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Taboo in cardiology: renin–angiotensin–aldosterone system antagonists worsening renal failure

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The renin–angiotensin–aldosterone system (RAAS) allows normal kidneys to maintain a stable function in every situation of daily life but also intervenes to help when critical situations occur that reduce the filtrate. A typical example is heart failure with reduced ejection function (HFrEF) which inexorably becomes complicated over time with renal failure in what is now commonly defined as cardiorenal syndrome. Renin–angiotensin–aldosterone system antagonists have long been irreplaceable in the treatment of HFrEF due to their beneficial haemodynamic and prognostic effects. However, their use often leads to an acute reduction in the filtrate which often scares the clinician and sometimes leads them to suspend their use. In reality, no guideline has ever clearly indicated when a decline in renal function in a patient taking RAAS antagonists should be acceptable and not lead us to fear the associated acute kidney injury. Usually the nephrologist, called for advice, recommends reducing or suspending the RAAS antagonists, knowing that this will improve the filtration and reassure everyone. But is this the right solution? Are we certain that this choice leads to a better prognosis? This article will try to give a reasonable answer to one of the most frequent doubts that arise in our daily practice.

Premises

Until the mid-1980s, heart failure was interpreted exclusively from a haemodynamic perspective; everything was related to reduced cardiac contractility and changes in pre- and afterload. In therapy, the only drugs available were digitalis and diuretics; beta-blockers were absolutely contraindicated, and just thinking about heart failure with preserved contractile function was an oxymoron.

But the neurohormonal arrangement of the patient with heart failure, chronically and exaggeratedly activated, soon focused medical research so much so that the renin–angiotensin–aldosterone system (RAAS) and sympathetic system (SS) became therapeutic targets and represented the rationale for the use of angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers (BB), sartans [angiotensin receptor blocker (ARB)], and antialdosterones [mineralocorticoid receptor antagonist (MRA)]. Antagonizing the RAAS and SS systems became the backbone of our therapeutic beliefs; we became familiar with the use of these drugs and learned to consciously manage their side effects. For RAAS antagonists, the most feared has been always the worsening of renal function which often led to their suspension. Indeed, no guideline has ever clearly indicated to us when a decline, often acute, in the estimated glomerular filtration rate (eGFR) should be considered acceptable and does not lead us to fear an associated episode of acute kidney injury (AKI) or, definitely, how long is an acute drop in eGFR acceptable that does not cause harm.

This is one of the most debated questions among cardiologists and nephrologists especially in patients with heart failure due to reduced ventricular ejection fraction (HFrEF). This clinical setting is dominated by haemodynamic changes (low flow rate with reduced renal perfusion and venous congestion) and by the fact that diuretics and renin–angiotensin–aldosterone system inhibitors (RAASI) are indispensable in the management of HFrEF.

Both of these drug classes have the potential to acutely modify glomerular filtration rate (eGFR) due to their

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effects on systemic blood pressure, vascular tone, peri-glomerular haemodynamics, and volume status. Therefore, the management between the optimization of renal function and the therapy of heart failure represents the keystone of that subtle balance that reigns between benefit and disaster, between art and medical fault.

For many years, large retrospective epidemiological studies have suggested that renal dysfunction is largely associated with a worse prognosis.[1] Because accurate assessment of intravascular volume status is an imprecise science and clinically difficult to diagnose at the bedside, clinicians have relied on ubiquitous serum creatinine values to determine titration of RAASIs and diuretics.

Specifically, positions between cardiologists and nephrologists often diverge regarding the management of patients with HFrEF. Usually, the nephrologist in the presence of a decompensated patient with reduced filtration suggests the cardiologist to reduce or more often suspend the RAAS antagonists, knowing that this will improve the eGFR and this will make everyone feel reassured.

Are we certain that this is the optimal solution? Are we certain that this choice will lead to a better prognosis? Part of the confusion derives from the term AKI (now universally accepted English acronym to define acute kidney injury) which is used without distinction to indicate both tubular renal damage and the fall in eGFR and which has become in common practice inappropriately synonymous with worsening of renal function.[2]

Let us try to ask ourselves to what extent a worsening of renal function is acceptable to improve prognosis without this leading to such a critical drop in filtration as to compromise, irreparably, the renal function itself. The doubt is legitimate, and the answer will have authoritative supporters for each of the parties involved; it is a bit like asking, Is Maradona better than Pelè? Is Panettone or Pandoro better?

Let us at least try to clarify.

Is Maradona or Pelè better?

The functional RAAS allows normal kidneys to maintain a stable GFR in the wide range of situations of daily life but also intervenes to help when critical situations occur.[3]

In fact, even in the presence of critical changes in pressure and/or volume, the kidney preserves its function by maintaining constant glomerular flow and therefore its GFR thanks to a fine mechanism called 'tubulo-glomerular feedback'. This is under the control of the macula densa and juxta-glomerular cells. Its armed wing will therefore be the RAAS.[4]

The macula densa is the renal sensor that controls the entire circulating volume thanks to the constant determination of the concentration of sodium which, filtered by the glomeruli, is present inside the lumen.

In HFrEF, since renal perfusion is reduced by the low flow rate, the sodium concentration will be lower and this will activate the macula densa which will promptly act to defend the GFR otherwise compromised by the reduction in flow. Through adenosine, it will cause vasodilation of the afferent arteriole and therefore increase the flow and perfusion pressure, and through the juxta-glomerular cells (they release renin; therefore, the terminal effector will be angiotensin II), it will cause vasoconstriction of the efferent arteriole. This will increase intra-glomerular pressure; the kidney will hyper-filter and preserve its function. The microalbuminuria that usually appears will be a direct consequence of hyper-filtration.

The mechanism is admirable and immediate but chronically activated as happens in decompensation; it will be highly deleterious over time especially due to the hyper-filtration that characterizes it; this will play a dominant role in that 'cascade' process which will then lead to terminal renal failure.

The entire process can be appreciated in Brenner's splendid editorial cited in the bibliography.[5]

It follows that any attempt to preserve renal function or slow down its decline must necessarily lead to a reduction in intra-glomerular pressure of which hyper-filtration is a consequence.

Is Panettone or Pandoro better?

Renin–angiotensin–aldosterone system inhibitors and, as we will see, also sodium/glucose co-transporter type 2 inhibitors (SGLT2i), more commonly called gliflozines (and even diuretics, although with a different mechanism), have in their very mechanism of action the ability to reduce glomerular hypertension and therefore hyper-filtration, thus slowing down the progression of renal failure but, in a context of decreased systemic blood pressure, compromising glomerular perfusion.[6–8] Any pre-existing low flow condition, including congestive heart failure (HFrEF), will increase the risk of a drop in GFR. They also contribute to the increase in systemic venous pressure which, in HFrEF, can in itself cause a drop in GFR by increasing renal interstitial pressure and activating the sympathetic nervous system.

Last but not least, the increase in intra-abdominal pressure, due to ascites in cases of severe HFrEF, can cause a reduction in GFR in patients causing functional urinary tract obstruction. A prolonged drop in habitual blood pressure beyond the autoregulatory range causes tubular ischaemia and injury ('true AKI'), from which recovery may take weeks and be incomplete.

Therefore, changes in renal function and GFR are complex in a patient with CHF and therapy must be individualized in each patient. The blockade of the RAAS system has several beneficial effects on the kidneys by reducing intra-glomerular hypertension through the vasodilation of the efferent arteriole and the consequent hyper-filtration, fighting inflammation, and increasing peri-tubular blood flow, and all this contributes to reducing the risk of AKI, even experimentally. Similarly, gliflozines in patients with HFrEF and reduced filtration preserve renal function, allowing us to continue using drugs and dosages of drugs that we would see precluded by the reduced filtration because they also reduce intra-glomerular pressure and therefore hyper-filtration, modulating the tubulo-glomerular feedback.[6]

However, treatment with diuretics does not prevent or improve AKI *per se*. Indeed, intravenous diuretics cause a reflex increase in the activity of the SS and RAAS, with a consequent reduction in GFR, but decongestion induced by diuretics can improve GFR by reducing renal venous pressure.[7]

The benefits of RAAS blockade in HFrEF have now been known for some time, making these drugs indispensable!

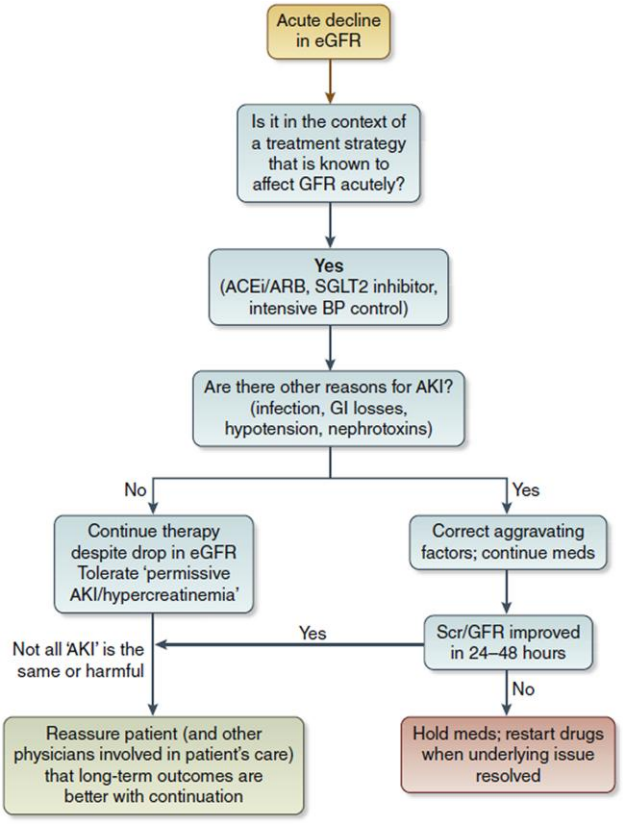

Figure 1 Modified from Parikh and Coca.[12]

Now, landmark randomized clinical trials convincingly demonstrate that RAAS agents confer greater reductions in mortality rates and hospitalizations for heart failure, as well as improved quality of life.[9,10] However, these studies excluded patients with eGFR < 30 mL/min, and therefore, there was no certainty that the advantages would be maintained even in the presence of lower filtrates, hence the tendency towards their suspension.

Reasonable certainties

In reality, rigorous evidence has long existed that the beneficial effect of RAASI is maintained even in the presence of low filtrates and therefore they should not be suspended.[11] This article is specifically referenced because it is unique from previous reports where the authors have attempted to address various biases that may emerge from *post hoc* analysis of data from other clinical trials. In fact, they evaluated whether and how much drops in GFR of different magnitudes, due to the action of the drug enalapril, led to differences in decline-related outcomes. The decreased risk of all-cause mortality, cardiovascular mortality, and hospitalization for heart failure, over a median follow-up of 2.8 years, was maintained across all levels of eGFR decline in patients with HFrEF, without any evidence of reduction in clinical benefit due to filtrate decline.

Interestingly, there were similar numbers of patients in the two arms of the trial for each level of GFR decline assessed. This suggests that changes in GFR are very common during the management of patients with HfrEF and that the data and concepts emerging from the work of Mc Callum *et al*. are a burning topic in daily practice. Acute decline in eGFR due to drugs known to modify renal perfusion (e.g. SGLT2i, intensive blood pressure control, and RAAS inhibitors) is usually well tolerated and should not be labelled for AKI.

These considerations led to the editorial accompanying the article intelligently speaking of 'permissive AKI'.[12]

Conclusions

So what to do in the presence of a patient with HFrEF who presents a drop in GFR after starting the RAAS inhibitor? Clinical evaluation is fundamental. In the absence of any other obvious cause of AKI due to infection, nephrotoxic drugs, or overt hypotension, the direction should be to continue RAAS inhibitors in the face of a decline in eGFR of up to 30–40%.

The scientific evidence produced by historical clinical studies supports this point of view,[9,10,13,14] and simple common sense rules (*Figure 1*) can help us clarify and lead to better results in the treatment of this population of fragile patients.

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