0.5 mg/dL or a relative >25% increase in creatinine) at discharge, respectively. 30-day co-primary outcomes were the out-of-hospital composites of death, myocardial infarction, or stroke (major adverse cardiovascular events, MACE), and net adverse cardiovascular events, (NACE), defined as the composite of MACE or BARC type 3-5 bleeding.
Results. Persistent and transient AKI occurred in 750 (9.1%) and 587 (7.2%) subjects, respectively. After multivariable adjustment, compared with patients without AKI, the risk of 30-day co-primary outcomes was higher in patients with persistent AKI (MACE, adjusted hazard ratio [adjHR]: 2.32; 95% confidence interval [CI]: 1.48-3.64; P<0.001; NACE,adjHR: 2.29; 95%CI: 1.48-3.52; P<0.001), mainly driven by all-cause mortality (adjHR: 3.43; 95% CI: 2.03-5.82; P<0.001), whereas transient AKI was not associated with higher rates of MACE or NACE. Results remained consistent by implementing the Kidney Disease Improving Global Outcomes (KDIGO) criteria.
Conclusions Among ACS patients undergoing invasive management, persistent, but not transient AKI at discharge, was associated with higher risks of 30-day MACE and NACE.

Trial Registration: clinicaltrials.gov NCT01433627

CONDENSED ABSTRACT (74 words)

In the MATRIX trial, persistent and transient AKI at discharge occurred in 9.1% and 7.2% of subjects, respectively. After multivariable adjustment, the risk of MACE and NACE was significantly higher in patients with persistent, but not transient AKI. By implementing KDIGO criteria, persistent AKI remained associated with higher hazards of MACE and NACE.

Keywords: transient acute kidney injury; persistent acute kidney injury; acute coronary syndrome; percutaneous coronary intervention.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication after percutaneous coronary intervention (PCI), ranging from 3% to 13%, and is associated with prolonged hospital stay and worse outcomes (1) (2). AKI occurs more frequently in patients with acute coronary syndrome (ACS) undergoing intervention (3–5) who incur, if develop AKI, a higher ischemic and bleeding events (6). Advocated mechanisms for AKI in ACS patients include the need for larger volume of contrast medium, hemodynamic instability, left ventricular (LV) dysfunction resulting in impaired systemic and renal perfusion and cholesterol embolization (3). Radial access, but not periprocedural anti-thrombotic selection (7), has been shown to mitigate the risk of AKI (8), most likely as a result of lower risk of cholesterol embolization to the renal circulation and/or as bleeding prevention strategy.

The increase in serum creatinine (SCr) levels may be transient in patients developing AKI, whereas a not negligible proportion of subjects may develop a ~~persistent~~ impairment of renal function which persists over time (9–11). Normalization of SCr levels in AKI patients may also underlie a subtle (but potentially clinically relevant) kidney damage, which similarly carry prognostic implications. Thus far, available literature data provided conflicting evidence regarding the impact of transient AKI on clinical outcomes, with some studies showing similar survival rates compared with no-AKI patients (9–11), while others did not (12). Additionally, these studies were retrospective, involved non-contemporary PCI cohorts and were limited by the small sample size, the different definitions of AKI recovery and the low proportion of ACS patients. Therefore, the differential impact of transient compared with persistent AKI at discharge on clinical outcomes remains uncertain.

Whether the predictors of persistent or transient AKI differ is also unclear, which might allow the implementation of dedicated preventive and treatment strategies.

We sought to investigate the predictors and prognostic relevance of transient versus persistent AKI at-hospital discharge in ACS patients who underwent invasive management from the *Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX* (MATRIX)- trial (13,14).

METHODS

Study design and population

This is a *post-hoc* analysis of the MATRIX trial, a program of 3 independent randomized controlled, multicenter, superiority trials (NCT 01433627) in patients with ACS undergoing invasive management (15). The first trial (MATRIX-Access) compared radial versus femoral access in 8,404 patients with ACS (14,16) and the effects of access site on AKI (AKI-MATRIX sub-study) have been previously reported (8). The MATRIX- Antithrombin and Treatment duration compared bivalirudin versus unfractionated heparin (UFH) and prolonged post-PCI bivalirudin infusion versus short-term bivalirudin administration in patients undergoing PCI (13). The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent.

The inclusion and exclusion criteria of the MATRIX trial were previously reported (15).

All patients enrolled in the MATRIX trial 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.

Transient and persistent AKI definitions

The primary AKI study definition was the incidence of either an absolute (>0.5 mg/dL) or a relative (>25%) increase in serum creatinine (sCr) at peak within hospitalization from the pre-intervention value. We also implemented the kidney disease improving global outcomes (KDIGO) criteria and staged for severity based on an absolute (≥ 0.3 mg/dl) or a relative (≥1.5 times) increase of sCr levels within hospitalization compared with baseline values. For both definitions, transient and persistent AKIs were those no longer or still fulfilling the criteria at discharge sCr value, respectively.

Follow-up and study outcomes

The outcomes of the MATRIX program and AKI-MATRIX study have been previously reported (8,13,14). The two co-primary endpoints of this sub-study were 30-day major adverse cardiovascular events (MACE), defined as the out-of-hospital composites of all-cause death, myocardial infarction (MI), or stroke, and net

adverse clinical events (NACE), defined as the out-of-hospital composite of MACE or major bleeding not related to coronary artery bypass grafting (Bleeding Academic Research Consortium [BARC] type 3 or 5) in patients with transient or persistent AKI according to the primary AKI-MATRIX definition (8). Secondary endpoints included each component of the co-primary outcomes, cardiovascular mortality, transient ischemic attack, and target vessel revascularization (TVR). As secondary endpoints, ischemic and bleeding events were also assessed at 1 year. Furthermore, primary and secondary endpoints were evaluated by implementing the KDIGO definition or in patients matching only the primary AKI definition (i.e., excluding those who matched AKI-KDIGO criteria). An independent clinical events committee, blinded to treatment allocation, adjudicated all adverse events.

Statistical analysis

All analyses were performed according to the intention-to-treat principle and clinical events at 30 days or 1 year after randomization were considered. 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. Primary and secondary outcomes were analyzed as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding 2-sided p values. For the present analysis, to take into account differences in baseline characteristics among study groups, dedicated multivariable models were implemented to obtain adjusted outcomes, including the following variables by pairwise selection: (1) Mehran Score, loop diuretics or other diuretics use, statins, beta-blockers, coronary artery bypass grafting (CABG), LV ejection fraction (EF) <35%, any crossover during index hospitalization, glycoprotein IIb/IIIa inhibitors (GPI) or bivalirudin use, UFH, Hb nadir < 9g/dL, access site-related BARC type 2, 3 or 5 bleeding; (2) gender, hypercholesterolemia, hypertension, family history of CAD, Mehran Score, LVEF < 30%, loop diuretics use, CKD, STEMI at clinical presentation, no significant lesions at baseline angiography, UFH total dose and Hb nadir < 9g/dL. Sensitivity analyses were also performed in patients who presented persistent or transient AKI according to modified AKI-KDIGO definition and in those who matched only the primary AKI definition (i.e. excluding those who matched the AKI-KDIGO criteria). In patients with AKI, continuous relation between creatinine values and estimated glomerular filtration rate

(eGFR) at discharge with MACE and NACE was assessed using restricted cubic splines. The analyses were done using Stata release 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

Study population

Among 8,404 patients enrolled in the MATRIX trial from 78 centers in Italy, the Netherlands, Spain, and Sweden between October 2011 and July 2014, 203 patients (2.4%) were excluded due to incomplete sCr data or end-stage renal disease on dialysis treatment. Among the 8,201 remaining patients, AKI occurred in 1,337 (16.3%) according to the primary definition, of whom 587 (7.2%) had transient and 750 had (9.1%) persistent AKI at discharge.

Clinical and procedural characteristics

Baseline and procedural characteristics of the study population are detailed in **Table 1** and **Supplementary Table 1**.

Patients with persistent AKI at discharge were older and more frequently female compared with transient AKI group. Diabetes mellitus, hypertension, peripheral vascular disease, STEMI at clinical presentation and advanced Killip class were more common in either transient or persistent AKI groups. Angiotensin II receptor antagonist and loop diuretics were more frequently used before catheterization in both AKI groups, whereas statins or beta-blockers were more frequently used in patients without AKI. Access site crossover, contrast media volume (CV) and CV/ eGFR ratio were higher in patients with compared with subjects without AKI (**Supplementary Table 1**). AKI patients presented more commonly complex coronary lesions involving the left coronary system and underwent more frequently > 1 vessel PCI. Intra-aortic balloon pump (IABP) use was 3-fold higher in AKI patients ($p< 0.001$). Hospitalization was longer in patients with AKI (median time 6 days, interquartile range [IQR]: 4 to 10 days) compared with no AKI subjects (median time: 4 days, IQR: 2 to 6 days, $p< 0.001$).

At baseline, patients with persistent AKI at discharge had lower sCr and higher eGFR compared with patients with transient AKI or no AKI (**Table 2**). Peak sCr and nadir eGFR did not differ after intervention between transient and persistent AKI group, whereas sCr and eGFR change from baseline to peak values

were significantly higher in patients with persistent compared with transient AKI (**Figure 1**). At discharge, sCr (1.4 ± 1.0 mg/dL) and eGFR (60.9 ± 26.4 ml/min/1.73 m^2) were respectively higher and lower in the persistent compared with transient AKI groups.

Clinical outcomes

Unadjusted outcomes at 30 days and 1 year

Compared with no-AKI **(Supplementary Table 5)**, persistent AKI at discharge was associated with higher hazards of 30-day (HR: 3.78; 95% CI: 2.54 to 5.63; P < 0.001) and 1-year (HR: 2.48; 95% CI: 1.95 to 3.15; P< 0.001) MACE, as well as 30-day (HR: 3.59; 95% CI: 2.45 to 5.26; P < 0.001) and 1 -year (HR: 2.40; 95% CI: 1.90 to 3.04; P<0.001) NACE, owing to higher risk of cardiovascular mortality and BARC 3 to 5 bleeding. Transient AKI resulted in comparable rates of 30-day MACE (HR]: 1.65; 95% confidence interval [CI]: 0.90 to 3.02; p=0.103) and NACE (HR: 1.60; 95% CI: 0.90 to 2.86; p=0.110) but higher risks of 1-year MACE (HR: 1.47; 95% CI: 1.06 to 2.04; P=0.019) and NACE (HR: 1.50; 95% CI: 1.10 to 2.04; P=0.011), due to higher risk of all-cause and cardiovascular mortality **(Figure 2, Supplementary Table 5)**.

Multivariable modeling for persistent and transient AKI

At multivariable logistic regression analysis, independent predictors of any (Table S2), persistent (Table S3) or transient (Table S3) AKI were in large overlap.

Adjusted outcomes

30-day outcomes

Compared with no-AKI group, persistent AKI was associated with a significantly higher risk for 30-day MACE (adjusted [adj] HR: 2.32; 95% CI: 1.48 to 3.52; p < 0.001) and NACE (adjHR: 2.29; 95% CI: 1.48 to 3.52; p< 0.001), owing to higher all-cause and cardiovascular mortality (**Table 3, Central illustration**). The rates of BARC type 3 or 5 bleeding did not significantly differ in patients who developed persistent AKI compared with no AKI (adjHR:1.22; 95% CI: 0.44 to 3.42; p= 0.700).

The risks for 30-day MACE (adjHR: 0.67; 95% CI: 0.31 to 1.43; p= 0.299) or NACE (adjHR: 0.71; 95% CI: 0.34 to 1.46; p= 0.353) and their individual components did not differ between transient AKI and no-AKI groups (**Table 3, Central illustration**).

Outcomes at 1 year

Compared with no-AKI group, persistent AKI was associated with a significantly higher risk for 1-year MACE (adjHR: 1.78; 95% CI: 1.38 to 2.30; p< 0.001) and NACE (adjHR: 1.77; 95% CI: 1.38 to 2.27; p< 0.001) as well as cardiovascular and non-cardiovascular mortality (**Table 3, Figure 2**). BARC type 3 or 5 bleeding did not significantly differ in patients who developed persistent AKI compared with no AKI (adjHR:0.99; 95% CI: 0.42 to 2.31; p= 0.975).

The risks for 1-year MACE (adjHR: 0.92; 95% CI: 0.64 to 1.33; p = 0.661), NACE (adjHR: 0.97; 95% CI: 0.68 to 1.38; p = 0.860), or its individual components did not differ between transient AKI and no-AKI groups (**Table 3, Figure 2**).

Sensitivity analyses and splines functions

By implementing the KDIGO criteria**,** AKI occurred in 451 patients (5.5%), of whom 189 (2.3%) with transient and 262 (3.2%) with persistent AKI at discharge. Independent predictors of transient or persistent AKI at discharge according to the AKI-KDIGO definition are displayed in the **Supplementary tables 6-8**. Sensitivity analyses by implementing the KDIGO criteria (**Table 4, Supplementary table 9**), or excluding AKI-KDIGO patients from those matching the AKI primary definition (**Supplementary table 10**) showed consistent results on primary and secondary outcomes, so that persistent but not transient AKI at discharge remained associated with worse outcomes, consistently across definitions. Spline functions show the continuous relationship between kidney function at discharge, in terms of creatinine values or eGFR in patients with persistent or transient AKI on 1-year MACE and NACE (**Supplementary Figures 1 and 2**).

DISCUSSION

The interplay between AKI and residual renal function impairment thereafter is likely multifactorial in etiology, involving multiple mechanisms which may ~~favor or~~ hinder a complete reversal of renal dysfunction. To the best of our knowledge, this is the largest and the only multi-center analysis disentangling

the impact of transient or persistent AKI at discharge on clinical outcomes in ACS patients undergoing invasive management. The main findings of the present study can be summarized as follows:

1. Persistent AKI at discharge was associated with higher risks of 30-day and 1-year MACE or NACE, mainly driven by >3-fold higher rates of all-cause mortality compared with no-AKI patients.
2. Transient AKI occurred in more than one third of AKI patients and did not affect the occurrence of MACE or NACE after multivariable adjustment.
3. These results remained consistent after implementing the AKI-KDIGO criteria and in patients matching only the AKI primary definition (i.e., excluding those matching the AKI-KDIGO criteria).
4. The risk factors for transient or persistent AKI largely overlapped.

The prevalence of AKI varies largely across studies depending on the definition and the investigated populations (3,4,8–12). Using the prespecified AKI definition, we found, in ACS patients undergoing invasive management, a rate of AKI of 16.3%, whereas the use of AKI-KDIGO criteria was associated with a roughly 3-fold lower prevalence of AKI. An additional finding of our study was that 56.1% of AKI patients according to the primary definition and 58.4% per the AKI-KDIGO criteria had persistent renal impairment at hospital discharge. Although the independent association between AKI and mortality has been previously reported, it is well known that the renal function recovers to (near)normal in a sizable proportion of patients thereafter. Only a paucity of prior single center studies has focused so far on the prognostic role of transient versus persistent AKI. It remained therefore unclear if AKI carries a different mortality risk depending on the degree of reversibility.

Evidence available prior to this study

In large single center prospective study of 7,763 consecutive patients undergoing PCI from 2000 to 2006, AKI, defined as ≥0.5 mg/dL increase in creatinine within 48 hours, occurred in 3.2 % of the patients overall and persisted at 2 weeks in 54.6% of the AKI patients (12). Both transient and persistent AKI patients suffered from similarly higher mortality risk at follow-up compared with no AKI patients after multivariable adjustment (12).

Wi et al reported on a single-center cohort of 1,041 AMI patients undergoing PCI, in whom the AKI definition was identical to our primary AKI study definition (9). AKI occurred in 148 (14.2%) patients, of whom 68 (45.9%) had persistent AKI at 1 month. AKI occurrence was independently associated with higher mortality at 2-year follow-up (9). While the highest unadjusted mortality risk was observed among patients with persistent AKI, transient AKI was also associated with higher risk compared with no-AKI patients. However, it remained unclear if transient AKI carries per se independent mortality risk as no multivariable adjustment was made separately for patients with or without persistent AKI. Maioli et al investigated the occurrence of AKI, defined as an absolute increase ≥0.5 mg/dL over baseline serum creatinine, in a single center cohort of 1,490 patients undergoing coronary angiography with preexistent moderate-to-severe renal dysfunction (10). The overall incidence of AKI was 12.1%, and persistent renal dysfunction at 3 months occurred in 18.6% of AKI patients (10). Similar to prior study, mortality was highest in patients with persistent renal dysfunction and intermediate in patients with transient AKI compared with no-AKI patients. Yet, this study did not specifically assess whether transient AKI was an independent mortality risk predictor. A subsequent retrospective single center study of 952 consecutive patients who underwent primary percutaneous coronary intervention for acute myocardial infarction suggested that persistent (at 2 weeks) but not transient AKI (using our primary study definition) was associated with higher mortality (11). However, no multivariable adjustment was implemented and the relatively low number of included AKI patients (55 with transient; 29 with persistent) suggests a cautious interpretation of the results given the chance of a type II error.

Evidence from the present study

In line with the majority of prior studies, we observed an increased risk of MACE and NACE at short and long-term follow-up in patients with both transient and persistent AKI at discharge. However, only persistent and not transient AKI at discharge remained associated with higher mortality rate after extensive multivariable adjustment, which was made possible thanks to the large number of persistent and transient AKI patients in our dataset. In the present study, both patients with transient and persistent AKI had more frequently diabetes mellitus, known CKD, previous MI, history of PCI or Killip class III or IV, higher Mehran score or were exposed to larger contrast volumes. However, after adjustments at multivariable

analysis, only persistent AKI remained associated with higher all-cause and cardiovascular mortality, suggesting that a persistent more than a transient renal damage could, interpedently form other risk factors, affect the risk of fatal events. Interestingly, the independent predictors of persistent AKI largely overlapped with those associated with transient AKI, whereas renal damage at peak, expressed either in terms of absolute creatinine or eGFR change, was greater in the former group.

Our findings were entirely corroborated using the AKI-KDIGO criteria, which identified a much lower prevalence of overall AKI, yet only patients with persistent AKI at discharge experienced higher mortality risk after multivariable adjustment. Since the AKI-KDIGO criteria are more stringent than our primary AKI definition for the identification of post-contrast exposure renal damage, we also investigated the consistency of the study results in patients fulfilling only the latter framework (i.e. patients with only milder renal damage). Even in the context of this selected AKI patient group, a milder degree of persistent renal damage at discharge independently identified patients with higher mortality risk whereas transient AKI patients did not incur worse prognosis.

These observations confirm previous findings suggesting that AKI is a global risk factor of mortality and extend previous observations by proposing that only residual renal damage, even if mild, at discharge, identifies a subset of AKI patients in whom AKI might per se contributes to the higher mortality risk.

It should be noted that the prevalence of persistent AKI was higher in our compared with previous studies. This most likely reflects the earlier time frame which was adopted here (i.e., at discharge) for the identification of persistent AKI compared with prior studies, which enforced renal function assessment at later follow-up times (from 2 weeks to 3 months). It is therefore likely that the prevalence of truly persistent AKI may further diminish over time after hospital discharge. Future research is needed to assess whether a reassessment of residual renal damage at time points later than discharge might further refine the population at risk after AKI for more personalized surveillance and therapeutic approaches.

Study limitations

Several limitations of this analysis should be considered. Firstly, the intensity of peri-procedural hydration or type of contrast media were not systematically collected in the study case report form (8), not allowing any adjustment of study outcomes according to these two variables. Secondly, the exact timing of sCr peak

during index hospitalization and sCr values after hospitalization were not collected. Thirdly, renal outcomes (as the need for renal replacement therapy or renal transplant) were not collected and the potential different impact of transient or persistent AKI on these endpoints at long-term could not be established. Fourth, patients with severe CKD (eGFR of less than 30 ml/min/1.73 m^2) or on dialysis treatment were excluded from the MATRIX trial, thus our results are not generalizable to that patient populations. Finally, persistent AKI at discharge might only be a proxy of truly residual renal impairment after AKI.

CONCLUSIONS

In a large cohort of ACS patients undergoing invasive management, persistent but not transient AKI at discharge was an independent risk factor for mortality at 1 year follow-up, despite sharing overlapping clinical and procedural features. Our results suggest that AKI during hospitalization is a global marker of greater mortality risk in ACS patients whereas only persistent renal damage at discharge seems to directly contribute to worse prognosis after an invasive management.

CLINICAL PERSPECTIVES

Competency in Patient Care and Procedural Skills: In invasively managed patients with ACS, persistent, (but not transient) AKI at discharge is associated with higher risks of MACE and NACE despite sharing overlapping clinical and procedural features.

Translational Outlook: AKI during hospitalization is a global marker of greater mortality risk in ACS patients whereas only persistent impairment of renal function at discharge seems to directly contribute to worse prognosis after an invasive management.

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FIGURE LEGENDS

Figure 1. Renal function variation from baseline to post-PCI values according to the AKI primary definition. Values are mean ± SD. Estimated glomerular filtration rate (eGFR) is calculated through MDRD (Modification of Diet in Renal Disease) formula. 8 patients with creatinine change of more than 5 mg/dl and eGFR change of more than 40 ml/min/1.73 m^2 in the persistent AKI group are not presented in the figure. *Abbreviations: PCI, percutaneous coronary intervention; AKI, acute kidney injury*.

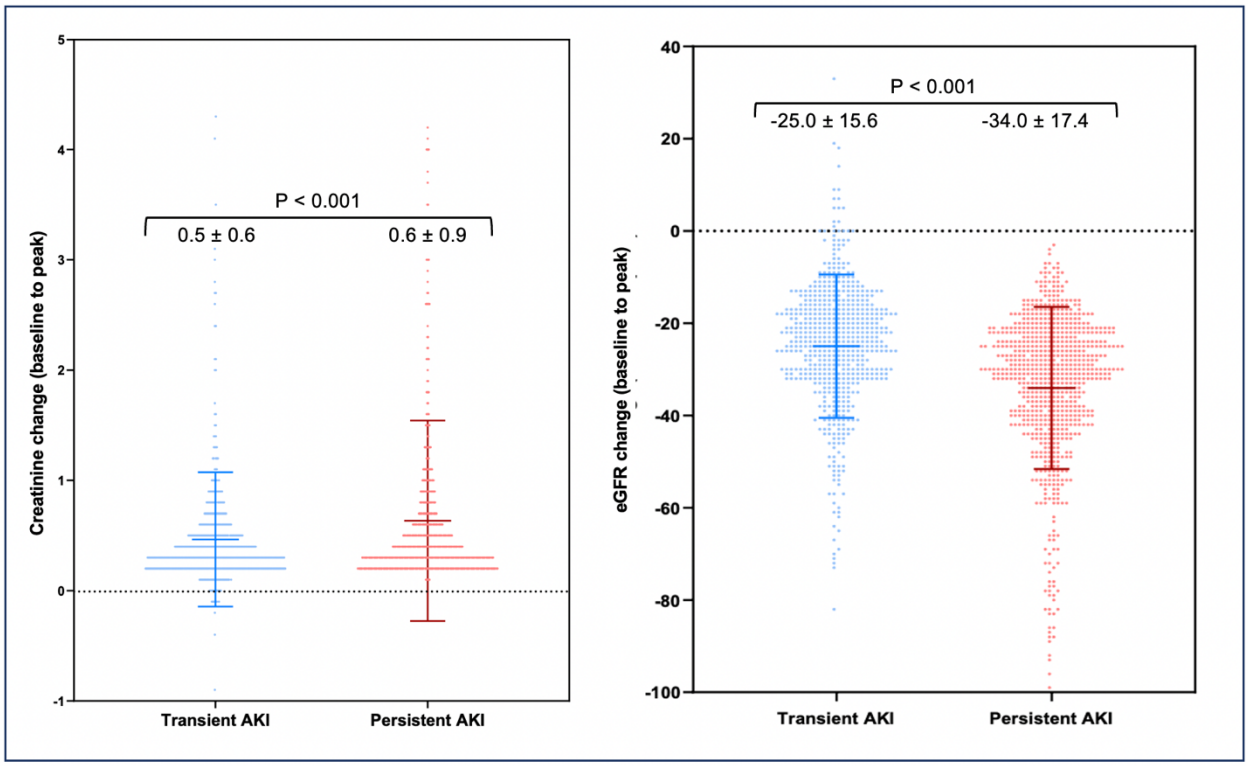
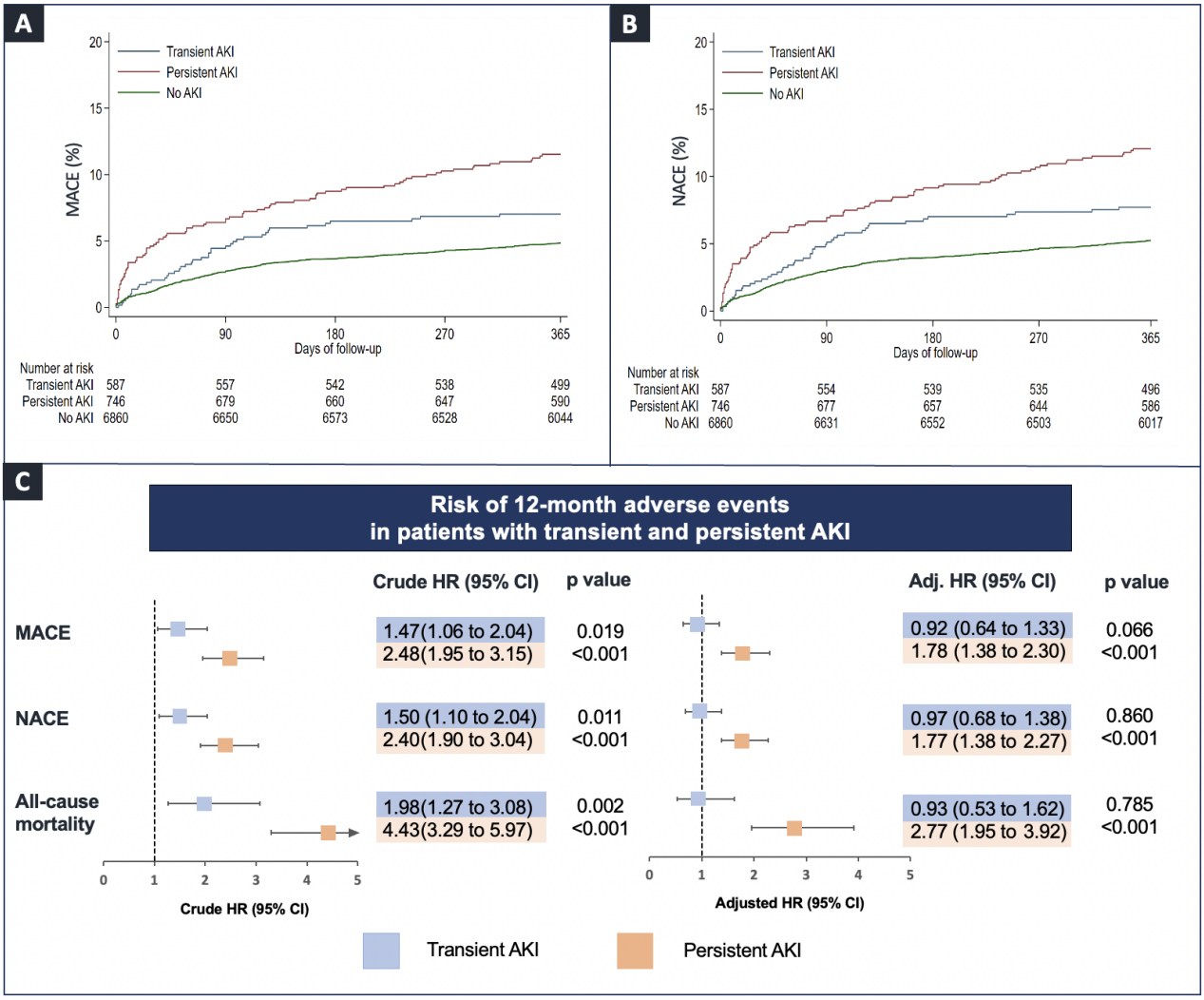


Figure 2. 1-year adverse events in patients with transient and persistent acute kidney injury (AKI) compared with no AKI patients. Kaplan-Meier estimates for major adverse clinical events (MACE) and net adverse clinical events (NACE) are presented in panels A and B, respectively. Unadjusted and adjusted adverse events are presented in panel C. *Abbreviations: HR= hazard ratio; CI= confidence interval.*



CENTRAL ILLUSTRATION. Adjusted clinical outcomes at 30 days and 1 year in patients with transient and persistent acute kidney injury (AKI). *Abbreviations: ACS, acute coronary syndrome; SCr, serum creatinine; Adj., adjusted; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; NACE, net adverse clinical events; BARC, bleeding academic research consortium.*

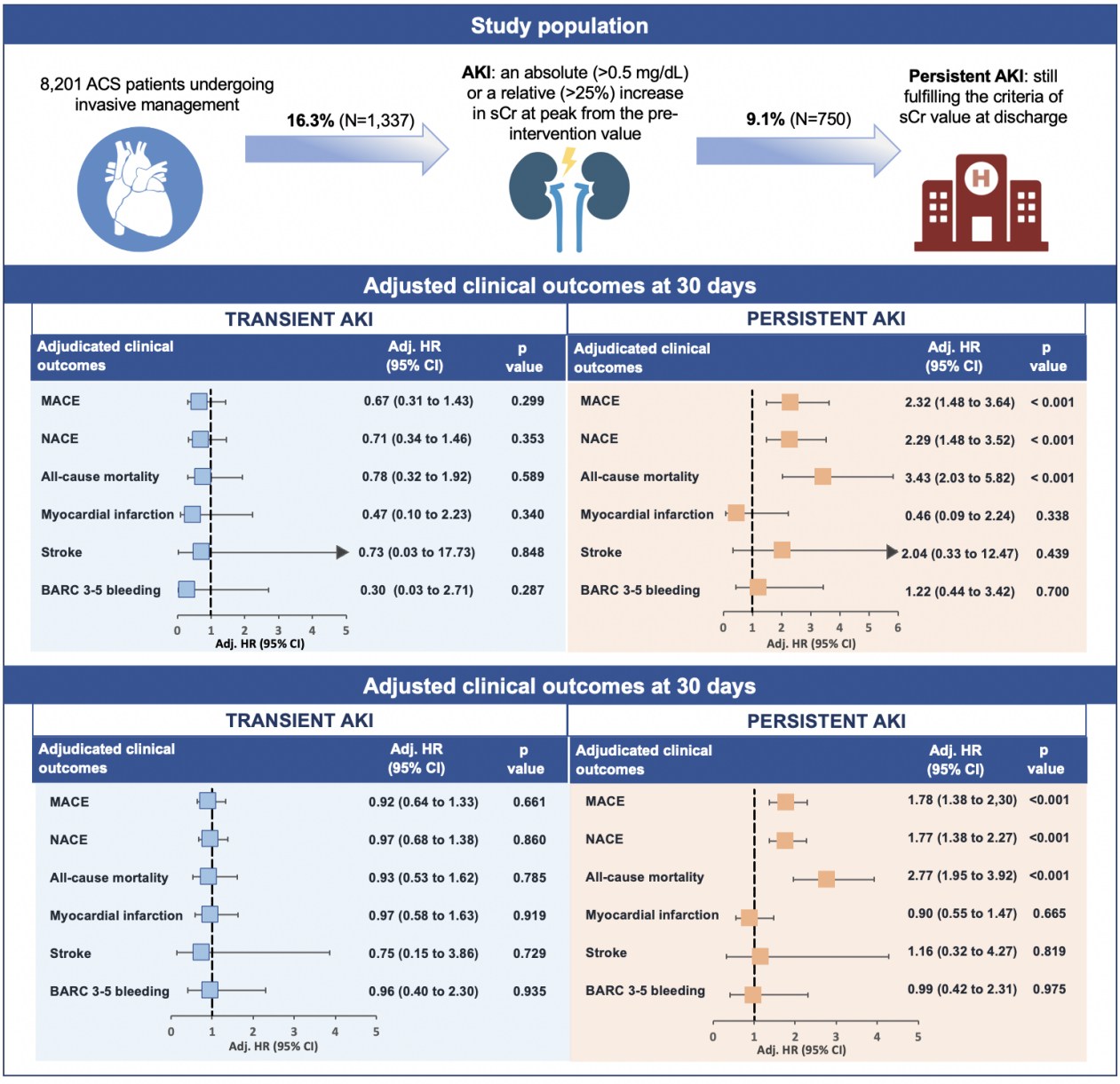


Table 1. Baseline characteristics. *Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndrome; LVEF= left ventricular ejection fraction; ACE= Angiotensin-converting enzyme.*

	Transient AKI (n= 587)	**Persistent AKI (n= 750)**	**No AKI (n= 6864)**	**p Value for trend**	**P value (Transient vs Persistent AKI)**
Clinical characteristics					
Age ≥ 75 years	212 (36%)	312 (42%)	1586 (23%)	<0.001	0.042
Male	415 (71%)	454 (61%)	5163 (75%)	<0.001	<0.001
BMI (kg/m^2)	27.0 ± 4.2	27.0 ± 4.2	27.1 ± 4.2	0.630	0.781
Diabetes mellitus	171 (29%)	221 (29%)	1459 (21%)	<0.001	0.904
Current smoking	184 (31%)	203 (27%)	2455 (36%)	<0.001	0.089
Hypercholesterolemia	243 (41%)	298 (40%)	3064 (45%)	0.016	0.575
Hypertension	406 (69%)	529 (71%)	4261 (62%)	<0.001	0.589
Family history of CAD	140 (24%)	166 (22%)	1932 (28%)	<0.001	0.471
Previous MI	94 (16%)	113 (15%)	967 (14%)	0.365	0.648
Previous PCI	75 (13%)	92 (12%)	1003 (15%)	0.123	0.803
Previous CABG	26 (4%)	26 (3%)	200 (3%)	0.100	0.394
Previous CVA	46 (8%)	53 (7%)	311 (5%)	<0.001	0.600
Peripheral Vascular Disease	68 (12%)	81 (11%)	545 (8%)	0.001	0.662
COPD	47 (8%)	67 (9%)	408 (6%)	0.002	0.556
Anemia †	144 (25%)	199 (27%)	1259 (18%)	<0.001	0.413
CKD (eGFR<60 mL/min)	143 (24%)	155 (21%)	1083 (16%)	<0.001	0.112
Creatinine at baseline >1.5 mg/dl	54 (9%)	51 (7%)	295 (4%)	<0.001	0.124
Mehran Score	5.6 ± 4.3	5.6 ± 4.4	3.7 ± 3.4	<0.001	0.986
Cardiac arrest	14 (2%)	14 (2%)	135 (2%)	0.761	0.566
Killip class III or IV	32 (5%)	44 (6%)	152 (2%)	<0.001	0.812
STEMI	338 (58%)	405 (54%)	3201 (47%)	<0.001	0.202
NSTE-ACS troponin negative	23 (4%)	31 (4%)	434 (6%)	0.005	0.889
NSTE-ACS troponin positive	226 (39%)	314 (42%)	3229 (47%)	<0.001	0.217
NSTE-ACS with T wave inversion	83 (14%)	97 (13%)	1113 (16%)	0.034	0.520
NSTE-ACS with ST deviation	132 (22%)	164 (22%)	1642 (24%)	0.360	0.791
Hypotension*	6 (1%)	9 (1%)	44 (1%)	0.152	0.801
LVEF <35%	87/567 (15%)	136 /733(19%)	473/6599 (7%)	<0.001	0.138
Medications administered before catheterization					
ACE inhibitors	164 (28%)	227 (30%)	2100 (31%)	0.405	0.364
Angiotensin II receptor antagonist	77 (13%)	95 (13%)	725 (11%)	0.046	0.806
Statins	197 (34%)	287 (38%)	3095 (45%)	<0.001	0.085

Beta blockers	188 (32%)	286 (38%)	2896 (42%)	<0.001	0.021
Loop Diuretics	94 (16%)	138 (18%)	702 (10%)	<0.001	0.275
Potassium-sparing diuretics	12 (2%)	23 (3%)	145 (2%)	0.231	0.301
Other diuretics	24 (4%)	23 (3%)	161 (2%)	0.023	0.370

Values are mean ± SD, n (%), n, or median (interquartile range). † <12g/dl for women, <13g/dl for men; § systolic blood pressure <80 mmHg.

Table 2. Laboratory data. Values are mean ± SD. *Abbreviations: eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention*

	Transient AKI (N=587)	**Persistent AKI (N=750)**	**No AKI (N=6864)**	**p Value for trend**	**P value (Transient vs Persistent AKI)**
Creatinine (mg/dL)	1.0 ± 0.5	0.9 ± 0.4	1.0 ± 0.3	<0.001	<0.001
Creatinine peak (mg/dL)	1.5 ± 0.9	1.5 ± 1.1	1.0 ± 0.3	<0.001	0.459
Creatinine at hospital discharge (mg/dL)	1.1 ± 0.5	1.4 ± 1.0	0.9 ± 0.3	<0.001	<0.001
Creatinine change (mg/dL, baseline to peak)	0.5 ± 0.6	0.6 ± 0.9	0.0 ± 0.1	<0.001	<0.001
eGFR at baseline	82.2 ± 31.1	92.1 ± 35.5	83.1 ± 23.3	<0.001	<0.001
eGFR post-PCI	57.3 ± 24.0	58.1 ± 26.7	83.1 ± 23.6	<0.001	0.531
eGFR at hospital discharge	77.9 ± 28.8	60.9 ± 26.4	87.0 ± 24.7	<0.001	<0.001
eGFR change (baseline to peak)	-25.0 ± 15.6	-34.0 ± 17.4	0.0 ± 13.3	<0.001	<0.001
Hemoglobin (g/dl)	12.8 ± 19.6	12.8 ± 19.3	11.8 ± 16.6	0.135	0.985
Hemoglobin nadir (g/dl)	11.9 ± 2.3	12.0 ± 2.2	12.9 ± 1.8	<0.001	0.249

Table 3. Adjusted clinical outcomes in acute kidney injury (AKI) patients according to the study primary definition. *Abbreviations: MACE, major adverse clinical events; NACE, net adverse clinical events; TVR, target vessel revascularization; BARC, Bleeding Academic Research Consortium; HR, hazard ratio; CI, confidence interval.* [x] Transient AKI vs no AKI; [y] Persistent AKI vs no AKI.

	Transient AKI (N= 587)	Persistent AKI (N=750)	No AKI (N= 6864)	p Value	Adjusted HR (95% CI)[x]	P Value	Adjusted HR (95% CI)[y]	P Value
30 days								
MACE	12 (2%)	34 (5%)	85 (1%)	<0.001	0.67 (0.31 to 1.43)	0.299	2.32 (1.48 to 3.64)	<0.001
NACE	13 (2%)	36 (5%)	95 (1%)	<0.001	0.71 (0.34 to 1.46)	0.353	2.29 (1.48 to 3.52)	<0.001
All-cause mortality	9 (2%)	31 (4%)	50 (1%)	<0.001	0.78 (0.32 to 1.92)	0.589	3.43 (2.03 to 5.82)	<0.001
Cardiovascular death	6 (1%)	29 (4%)	43 (1%)	<0.001	0.51 (0.18 to 1.45)	0.205	3.24 (1.88 to 5.58)	<0.001
Non-cardiovascular death	0 (0%)	1 (0%)	5 (0%)	0.668	-	-	2.63 (0.27 to 25.11)	0.402
Myocardial infarction	2 (0%)	2 (0%)	33 (0%)	0.653	0.47 (0.10 to 2.23)	0.340	0.46 (0.09 to 2.24)	0.338
Stroke	1 (0%)	2 (0%)	5 (0%)	0.226	0.73 (0.03 to 17.73)	0.848	2.04 (0.33 to 12.47)	0.439
Urgent TVR	2 (0%)	0 (0%)	16 (0%)	0.351	0.93 (0.18 to 4.91)	0.932	-	-
BARC type 3 or 5 bleeding	1 (0%)	7 (1%)	24 (0%)	0.034	0.30 (0.03 to 2.71)	0.287	1.22 (0.44 to 3.42)	0.700
1 year								
MACE	41 (7%)	84 (11%)	331 (5%)	<0.001	0.92 (0.64 to 1.33)	0.661	1.78 (1.38 to 2.30)	<0.001
NACE	45 (8%)	88 (12%)	358 (5%)	<0.001	0.97 (0.68 to 1.38)	0.860	1.77 (1.38 to 2.27)	<0.001
All-cause mortality	23 (4%)	63 (8%)	138 (2%)	<0.001	0.93 (0.53 to 1.62)	0.785	2.77 (1.95 to 3.92)	<0.001
Cardiovascular death	14 (2%)	44 (6%)	76 (1%)	<0.001	0.89 (0.43 to 1.83)	0.750	3.06 (2.00 to 4.68)	<0.001
Non-cardiovascular death	6 (1%)	15 (2%)	33 (0%)	<0.001	1.40 (0.53 to 3.65)	0.495	3.72 (1.82 to 7.60)	<0.001
Myocardial infarction	18 (3%)	20 (3%)	192 (3%)	0.909	0.97 (0.58 to 1.63)	0.919	0.90 (0.55 to 1.47)	0.665
Stroke	2 (0%)	3 (0%)	17 (0%)	0.697	0.75 (0.15 to 3.86)	0.729	1.16 (0.32 to 4.27)	0.819
Urgent TVR	12 (2%)	7 (1%)	91 (1%)	0.211	1.09 (0.56 to 2.12)	0.790	0.66 (0.29 to 1.50)	0.326
BARC Type 3 or 5 bleeding	6 (1%)	9 (1%)	51 (1%)	0.337	0.96 (0.40 to 2.30)	0.935	0.99 (0.42 to 2.31)	0.975

Table 4. Adjusted clinical outcomes in acute kidney injury (AKI) patients according to KDIGO definition (persistent AKI= persistence of absolute (≥ 0.3 mg/dl) or a relative (≥1.5 times) increase of SCr levels at discharge compared to baseline values). *Abbreviations: MACE, major adverse clinical events; NACE, net adverse clinical events; TVR, target vessel revascularization; BARC, Bleeding Academic Research Consortium; HR, hazard ratio; CI, confidence interval.* [x] Transient AKI vs no AKI; [y] Persistent AKI vs no AKI.

	Transient AKI (N= 189)	Persistent AKI (N=262)	No AKI (N= 7744)	p Value	Adjusted HR (95% CI) [x]	P Value	Adjusted HR (95% CI)[y]	P Value
30 days								
MACE	9 (5%)	18 (7%)	106 (1%)	<0.001	1.17 (0.50 to 2.77)	0.718	2.21 (1.18 to 4.14)	0.013
NACE	10 (5%)	20 (8%)	116 (1%)	<0.001	1.31 (0.58 to 2.96)	0.522	2.37 (1.31 to 4.31)	0.005
All-cause mortality	9 (5%)	18 (7%)	65 (1%)	<0.001	1.70 (0.67 to 4.33)	0.264	3.19 (1.61 to 6.33)	0.001
Cardiovascular death	6 (3%)	18 (7%)	56 (1%)	<0.001	1.16 (0.41 to 3.31)	0.782	3.26 (1.60 to 6.66)	0.001
Non-cardiovascular death	0 (0%)	0 (0%)	6 (0%)	0.840	-	-	-	-
Myocardial infarction	0 (0%)	0 (0%)	37 (0%)	0.339	-	-	-	-
Stroke	0 (0%)	0 (0%)	8 (0%)	0.792	-	-	-	-
Urgent TVR	0 (0%)	0 (0%)	18 (0%)	0.591	-	-	-	-
BARC type 3 or 5 bleeding	1 (1%)	4 (2%)	27 (0%)	0.010	0.96 (0.10 to 8.87)	0.974	1.33 (0.30 to 5.88)	0.709
1 year								
MACE	23 (12%)	43 (16%)	392 (5%)	<0.001	1.33 (0.80 to 2.20)	0.274	2.09 (1.48 to 2.95)	<0.001
NACE	26 (14%)	45 (17%)	422 (5%)	<0.001	1.47 (0.92 to 2.36)	0.107	2.11 (1.51 to 2.95)	<0.001
All-cause mortality	17 (9%)	36 (14%)	173 (2%)	<0.001	1.42 (0.71 to 2.84)	0.326	3.00 (1.94 to 4.64)	<0.001
Cardiovascular death	11 (6%)	28 (11%)	97 (1%)	<0.001	1.43 (0.61 to 3.37)	0.410	3.76 (2.22 to 6.34)	<0.001
Non-cardiovascular death	3 (2%)	7 (3%)	44 (1%)	<0.001	1.45 (0.41 to 5.15)	0.570	2.89 (1.16 to 7.15)	0.022
Myocardial infarction	6 (3%)	8 (3%)	216 (3%)	0.923	1.08 (0.46 to 2.52)	0.863	0.99 (0.47 to 2.11)	0.983
Stroke	2 (1%)	0 (0%)	20 (0%)	0.077	2.66 (0.40 to 17.53)	0.310	-	-
Urgent TVR	4 (2%)	1 (0%)	105 (1%)	0.260	1.17 (0.41 to 3.37)	0.766	0.25 (0.03 to 1.88)	0.176
BARC Type 3 or 5 bleeding	6 (3%)	4 (2%)	56 (1%)	<0.001	3.23 (1.27 to 8.22)	0.014	0.99 (0.28 to 3.55)	0.989