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It is with great pleasure that we introduce to you to this issue of *Cardiac Failure Review*. In this issue, we focus on clinical practice research and observations in advanced heart failure, a topic of increasing interest to triallists, innovators and practising physicians alike. We know the prognosis and outlook remains poor for advanced heart failure, especially if the patient is unlikely receive a cardiac transplant, due to a lack of donor organs, but there is much more we may be able to do if some of the new approaches to advanced heart failure therapy establish themselves as being effective in future trials.

In this issue, Rosano and colleagues review the interrelated phenomena of low dosing of renin–angiotensin–aldosterone system inhibitor (RAASi) drugs and the perceived risk and dangers of RAASi-induced hyperkalemia. Although RAASi agents are well known to improve outcomes in heart failure with reduced ejection fraction (HFrEF), this has been proven in randomised controlled trials (RCTs) where protocol and processes force the physicians to make multiple attempts to up-titrate the drugs to a target dose. Such prompting rarely happens in real-world practice, so that the eventual doses taken in real life are well below the doses we know are effective from the RCTs. The maximally tolerated dose is a rarity in most registries that have reported, despite being achievable in 50% or more of patients in RCTs. The well-known RAASi side-effect of hyperkalemia often leads to down-titration or even discontinuation of RAASis.[1] As Rosano and colleagues explain, this and other complaints that could be linked to RAASi use, such as symptomatic hypotension, syncope, hypoperfusion and reduced kidney function, are often quoted as a reason to reduce or stop RAASi drugs. This RAASi under-dosing is not innocent. It can itself lead to adverse outcomes and increased death rates. Thus, novel ways to manage common RAASi side-effects may allow the use of higher and more effective RAASi dosages in HFrEF. Foremost of these are two newly registered agents to manage hyperkalemia, zirconium cyclosilicate and Patiromer. They conclude that these agents, which have been shown convincingly to be able to control serum potassium in patients with hyperkalemia on RAASis, may in fact help allow RAASi therapies to be used at the effective doses shown from trials. They warn, however, that large-scale clinical trials will be needed to prove safety and resulting outcomes from this approach.

Next, the team of John Parissis reviews the use of inotropes in acute heart failure covering what is said in guidelines through to what we know about their use in routine clinical practice. They review the use of inotropic agents (the main ones being beta-receptor agonists, phosphodiesterase 3 inhibitors and calcium sensitisers), which remain indicated to a limited extent to treat the complications of acute decompensated heart failure (ADHF), where hypoperfusion is a clinical problem when due to a decrease in cardiac pumping capacity because of left ventricular systolic dysfunction. As there is no evidence that these agents improve long-term outcomes – in fact, many are associated with a risk of dangerous ventricular arrhythmias – their use is restricted to short periods to allow haemodynamic stabilisation if it cannot be sensibly achieved by other procedures (such as surgery or mechanical circulatory support). Another clinical situation where their use is justifiable is to support patients as a bridge to a more definitive treatment, such as cardiac transplantation or a left ventricular assist device (LVAD). Newer inotropic agents remain under development and there remains an urgent need for a safe, effective and long-term beneficial positive inotropic agent. The most advanced of these is omecamtiv mecarbil, the first cardiac myosin activator, with an intriguing mechanism of action, priming the myosin head, which may be safer than conventional inotropes by being free of significant calcium or cAMP effects.[2] A second approach under clinical trial evaluation is that of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) 2a modulation, a sarcolemmal membrane-bound enzyme that handles free calcium influx back in the sarcoplasmic reticulum, including via SERCA2a direct gene therapy, although the CUPID II trial with 250 HF patients did not significantly decrease heart failure-related endpoints.[3]

Ruschitzka and colleagues consider the role of the right ventricle (RV) in heart failure syndromes. They review the distinct and complex anatomy and physiology of the RV and explain how it has been relatively neglected compared to the left ventricle for many years. They discuss the important interactions between preload, contractility, afterload, ventricular interdependence and heart rhythm in assessing RV function. They present a recommended treatment algorithm for acute RV failure that takes you through the steps of diagnosis

and identification of the cause of the RV disorder (including the most appropriate imaging techniques to understand the specific pathophysiological mechanisms operative), and then proceeding to optimising the patient's volume status, restoring perfusion pressures, correcting any contractility deficiency and lastly considering specialist procedures for RV failure, such as inhaled NO, inhaled prostacyclins or the use of mechanical circulatory support.

Park and Suradi review the rapidly developing field of structural interventions for heart failure. They explain how, following decades of advances in the pharmacological treatment of heart failure, we are now seeing the emergence of structural heart interventions to improve our heart failure patients with devices and procedures with the potential to improve exercise capacity, quality of life and maybe even survival and outcomes. They consider transcatheter interventions for severe aortic stenosis, including balloon aortic valvuloplasty and transcatheter aortic valve replacement, the latter of which has been demonstrated of increasing clinical value in multiple clinical trials. The article then considers mitral stenosis and mitral and tricuspid regurgitation and the interventional options for their correction. Most recent attention has been given to the possible benefits of correcting functional mitral regurgitation (FMR) secondary to HFrEF. Guideline-directed medical therapy and cardiac resynchronisation therapy may reduce the severity of FMR in some patients, but residual FMR remains a risk factor for increased mortality, spiking interest in percutaneous options for its amelioration. In this regard, there has been considerable interest in the results of the MitraClip procedure. The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial recruited patients with HFrEF and moderate-to-severe or severe secondary mitral regurgitation. In this study, MitraClip was associated with a reduced rate of hospitalisation for heart failure and improved all-cause mortality, although neutral results were seen in another study of the same device.[4,5]

Continuing the theme of the management of advanced and complicated heart failure, Agostoni and colleagues review the role of the calcium sensitiser, levosimendan, in achieving haemodynamic balance in the setting of acute and advanced heart failure. They remind us of the difficult and complicated task of restoring haemodynamic stability and organ perfusion in the setting of ADHF, juggling the use of IV vasodilators and inotropes. Of the inotropic agents, levosimendan, they argue, is best suited to the needs of the patients, for it is free of the increased mortality seen with of the beta-adrenergic receptor agonists and phosphodiesterase 3 inhibitors reviewed earlier by Parissis. The intermittent use of levosimendan in advanced heart failure has received some recent attention. Van Iterson reviews the complex interactions between LVAD support and exercise cardiopulmonary physiology and oxygen transport and uptake in advanced heart failure. We also have excellent reviews of sodium-glucose co-transporter-2 inhibitors and heart failure prevention in type 2 diabetes by Khan and Butler and of iron deficiency and its treatment in heart failure by Ebner and von Haehling. We do hope you enjoy the issue. ■

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