Renal dysfunction and heart failure: things are seldom what they seem

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This editorial refers to ‘Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis’, by K. Damman et al. on page 455

Heart failure (HF) is a risk factor for the development of chronic kidney disease (CKD) and vice versa, while the two conditions quite often co-exist. About one-third of HF patients suffer from at least mild to moderate CKD and about a quarter of them develop worsening renal function (WRF) during their hospitalization for HF.1–4 Renal dysfunction is an independent predictor of adverse prognosis in HF, but the significance of transient WRF during hospitalization for HF has not been fully investigated.1–4 The potential pathogenetic pathways linking HF with renal dysfunction are outlined in Figure 1.

In their comprehensive meta-analysis of studies on the association between renal dysfunction and HF outcomes, Damman et al. provide updated evidence covering the wide spectrum of HF in its acute and chronic setting.4 Pooled data from > 1 million HF patients showed that CKD was present in 32% of cases and conferred a double risk of all-cause mortality.4 In an additional pooled analysis of nearly 50 000 HF patients, WRF occurred in 23% of cases during their hospitalization, and was also associated with a 1.5-fold higher risk of all-cause mortality.4 Furthermore, baseline CKD, diabetes, hypertension, and use of diuretics were shown to be predictors of WRF.4

Although the association between HF and renal dysfunction is undoubtedly important, there are several issues that deserve further consideration. First, although the definition of CKD is well established and generally accepted, the same does not apply to WRF. There are many definitions for WRF that use different absolute or relative increases in serum creatinine (Table 1). The glomerular filtration rate (GFR), which is used in the case of CKD and provides more objective evidence of renal function, cannot be easily used and evaluated in the acute setting. In addition, the baseline renal function is obviously crucial. It is known that baseline CKD is a risk factor for WRF, but studies have not generally addressed the differential outcome of WRF in patients with and without CKD. A particular increase in serum creatinine has a different significance for patients with baseline CKD compared with those without. To complicate things further, not only the extent but also the timing and the duration of decline of renal function are important components that are not usually taken into consideration. For example, data from the DOSE trial suggest that an early and transient WRF during hospitalization for acute HF may not have any prognostic significance, while a subanalysis of the ESCAPE trial showed that HF patients with WRF during hospitalization had an even better outcome than those without, as WRF was an indicator of effective management of congestion.5,6 Moreover, in the EVEREST trial, haemoconcentration, a marker of decongestion, has been found to be associated with decreased mortality and HF re-hospitalization despite in-hospital WRF.7 Thus, to be clinically meaningful, the definition of WRF should differentiate between a transient derangement that results from intensive therapy, is followed by favourable response of symptoms and signs of congestion to treatment, and thus lacks negative prognostic significance, and a more profound and persistent dysfunction that is associated with resistant congestion and is followed by an adverse outcome (Figure 2). Thus, besides the extent, timing, and duration of renal dysfunction and the monitoring of cardiac and renal haemodynamic parameters, the evaluation of symptoms and signs of congestion and their response to the applied therapy may help in differentiating the two forms of WRF. This consideration of WRF would further allow clinicians to enhance their therapeutic approach. The emerging renal biomarkers that provide earlier and/or more sensitive identification of kidney dysfunction may prove useful in this respect. However, we still require clinical trials to evaluate their use in the context of structured diagnostic and management strategies (Figure 2).

Therapy is the second important issue concerning the association of HF with renal dysfunction. Although the latter is generally believed to be an important contributor to the progression of the HF syndrome, it has rarely been used as a therapeutic target in HF. The limited number of trials that have followed such an approach have failed to provide any encouraging data either with drugs or with...
renal replacement therapy. In the PROTECT and RENO-DEFEND trials, the adenosine A1 receptor antagonists rololofylline and SLV320 failed to prevent WRF in decompensated HF patients with renal dysfunction.8,9 Similarly, according to the CARRESS-HF trial, ultrafiltration was inferior to a structured pharmacological approach in preventing WRF and relieving congestion in decompensated HF patients with renal dysfunction. Ongoing trials will clarify if this management strategy is useful.10 Anaemia is another frequent co-morbid state in HF that is closely related to renal dysfunction and emerged some years ago as another potential therapeutic target in HF. However, despite initial enthusiasm, the treatment of anaemia with erythropoietin-stimulating agents in HF is not strongly supported by the available evidence, while the interest of clinical research has lately been redirected to iron deficiency rather than anaemia.11

The meta-analysis of Damman et al. reinforces the already substantial epidemiological evidence linking HF and renal dysfunction, but...
also stresses the current gaps in evidence and our understanding of this association. HF is rather a systemic condition affecting and being affected by several organs as a result of the bidirectional relationship between the cardiovascular symptoms and other systems. For example, HF affects the hepatic function by increasing central venous pressure, while hepatic dysfunction may affect the cardiovascular system by impairing the metabolism of circulating vasoactive substances. In addition, renal function is also as closely related to hepatic function as to cardiac function. Similar multi-bidirectional relationships exist between the heart on one hand and the lungs, the central nervous system, the haematopoietic system, and several other systems on the other. As a result, the approach of isolating a certain two-organ relationship from a complex multisystem entity seems like trying to figure out the layout of a large room through a keyhole.

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