Best of European Journal of Heart Failure at the ESC/HFA Heart Failure Congress 2021

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The *European Journal of Heart Failure* (EJHF) has recently been confirmed as top ranked specialty journal on heart failure (HF) with an impact factor of 15.534 in 2020. For an ad-hoc session during the Congress organized by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in 2021, we selected major studies published in EJHF in 2020 based on their novelty, citations and the potential impact on current (and future) clinical practice in the fields of epidemiology, biomarkers, imaging, and medical treatments and devices.

Epidemiology

Among the selected best studies on HF epidemiology, the HFA Atlas reporting HF epidemiology and management data for 2019 deserves acknowledgment since it represents the first attempt to provide a comprehensive estimate of the HF burden in Europe.[1] It highlighted a median HF prevalence of 17.2 cases per 1000 people, a median HF incidence of 3.2 per 1000 person-years, a median number of HF hospitalizations of 2671 per million people annually, and a median length of hospital stay for HF of 8.5 days across the ESC countries participating in the project. There was great geographical variability in epidemiological data, diagnostic and management resources, which allows to capture inequalities and needs of improvement across the participating countries. The HFA Atlas is a major step forward as it captures, for the first time, real data about HF epidemiology and treatment across Europe. Until now, we had only analyses based on isolated registries and trials.[2,3]

The second study providing important insights into HF epidemiology comes from Australia and New Zealand and considered ~150 000 patients hospitalized for HF in all the public and private hospitals of these countries between 2010 and 2015.[4] Thirty-day mortality was 10.7% and 30-day hospitalization rate was 22.3%, with risk standardized rates declining over time, and risk estimates varying among hospitals. Beyond significantly contributing to highlight the burden of HF in Australia and New Zealand, this study suggests disparities in quality of care among the hospitals in these countries.

Further data on the burden of HF hospitalizations come from the Cardiovascular Disease in Norway (CVDNOR) project.[5] Between 2000 and 2014 there were ~140 000 hospitalizations with a primary diagnosis of HF in Norway. Age-standardized rates for incident HF hospitalizations declined by 1.9% per year in men and 1.8% per year in women, whereas the risk of recurrent HF hospitalizations at 30 days and 3 years increased only in men and by 1.7% and 1.2% per year, respectively. In-hospital mortality for an HF hospitalization declined in both men and women. These data highlight the increase in recurrent HF hospitalizations, which parallels the reduction in in-hospital mortality for HF.

The same topic was addressed in a nationwide observational cohort study from Denmark including 17 176 patients with a first hospital admission for HF in the period 2013–2015, 52% patients with new-onset HF and 48% with worsening of chronic HF. Compared with patients with new-onset HF, those with worsening of chronic HF had a greater comorbidity burden and a higher rate of all-cause mortality or HF readmission.[6]

An analysis of the Women's Health Initiative including ~150 000 post-menopausal women enrolled in 1993–1998 and followed through 2015 assessed the longitudinal relationship between incident HF and incident cancer.[7] Incident HF was associated with a 28% higher risk of incident cancer, but this association was observed only for obesity-related, lung and colorectal cancers, and for HF with preserved (HFpEF) but not for HF with reduced ejection fraction (HFrEF). Due to the lack of an association between HF and incident cancer in male populations from previous studies, the current analysis highlights that gender-related differences in this field might exist, which calls for unselected community-based studies including both genders and more translational research in cardio-oncology to adequately address the relationship between HF and malignancy.[8]

COVID-19

In 2020/2021, EJHF has contributed with top science about the relationship between COVID-19 and cardiovascular diseases. A multicentre study from Italy, the Cardio-COVID-Italy, analysing data from 692 patients admitted for COVID-19 in March–April 2020, assessed the prognostic impact of a history of HF on COVID-19.[9] As much as 13% of the study population had HF and the median hospitalization length was 14 days. Crude in-hospital mortality was twofold higher in patients with vs. without a history of HF (41% vs. 21%), which remained statistically significant after extensive adjustments. Additionally, risk of acute HF, sepsis, acute renal failure and multiorgan failure was higher in patients with concomitant HF. Notably, in-hospital use of corticosteroid and heparin predicted lower in-hospital mortality rates. Similar data regarding the deleterious effects of concomitant HF and COVID-19 came from Spain, United Kingdom (UK) and Germany.[10–13]

One registry-based study on cardiovascular diseases and COVID-19 came from the National Patient Registry in Sweden, considering 1.4 million patients with hypertension, HF, kidney disease, ischaemic heart disease and diabetes.[14] In this population, after extensive adjustments, use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) was associated with lower risk of hospitalization or death from COVID-19, and consistently, in patients hospitalized for COVID-19 the use of these medications was associated with lower mortality, whereas no associations were observed for mineralocorticoid receptor antagonists (MRA). Similar results were observed across subgroups, including also HF. These data and other similar studies[15] highlighted the lack of any signal of a harmful association between ACEi/ARB and MRA use and incident hospitalization/death for COVID-19, or risk of all-cause death in patients with COVID-19, providing reassuring evidence at a time when it was hypothesized these drugs might favor COVID-19.[16–18]

Biomarkers

In the field of cardiac biomarkers, a large meta-analysis of 61 trials including ~6000 patients showed that high troponin levels in patients receiving chemotherapy or human epidermal growth factor receptor 2 inhibitor therapy predicted left ventricular dysfunction with a 93% negative predictive value, whereas natriuretic peptide levels [N-terminal pro-B-type (NT-proBNP) and B-type natriuretic peptide (BNP)], although increased post-treatment, did not have a similar predictive value.[19] Beta-blockers and ACEi during cancer therapy were associated with decreasing levels of troponins. Importantly, this study highlighted a role for troponins to identify those patients more in need of referral to cardio-oncology and of preventive strategies following chemotherapy. This topic has been also reviewed in a position paper.[20]

On a different topic, high-sensitive troponin T (hsTnT) and NT-proBNP identified patients at higher risk of cardiovascular death/HF hospitalization in the DECLARE-TIMI 58 trial.[21] Dapagliflozin reduced the relative risk of cardiovascular death/HF hospitalization regardless of the levels of these biomarkers, although the absolute risk reduction was greater in patients with high levels of NT-proBNP and/or hsTnT. Similar data were recently issued from EMPEROR-Reduced with a linear positive association between higher hs-TnT levels and HF severity and worse outcomes, but a similar efficacy of empagliflozin independently of hsTnT levels.[22]

One more important study on biomarkers focused on high soluble transferrin receptor (sTfR) as a measure of iron deficiency (ID) and predictor of mortality in HF.[23] In patients with HF and ejection fraction ≤45%, sTfR had better accuracy in predicting ID in bone marrow compared with ferritin, transferrin saturation or serum iron levels, and a sTfR ≥1.25 predicted a 74% higher risk of 3-year mortality on top of other common prognostic factors in HF, including NT-proBNP.

Management

In the field of medical treatments, the EMPA-RESPONSE-AHF trial deserves attention.[24] In this trial, 80 patients with acutely decompensated HFrEF were randomized to empagliflozin or placebo and followed up for 60 days. Treatment with empagliflozin reduced the risk of death or worsening/hospitalization for HF and was safe. This study paves the way towards larger trials on the use of sodium–glucose co-transporter 2 inhibitors in the setting of acute decompensated HF.[25]

In another interesting trial randomizing 36 patients with HFrEF and insulin resistance, metformin improved myocardial efficiency by 20%, as evaluated by the work metabolic index, and reduced myocardial oxygen consumption.[26] These energy-sparing effects encourage further large-scale investigations on this drug in HFrEF.

Finally, the results of the 4-year follow-up of the MSC-HF trial are of great interest.[27] In this trial, 40 patients with ischaemic HF and ejection fraction <45% were randomized to receive intramyocardial injections of autologous bone marrow-derived mesenchymal stromal cells (MSCs) whereas 20 patients received placebo. After 12 months, MSCs reduced left ventricular end-systolic volume, which was the primary outcome of the trial, improved LVEF by 6.2% and also stroke volume, and reduced the amount of scar tissue and myocardial mass, without any concern on safety but also without any long-term (4-year) effect on hospitalizations/survival.

Registries represent an important tool to evaluate real-world management of HF patients and monitor the implementation of treatments and diagnostic procedures in daily clinical practice.

In this perspective, an elegant analysis of the ESC-EORP Heart Failure Long-Term Registry assessed the prognostic impact of loop diuretic down-titration.[28] Analyzing more than 8000 patients, this study showed that in the majority of cases (76%) the used loop diuretic doses remained unchanged over time. However, when down-titration was achievable, a trend towards lower HF and cardiovascular mortality was observed. Important predictors of loop diuretic dose decrease were higher systolic blood pressure and absence of sleep apnoea, peripheral congestion, and moderate/severe mitral regurgitation. On the contrary, up-titrating loop diuretics was associated with a significantly higher mortality.

Regarding HF devices, in the MEMS-HF study physician-directed treatment modifications based on pulmonary artery pressures

(PAP) values obtained remotely by CardioMEMS, an implantable device allowing haemodynamic-guided HF management, were associated with a reduction in risk of HF hospitalization, a decrease in PAP and better quality of life.[29]

Finally, the long-term extension study of ATTR-ACT trial showed that tafamidis, both 80 and 20 mg/day, reduced mortality and risk of cardiovascular hospitalization in patients with transthyretin-related (TTR) amyloidotic cardiomyopathy.[30] The long-term survival data and the lack of dose-related safety concerns support 80 mg as the optimal dose. An association between tafamidis treatment and a lower occurrence of cardiovascular outcomes was also shown in a real-life population including 648 consecutive patients with TTR amyloidosis.[31]

These studies represent only the tip of the iceberg of the great science published over the last year in EJHF, contributing to the extraordinary growth of the journal and, we retain, in the knowledge and treatment of HF, the ultimate goal of our journal and HFA itself.

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