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Review

Renin–angiotensin system inhibitors (RASi) are not nephrotoxic – they protect the kidneys and the heart

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ABSTRACT

Healthcare professionals should not label medications as 'kidney toxins' unless this is actually the case, especially medications that instead confer clear prognostic benefit, such as renin–angiotensin system inhibitors (RASi). This is imperative when discussing treatments with people with long-term health conditions, for whom RASi significantly reduce death, progression of chronic kidney disease (CKD) and hospitalisation. RASi are fundamental to management of heart failure with reduced ejection fraction (HFrEF) and CKD with proteinuria, yet are frequently called 'nephrotoxic'. The association between RASi use and acute kidney injury (AKI) is too often mistaken for 'causation'; it is largely driven by the use of RASi to treat long-term conditions that increase AKI risk, such as HFrEF, CKD and diabetes mellitus. Mislabelling RASi as 'nephrotoxic' adversely affects vital decision making, driving a tendency for RASi avoidance, even when RASi use has clear prognostic benefit. Healthcare education must embed this clinically important change to convention.

Background: RASi and other disease-modifying medicines for serious long-term cardiorenal disease

RASi confer significant prognostic benefit for many people living with serious long-term conditions, including HFrEF, CKD and diabetes mellitus.[1] RASi use is therefore first line within international guidelines[2–4] and these outcome-improving medications are among the most commonly prescribed worldwide.[5,6] The focus of this article is on RASi, but the principles apply to other medicines used for prognostic advantage in cardiorenal disease, including mineralocorticoid receptor antagonists (MRAs) and sodium glucose co-transporter 2 inhibitors (SGLT2i).

Heart failure is the commonest cause of hospitalisation in older people, and a comorbid finding in 14% of inpatients.[7] People with heart failure are at greater risk of AKI than the general population, especially during acute illness. Large observational analyses suggest that their increased AKI risk is predominantly associated with patient characteristics and comorbidities, with smaller risks associated with RASi therapy.[8] Moreover, RASi use is *not* associated with substantially greater risk of AKI than use of other antihypertensive medications in people with heart failure (Fig. 1). Similarly, systematic review and meta-analysis suggest that SGLT2i use does not increase incidence of AKI among patients treated for heart failure with these disease-modifying medications.[9]

When people with HFrEF sustain AKI, balancing the need to maintain kidney perfusion while achieving fluid loss requires timely and regular assessment by senior decision makers. It is often assumed that RASi withdrawal is required to achieve both goals, but RASi

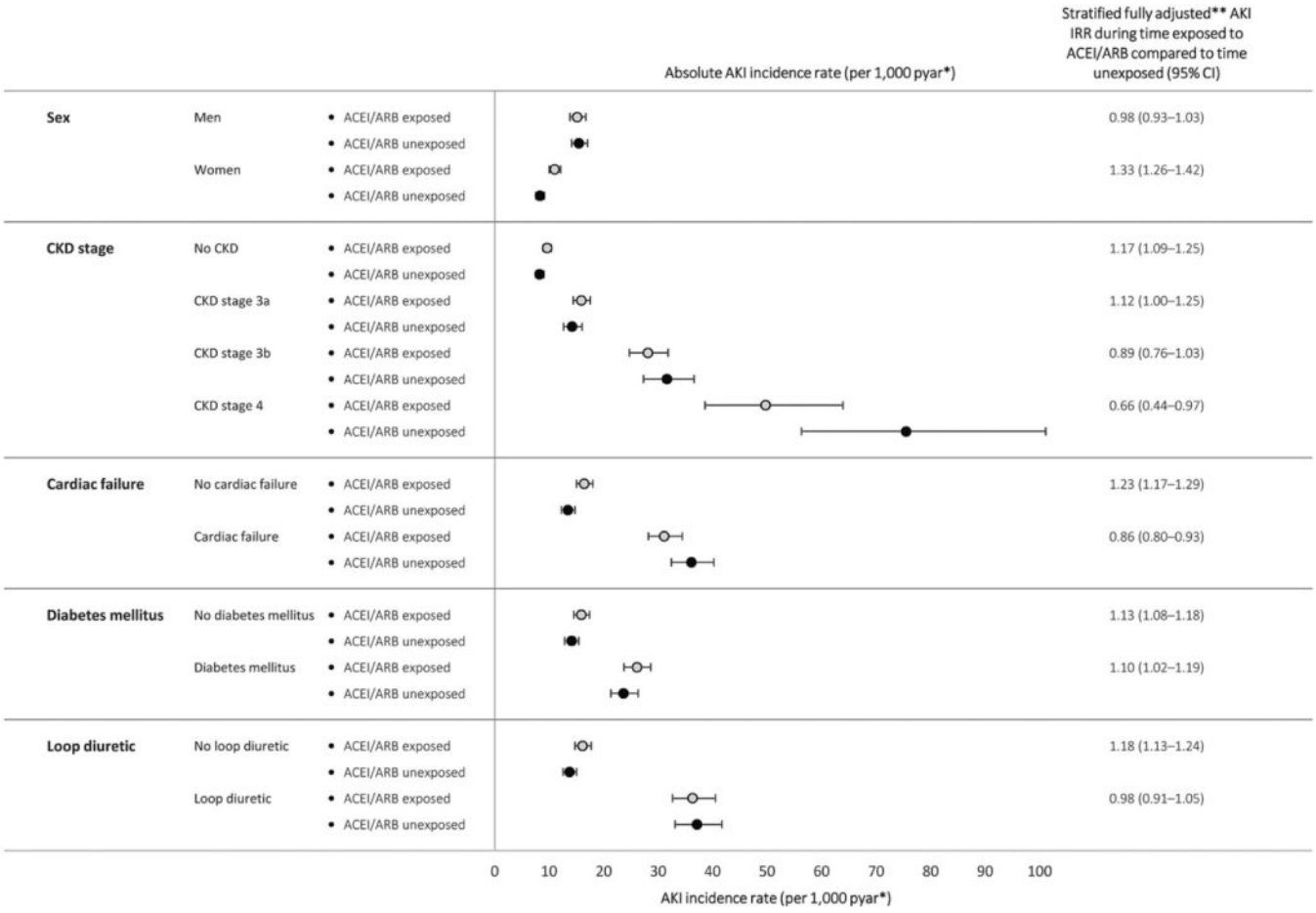


Fig. 1. Modelled rates of AKI per 1,000 person years at risk for AKI during time exposed to antihypertensive treatment including angiotensin converting enzyme inhibitors / angiotensin II receptor blockers (ACEI/ARB) compared to time exposed to antihypertensive treatment excluding ACEI/ARB, stratified by characteristics and comorbidities.
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continuation or dose reduction may be preferable to discontinuation, even in the face of AKI.[10] Exceptions to this include severe hypotension or moderate to severe hyperkalaemia[11] (Fig. 2).

RASi exert renal haemodynamic effects that reduce intraglomerular pressure and thereby slow progressive nephron loss associated with glomerular hyperfiltration during CKD. This underpins why RASi are a cornerstone therapy for CKD and should generally be considered nephro-*protective* rather than nephro-*toxic*, a concept that is supported by several large-scale studies.

RASi have been shown to significantly slow progression of mild to moderate CKD, especially diabetic kidney disease, an effect that is independent of blood pressure lowering.[12,13] Meta-analysis suggests that starting RASi therapy in people with more advanced CKD is similarly associated with reduced rates of CKD progression,[14] while the *STOP-ACEi* trial found that withdrawing RASi did not slow CKD progression in people with stage 4 or 5 CKD.[15] Moreover, in a large Swedish emulation of STOP-ACE, stopping RASi in patients with advanced CKD was associated with higher absolute risks of mortality and major adverse cardiovascular events, but with lower absolute risk of initiating dialysis.[16]

RASi are also widely used in children with heart failure and/or CKD. Much paediatric RASi therapy is 'off-label' and extrapolated from adult practice; the little paediatric-specific evidence available does not suggest that RASi are 'nephrotoxic' for children.[17,18]

Medications that can affect kidney function: nephrotoxins and renal blood flow modulators

Nephrotoxicity is a term conventionally used to describe *structural kidney damage* that occurs following use of various medications.[19]

Truly nephrotoxic medications or substances cause structural kidney damage or inflammation, *regardless of clinical context*. Nephrotoxin-induced kidney dysfunction (reduced glomerular filtration rate, GFR) can thereby occur in people who are otherwise well and may be irreversible, even after drug discontinuation. Examples include aminoglycoside antibiotics and some chemotherapeutics.

In contrast to nephrotoxins, RASi modulate renal blood flow, reducing efferent arteriolar tone and intraglomerular perfusion pressure, but do not cause structural kidney damage or inflammation. The degree and clinical implications of RASi-associated haemodynamic changes upon kidney function (GFR) may be *affected by clinical context*.

A modest and relatively stable GFR drop is commonly observed after RASi initiation or dose increase in *stable clinical circumstances*. This GFR change is usually predictable and acceptable, as it typically reflects a reversible and nephro-protective reduction in intraglomerular perfusion pressure. A *very rare exception* can arise in people with haemodynamically significant renovascular disease; RASi may cause more marked and *rapidly progressive* reduction of GFR in this context.

RASi-associated haemodynamic changes can affect autoregulation of renal blood flow, which may be required to maintain adequate intraglomerular perfusion pressure, during some *unstable clinical circumstances*. This concept underpins why AKI associated with severe hypotension, hypovolaemia or sepsis may be exacerbated by RASi and, if suspended, RASi can usually be restarted promptly after acute illness recovery. Moreover, incomplete recovery of renal function should not preclude timely reinitiation of RASi therapy, especially when otherwise clinically indicated.[20]

Patient safety risks associated with referring to RASi as nephrotoxins

Mislabelling RASi medication as 'nephrotoxic' risks patients and healthcare professionals misunderstanding the overall clinical 'benefit

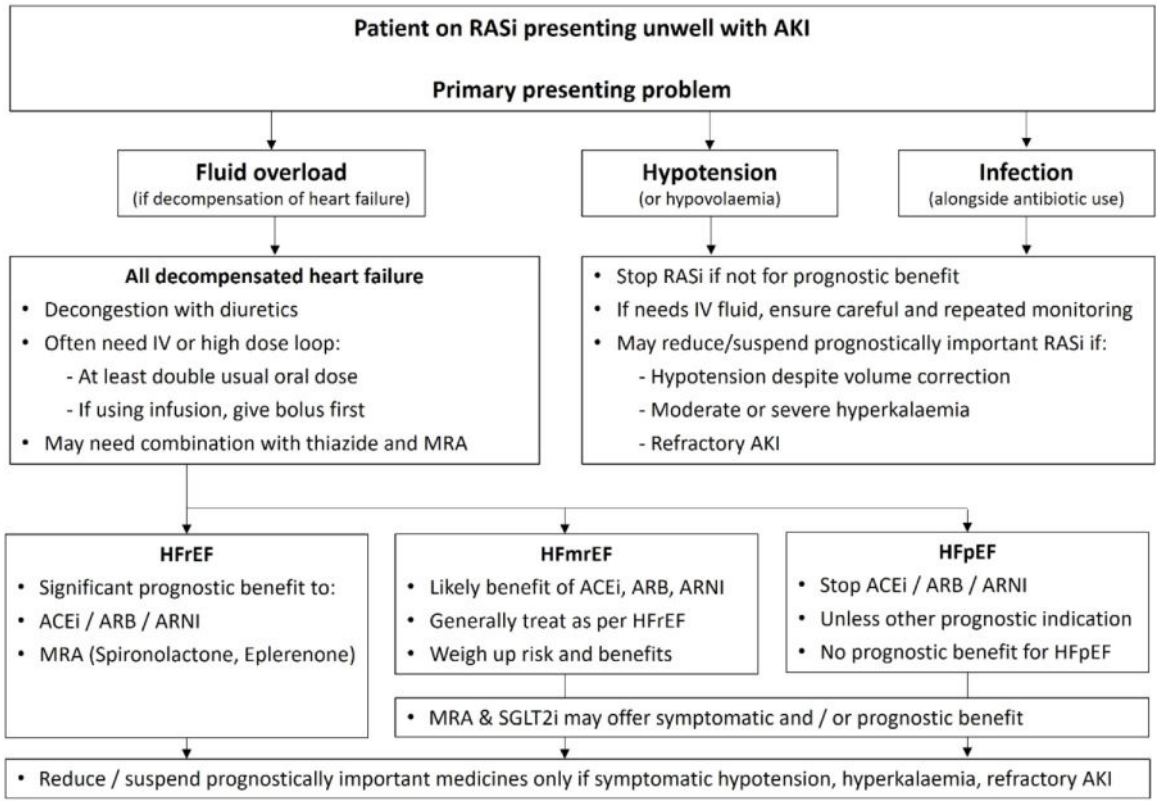


Fig. 2. Management of patients with AKI or worsening renal function who are receiving RASi. IV, intravenous; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist; ARNI, angiotensin receptor/neprilysin inhibitor; SGLT2i, Sodium Glucose Co-transporter 2 inhibitors; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.
Adapted from Clark *et al.*,[11] distributed under the terms of the Creative Commons Attribution Non-Commercial (CC BY NC 4.0) licence.

over risk' profile of these medications. This can negatively influence clinical decision making, therapeutic trust and practice; healthcare professionals and patients will be understandably reluctant to use medications considered 'toxic to their kidneys'.

Despite clear evidence and recommendations supporting RASi use, RASi are frequently avoided, or suspended and not restarted within a clinically effective timeframe. In a large Canadian cohort, post-discharge RASi use was associated with lower mortality among patients hospitalised with AKI.[21] However, discharge communication following AKI in hospital is often inadequate or untimely[22] and in England only 60% of patients hospitalised with AKI had RASi restarted within 90 days of discharge.[23] This risks destabilisation of common long-term health conditions[24] and may thereby underlie many serious adverse patient outcomes that often occur post AKI, including high mortality and emergency hospital readmission, often due to acute pulmonary oedema.[25] Considerations to support safe and timely RASi reintroduction in such circumstances are summarised in Table 1.

RASi and sick day advice

Generic sick day advice (SDA) incorporating medication changes aims to limit patient harm during acute illness episodes.[30,31] While *disease-specific* SDA, for example in Addison's disease or type I diabetes, can be critical, evaluation suggests that SDA understanding and application is less clear when aiming to prevent AKI and its complications.[32–34] Furthermore, there is little evidence that *RASi-specific* SDA prevents AKI,[35,36] even for people with CKD.[37]

Inappropriate suspension of medications may further risk patient safety and increase overall healthcare service use. For example, the Stopping Perioperative ACE-inhibitors or angiotensin-II receptor blockers (SPACE) trial found that suspending RASi before non-cardiac surgery may be associated with increased risk of clinically significant acute hypertensive episodes, without reducing AKI rates,[38] while the much larger Stop-or-Not Trial in cardiac surgery showed that stopping RASi made no difference to outcomes or AKI rates.[39]

In summary, while it may be appropriate to suspend or reduce RASi during AKI associated with severe hypotension, hypovolaemia, sepsis or moderate to severe hyperkalaemia, there is little evidence to show that routine adoption of SDA for this purpose is of overall benefit. Furthermore, SDA may risk overall patient harm if applied indiscriminately in heterogeneous and complex clinical scenarios associated with AKI, especially if SDA does not include if/when to restart RASi and/or implies that these medications are nephrotoxic.

Discussion

Healthcare professionals should avoid misinforming patients or colleagues that RASi are 'nephrotoxic', as this risks patient harm due to suboptimal treatment of common and serious long-term conditions.

Unlike truly nephrotoxic medications, RASi do not cause structural kidney damage. Changes to kidney function associated with RASi reflect changes to renal blood flow that are usually nephroprotective. This fundamental concept is supported by large studies showing that RASi slow progression of CKD, underlining that a creatinine rise associated with RASi use is generally safe and beneficial, as it reflects a protective effect upon renal blood flow for most patients.

While it may be appropriate to reduce or suspend RASi during acute illness in the context of a clear and objective indication, such as severe hypotension or hyperkalaemia, timely RASi reinitiation following recovery is often crucial, and if otherwise indicated, should not be delayed due to incomplete renal recovery. Timely individualised communication between patients and healthcare professionals is essential to ensure this.

Undergraduate and postgraduate multiprofessional training must embed these significant changes to convention, to optimise contemporary clinical practice and reduce patient safety risks.

Take-home messages

1. Healthcare professionals must avoid informing patients that medications are 'toxic to their kidneys' unless this is actually the case. Mislabelling RASi as 'nephrotoxic' seriously risks patient safety by (a) driving a tendency for these disease-modifying medications to be avoided and (b) the correct cause and treatment of AKI episodes being delayed or missed if AKI episodes are inappropriately attributed to RASi use.

Table 1
Considerations to support safe and timely reintroduction of RASi if suspended during AKI (adapted from 10,26,27).

Consideration	Key points
1. General principles	• Use overall clinical judgement and individualise decisions. • Many patients receiving RASi are at ongoing high AKI risk because of their comorbidities, but also gain major prognostic benefit from RASi. • Restart should be prioritised for HFrEF, CKD and diabetes to prevent destabilising these conditions, as soon as clinically appropriate, and not delayed by incomplete renal recovery.
2. Holistic and shared decisions	• Wherever possible, stopping or restarting should be agreed with the patient, documented, and communicated with a clear follow-up plan (who reviews, where and when, ideally within 2 weeks for high-risk patients[28]). • Omitting restart without discussion or documentation should be avoided.
3. Indications for RASi	• Strongly prioritise restart when there is a compelling indication: HFrEF, proteinuric CKD or diabetes.
4. Clinical status	• Restart once the acute illness/instability has resolved. • Assess fluid status; in congestion (especially HFrEF), consider optimising diuretics alongside/before RASi.
5. Blood pressure	• Restart at a low threshold if blood pressure is elevated or at the patient's usual level. • Low blood pressure may be the patient's baseline, and RASi benefit in HFrEF/CKD is often independent of blood pressure lowering.
6. Kidney function	• Do not delay restart solely because renal function has not fully returned to baseline. Interpret current kidney function in the context of baseline and prior trajectory. • Consider renal advice if there is new or rapidly progressive CKD after acute illness recovery, particularly with proteinuria, as per CKD guidelines[29]
7. Serum potassium	• Review recent potassium values. If previously high, address modifiable factors (diet, interacting drugs, potassium binders) and arrange early repeat blood tests.
8. Other drugs	• If other disease-modifying agents were held during AKI (eg MRAs, SGLT2 inhibitors), consider phased reintroduction. • Aim for at least low doses of all indicated classes (eg in HFrEF), balancing blood pressure and potassium. • SGLT2 inhibitors have minimal blood pressure effect and may help limit potassium rise, supporting reintroduction of RASi and/or MRAs.

RASi, renin-angiotensin system inhibitor; AKI, acute kidney injury; CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, Sodium Glucose Co-transporter 2 inhibitor.

2. The term 'nephrotoxin' should be reserved for medications that commonly cause structural injury or inflammation to nephrons, regardless of clinical context. True nephrotoxins can cause structural kidney damage and dysfunction in people who are otherwise well. RASi do not exert any toxic effect upon nephrons, and changes to kidney function associated with RASi use reflect modulation of renal blood flow that is usually nephroprotective.
3. Observational data and large-scale studies show no significant increase in AKI among people treated with RASi compared to those treated with other antihypertensive medications, including people with common and serious long-term health conditions, for whom RASi therapy confers significant prognostic benefits.
4. While it may be appropriate to suspend or reduce RASi dose during AKI episodes associated with severe hypotension, hypovolaemia or moderate to severe hyperkalaemia (Fig. 2), there is little evidence to support routine use of RASi sick day advice to prevent AKI, and some evidence to suggest that stopping RASi inappropriately may cause patient harm.
5. If suspended during AKI, a plan should be documented to restart RASi and other guideline-indicated medications as soon as clinically appropriate, to avoid decompensation of serious long-term conditions. This requires clear and timely communication between healthcare professional teams and patients, including at the point of hospital discharge. Incomplete recovery of renal function post-AKI should not preclude timely reintroduction of RASi, unless the patient remains at high risk of recurrent AKI due to volume depletion, in the context of a high-output stoma, for example.[40]

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Declaration of competing interest

JSM is co-chair for the UK Kidney Association (UKKA) Acute Kidney Injury Specialist Interest Group and an expert nephrology adviser for the *British Medical Journal* (both unpaid roles). His contribution to this article is in a personal capacity and the content of the article does not necessarily reflect the position of the UKKA or *British Medical Journal*.

DG reports a relationship with AstraZeneca UK Limited that includes: consulting or advisory and speaking and lecture fees. DG reports a relationship with Boehringer Ingelheim Ltd that includes: consulting or advisory and speaking and lecture fees. DG reports a relationship with Bayer plc that includes: consulting or advisory and speaking and lecture fees. He reports a relationship with Novartis Pharmaceuticals UK that includes: speaking and lecture fees. His contribution to this article is in a personal capacity and the content of the article does not necessarily reflect the position of these roles.

LJA reports a relationship with the British Society for Heart Failure that includes: board membership. Her contribution to this article is in a personal capacity and the content of the article does not necessarily reflect the position of the British Society for Heart Failure.

PRK reports a relationship with FIRE-1 that includes: funding grants. PRK reports a relationship with Pharmacosmos AS that includes: consulting or advisory, funding grants, and speaking and lecture fees. PRK reports a relationship with AstraZeneca that includes: consulting or advisory and speaking and lecture fees. PRK reports a relationship with Boehringer Ingelheim GmbH that includes: consulting or advisory. PRK reports a relationship with Bayer AG that includes: speaking and lecture fees. PRK reports a relationship with Vifor Pharma Switzerland SA that includes: consulting or advisory and speaking and lecture fees. PRK reports a relationship with Novartis that includes: speaking and lecture fees.

SB declares that she is current National Acute Kidney Injury Community of Practice Lead for the Association of Nephrology Nurses UK (unpaid). Her contribution to this article is in a personal capacity and the content of the article does not necessarily reflect the position of the Association of Nephrology Nurses UK.

PC reports the following advisory or leadership roles: past president and trustee UK Kidney Association; other interests or relationships: Boehringer Ingelheim – non-remunerated research collaboration, AstraZeneca – clinical development programme and advisory board, Vifor, advisory board.

TB declares no financial competing interests, though declares the following (non-funded) positions: NHS England Think Kidneys Programme Board Member (2014–17); Royal College of General Practitioners' AKI Clinical Champion (2017–20); NHSE Renal Services Transformation Programme Post-AKI care Lead (2021–23); Specialist Committee Member for NICE AKI Quality Standard (QS76) (2022–23); Kidney Disease Improving Global Outcomes (KDIGO) AKI Guideline Work Group (2023-To date). His contribution to this article is in a personal capacity and the content of the article does not necessarily reflect the position of these roles.

CM is a consultant renal pharmacist, co-chair for the UK Kidney Association (UKKA) Acute Kidney Injury Specialist Interest Group and president of the UKKA. Her contribution to this article is in a personal capacity and the content of the article does not necessarily reflect the position of the UKKA.

MW, AH, WTH, NMS, WSM, SS, KN, LAT, NVK, MO, SJM, MTJ, JDD, AJPL and SJS declare no conflicts of interest.

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