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Editorial Comment



EDITORIAL COMMENT

# Stopping kidney protection in the elderly following acute kidney injury: think mortality

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## ABSTRACT

Chronic kidney disease (CKD) is projected to become the fifth most common global cause of death by 2040. This illustrates a key consequence of CKD, i.e. premature mortality. Since nephroprotective drugs such as renin–angiotensin system (RAS) blockers and sodium–glucose transport protein 2 (SGLT2) inhibitors decrease glomerular hyperfiltration, they may be stopped following an episode of acute kidney injury (AKI). This may theoretically modify the risks of subsequent events, ranging from hyperkalaemia to CKD progression to cardiovascular events, but the evidence so far has been inconsistent. Roemer *et al.* have now addressed the shortcomings of prior studies. In a population of mostly elderly (median age 78 years) prevalent users of RAS blockers with an indication for this therapy and who survived for at least 3 months after discharge following a hospitalization characterized by moderate to severe AKI, roughly 50% had stopped RAS blockade at 3 months. Stopping RAS blockade was associated with an increased risk of a primary composite outcome of death, myocardial infarction and stroke, of which a large majority (80%) of events were deaths. In contrast, the risk of hyperkalaemia was reduced and the risk of repeated AKI, CKD progression or heart failure hospitalization was unchanged in patients who stopped RAS blockers. These findings call for a re-evaluation of the practice of stopping RAS blockers in the long-term following AKI and suggest that studies are needed regarding similar practices for SGLT2 inhibitors.

**Keywords:** acute kidney injury, chronic kidney disease, elderly, hyperkalaemia, mortality, renin–angiotensin system blockers

Chronic kidney disease (CKD) is projected to become the fifth most common global cause of death by 2040 and the second leading cause of death before the end of the century in countries with long life expectancy [1, 2]. This illustrates a key consequence of CKD, i.e. premature mortality. Health authorities mainly assess the burden of CKD as the need for kidney replacement therapy (KRT), but premature mortality is a more common outcome than KRT in non-dialysis patients with CKD and remains extremely high in patients on KRT, resulting in a reduction of life expectancy of up to 70% (i.e. 40 years) for younger patients on dialysis [3–5]. Thus therapeutic intervention should aim at both decreasing mortality and delaying or avoiding the need for KRT. These aims also apply to the elderly, since the absolute increase in the risk of death associated with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$ is several-fold higher in those >75 years of age than in younger individuals [6]. However, the elderly may be more prone to deprescribing for reasons ranging from efforts to simplify therapy and decrease the pill burden to perceived safety concerns, especially after certain events such as hyperkalaemia or acute kidney injury (AKI) episodes. It is thus key to understand the potential consequences of deprescribing nephroprotective drugs, such as renin–angiotensin system (RAS) blockers or sodium–glucose transport protein 2 (SGLT2) inhibitors, especially in the elderly.

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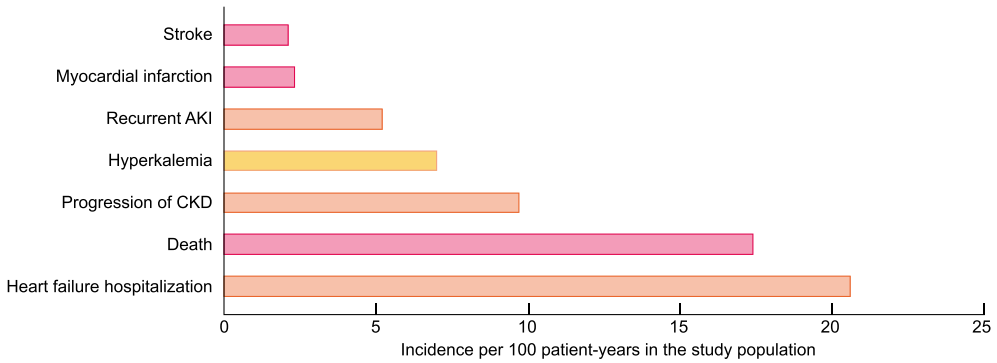


**FIGURE 1:** Incidence per 100 patient-years of individual events during follow-up in the study population. Incidence for individual events in the primary outcome were estimated from data from Janse *et al.* [8] on the overall incidence of the primary outcome (21.8/100 patient-years) and the event distribution within the primary outcome (4489 deaths, 591 myocardial infarctions, 553 strokes). Note the large contribution of deaths to the primary outcome. The figure is colour coded. Red represents events that were more common in patients who stopped RAS blockade for >3 months after AKI than for patients who continued on RAS blockade. Black represents events for which there were no significant differences between the groups and green represents events less common among those stopping RAS blockade.

Under some circumstances, RAS blockade may be temporarily withheld. Thus, according to the British Society for Heart Failure and the Renal Association, among patients with reduced left ventricular ejection fraction, with intercurrent illness, there is no evidence that stopping RAS blockade is beneficial, but if potassium increases above 6.0 mmol/L or creatinine increases >30%, RAS blockade should be temporarily withheld [7]. The keyword here is 'temporarily'.

In this issue of *CKJ*, Roemer *et al.* report on the association with outcomes of stopping RAS blockers following a hospitalization episode characterized by the development of moderate to severe AKI in the Stockholm CREAtinine Measurements (SCREAM) database [8, 9]. Participants were prevalent users of RAS blockers who had an indication for this therapy and who survived for at least 3 months after discharge. Thus the study does not address the acute impact of stopping RAS blockers during hospitalization or shortly thereafter. Participants were mostly elderly (median age 78 years) and 60% had a baseline eGFR <60 mL/min/1.73 $m^2$. Data were collected between 2007 and 2018, i.e. before the era of widespread use of SGLT2 inhibitors. Roughly 50% of patients had stopped RAS blockade at 3 months. Thus the study does not addressing the impact of short-term discontinuation of RAS blockers during hospitalization, but a more prolonged discontinuation, persisting 3 months after the event.

Stopping RAS blockade was associated with an increased risk of the primary composite outcome of death, myocardial infarction and stroke, a similar risk of recurrent AKI, hospitalization for heart failure or CKD progression and lower risk of hyperkalaemia ≥5.5 mmol/L. The risk for the primary outcome may be even higher for patients who had not reinitiated RAS blockade 6 months after the AKI episode. The incidence of the primary outcome as well as of heart failure hospitalization increased steeply for the first few months of follow-up. However, the risk curves for the primary endpoint are separated over the first year and then run parallel to each other. This may suggest that RAS blockade should be reinitiated as soon as possible after the AKI episode, if not already initiated by 3 months, as the difference in events between RAS blockers or no RAS blockers becomes apparent during the first few months after hospitalization. The incidence rate of the primary study outcome was 20/100 person-years among patients who continued RAS blockade and 25/100 person-years among those who stopped RAS blockade. However, 80% of the events in the primary composite outcome were death (Figure 1).

As the authors discuss, previous studies with different designs and population characteristics have reported contradictory results for the risk of heart failure hospitalization, recurrent AKI and CKD progression [10–14]. However, all of them agree on the increased risk of death in a patient in whom RAS blockade is stopped, the only exception being the Swedish arm of one of the studies that corresponds to an earlier (2006–2011) Stockholm cohort [11] and thus this population is better represented by the population reported by Roemer *et al.* Thus an increased risk of death is a consistent association of stopping RAS blockade following AKI in different populations and for different study designs. These results are also consistent with those observed after stopping RAS blockade because of hyperkalaemia [15].

Albuminuria merits a specific comment, as it raises questions about how complete cardiovascular risk assessment in this population is. In a prior report from the SCREAM database, it became clear that CKD is underdiagnosed in Sweden, as only 20% of patients who fulfilled both the low eGFR (<60 mL/min/1.73 $m^2$) and the temporal criterion (>3 months) for CKD had a diagnosis of CKD in their electronic health records [16, 17]. This underdiagnosis had potential consequences for health, as CKD patients lacking a CKD diagnosis were more frequently prescribed nephrotoxic medications [16]. In the current report, ∼25% of participants had an RAS blockade indication for albuminuria. However, urinary albumin:creatinine ratio values were missing in 74%, suggesting further underdiagnosis of CKD; if albuminuria is assessed, CKD cannot be diagnosed based on albuminuria criteria. This is striking for a high cardiovascular risk population based on age and the prevalence of hypertension (91%), diabetes (54%) and cardiovascular disease (>54%). Major changes in patient care should be expected in the Stockholm area in the next few years, as both albuminuria and eGFR are needed for correct cardiovascular risk assessment as per the 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice [18]. It will be of interest to monitor the uptake of the guideline and its impact on the availability of albuminuria values in electronic health records.

The present study offers lessons to be learned for SGLT2 inhibitors. As for RAS blockers, SGLT2 inhibitors also decrease eGFR when started [19]. Decreasing hyperfiltration is part of the kidney protection mechanism. Thus physicians may feel

inclined to stop SGLT2 inhibitors after an AKI episode, even when the incidence of AKI in major trials of SGLT2 inhibitors was even lower than in placebo patients. Moreover, prescription of dapagliflozin in acute coronavirus disease 2019 (COVID-19) patients was associated with a numerical decrease in the risk of AKI as compared with placebo [hazard ratio 0.65 (95% confidence interval 0.38–1.10)], although the trial was not powered to detect differences [20]. Indeed, the mechanism of kidney protection by SGLT2 inhibitors would have been consistent with kidney protection in this setting [21]. Thus there is no clear safety reason to stop SGLT2 inhibitors during AKI, but if this is done based on efficacy or concerns about the number of pills, they should be restarted thereafter. Clinical practice should be monitored, and if, as shown by Roemer *et al*. for RAS blockers, a significant number of patients are not restarted on SGLT2 inhibitors, then the impact over longer-term outcomes should be assessed.

In conclusion, the largest impact of long-term deprescription of RAS blockade in the elderly following hospitalization characterized by AKI appears to be an increased risk of cardiovascular events and death, mainly driven by an increased death risk. This increased risk is evident in the first few months after stopping RAS blockade. These findings may influence clinical practice and additionally may guide research into the consequences of stopping SGLT2 inhibitors following AKI in a similar population.

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## CONFLICT OF INTEREST STATEMENT

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