Is substantial renal dysfunction in patients with heart failure no longer a contraindication for RAS inhibition? The power of a large, high-quality registry to illuminate major clinical issues

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This editorial refers to ‘Association between renin–angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study’, by M.Edner et al., on page 2318.

Published Guidelines uniformly provide renin–angiotensin system (RAS) inhibitors with a class IA recommendation for the treatment of patients with symptomatic heart failure (HF) due to systolic dysfunction. However, the Guidelines reflect the lack of evidence in patients with moderate to severe renal dysfunction and do not recommend the use of RAS inhibitors in this large patient population. The text in the current ESC Guidelines reads: ‘An ACE inhibitor should only be used in patients with adequate renal function (creatinine <221 mmol/L or <2.5 mg/dL, or eGFR ≥30 mL/min/1.73 m² and a normal serum potassium level’. This caveat was adopted in clinical practice both in hospitalized patients and in primary care. ‘Caution/specialist advice’ is recommended when considering initiation of these agents both in patients with evidence of renal dysfunction and in the elderly.

Fifteen years ago, a paper reported some surprising, unexpected results in important subgroups in the HOPE trial. The improvement in clinical outcomes (both all-cause and cardiovascular death) with ramipril in this large heterogeneous population was almost entirely due to highly significant favourable outcomes in the patients with evidence of moderate renal dysfunction (serum creatinine >1.4 mg/dL). Several encouraging retrospective analyses were published demonstrating the safety and efficacy of RAS inhibition in elderly patients with HF and moderate to severe renal dysfunction. Subsequently, similar findings evaluated by rigorous propensity analyses were reported in patients with HF and chronic kidney disease (CKD) treated with RAS inhibitors. These and other publications encouraged many of us to trust our anecdotal experience and cautiously treat these patients with perceived contraindications. Such patients were excluded from the large randomized controlled trials (RCTs) with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

The study by Edner et al. published in this issue of the journal contains real-life clinical data which could potentially improve care of the large population with renal dysfunction due to cardio-renal syndrome or concomitant kidney disease. The data stem from the Swedish Heart Failure Registry and demonstrate the power of a large, high-quality registry to bring clarity to important clinically relevant issues and generate hypotheses that deserve to be tested prospectively. The authors assessed data from a HF registry collected between 2000 and 2013. Approximately 80 variables were recorded at discharge or outpatient visit upon entry into the registry. Out of 24283 patients, 2410 patients had a creatinine >221 mmol/L or creatinine clearance <30 mL/min (Cockcroft–Gault method). Approximately two-thirds of these patients were treated with a RAS inhibitor despite the caveats in the guidelines. The authors created a matched cohort based on propensity scores for RAS antagonist use and demonstrated that the hazard ratio (HR) for 1-year survival in treated patients was almost identical whether or not severe renal insufficiency was present. This is an important and encouraging finding.

A propensity score with 602 patients in each matched arm was developed using 36 clinically relevant baseline variables. All patients had an ejection fraction (EF) ≤39% and approximately half had an EF <30%. The mean creatinine clearance was 23 mL/min. Approximately 94% of patients were concurrently treated with a diuretic, 88% with a beta-blocker, and 25% with a mineralocorticoid receptor antagonist. In the RAS inhibitor arm, 67% were treated with an ACE inhibitor, 31% with an ARB, and 2% with both. About half of RAS inhibitor-treated patients received ≥50% of target doses. Patients with CKD class 4–5 were also notably older than the remainder of the cohort (mean age 82 vs. 71 years) but, even in the CKD
4–5 group, there was no interaction with age, suggesting that RAS antagonists may be associated with benefit not only in CKD 4–5 but also in elderly patients.

This analysis from the Swedish HF Registry based at UCR in Uppsala evaluates patients diagnosed with HF, an EF $\leq 39\%$ and CKD class 4–5 (moderate/severe) defined as a creatinine clearance $<30$ mL/min or serum creatinine $>221$ μmol/L. Such patients have been routinely excluded from trials of RAS inhibitors in patients with cardiovascular disease. A total of 24 283 patients out of the 85 291 in the Registry had systolic dysfunction and a first registration with sufficient information for evaluation, and, of those, 2410 patients satisfied the CKD 4–5 criteria. The association between RAS inhibitor use and all-cause mortality was assessed by Cox regression in a cohort matched 1:1 based on age and the propensity score. The results were consistent across the major subgroups including diabetes and ischaemic heart disease. In the propensity score-matched cohort with CKD 4–5, the HR for all-cause mortality associated with RAS antagonist use was 0.76, $P < 0.001$. Strengthening these findings, a ‘positive control’ analysis in patients without CKD 4–5 demonstrated a HR of 0.79, $P < 0.001$, which is similar both to the CKD 4–5 group in this paper and to results from RCTs in patients without CKD 4–5.

The effect of RAS inhibition on renal function is not a side effect but rather a direct pharmacodynamic action inhibiting the vasoconstrictor effects of angiotensin II on effenter glomerular arterioles. In patients with HF this will serve to reduce hydrostatic pressure within in the glomerulus with a concomitant reduction in filtration fraction.

This reduction will routinely result in a modest and sustained increase in serum creatinine and corresponding decrease in estimated glomerular filtration rate (eGFR), which is typically reversible following dose reduction or discontinuation of the RAS inhibitor. Rarely, this compromise in renal function can become clinically important and it is essential to follow patients routinely to screen for evidence of progressive renal dysfunction and the potential development of hyperkalaemia. This is especially important during the initiation and up-titration phase.

So do these results from the Swedish Registry have ‘game-changing’ impact? From my vantage point, the answer is yes. Substantial renal dysfunction should not be considered a contraindication to the judicious use of RAS inhibitors in patients with symptomatic HF. However, healthcare professionals have an obligation to confirm that the treatment strategy includes an adequate follow-up plan.

There are a number of major limitations that must be considered when interpreting these results. This was not a randomized trial of RAS antagonists in patients with HF and renal dysfunction. Notable demographic characteristics include a mean age of 82 years in the matched cohort, mean creatinine clearance of 23 mL/min, and reduced EF, with almost half the patients having an EF $<30\%$. Patients with a preserved EF were not included. Important confounding factors include potential selection bias that cannot be completely accounted for by a propensity analysis. Unfortunately, the only outcome reported is all-cause death. There is no measure of morbidity such as evidenced by all-cause or cardiovascular hospitalization. Notably, essential longitudinal data on safety and adverse events such as progressive renal dysfunction, hyperkalaemia, and asymptomatic hypotension are lacking. Less than 1% of patients were on haemodialysis. Compliance with therapy and the extent of crossover during follow-up were not assessed. Accurate information on up- or down-titration and dosages of different agents is limited to baseline information.

The authors should be gratified by these results, which should provide cardiologists with ammunition when discussing such patients with colleagues who are traditionally conservative in the use of RAS inhibitors in patients with severe renal dysfunction. These results, of course, generate a hypothesis that deserves to be addressed ideally in a prospective, appropriately designed RCT. However, it would be difficult to recruit symptomatic patients into a long-term placebo-controlled trial when clinical experience and data such as contained in the paper by Edner et al. suggest a net favourable safety and efficacy in this population. The recent evidence demonstrating the efficacy of a novel angiotensin receptor–neprilysin inhibitor (ARNI) as compared with ACE inhibition in patients with HF excluded patients with evidence of renal dysfunction. However, there is some evidence that the preferential vasorelaxation of the pre-glomerular arteriole and a relative vasoconstriction of the post-glomerular arteriole may serve to attenuate the effects of ARBs on filtration fraction and GFR.

It may not be easy to find a sponsor for a conventional RCT but, as the authors suggest, the novel registry-randomized clinical trial (RRCT) concept provides a potential platform for addressing such important clinical questions. Nevertheless, long-term experience is the acid test and will ultimately determine clinical practice.

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**References**


