

# The unbearable underreporting of comorbidities in heart failure clinical trials

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**This article refers to 'Trends in prevalence of comorbidities in heart failure clinical trials' by M.S. Khan et al., published in this issue on pages 1032–1042.**

Comorbidities have a profound impact on the pathophysiology, clinical presentation, management, and outcome of heart failure (HF).<sup>1,2</sup> The relationship between HF and comorbidities differs substantially between HF with reduced (HFrEF) and mid-range (HFmrEF) or preserved ejection fraction (HFpEF). In HFrEF, comorbidities increase the risk of HF decompensation, are associated with a worse quality of life and prognosis.<sup>1,2</sup> Treatment of comorbidities is warranted, though it has not always been shown to improve HF-related outcomes, with the exception of therapy of diabetes with sodium–glucose co-transporter 2 inhibitors.<sup>3,4</sup> In HFmrEF/HFpEF, comorbidities (most notably hypertension and diabetes) are considered crucial determinants of cardiac dysfunction and symptoms, the mechanisms being represented by impaired nitric oxide bioavailability and endothelial dysfunction, oxidative stress, and low-grade systemic inflammation.<sup>5</sup> Treating comorbidities and diuretic therapy for symptom relief are the only recommended approaches for HFmrEF/HFpEF.<sup>6</sup>

Data from population registries or observational studies show a high burden of comorbidities in patients with HF, increasing with age and symptom severity.<sup>7</sup> Most notably, the European Society of Cardiology (ESC) HF Pilot Survey assessed 3226 HF outpatients and reported that nearly 75% have at least one of seven non-cardiac comorbidities [diabetes, stroke, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), anaemia, thyroid disease, or sleep apnoea], the most prevalent being CKD (41%), diabetes and anaemia (both 29%), with a similar burden of comorbidities between HFrEF and HFmrEF/HFpEF.<sup>7</sup> Much less attention has been paid to the prevalence of comorbidities in patients from randomized controlled trials (RCTs), possibly because the pool of patients meeting the stringent inclusion and exclusion criteria are not representative of the general population of HF

patients.<sup>8</sup> On the other hand, comparing the prevalence and burden of comorbidities in an RCT and a reference population could provide a surrogate measure of the discrepancy between RCTs and real-world data. Understanding the current state of comorbidity reporting in RCTs would be a first step in this direction.

In this issue of the Journal, Khan and co-workers assess the prevalence of 10 chronic comorbidities in RCTs published from 2001 to 2016, and enrolling more than 400 patients.<sup>9</sup> Cardiac comorbidities, i.e. cardiovascular risk factors or manifestations of heart disease [current and former smoking habit, diabetes, hypertension, dyslipidaemia, CKD, alcohol intake, coronary artery disease (CAD), atrial fibrillation (AF)], and non-cardiac comorbidities (cancer, stroke, chronic liver disease, peripheral artery disease, anaemia, COPD, obstructive sleep apnoeas, depression, and dementia) were considered. Overall, 118 studies were evaluated, for a total of 215 508 patients. Data on the above comorbidities were reported in a mean of 35% of trials, with no significant increase during the 2001–2016 timespan, and more commonly in RCTs on HFrEF (51%) than in those on HFpEF (which nevertheless was variably defined across different trials; 27%). When reported, the prevalence of several comorbidities was sizable (two in three with systemic hypertension, one in two patients with CAD, one in three patients with diabetes, and one in four patients with AF or CKD), and often tended to increase over time. Almost 75% of trials excluded patients with one or more among 10 common comorbidities (dementia, anaemia, diabetes, severe or uncontrolled hypertension, CKD, AF, chronic liver disease, stroke, cancer, COPD), with an increase to 88% in the 2013–2016 period.<sup>9</sup> Overall, the main message of the study is that comorbidities are underreported in HF RCTs, and should receive more attention in future investigations.

A first observation on these findings is the striking discrepancy between 'cardiac' and 'non-cardiac' comorbidities, the latter being reported in a markedly lower percentage of trials. For example, obstructive sleep apnoeas and dementia were basically overlooked,

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.1818

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and anaemia was never reported in RCTs before 2005, despite its crucial clinical and prognostic relevance.<sup>10</sup> Some possible reasons of the underreporting of 'non-cardiac' comorbidities are the perception of a lower relevance of conditions that are less directly related to cardiac disease, the lack of standardized definitions (as in the case of 'chronic liver disease'), and the notion that some comorbidities (e.g. cancer, depression or dementia) would have discouraged patient enrolment, even when not representing exclusion criteria. As underscored by Khan and co-workers, among 'non-cardiac' comorbidities, there is also an almost complete lack of data on frailty among HF patients in RCTs, although this condition is highly prevalent especially in elderly HF patients and represents a major determinant of prognosis.<sup>11,12</sup> As for 'cardiac' comorbidities, a comparison with the ESC HF Pilot Survey can be made only for diabetes and CKD, also because this survey focused on several conditions that were considered as 'non-cardiac' disorders.<sup>7</sup>

The problem of underreporting of comorbidities in RCTs would be best addressed by an international panel of experts, who should issue recommendations regarding standardization of trial design, data analysis and reporting. These recommendations should include a list of comorbidities that should be mandatorily reported, and propose standardized definitions of these conditions. Should HF registries apply the same criteria for comorbidity reporting, the representativeness of RCT populations, and then the external validity of results from RCTs, could be ultimately evaluated. We may add that, besides mere reporting of comorbidity status at baseline, both retrospective studies and RCTs should pay attention to baseline comorbidity severity, as well as their change over time, often overlooked, but with a profound impact on compliance and response to treatment as well as on prognosis in HF patients.<sup>13</sup>

**Conflict of interest:** none declared.

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