Renin-angiotensin-aldosterone system blockers after KDIGO stage 3 acute kidney injury: use and impact on 2-year mortality in the AKIKI trial

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Dear Editor,

Acute kidney injury (AKI) carries high mortality and morbidity [1, 2]. Two studies recently suggested the potential benefit of renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)) after AKI [3, 4]. The first one reported a lower mortality after 1 year of follow-up in patients receiving an ACEI or ARB after an episode of AKI (KDIGO stages 1 to 3) at ICU discharge (20/109 (18%) vs 153/502 (31%), \(p = 0.001\)) [3].

The second one was a retrospective cohort study including adults after an episode of AKI during hospital stay (with 18% only of ICU-patients and only 7% of KDIGO stage 3) [4]. It concluded that exposure to an RAS blocker within the first 6 months after hospital discharge was associated with a 15% decrease in all-cause mortality (HR, 0.85; 95%CI, 0.81–0.89).

We performed an ancillary of the AKIKI trial [5], which included 619 ICU patients with severe AKI (KDIGO stage 3) in order to evaluate the potential effect of RAS blockers on long-term mortality.

All patients discharged alive from ICU were included, and their long-term prognosis (2-year all-cause mortality) was assessed according to treatment with ACEi/ARB at ICU discharge using both univariate and multivariate analyses.

Among 348 patients discharged alive from ICU, 45 (12.9%) received an ACEi/ARB at ICU discharge (see Table 1 for patient characteristics). Patients without ACEi/ARB were more severe as attested by a higher SAPS 3 (\(p = 0.02\)) and a higher rate of catecholamine infusion (\(p = 0.008\)) during AKI. However, 2-year all-cause mortality did not significantly differ between the two groups (12/45 (27%) with ACEi/ARB vs 55/303 (18%) without, \(p = 0.18\)). Mortality risk was not associated with non-prescription of ACEi/ARB after adjustment for prognostic variables (\(p = 0.21\)) (Table 2).
We acknowledge that our study did not assess introduction nor interruption of ACEi/ARB after ICU discharge. One consequence of the severity of AKI in our study is that most patients had not fully recovered at ICU discharge. In this condition, physicians in charge could be reluctant to initiate ACEi/ARB in ICU but treated the patients later.

Our study does not confirm findings from two recent studies [3, 4]. This discrepancy could be explained by a different population (less severe AKI in previous studies) and/or a lack of power of our study but in any case warrant the performance of a randomized controlled trial of ACEi/ARB at ICU discharge after an episode of severe AKI.

Abbreviations
ACEi: Angiotensin-converting enzyme inhibitors; AKI: Acute kidney injury; ARBs: Angiotensin receptor blockers; ICU: Intensive care unit; KDIGO: Kidney Disease Improving Global Outcomes; RAS: Renin-angiotensin system

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
SG, DD, and MS conceived the study. AO and KC managed the data. AO contributed substantially to the revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The original trial was approved by the ethical committee of the French Society of Intensive Care Medicine and by the competent French legal authority (Comité de Protection des Personnes d’Ile de France VI, ID RCB 2013-A00765-40, NCT01932190) for all participating centers. According to French law, because the treatments and strategies used in the study were classified as standard care, there was no requirement for signed consent, but the patients or next of kin were informed about the study before enrolment and confirmed this fact in writing.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
References

1. Fortrie G, de Geus HRH, Betjes MGH. The aftermath of acute kidney injury: a narrative review of long-term mortality and renal function. Crit Care. 2019; 23(1):24.

2. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.

3. Gayat E, Hollinger A, Cariou A, Deye N, Vieillard-Baron A, Jaber S, et al. Impact of angiotensin-converting enzyme inhibitors or receptor blockers on post-ICU discharge outcome in patients with acute kidney injury. Intensive Care Med. 2018;44(5):598–605.

4. Brar S, Ye F, James MT, Hemmelgarn B, Klarenbach S, Panru N, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. JAMA Intern Med. 2018;178(12):1681–90.

5. Gaudry S, Hajage D, Schortgen F, Martin-Lefèvre L, Pins B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33.