Cardiologia Hungarica
2023; 53: 309–312.

The year in cardiovascular medicine 2022: the top 10 papers in heart failure and cardiomyopathies

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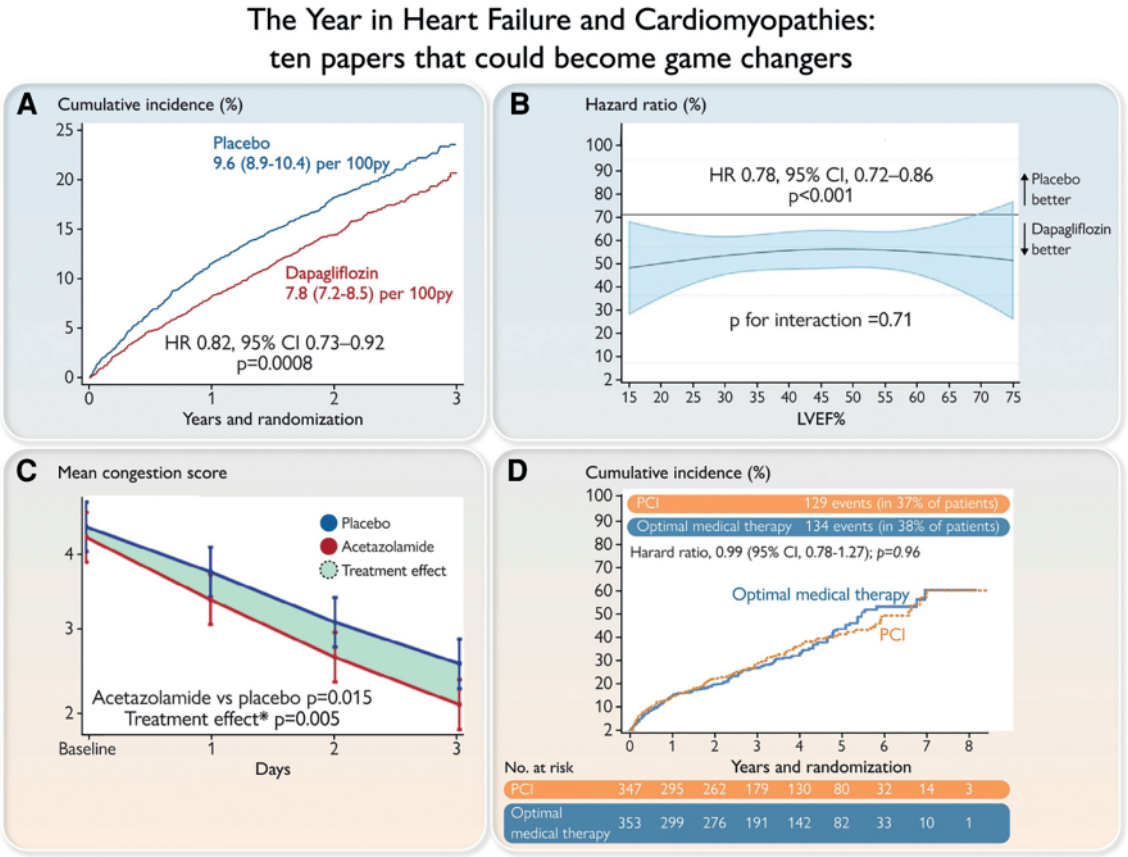

GRAPHICAL ABSTRACT: PANEL A. Primary endpoint of DELIVER [cardiovascular (CV) death or heart failure (HF) hospitalization] in the entire population (left) and in the population with LVEF <60%. Reprinted with permission (2). PANEL B: A pooled analysis of patients enrolled in the DAPA-HF and DELIVER trials reveals a consistent benefit of dapagliflozin on the primary endpoint (CV death or HF hospitalization) across the entire spectrum of LVEF, with no signs of attenuation of the effect in the higher LVEF range. Reprinted with permission (3). PANEL C: Effect of acetazolamide on congestion in the ADVOR trial. From Day 1 onwards, the use of acetazolamide on top of regular loop diuretics resulted in accelerated decongestion. Reprinted with permission (6). PANEL D: Kaplan–Meier estimates of all-cause mortality or HF hospitalization for patients receiving PCI or optimal medical therapy in the REVIVED trial. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention. Reprinted with permission (8)

Received 22 September 2022; revised 20 November 2022; accepted 12 December 2022;
Reproduced from: European Heart Journal, Volume 44, Issue 5, 1 February 2023, online publish-ahead-of-print 2 January 2023 Pages 342–344, https://doi.org/10.1093/eurheartj/ehac781

The year of 2022 has been an exciting year in heart failure (HF). In this brief report, we will highlight some of the most provocative and impactful papers in the field.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors are becoming one of the main treatments for patients with cardiorenal disease. Some uncertainties remained, e.g. if SGLT2 inhibitors were effective in patients with acute HF (AHF), or in HF with a left ventricular ejection fraction (LVEF) >40%, or in patients with improved LVEF. The Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE; NCT04157751) trial enrolled 530 patients with acute de novo or decompensated HF to receive empagliflozin 10 mg once daily or placebo (1). The unique aspect of EMPULSE was that patients were randomized in hospital, when clinically stabilized (median time to randomization: 3 days), and were treated for up to 90 days. More patients treated with empagliflozin had clinical benefits compared with placebo (this was assessed by a 'win' ratio). Mortality and HF readmissions were also reduced.

The Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER, NCT03619213) study was a randomized double-blind clinical trial in 6263 patients with chronic symptomatic HF, LVEF >40%, and elevated natriuretic peptides comparing the effect of dapagliflozin 10 mg once daily vs. placebo, in addition to standard of care (2). After a median follow-up of 28 months, the primary outcome [death from cardiovascular (CV) causes or HF hospital admissions] occurred in 16.4% in the dapagliflozin group and in 19.5% in the placebo group [hazard ratio (HR) 0.82; 95% confidence interval (95% CI): 0.73–0.92; P<0.001, *Panel A*]. Findings were similar in prespecified subgroups. The frequency of adverse events leading to treatment discontinuation, related to volume depletion, and hypoglycaemia were similar between groups.

A prespecified patient-level pooled analysis (n = 11 007) of the DAPA-HF (NCT03036124) and DELIVER trials (3) found that the benefits of dapagliflozin were similar regardless of LVEF. Dapagliflozin reduced the risk of the composite of HF hospitalizations or CV death (Panel B), and of CV death alone (HR = 0.86; 95% CI: 0.76–0.97; P = 0.01), death from any cause (HR = 0.90; 95% CI: 0.82–0.99; P = 0.03), total hospitalizations for HF (HR = 0.71; 95% CI: 0.65–0.78; P<0.001), and MACE (HR = 0.89; 95% CI: 0.80–0.99; P = 0.02). In this patient-level meta-analysis, there was no evidence that the effects of dapagliflozin differed by LVEF.

Several papers addressed the issue of diuresis, renal function, sodium, and potassium.

The issue of sodium restriction in HF has been disputed for long, and the study of dietary intervention under 100 mmol in heart failure (SODIUM-HF) was designed to test whether or not a reduction in dietary sodium reduces the incidence of future clinical events (4). SODIUM-HF enrolled 806 patients with chronic HF receiving guideline-directed medical treatment, and randomized them to either usual care according to local guidelines or a low sodium diet (LSD) of <100 mmol (this is <1500 mg/day). The median sodium intake decreased from 2286 mg/day (interquartile range 1653–3005) to 1658 mg/day (1301–2189) in the low sodium group and from 2119 mg/day (1673–2804) to 2073 mg/day (1541–2900) in the usual care group. By 12 months, the primary composite endpoint of CV-related admission to hospital, CV-related emergency department visit, or all-cause death had occurred in 15% of patients in the LSD group and 17% in the usual care group (HR=0.89; 95% CI: 0.63–1.26; P = 0.53). So, a dietary intervention to reduce sodium intake does not reduce clinical events.

Patiromer is a potassium lowering agent, and the Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND, NCT03888066) trial investigated the effects of patiromer on serum potassium level, and if its use would enable target doses of renin–angiotensin–aldosterone system inhibitors (RAASi) use in patients with HFrEF (5). A total of 1195 patients were enrolled during the run-in phase with patiromer and optimization of RAASi therapy [≥50% recommended dose of RAASi and 50 mg of mineralocorticoid receptor antagonist (MRA)]; this was achieved in 878 (84.6%) of the patients who were 1:1 randomized. At the end of the treatment, the adjusted mean change in potassium was +0.03 mmol/L in the patiromer group and +0.13 mmol/L in the placebo group [difference: −0.10 (95% CI −0.13, −0.07), P<0.001]. This was accompanied by lower risk of hyperkalaemia (>5.5 mmol/L) and less reductions in MRA dose. Strikingly, a large proportion of the patients with hyperkalaemia in the past whose RAASi or MRA was downtitrated could tolerate adequate dosages of RAASi and/or MRA during the run-in phase of the DIAMOND trial. In any way, patiromer enables adequate titration of RAASi and MRA in patients with hyperkalaemia, although the number needed to treat to prevent hard clinical outcomes by this strategy appears to be rather high.

Diuretic resistance is another clinical dilemma which was addressed by two interesting trials. The Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial (6) evaluated if acetazolamide, a carbonic anhydrase inhibitor, reduces proximal tubular sodium reabsorption, on top of loop diuretics in patients with AHF; 519 AHF patients and clinical signs of volume overload and an NT-proBNP level of more than 1000 pg/mL were randomized to either intravenous acetazolamide (500 mg once daily) or placebo added to standardized intravenous loop diuretics. Successful decongestion was more often achieved in the acetazolamide group compared with the placebo group [risk ratio (RR) 1.46, 95% CI: 1.17–1.82; P<0.001; *Panel C*]. Acetazolamide treatment was associated with higher

cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. However, neither changes in symptoms, nor weight, nor the EuroQoL outcomes were reported and may complement the published data. The incidence of worsening kidney function, hypokalaemia, hypotension, and adverse events was similar in the two groups. These data likely will shift the standard diuretic regimen in AHF.

The Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC trial; NCT01647932) (7) evaluated if addition of hydrochlorothiazide (HCT) to intravenous furosemide is a safe and effective strategy for improving diuretic response in patients with AHF. In total, 230 patients (48% women, 83 years) were randomized to HCT or placebo; those on HCT lost more weight at 72 h [−2.3 vs. −1.5 kg; −1.14 (95% CI: −1.84 to −0.42); P = 0.002], but there were no significant differences in patient-reported dyspnoea. Mortality or HF rehospitalization rates were similar between HCT and placebo. Patients with HCT more often had a significant increase in creatinine (46.5% vs. 17.2%; P<0.001).

Several other interesting articles were published.

First, the long-standing dispute about whether or not patients with ischaemic cardiomyopathy may benefit from revascularization by percutaneous coronary intervention (PCI), when compared with optimal medical therapy (OMT) (i.e. individually adjusted pharmacologic and device therapy for HF), was addressed by the Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2; NCT01920048) (8). Patients with an LVEF of 35% or less, extensive coronary artery disease that could be treated by PCI, and demonstrable myocardial viability were randomized to either PCI plus OMT (PCI group) or OMT alone. Totally, 347 were assigned to the PCI group and 353 to the OMT group. Over a median of 41 months, a primary outcome (death from any cause or HF hospitalization) occurred in 37.2% in the PCI group and in 38.0% in the OMT group (HR = 0.99; 95% CI: 0.78–1.27; P = 0.96; *Panel D*). The LVEF was similar in the two groups at 6 and 12 months. So, revascularization by PCI has no benefit in these patients on top of medical therapy.

Finally, two interesting articles addressed how drug titration in patients with HF may be handled. Until recently, the guidelines recommended initiating therapy in patients with HF in a historical sequence, with slow and controlled up-titration of individual classes of drugs. However, the newest guidelines state that four classes of drugs should be titrated on a faster schedule; however, the order and speed of titration remained unaddressed.

A first study (9) to address this was a retrospective study analysing data from six major mortality trials in HF: the SOLVD-Treatment trial (angiotensin-converting enzyme inhibition, enalapril), the MERIT-HF trial (beta-blockade, metoprolol), EMPHASIS-HF (MRA, eplerenone), the PARADIGM-HF trial (angiotensin receptor–neprilysin inhibition), DAPA-HF (SGLT2 inhibition, dapagliflozin), and CHARM (angiotensin receptor blocker, candesartan). The authors modelled the potential reductions in CV events that might be expected from more rapid up-titration in the conventional order (based on a chronology of trials), and compared this to accelerated up-titration, using treatments in different orders than currently is conventional. Indeed, a rapid up-titration schedule was associated with fewer HF hospitalization or CV death. Furthermore, an optimal ‘alternative’ sequence of drugs was identified, which proposed SGLT2i and an MRA as the first two therapies.

A second study addressing this pressing issue was the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies (STRONG-HF; NCT03412201) (10). STRONG-HF randomized patients who were admitted to the hospital with AHF, who were not treated with full doses of guideline-directed drug treatment, to usual care or high-intensity care (HIC). HIC was defined by the up-titration of treatments to 100% of recommended doses within 2 weeks of discharge, with four scheduled outpatient visits over the 2 months after discharge, to closely monitor

Reproduced from: European Heart Journal, Volume 44, Issue 5, 1 February 2023, https://doi.org/10.1093/eurheartj/ehac781

clinical status, laboratory values, and biomarkers. The primary endpoint was 180-day readmission for HF or all-cause death. In total, 1078 patients were randomized to HIC (n = 542) or usual care (n = 536). The study was stopped prematurely by the DSMB because of greater than expected between-group differences. A higher proportion of HIC patients had been up-titrated to full doses of prescribed drugs. HF readmission or all-cause death up to day 180 occurred in 74 (15.2%) of 506 patients in the HIC group and 109 (23.3%) of 502 patients in the usual care group (difference: 8.1%; RR = 0.66, 95% CI: 0.50–0.86). Patients receiving HIC thus ended up having both more medical attention and visits as well as higher dosages of drugs – it remains uncertain what part of the benefit is explained by what element. More adverse events by 90 days occurred in the HIC group (41%) than in the usual care group (29%), but similar incidences of serious adverse events were reported in each group.

Overall, these two trials provide strong support for accelerated titration of guideline-directed drug treatment, while the order of drugs installed does not need to be based on historical grounds.

Funding

All authors declare no funding for this contribution.

Data availability. No new data were generated or analysed in support of this research.

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