

The importance of registries in today's heart failure therapies

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Heart failure (HF) research and treatment have become an important part of modern day medicine. Over 23 million people worldwide suffer from HF today. Each hospitalisation for congestive HF amounts to an average treatment costs of \$ 8000 [1]. HF is currently divided according to the range of left ventricular ejection fraction (LVEF) into three subcategories: HF with reduced (LVEF < 40%), mid-range (40%–49%), and preserved ejection fraction (\geq 50%) [2]. The frequency of these three groups is 50%, 25%, and 25%, respectively [3]. We continue to gain more insight into these HF syndromes from contemporary registries [4–6]. While one-year and five-year mortality rates of patients with HF remain unacceptably high at about 15% and 50%, respectively [7–10], awareness about HF management and prognosis in the general population is still low [11].

It is important to have new therapeutic developments, and prospective randomised controlled trials (RCTs) are the gold standard in providing evidence of efficacy. Registries, however, also play an enormously important role. They can support our understanding of the characteristics of HF patients and currently prescribed treatments across a range of health care systems. Registries can also provide information about the safety of drugs and, importantly, in larger cohorts of patients, over longer periods of follow-up, and in more complex cases (such as patients with comorbidities) than can RCTs. The limitations of registry-derived data on assessing the risk and efficacy of therapies are well known. There are potentially many reasons why patients do or do not receive specific therapies, and only a few of these factors can be measured and adjusted for (e.g. by using propensity score matching) [12]. However, the advantages of registries, such as the ability to study rarer syndromes [13], should not be forgotten.

A very important feature of the current paper by Migaj et al. [14] is the focus on comorbidities in HF. Here atrial fibrillation was considered, but there are many other important ones that require our attention. These include anaemia [15], iron deficiency [16], chronic obstructive pulmonary disease [17], liver dysfunction [18], chronic kidney disease [19], central sleep apnoea [20], along with sarcopaenia [21], cachexia [22], anorexia [23], and even sexual dysfunction [24].

Among these, an important field of research development is the area of central sleep apnoea in HF. It is a problem in about one-third of patients [25] and is associated with worse outcomes [26]. RCTs of positive airway pressure therapies for the treatment of central sleep apnoea in HF patients, including Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) [27] and Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnoea and Heart Failure (CAN-PAP) [28], resulted in no benefit for the patients, and indeed SERVE-HF showed an increase in cardiovascular mortality. Newer therapies currently being investigated include stimulation of the diaphragm by phrenic nerve stimulation [29].

There is also a lot of research focusing on the development of medical therapies for cachexia [30, 31]. Cachexia is defined as weight loss of \geq 5% [32] or a body mass index below 20 kg/m² combined with weight loss of 2% to 5% and biochemical abnormalities [33]. It occurs in 5% to 15% of patients with advanced chronic HF [34, 35], as it does in other chronic disorders [36, 37], and is associated with increased mortality [38]. Regarding possible treatment options, firstly, it has been shown that patients with HF and cachexia benefit from a high-caloric diet in terms of weight gain and increased quality of life [39]. Secondly, promising new research has shown

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that treatment with a non-specific β -blocker (carvedilol) in chronic HF patients reduces the burden of cachexia [40]. More research into this area is needed to show whether this is a class effect of all β -blockers.

Likewise, the treatment for sarcopaenia as a comorbidity in HF remains challenging. Sarcopaenia frequently occurs in people of older age [41]. When present it is associated with a worse outcome [42] and a lower quality of life [43]. Interestingly, in addition to absolute muscle mass reduction in sarcopaenia, there is also an impairment of muscle function, both of which combine to translate into poor physical independence [44]. In chronic HF, depending on many co-factors such as age and disease severity, sarcopaenia occurs in 20% to 50% of patients [45, 46]. The main treatment approach currently includes resistance and endurance training [47] combined with nutritional support [48] and possible drug treatment with testosterone [49], growth hormones [50], and megestrol [51]. Unfortunately, registries on sarcopaenia and cachexia in HF are lacking. It is unclear whether the European Society of Cardiology (ESC) Heart Failure Long-Term Registry that was used by Migaj et al. [14] can help in this area, but it would be a helpful start for future registries to include more data on comorbidities.

When using today's cardiovascular treatments, we also have to consider the aetiology of HF (hypertensive, ischaemic, valvular, or idiopathic dilated [52]) because this may affect the outcome and the range of treatment options for our patients. It is noteworthy that we are also seeing the emergence of more iatrogenic HF. Most commonly it is observed after oncology and haematology treatments, which, depending on the kind and dose of chemo-, immune-, or radiotherapy used, can cause cardiac dysfunction in up to 48% of patients [53, 54]. Early recognition of left ventricular dysfunction is a key component in initiation of adequate treatment for these patients [55]. Nevertheless, there remains more to be learnt in this field of research because even chemotherapy-naïve tumour patients show a mildly but significantly reduced LVEF [56], and higher resting heart rates in cancer patients are associated with increased mortality [57]. We think the latter is associated with an increased activation of the sympathetic nervous system in these patients and therefore might represent a new therapeutic target — similar to the situation in HF patients [58].

Lastly, we should not forget that psychological characteristics of our patients are also important in the treatment and course of the disease. Patients with inadequate self-care parameters in psychological testing show higher probabilities of recurrent HF hospitalisations [59]. Therefore, we have to teach our patients how to recognise early signs of worsening HF and at the same time ensure adequate ambulant monitoring by skilled medical staff. In this regard, we believe that in the future virtual consultations [60] of patients will become more important in order to ensure extensive medical support in less populated areas and at the same time cut the costs of the healthcare system. Again, the ESC-registry group may

also want to add these aspects of focused research in their future research plans.

Conflict of interest: Markus S. Anker reports no conflict of interest. Andrew J.S. Coats reports receiving lecture and consultancy fees from Resmed, Respicardia, Impulse Dynamics, Vifor, Verona, Actimed, Servier, and Astra Zeneca. Stefan D. Anker has received honoraria for clinical trial committee work, consultancy, and lectures from Bayer, Boehringer Ingelheim, BRAHMS, Actimed Therapeutics, V-Wave, Impulse Dynamics, Novartis, Respicardia, Servier, and Vifor and reports grant support for IITs from Abbott Vascular and Vifor.

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