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August 2023 at a glance: Focus on epidemiology and medical therapy

Daniela Tomasoni, Marianna Adamo, and Marco Metra

Cardiology and Cardiac Catheterization Laboratory, Cardio-Thoracic Department, Civil Hospitals; Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

HFA clinical consensus statement

An early diagnosis, and hence treatment, of heart failure (HF) may have a major impact on health care resources and patients' longevity and quality of life.[1] The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) provided a clinical consensus statement addressed to general practitioners and to non-cardiology physicians to facilitate the early diagnosis of HF with a major role to screening strategies, including the measurement of brain natriuretic peptides (BNP).[2]

Epidemiology

Myocardial infarction is one of the most common causes of HF.[3–6] Docherty *et al.*[7] examined changes in the risk of HF hospitalizations (HFH) following a first acute myocardial infarction (AMI) in Scotland in the years 1991 to 2016. Overall, 175 672 patients with no previous HF who survived the first hospitalization were included. Overall, there was a 12.2% HFH rate post-AMI. Incidence of HFH at 1 year following discharge after a first AMI decreased from 5.9% in 1991 to 3.1% in 2015 corresponding to a 53% decrease in these years, after adjustment for covariates. Similar trends were observed also for HFH at 5 and 10 years after AMI. Annualized mortality remained, however, five-fold greater in those after a first HFH, compared to those who were never hospitalized for HF, with a fatality rate per 1000 patient-years of 254.2 (95% confidence interval 250.5–258.0) for patients following a first HFH vs. 53.7 (53.3–54.1) for those never hospitalized for HF (*Figure 1*).[7,8]

A secondary analysis of the PARADISE-MI trial[5,9] highlighted the geographical differences in characteristics, management and prognosis of the patients enrolled. Rates of the primary composite outcome of cardiovascular (CV) death or incident HF varied among regions, with the lowest rates in South Asia (4.6/100 person-years) and the highest ones in Latin America (9.2/100 person-years). Rates of incident HF were 1.0/100 person-years in South Asia and 5.9/100 person-years in Northern Europe.[9]

Patient profiling is useful for tailoring medical therapy in patients with HF and reduced ejection fraction (HFrEF).[10] Of 108 profiles generated by combining different strata of renal function based on estimated glomerular filtration rate (eGFR), systolic blood pressure, heart rate, atrial fibrillation and presence of hyperkalaemia, 93 were identified among patients with HFrEF enrolled in the Swedish Heart Failure Registry (SwedeHF) between 2013 and 2021. Most patients fit in a few easily identifiable profiles; the nine profiles at highest risk of mortality/morbidity accounted for only 5% of the population.[11]

A post-hoc analysis of PARADIGM-HF was performed to unveil prevalence of pathogenic variants in genes associated with dilated cardiomyopathy. A total of 44 genes were assessed for rare predicted loss-of-function (pLoF) variants. Among 1412 HFrEF patients with whole-exome sequence data, about 5% presented at least one pLoF variant with definitive/strong association with dilated cardiomyopathy, with titin being the most common. Such patients were younger, had a lower left ventricular ejection fraction (LVEF) and were less likely to have an ischaemic aetiology.[12]

Iron deficiency (ID) is common in HF patients and should be treated with intravenous iron.[3,13,14] An analysis from SwedeHF reported an improvement in iron screening since 2016, even if it remained <25% as in 2018. In 1486 patients with iron biomarkers at baseline, the prevalence of ID was 55%. ID was independently associated with a greater risk of CV death or HFH.[15]

Imaging

Machine learning is now often used for risk stratification and possibly improve clinical trials' efficiency.[16–18] This technique was applied to echocardiographic parameters to predict the effects of spironolactone in patients at risk for HF investigated in the HOMAGE trial.[19] Different echocardiographic phenotypes were identified. Spironolactone significantly reduced E/e' and BNP concentrations only in subjects with the diastolic and structural changes specific phenotype, but not in those with other phenotypes.[20]

The diagnosis of HF with preserved ejection fraction (HFpEF) remains challenging.[3,21,22] Harada *et al.*[23] examined 225 patients with HFpEF and 262 controls with non-cardiac dyspnoea (NCD) who underwent exercise stress echocardiography. As compared with NCD, patients with HFpEF demonstrated decreased left atrial (LA) reservoir strain and compliance at rest; these differences further increased during exercise. Exercise LA compliance discriminated HFpEF from NCD (area under the curve 0.87, $p < 0.0001$), with a superior diagnostic ability than exercise E/e' ratio (DeLong

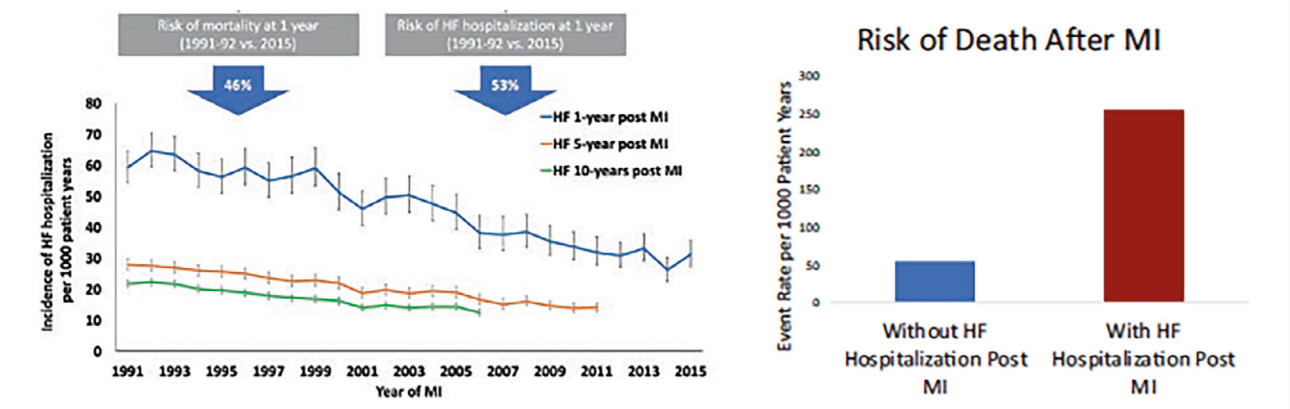

Figure 1 Declining risk of hospitalizations for heart failure (HF) after a first acute myocardial infarction (MI) in Scotland in the years 1991 to 2016 (*left*) and persistent high risk of death after HF hospitalization (*right*). Redrawn from[7,8]

$p = 0.005$) and demonstrated incremental diagnostic value over clinical factors and resting LA compliance.

Medical treatment

Diuretics

A pre-specified analysis of the ADVOR trial assessed the effects of acetazolamide on sodium and potassium concentrations.[24] Acetazolamide was associated with a slight decrease in potassium concentrations, compared to placebo, and had no significant impact on hypokalaemia incidence ($p = 0.061$). Acetazolamide was not associated with hyponatraemia. Decongestion was improved irrespective of baseline sodium and potassium levels.[25]

A prospective observational study including 50 patients with acute HF, divided into two groups according to the previous use of furosemide (naïve vs. chronic users), showed that the naïve group had a better diuresis and natriuresis compared to the chronic users. Urine furosemide delivery was similar between groups. However, the tubular response to delivered diuretic was higher in diuretic naïve versus chronic users showing the central role of the tubule in diuretic resistance.[26]

Sodium–glucose cotransporter 2 inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are mandatory in the treatment of HF,[3,27–29] and their administration is also cost-effective, as more recently shown.[30]

A secondary analysis of EMPEROR-Preserved assessed the effects of empagliflozin across the spectrum of kidney function. Overall, 5988 patients were included and categorized according to concomitant chronic kidney disease (CKD) at baseline ($n = 3198$, 53.5% with CKD). The efficacy of empagliflozin on the primary outcome of HFH or CV death was significant irrespective of CKD. Empagliflozin also reduced the progression to macroalbuminuria and the risk of acute kidney disease.[31]

The interaction between liver function and the efficacy of SGLT2 inhibitors has been also investigated.[32] A further analysis of EMPEROR-Preserved is focused on the role of liver function. High alkaline phosphatase, low albumin and high bilirubin concentrations were associated with poorer outcomes. Empagliflozin, compared to placebo, showed an effect on albumin levels, which were significantly increased, and reduced the primary outcome irrespective of baseline liver function.[33]

The DAPA-MODA trial was a multicentre, single-arm, open-label, prospective and interventional study involving 162 patients evaluating the effect of dapagliflozin on cardiac remodelling parameters over 6 months. Echocardiography was performed at baseline, at 30 and 180 days in a core echo-lab with blinded measurements. Treatment with dapagliflozin showed a global reverse modelling with a reduction in LA volumes and improvement in left ventricular geometry and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.[34]

Chatur *et al.*[35] assessed the impact of dapagliflozin on different ranges of complexity and length of HFH using data from the DELIVER and DAPA-HF trials. HFH were classified as 'complicated' or 'uncomplicated'. About 30% and 40% of incident HFH were defined as complicated in the two trials, respectively. Dapagliflozin significantly reduced HFH, irrespective of baseline severity of inpatient course or length of stay.

Heart damage is characterized by multiple molecular pathological pathways, leading to cardiac dysfunction.[36] Packer[37] reviewed the intrinsic molecular pathways of cardiac injury, mimicking foetal processes. This signalling programme, although adaptive in the short term, is highly deleterious when prolonged for a long time. SGLT2 inhibitors exert a cardioprotective action limiting such foetal processes.

Sacubitril/valsartan and plasma biomarkers

Adrenomedullin plays a role in microcirculatory and endothelial homeostasis and it is a substrate of neprilysin.[38] Mid-regional

pro-adrenomedullin levels were measured in 156 HFrEF patients treated with sacubitril/valsartan and 264 patients with HFpEF randomized to treatment with sacubitril/valsartan or valsartan. Mid-regional pro-adrenomedullin levels showed a significant increase following the sacubitril/valsartan administration regardless of LVEF, while no changes occurred with valsartan alone. No association between these changes and cardiac structure and function or health status was noted.[39]

The search for new biomarkers as diagnostic and prognostic tools for patients with HF remains active.[36,40] McDowell *et al.*[41] examined among 1559 HF patients from the PARADIGM-HF trial whether a panel of several biomarkers improved the performance of the PREDICT-HF prognostic model, which includes clinical, routine laboratory, and BNP data. Aldosterone, cystatin C, high-sensitivity troponin T (hs-TnT), galectin-3, growth differentiation factor-15, kidney injury molecule-1, matrix metalloproteinase-2 and -9, soluble suppression of tumourigenicity-2, tissue inhibitor of metalloproteinase-1 and urinary albumin to creatinine ratio were tested individually and collectively, but none of them led to a meaningful improvement compared to standard tests.

Eplerenone

Monzo *et al.*[42] investigated time to benefits after the initiation of eplerenone in 2737 patients from the EMPHASIS-HF trial. A significant reduction in the primary endpoint, a composite of CV death or first HFH, was observed 26 days after randomization. Most subgroups of patients, characterized by a different clinical history and comorbidities, showed benefits within 35 days after eplerenone initiation.

Other medications

The eligibility for vericiguat in a real-world HFrEF population according to VICTORIA trial criteria, guidelines and product labelling was assessed in 23 573 patients from the SwedeHF. Only 21.4% of patients would be eligible to receive vericiguat according to VICTORIA trial selection criteria, while 47.4% of patients according to guidelines and labelling. HFH in the prior 6 months was the main limiting factor for eligibility.[43]

EVO-HF was a multicentre prospective randomized trial comparing the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab (420 mg/month administered subcutaneously) plus guideline-directed medical therapy (GDMT; $n = 17$) versus GDMT alone ($n = 22$) for 1 year in patients with stable coronary artery disease and LVEF <40%, New York Heart Association class II, NT-proBNP ≥400 pg/ml, hs-TnT >10 pg/ml and low-density lipoprotein cholesterol ≥70 mg/dl. No significant changes in hs-TnT levels (primary endpoint) were observed in any group at 1 year.[44]

Disease management

Influenza vaccination reduces the risk of CV events, including HFH, and is strongly recommended in HF patients.[3,4] The nationwide NUDGE-FLU trial randomized 964 870 Danish citizens ≥65 years to usual care or nine different electronic nudging letter strategies, with the aim to test the effectiveness of a nudging system on influenza vaccinations. About a quarter of HF patients in Denmark did not get vaccinated. Vaccination uptake was higher among those on higher levels of baseline GDMT. HF status did not modify the effects of the two overall successful nudging strategies on influenza vaccination.[45]

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