Change in renal function associated with drug treatment in heart failure: national guidance

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ABSTRACT

Inhibitors of the renin–angiotensin–aldosterone (RAAS) system are cornerstones of the management of patients with heart failure with reduced left ventricular ejection fraction (HFrEF). However, RAAS inhibitors may cause decline in renal function and/or hyperkalaemia, particularly during initiation and titration, intercurrent illness and during worsening of heart failure. There is very little evidence from clinical trials to guide the management of renal dysfunction. The Renal Association and British Society for Heart Failure have collaborated to describe the interactions between heart failure, RAAS inhibitors and renal dysfunction and give clear guidance on the use of RAAS inhibitors in patients with HFrEF. During initiation and titration of RAAS inhibitors, testing renal function is mandatory; a decline in renal function of 30% or more can be acceptable. During intercurrent illness, there is no evidence that stopping RAAS inhibitor is beneficial, but if potassium rises above 6.0 mmol/L or creatinine rises more than 30%, RAAS inhibitors should be temporarily withheld. In patients with fluid retention, high doses of diuretic are needed and a decline in renal function is not an indication to reduce diuretic dose: if the patient remains congested, more diuretics are required. If a patient is hypovolaemic, diuretics should be stopped or withheld temporarily. Towards end of life, consider stopping RAAS inhibitors. RAAS inhibition has no known prognostic benefit in heart failure with preserved ejection fraction. Efforts should be made to initiate, titrate and maintain patients with HFrEF on RAAS inhibitor treatment, whether during intercurrent illness or worsening heart failure.

BACKGROUND

One of the great triumphs of modern medicine is the therapy of patients with chronic heart failure (CHF) due to reduced left ventricular ejection fraction (HFrEF). Treatment with ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), sacubitril/valsartan, beta-blockers and mineralocorticoid receptor antagonists (MRAs) (together with appropriate device therapy) increase life expectancy markedly, with the combination of sacubitril/valsartan, beta-blocker and MRA reducing all-cause mortality with a HR of 0.37 against placebo.1 However, there is frequently a conflict between renal function and heart failure therapy. Renal dysfunction is extremely common in patients with CHF (figure 1) and associated with a worse outcome.2 Most of the treatments used for CHF can cause worsening renal function.

Anxiety about rises in creatinine (and the associated falls in estimated glomerular filtration rate [eGFR]) can lead to underprescription of ACEI and ARBs. The tendency to withdraw ACEI and ARB has been exacerbated by the international adoption of the term ‘acute kidney injury’ (AKI) to describe acute changes in kidney function and by the inclusion of these drugs, which can also protect against progressive proteinuric kidney damage, in lists of drugs termed ‘nephrotoxic’. The British National Formulary and guidelines on chronic kidney disease (CKD) published by the National Institute for Health and Care Excellence (NICE) advise dose reduction or even stopping ACEI or ARB if serum creatinine rises by >30% without another explanation. The NICE heart failure guideline3 recommends regular biochemical monitoring but refers to the NICE CKD guidelines on how to respond to changes in biochemistry. In contrast, the European Society of Cardiology heart failure guidelines advise dose reduction or withdrawal only if serum creatinine rises by >50% or reaches a limit of 266 μmol/L.4 (The arbitrary nature of some cut points is shown by the peculiar numbers that sometimes appear. They appear less peculiar when it is appreciated that they are conversions of round numbers of mg/dL.)

The results from clinical trials suggest that fears about renal function may be misplaced: in the Studies of Left Ventricular Dysfunction (SOLVD) trial, 16% of patients in the enalapril arm had a rise in serum creatinine >44 μmol/L but so did 12% of patients in the placebo arm.5 Patients whose renal function declines on placebo have a much greater increase in their risk of mortality than those whose renal function declines on ACEI or ARB.8 However, patients are usually excluded from CHF trials if they have major renal dysfunction at baseline, making it difficult to be certain that the advice is appropriate in all patients.

Clinicians receive varying advice from cardiologists, nephrologists and other physicians. The variation reflects the lack of robust evidence: designing and delivering randomised studies with management strategies directed both by changes in renal function and clinical response would be very complex. The different sources of advice can adversely affect patient care. Here, we outline consensus recommendations agreed by the Renal Association and the British Society for Heart Failure on the management of renin–angiotensin–aldosterone system (RAAS) blockers in patients with heart failure. Any guidance is based on very limited observational evidence and cut-offs are necessarily arbitrary.

CHANGES IN KIDNEY FUNCTION DURING TREATMENT OF CHF

In the absence of evidence from trials, understanding how changes in the systemic circulation...
may affect kidney function is important in informing clinical recommendations.

Effects of systemic blood pressure on glomerular filtration rate (GFR)
The normal kidney maintains a stable GFR across a wide range of systemic blood pressure due to the effect of an intact RAAS. However, in CKD and in long-standing hypertension, the blood pressure range for autoregulation is smaller, and GFR becomes more pressure dependent, so that a drop in systemic blood pressure results in a fall in GFR, without tubular injury. RAAS inhibitors make GFR much more dependent on systemic arterial pressure. A sustained drop in usual blood pressure beyond the autoregulatory range causes AKI,10 from which recovery may take weeks and may be incomplete. Pre-existing low-flow states, including CHF, increase the risk of normotensive AKI.11

Effects of renal artery stenosis and intrarenal vascular disease
Angiotensin II causes a preferential increase in efferent arteriolar tone, helping to maintain GFR when afferent arteriolar pressure is low, as in renal artery stenosis and severe generalised intrarenal arteriosclerosis. In these settings, inhibition of angiotensin II production by ACEI or ARB can lead to acute renal failure, which is not always reversible.12

Effects of venous congestion and fluid overload
Increased systemic venous pressure can cause a decline in GFR by increasing renal interstitial pressure. Congestion per se is a key driver of change in renal function. Venous congestion also causes an inflammatory response within the renal parenchyma. Decongestion by diuretics can thus result in an increase in GFR,15 and withdrawal of diuretics from patients with stable chronic heart failure can cause tubular injury.15

Effects of increased intra-abdominal pressure
Increased intra-abdominal pressure, for instance, due to tense ascites, can cause a reduction in GFR in patients with CHF by causing functional ureteric obstruction; the precise mechanism is unclear.16

Effect of neurohormonal activation on GFR
Reduced cardiac output causes neurohormonal activation. Sympathetic stimulation causes renal vasoconstriction and a fall in GFR. Increased activity of the RAAS causes glomerular arteriolar vasoconstriction that is more marked in the efferent than the afferent arteriole, helping to preserve GFR. Non-osmotic anti-diuretic hormone (ADH) release contributes to hyponatraemia and also to increased urea reabsorption in the collecting duct: a disproportionate rise in blood urea is a marker of poor prognosis in patients with acute decompensated heart failure. Other neurohormones, particularly natriuretic peptides, counteract the effects of RAAS activation. GFR is also dependent on the vasodilator effects of prostaglandins. Non-steroidal anti-inflammatory drugs can therefore cause a marked fall in GFR.

Effects of diuretics on GFR in CHF
Diuretic treatment does not prevent or ameliorate AKI.18 Although higher diuretic dose in CHF is associated with worse outcome,19 the reason is that higher doses of diuretics are a marker of more severe heart failure. Intravenous diuretics cause increased activity of the sympathetic nervous system and the RAAS, resulting in a fall in GFR, but diuretic-induced decongestion can improve GFR by reducing renal venous pressure.18

Additional effects of RAAS blockade
RAAS blockade might have beneficial renal effects. It reduces inflammation, ameliorates experimental AKI and increases tubular blood flow.20–22

HEART FAILURE WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION (HFrEF) AND HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION (HFpEF): EVIDENCE FOR RAAS BLOCKADE
Patients with heart failure can be categorised on the basis of left ventricular (LV) systolic function into those with HFrEF and those with HFpEF. In HFrEF, the primary cardiac abnormality is major impairment in LV systolic function. In HFpEF, LV systolic function is not necessarily normal but the ejection fraction is.

Both ACEIs and MRAs reduce mortality and HF hospitalisations in patients with HFrEF when compared with placebo. The combination of the neutral endopeptidase (neprilysin) inhibitor, sacubitril, with the ARB, valsartan, reduced mortality and HF hospitalisations compared with the previous gold standard, enalapril. Quality of life is also improved by the RAAS inhibitors. All are at least as effective in patients with mild degrees of renal impairment as those with normal renal function (among those who met the inclusion criteria of the trials). For example, enalapril, spironolactone, eplerenone and sacubitril/valsartan in HFrEF all confer similar or greater reduction in mortality and heart failure hospitalisation in those with an eGFR below 60 mL/min/1.73 m² compared with those with normal renal function. Patients with severe renal disease at baseline were excluded from the definitive HFrEF trials. In SOLVD Treatment and Randomised Aldactone Evaluation Study (RALES), patients with a creatinine of >221 μmol/L were excluded; in Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure with Preserved Ejection Fraction, patients with a baseline eGFR <40 mL/min/1.73 m² and an estimated creatinine clearance of >60 mL/min were excluded.

Figure 1 Distribution of estimated glomerular filtration rate (eGFR) among 1216 patients with chronic stable heart failure. Data from *Eur Heart J* 2006;27:569–81. AKI, acute kidney injury; CKD, chronic kidney disease; HFREF, heart failure with reduced left ventricular ejection fraction; MI, myocardial infarction; RAAS, renin–angiotensin–aldosterone.
(PARADIGM), those with an eGFR below 30 mL/min/1.73 m² were excluded. As a result, there is no certainty of benefit from RAAS blockers for patients with severely impaired renal function.

In contrast to the large body of evidence of the benefit of RAAS blockade in HFrEF, there is no convincing evidence of benefit in HFrpEF. The only trial to suggest possible benefit was the post hoc analysis by region of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (spironolactone versus placebo in HFrpEF).19,20

► There is unequivocal evidence that inhibitors of the RAAS improve survival in patients with HFrEF.
► All such patients should be offered RAAS inhibitors.
► There is no such evidence for patients with HFrpEF.

CHANGES IN KIDNEY FUNCTION AFTER INITIATION OF DRUG TREATMENT

A decline in renal function is commonly seen in patients when they start an ACEI, ARB or sacubitril/valsartan and is usually modest. The decline is attributable to loss of renal efferent arteriolar vasoconstriction and an acute decrease in intraglomerular pressure, with subsequent fall in GFR.29 Renal function may actually improve: in Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), although the average increase in creatinine was 44 μmol/L at 2 weeks, in nearly a quarter of patients creatinine declined.30 RAAS inhibitors can decrease the rate at which renal function subsequently declines, despite an apparent initial worsening.

The deterioration in renal function may also indicate haemodynamically significant renal artery stenosis or intrarenal vascular disease. For a small proportion of patients, particularly those with bilateral renovascular disease, initiation of ACEI/ARB can result in substantial and irreversible declines in renal function or life-threatening hyperkalaemia.31 In those rare cases with profound decline in GFR post-RAAS inhibitor, renal artery stenosis should be actively sought with decision on revascularisation made on an individual patient basis.

Important questions are: (1) whether there is a level of decline in renal function related to ACEI/ARB initiation beyond which the risk of continuing treatment outweighs the benefits; and (2) whether the risk/benefit balance depends on the indication for treatment.

One of the pitfalls in caring for patients with heart failure is premature discontinuation of RAAS inhibitors when renal function declines during initiation or up titration of the drugs. Worsening renal function is more common in patients treated with ACEI and ARB. Among patients with HFrEF, those with worse renal function at baseline, and those who have a greater decline in renal function during initiation of RAAS inhibitors, have a worse prognosis than those who do not; however, they gain a greater relative benefit from RAAS inhibitors.32,33

In patients with HFrpEF, worse renal function is again associated with higher mortality, but in contrast to patients with HFrEF, worsening renal function on RAAS inhibitors is associated with increased mortality.8

A note on AKI

The term ‘acute kidney injury’ is used to describe changes in renal function over a short period of time. The introduction of ‘AKI e-alerts’ based on automated recognition of changes in creatinine (a rise in serum creatinine from baseline of ≥50% or an absolute increment of 26 μmol/L within 48 hours is defined as ‘stage 1 AKI’) is intended to prompt clinicians to seek and treat promptly such reversible causes as sepsis or obstructive nephropathy; in these settings, the e-alerts have proved helpful.33

However, in patients with heart failure, the initial rise in creatinine is usually not due to intrinsic kidney injury but to a change in haemodynamics. Because patients with heart failure commonly have reduced renal function, even a small decline in renal function may produce a rise in creatinine large enough to trigger an e-alert and the stopping of prognostically vital medication. An ‘AKI’ alert in a patient starting RAAS inhibitors in a patient with HFrpEF does not mean the RAAS inhibitor should be stopped but should stimulate a careful search for potentially reversible causes of renal decline.

► A fall in eGFR (and rise in creatinine) is very common after initiation of RAAS inhibitors but usually stabilises.
► A progressive fall in GFR on RAAS inhibition suggests primary renal disease, including extrarenal and intrarenal vascular disease.
► For patients with HFrEF, the benefit of RAAS inhibitors is greater in patients with worsening renal function during RAAS inhibition despite their worse prognosis relative to those with no decline.
► A moderate, asymptomatic decline in renal function is not an indication to stop RAAS inhibitors.
► Further guidance from the Renal Association and British Society for Heart Failure on managing changes in kidney function and serum potassium during RAAS inhibition is given in table 1 and https://tinyurl.com/y7yrYk69.

CHANGES IN KIDNEY FUNCTION DURING INTERCURRENT ILLNESS

Regardless of whether patients are treated with RAAS inhibitors, changes in renal function are common during acute intercurrent illness; the incidence of AKI is between 7% and 18% of hospitalised patients. AKI is a powerful risk marker for poor outcome and is strongly associated with an increase in the risk of subsequent admission for heart failure.40 Renal function often does not return to baseline level in survivors of AKI, especially in those with pre-existing CKD.33

The incidence of AKI as defined by hospital coding is rising rapidly, which may reflect a genuine increase or simply greater awareness. Conditions associated with the development of AKI (such as diabetes and CKD) are also common indications for RAAS inhibitors and thus AKI in association with RAAS blockade is a common clinical scenario. However, it is not clear that ACEI/ARB therapy alone is associated with a substantially increased risk of AKI.36

When AKI is associated with overt hypovolaemia, hypotension or sepsis, it is axiomatic that prompt correction of these abnormalities will improve outcome. However, the reflex inclusion of patients with HFrEF in treatment algorithms for AKI is dangerous. Administration of crystalloids to patients who are already fluid overloaded defies common sense. There is no good evidence that temporary cessation of RAAS therapy given for HFrEF during hospitalisation or perioperatively reduces rates of AKI.37 Among patients hospitalised with AKI, treatment with ACEI or ARB is associated with a lower risk of death.38

In patients on a RAAS inhibitor, intercurrent illness commonly causes AKI, but there is no evidence that stopping the RAAS inhibitor is beneficial.

► If a patient with HFrEF develops hyperkalaemia (table 2):
  – Potassium ≥5.5 mmol/L, monitor closely, medication review and consider suspending RAAS inhibitor(s).
  – Potassium ≥6.0 mmol/L, stop RAAS inhibitor(s).
Table 1  Management of RAAS inhibitors in response to change in renal function

<table>
<thead>
<tr>
<th>Change in renal function compared with baseline</th>
<th>Recommendations for RAAS inhibitors</th>
<th>HFpEF (assuming no other prognostic indication)</th>
<th>HFREF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in serum creatinine by &lt;30%</td>
<td>Consider stop ACEI/ARB/ARNI</td>
<td>Continue unless symptomatic hypotension.</td>
<td></td>
</tr>
<tr>
<td>Increase in serum creatinine 30%–50%</td>
<td>Stop RAAS inhibitor.</td>
<td>Consider reducing dose or temporary withdrawal.</td>
<td></td>
</tr>
<tr>
<td>Increase in serum creatinine &gt;50%</td>
<td>Stop RAAS inhibitor.</td>
<td>Temporarily stop RAAS inhibitor.*</td>
<td></td>
</tr>
<tr>
<td>Severe renal dysfunction, for example, eGFR &lt;20</td>
<td>Stop RAAS inhibitor.</td>
<td>Stop RAAS inhibitor if symptomatic uraemia irrespective of baseline function.</td>
<td></td>
</tr>
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*Reinitiate/restart when renal function improved in patients with HFpEF.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved left ventricular ejection fraction; HFREF, heart failure with reduced left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; RAAS, renin–angiotensin–aldosterone.

If the patient with HFpEF has a rise in creatinine during intercurrent illness:
- By less than 30%, continue RAAS inhibitor(s) but monitor closely.
- Stop any other medication that may worsen renal function, including diuretic if clinically appropriate.
- If by ≥30%, RAAS inhibitor(s) should be stopped.

There must be robust arrangements to make certain that the reduced or stopped RAAS inhibitors prescribed for HFpEF are reintroduced and/or reuptitrated once the intercurrent illness is over.

CHANGES IN KIDNEY FUNCTION DURING WORSENING HEART FAILURE
The consequences of a decline in renal function in a patient with heart failure depend on the clinical setting.39 Patients with hypotension or shock behave differently from those with progressive hypovolaemia.

Table 2  Considerations when managing a patient with heart failure who develops hyperkalaemia

<table>
<thead>
<tr>
<th>Serum K+</th>
<th>All patients</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>Serum K+</th>
<th>Mild hyperkalaemia 5.5–5.9 mmol/L</th>
<th>Moderate hyperkalaemia 6.0–6.4 mmol/L</th>
<th>Severe hyperkalaemia &gt;6.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient clinically well, no AKI</td>
<td>Increase frequency of biochemical monitoring but do not stop RAAS inhibitors. Consider reducing dose.</td>
<td>Stop RAAS inhibitor(s), repeat test Re-start at lower dose once K+&lt;5.5 Re-start one drug at a time, with biochemical monitoring, if the patient was previously on a combination of ACEI/ARB/ARNI plus MRA.</td>
<td>Admit to hospital for immediate K+-lowering treatment Stop RAAS inhibitor(s). Repeat blood test 24 hours later. Restart at lower dose once K+&lt;5.5 Restart one drug at a time, with biochemical monitoring, if the patient was previously on a combination of ACEI/ARB/ARNI plus MRA.</td>
</tr>
<tr>
<td>Patient clinically unwell with sepsis or hypovolaemia and/or AKI.</td>
<td>Withhold RAAS inhibitors until sepsis/hypovolaemia corrected, then restart.</td>
<td>Withhold RAAS inhibitor(s) until sepsis/hypovolaemia corrected, then restart once K+&lt;5.5.</td>
<td>Withhold RAAS inhibitor(s) until sepsis/hypovolaemia corrected, then restart once K+&lt;5.5. Restart one drug at a time, with biochemical monitoring, if the patient was previously on a combination of ACEI/ARB/ARNI plus MRA.</td>
</tr>
<tr>
<td>Patient clinically unwell with decompensated heart failure with/without AKI.</td>
<td>Do not withhold RAAS inhibitors. Consider reduce dose. Treat congestion with loop diuretics or combination of loop and thiazide diuretics. Reduce dose of RAAS inhibitor(s) and monitor frequently. Treat congestion with loop diuretics or combination of loop and thiazide diuretics.</td>
<td>Withhold RAAS inhibitor(s) and restart at lower dose when serum K+&lt;6.0. Restart one drug at a time, with biochemical monitoring, if the patient was previously on a combination of ACEI/ARB/ARNI plus MRA.</td>
<td></td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ARNI angiotensin receptor-neprilysin inhibitor; RAAS, renin–angiotensin–aldosterone; MRA, mineralocorticoid receptor antagonist.
symptoms but who are euvoletic and differently again from those with fluid retention (decompensation with congestion) as discussed here.

Congestion
CKD and AKI are undoubtedly associated with a poor prognosis in patients with HF, but it is far from clear that worsening renal function drives the association. Worsening renal function is only associated with a worse prognosis in patients whose signs of congestion persist at discharge. It feels intuitively obvious that an improvement in eGFR must be related to better outcome, but improving renal function is, in fact, associated with worse outcome. Figure 2 shows data from a post hoc analysis of the Diuretic Strategies in Patients with Acute Decompensated Heart Failure trial, in which patients who were hospitalised with congestion were randomised to a high versus low dose intravenous diuretic regimen. Improvement in eGFR at 72 hours was independently associated with increased risk of the composite end point of death, hospitalisation for HF or visit to the emergency department. The association may reflect inadequate optimisation of fluid balance.

Achieving clinical euvolaemia is a fundamental goal to improve symptoms and to improve outcome. Patients presenting with congestion (unless they are diuretic naive) often need high doses of intravenous diuretics to achieve fluid loss. Patients with fluid overload should have their diuretics increased whether or not their renal function is impaired (and not stopped as is sometimes practice in the hands of non-specialists).

The pharmacological therapy arm of the CARESS study provides a useful protocol for managing difficult congestion. Doses as high as 30 mg frusemide per hour together with a thiazide were used successfully. In clinical practice, the initial diuretic doses prescribed are often far too low, perhaps driven by (an inappropriate) fear of an adverse impact on renal function. Clinical assessment is key. If the patient is improving clinically, declines in renal function are of secondary importance. Current renal function should be assessed in the context of ‘baseline’ values (ideally reflecting longer-term serial evaluations).

End-of-life care
When a patient with HF is approaching end of life, symptom control overrides treatment with potential prognostic impact. Deteriorating renal function is common. Diuretics should be titrated to prevent distress from fluid overload, irrespective of

Figure 2  Relationship between change in eGFR during hospitalisation and subsequent 60-day hazard for adverse events. Data from 303 patients in the DOSE trial. J Card Fail 2016;22:753–760. DOSE, Diuretic Strategies in Patients with Acute Decompensated Heart Failure; eGFR, estimated glomerular filtration rate; ER, emergency room.

Figure 3  Management of patients with AKI or worsening renal function who are receiving RAAS inhibitor. Clinical assessment of the individual patient is key. In all cases consider original indication for RAAS inhibitor. Major prognostic benefit: HFrEF; post MI and left ventricular systolic dysfunction (LVSD), CKD and albuminuria. No/little prognostic benefit: hypertension (other drug options available) and HfPEF. Please refer to table/text box for management of moderate to severe hyperkalaemia or progressive worsening renal function (WRF). ACEI, ACE inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone.
renal function. If there is symptomatic hypotension, discontinuation of RAAS blockade is appropriate.

- Higher doses of diuretics than are commonly used are needed to treat congestion in the fluid overloaded patient.
- A decline in renal function is not an indication to reduce diuretic dose if the patient remains congested.
- Consider stopping RAAS inhibitors towards the end of life.

CONCLUSIONS

The interaction between treatment for heart failure and decline in renal function is frequently misunderstood and commonly used as a reason to withhold potentially life-prolonging therapy. The misunderstanding is not helped by referring to RAAS inhibitors as ‘nephrotoxic’ drugs, which they most emphatically are not. Well-meaning but poorly evidenced recommendations to give patients ‘sick day rules’ have the potential to cause harm when patients stop their medication for minor illness (or fail to restart them once illness has passed). Perhaps of even greater concern is inaccurate advice given by bodies such as the Medicines and Healthcare products Regulatory Agency, which suggested ‘concomitant use of spironolactone with ACEi or ARB is not routinely recommended’. The combination is, of course, of vital importance to patients with symptomatic HFpEF; however, close monitoring of renal function and potassium is vital when using MRA and other RAAS inhibitor together.

There is a danger that concerns over renal function may prevent patients receiving medication beneficial to their long-term outcome. While decline in renal function is important and may require drugs to be stopped, that should only be after very careful consideration of the risks and benefits to the individual patient (Figure 3).

Contributors Each author was involved in the conception and planning of the article. Each author was the primary writer of one of the sections of the document, but each section has in turn been edited and approved by all the other authors. ALC and CT are responsible for the overall content as guarantors on behalf of, respectively, the British Society for Heart Failure and the Renal Association.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MCP has received support from Boehringer Ingelheim, Novartis and AstraZeneca. PK has received speaker and advisory board fees from: AstraZeneca, Novartis and Vifor Pharma. MCP has received speaker and advisory board fees from: Vifor Pharma, AstraZeneca and Novartis. ALC has received speaker and advisory board fees from: Novartis and AstraZeneca. PK has received speaker and advisory board fees from: Vifor Pharma, AstraZeneca and Novartis. LT and CT have no conflicts of interest to declare.

Provenance and peer review Not commissioned; externally peer reviewed.

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