CKD and CKD-ism in heart failure – what a mess!

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Heart failure is a cardio-renal syndrome due to cardiac dysfunction associated with renal retention of salt and water (1). Many patients with heart failure have a low estimated glomerular filtration rate (eGFR), which may be due, in part, to chronic kidney disease (CKD). The term implies that there is long-standing, probably irreversible, structural damage to the renal parenchyma. Assigning a CKD stage requires two consistent measurements of eGFR made at least 90 days apart (2); criteria that are rarely met in studies of heart failure. The term CKD may be unhelpful and misleading when managing patients with heart failure. There may be a reluctance to prescribe guideline recommended therapy for patients with concurrent renal impairment (leading to sub-optimal clinical consequences), which could be called “CKD-ism”.

Renal damage (true CKD) may be due to hypertension, diabetes or atherosclerosis and may have preceded the onset of, and perhaps contributed to, the development of heart failure. When heart failure is diagnosed, an array of guideline-recommended pharmacological therapies should be initiated, all of which are likely to cause an abrupt fall in eGFR (3,4). Consequently, patients with pre-existing renal impairment and very low eGFR are often excluded from randomised trials of heart failure and thus from guideline recommendations. In fact, the fall in eGFR rarely indicates worsening CKD. If it is important to know how severe any underlying CKD is, then a few days therapeutic ‘holiday’ will usually reverse any decline in eGFR, providing some idea of the degree to which the renal dysfunction is fixed (i.e.: CKD) or functional (5). GFR will often improve dramatically if cardiac function recovers (6). However, withdrawal of treatment on a more permanent basis is likely to accelerate progression of heart failure and increase mortality (7).

Due to the lack of evidence, heart failure guidelines emphasise that recommended treatments should be used with caution when eGFR is <30 ml/min/1.73 m^2 (8). However, sub-group analyses of landmark trials strongly support the notion that standard therapy is effective even when the GFR is lower than normal (central figure). Despite any initial dip, heart failure therapy reduces the subsequent rate of decline in GFR (3). Although most patients with heart failure will die before they progress to end-stage CKD, some with ‘terminal’ heart failure do develop a very low eGFR but will usually be refused dialysis due to the risk of hypotension, advanced age and frailty.

In this issue, using a large Swedish database (SwedeHF), Janse and colleagues report that, for patients with heart failure and a reduced (HFrEF) or mildly-reduced (HFmrEF) left ventricular ejection fraction, use of angiotensin-converting enzyme-inhibitors (ACEi)/ angiotensin receptor blockers (ARB)/ angiotensin receptor neprilysin inhibitor (ARNI) (AAA) and mineralocorticoid receptor antagonists (MRAs) was declined when eGFR was low (9). These findings are not novel (10) but the authors now address three additional important points:

- how likely were patients to go to the pharmacy to get their initial prescriptions?

- how many patients had guideline recommended therapy interrupted in the following year and, if so, how often was it restarted?
- If prescribed, how many patients claimed enough prescriptions to enable them to take medicines as recommended on ≥80% of days in the following year?

The results were shocking. In brief, AAAs were prescribed initially for >90% of patients with HFrEF and an eGFR >45 ml/min/1.73 m^2 but also for 68% of those whose eGFR was below <30 ml/min/1.73 m^2. Of concern, 10% of patients prescribed AAA did not claim their prescription, which was similar regardless of eGFR. The first big shock was that prescriptions for AAA were interrupted in about 50% of patients over the following year, rising slightly to 59% in those with an eGFR <30 ml/min/1.73 m^2, although AAAs were more likely to be re-initiated in those with a normal eGFR (82%) than those with a very low eGFR (58%). The second big shock was that fewer than 15% of patients with a normal eGFR claimed enough prescriptions to permit >80% adherence in the following year; the rate was only slightly worse (9%) for those with an eGFR <30 ml/min/1.73 m^2. Many patients will not have consumed all the tablets they *did* obtain and so actual adherence will have been even lower.

For beta-blockers, the picture was different. Beta-blockers were prescribed initially for >90% of patients regardless of eGFR, perhaps because guidelines do not counsel caution against their use when eGFR is low. However, about 20% of patients, regardless of eGFR, did not claim their initial prescription. Why patients prescribed both AAA and beta-blockers should preferentially claim AAA is not clear but might reflect patient disinformation about side effects. In the following year, regardless of eGFR, beta-blockers were stopped, at least temporarily, in 20% of patients and reinstituted in about 70% of these. Adherence appeared rather better for beta-blockers (when prescribed) than for AAA, perhaps because those most reluctant to take beta-blockers were not prescribed them in the first place. About 50% claimed enough prescriptions to permit >80% adherence, with only slightly worse rates for those with a low eGFR.

Only 45% of those with a normal eGFR were initially prescribed an MRA and the rate was even lower (24%) for those with an eGFR below 30 ml/min/1.73 m^2. As for AAA, patients generally claimed their initial prescriptions. Over the following year, regardless of eGFR, prescriptions for MRA were interrupted less often than for AAA (~30% of patients), perhaps reflecting the low rate of initiation. MRAs were reinstated in half of those with a normal eGFR, but in only 27% of those with an eGFR <30 ml/min/1.73 m^2. For those prescribed an MRA, adherence was about 50% for those with an eGFR >45 ml/min/1.73 m^2 and only slightly worse, at 41%, for those with an eGFR <30 ml/min/1.73 m^2.

In brief, physicians were highly likely to prescribe both AAAs and beta-blockers, but much less likely to prescribe MRAs. They commonly withdrew recommended therapies during the first year, and re-started them preferentially in those with a normal eGFR. Patients generally cashed their initial prescriptions but had sub-

optimal adherence thereafter. Patients with a low eGFR were less likely to be initiated on an AAA or MRA, were somewhat more likely to be withdrawn from these agents and, when treatments were withdrawn, were less likely to have them reinstated. However, absolute differences in prescribing according to eGFR were modest.

The data reported here are much more important than simply reporting the relation between renal function and either prescription rates or adherence. The data show that even in a well-resourced healthcare system, even in the absence of substantial renal impairment, there is a large deficit in the pharmacological management of heart failure. Of the more than 30,000 patients with HFrEF included in SwedeHF, fewer than 10% had an eGFR below 30 ml/min/1.73 m^2. For those with an eGFR >45 ml/min/1.73 m^2, about 2,000 patients did not receive an initial prescription for AAA and a further 2,000 did not claim their initial prescription; and about 10,000 had their prescriptions interrupted in the first year, which will have been permanent in about 2,000. More than 17,000 might have not taken their AAA for at least 70 days in the following year. A huge proportion of patients thus received sub-optimal care *regardless of renal dysfunction*.

Only if guideline-recommended therapy is adequately implemented can we expect to deliver the benefits observed in clinical trials. The one-year median survival of older patients with heart failure and an eGFR <30 ml/min/1.73 m^2 might be worse than 50% (11), and may not be improved by guideline recommended therapy. Even if guideline recommended therapy does improve outcome in relative terms, this may equate, on average, only to a few extra weeks of life. In contrast, the median one-year survival for patients with an eGFR >60 ml/min/1.73 m^2 might be 90%, or higher (11); even a modest reduction in relative risk may prolong life expectancy by several years (12). Failure to prescribe, de-prescribing and lack of adherence has far greater consequences for this group of patients.

In summary, a distinction must be drawn between a low eGFR and CKD in heart failure. Renal dysfunction often reflects cardiac dysfunction rather than disease of the renal parenchyma. In patients with an eGFR <30 ml/min/1.73 m^2, the risk is high and the benefits of recommended treatments is less certain. In contrast, we must not neglect the needs of the majority with an eGFR >45 ml/min/1.73 m^2 who probably have more to gain from the treatments we have to offer. For patients with heart failure, a reduction in eGFR associated with initiation of therapy might be a marker of adherence to treatment rather than a signal of concern (13). The patient's needs should guide decisions, rather than a measurement of renal function; listening to their wishes, explaining the reasons for treatments and how to recognise their side-effects, might improve trust, adherence and outcomes.

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Legend to figure: treatment effect according to estimated glomerular filtration rate (eGFR) in heart failure with reduced ejection fraction (HFrEF) clinical trials. Abbreviations used: SGLT2i - Sodium-glucose co-transporter-2 (*SGLT2*) inhibitors*;* ARNI - angiotensin receptor neprilysin inhibitor; MRAs - Mineralocorticoid receptor antagonists; CVD – cardiovascular death; HFH – Heart failure hospitalisation; uHFV – urgent heart failure visit; HR- hazard ratio; IPM –individual patient meta-analysis; Pi – p for interaction; ACM – all cause mortality; AF – atrial fibrillation; SR – sinus rhythm. References to this table are reported in supplementary material.