In the year 2022 a large number of remarkable scientific papers were published in the field of heart failure and heart muscle disease, to which the Hungarian Heart Failure community contributed with influential scientific activity. Results of landmark randomized clinical trials were published, and in recognition of the clinical and scientific activity of the Hungarian centers, notable activity was also demonstrated publishing these studies.

In the field of cardiomyopathies several novel results were published in 2022. In connection with hypertrophic cardiomyopathy (HCM) a landmark paper described the genetic architecture of the affected Hungarian population. An editorial comment was published in a highly ranked journal describing the myosin motor inhibition concept. An interesting paper about a retrospective analysis of cardiac amyloidosis patients, and MR specific differences between left ventricular noncompaction and dilated cardiomyopathy was published.

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was an ongoing pandemic in 2022 resulting in millions of deaths worldwide, affecting the heart of as much as 20–25% of those infected and causing several cardiac complications. Studies were published about the screening for myocardial injury and about the immunological response on disease itself and the vaccination against the virus. A joint scientific statement by the ESC also dealt with this topic. An impressive study was published about the prognostic value of anemia in patients with preserved, and mildly reduced and recovered ejection fraction and about the feasibility of baroreflex sensitivity measurements in heart failure subjects. In relation to drug therapy, a study is also worth mentioning about the cardiac efficacy and overall safety of SGLT2 inhibitors in patients treated with anthracyclines, and a network meta-analysis of randomized trials, analyzing the cardiovascular outcomes in patients treated with gliflozins.

Finally, a focused issue of Cardiologia Hungarica on heart failure and myocardial diseases should be highlighted.

**Keywords:** Heart failure, Myocarditis, SARS-CoV-2, Cardiac resynchronization therapy, SGLT2 inhibition, Renin–angiotensin–aldosterone system inhibitor (RAASI), Angiotensin receptor–neprilysin inhibition, Randomized clinical trial, Cardiomyopathy, Cardiac imaging
The year 2022 yielded remarkable scientific activities from Hungary in the field of heart failure and cardiomyopathies. In the current review we summarize those with highest impact that were at least partly written by Hungarian author(s), the work included in the report was at least partially carried out at a Hungarian research site(s), and were published in international, peer-reviewed journals. Original research papers are predominantly included, spectacular case reports or reviews with special impact are also presented. Due to their outstanding scientific importance and major impact on the daily clinical practice, we highlight the results of major phase III randomized controlled clinical trials with Hungarian contribution also.

### Management of heart failure patients

Requires multidisciplinary approach, and involving subspecialties such as imaging specialists, electrophysiologists, etc. Experimental and translational activities of Hungarian scientists are also extensive, and their publication activities are noteworthy. Therefore, this review does not focus on these activities that have already been published or will be published in the future in a separate issue of Cardiologia Hungarica.

### Contribution in randomized controlled clinical trials

#### SGLT2 inhibitors
Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction (LVEF) of 40% or less (HFrEF). Whether SGLT2 inhibitors are effective in patients with a higher LVEF remains less certain until recent years. In the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) Trial, based on randomization of 6263 patients with heart failure and a LVEF of more than 40%, 10 mg once-daily dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001) among patients with heart failure and a mildly reduced or preserved EF (HFpEF) (1, 2). Several substudies were also published with involvement of Merkely B. which verified the consistent effect of dapagliflozin in all age groups (3), and across the range of frailty studied. The improvement in health-related quality of life with dapagliflozin occurred early and was greater in patients with a higher level of frailty (4).

Until the EMPULSE study was published, it had been unknown whether SGLT2 inhibitors also improve clinical outcomes when initiated in patients who are hospitalized for acute heart failure. In this trial Hungarian centers were also involved, and Kiss R. G. was one of the authors of the publication. With 10 mg of empagliflozin therapy a clinical benefit was observed in the composite endpoint (stratified win ratio, 1.36; 95% confidence interval, 1.09–1.68; P = 0.0054) for both acute...
de novo and decompensated chronic heart failure and was observed regardless of EF or the presence or absence of diabetes (5).

**ARNI (sacubitril-valsartan)**

PARADISE-MI (Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction) trial was published in 2021 with the result, that sacubitril–valsartan was not associated with a considerably lower incidence of death from cardiovascular causes or incident heart failure than ramipril among patients with acute myocardial infarction (6). In 2022 Merkely B. and co-workers published two post-hoc analyses of the PARADISE-MI trial. They used the win ratio method to enhance statistical power. The principal composite outcome was analyzed in the hierarchical order of death due to cardiovascular causes, first hospitalization for heart failure, and first outpatient episode of symptomatic heart failure. The analysis demonstrated a larger number of wins (1,265,767 [15.7%]) than losses (1,079,502 [13.4%]) in the sacubitril/valsartan group (win ratio of 1.17, 95% confidence interval [CI] 1.03–1.33; p = 0.015) (7). In a research letter they provide analyses regarding more expansive evaluations of clinical outcomes. Although these exploratory analyses do not alter the primary neutral findings, in all subgroups:

- Investigator-reported time-to-first event;
- CEC adjudicated total (first and recurrent) events;
- Investigator-reported total (first and recurrent) events they found substantial benefit in the sacubitril/valsartan group (8).

It is also worth mentioning that Kovacs A. was involved in the PARADISE-MI Echocardiographic Substudy. They found no changes in EF, but patients randomized to sacubitril/valsartan demonstrated less increase in LV end-diastolic volume (P=0.025) and greater decline in LV mass index (P=0.037), increase in tissue Doppler e’ lat (P=0.005), decrease in E/e’ lat (P=0.045), and decrease in tricuspid regurgitation peak velocity (P=0.024) than patients randomized to ramipril (9).

**Patiromer**

Hyperkalemia, or the fear of inducing it, often leads to suboptimal use and dose of RAASi, especially mineralocorticoid receptor antagonists (MRAs), placing patients at an increased risk for adverse outcomes. Patiromer is a novel potassium-binder that exchanges potassium for calcium in the gastrointestinal tract that decreases natriuretic peptide concentrations in patients with HFpEF. Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) trial was published in 2021. Tomcsányi J. contributed to this current post hoc analysis and evaluated the efficacy and safety of OM therapy among patients classified as having severe HF compared with patients without severe HF (11). Severe HF was defined as the presence of all of the following criteria: New York Heart Association symptom class III to IV, left ventricular ejection fraction of 30% or less, and hospitalization for HF within the previous 6 months. Among 8232 patients enrolled in the GALACTIC-HF clinical trial, 2258 patients met the specified criteria for severe HF. Patients with severe HF who received OM experienced a major treatment benefit for the primary end point (hazard ratio [HR] = 0.80; 95% CI: 0.71–0.90), whereas patients without severe HF had no significant treatment benefit (HR = 0.99; 95% CI: 0.91–1.08; P=0.005 for interaction). For CV death, the results were similar (HR for patients with vs. without severe HF: 0.88 [95% CI: 0.75–1.03] vs. 1.10 [95% CI: 0.97–1.25]; P=0.03 for interaction). OM therapy was well tolerated in patients with severe HF, with no substantial changes in blood pressure, kidney function, or potassium level compared with placebo.

**Cardiomyopathies**

In the field of cardiomyopathies novel results were published in 2022. In connection with hypertrophic cardiomyopathy (HCM) a landmark paper from Sepp R. and co-workers demonstrated the genetic architecture of the affected Hungarian population (12). A total of 242 HCM patients (127 men, 44±11 years) were studied with next generation sequencing using a custom-designed gene-panel comprising 98 cardiomyopathy related genes. Results showed that 90 patients (37%) carried pathogenic/likely pathogenic (P/LP) variants, most of them had mutations in MYBPC3 (55 pts. 61%) and in MYH7 (21 pts. 23%) genes. Frameshift, nonsense, and splice variants made up 82% of all P/LP MYBPC3 variants. The MYBPC3 p.Gln1233Ter, the MYBPC3 p.Pro955ArgfsTer95, and the MYBPC3 p.Ser593ProfsTer11 variants were identified in 12, 7 and 13 patients, respectively. The high prevalence of these three MYBPC3 mutations...
raises the possibility of a founder effect in the HCM population. An editorial comment (13) was published by Papp Z. describing the myosin motor inhibition concept with aficamten, a second-generation cardiac myosin inhibitor drug developed for the treatment of HCM and tested in a phase 1 double blind, randomized, placebo-controlled, first-in-human study. Results showed that aficamten therapy yielded a small but significant reduction in left ventricular ejection fraction and was well tolerated by healthy participants. The clinical applicability of aficamten now appears to be superior to that of mavacamten, a first-generation cardiac myosin inhibitor. A retrospective analysis (14) of cardiac amyloidosis (CA) patients with (>12 mm) or without (<12 mm) increased left ventricular wall thickness (IWT) was made focusing on prevalence, clinical characteristics, and outcome. Nagy D. and co-authors identified 89 patients with CA and IWT and 9 patients without IWT (9%). In total, 70 patients had light chain and 27 had transthyretin amyloidosis, while all non-IWT patients had light chain type CA. Both groups had a clinically significant disease supported by the elevated cardiac biomarker levels. There was no difference between the outcomes of the two groups. These results raise the significance of the non-IWT CA subgroup; thus, the diagnostic algorithms and criteria should take these individuals into consideration before therapy initiation.

MR specific differences between left ventricular non-compaction (LVNC) and dilated cardiomyopathy were investigated by Gregor Zs. and co-workers (15). While the left ventricular volumetric and myocardial mass parameters and the global longitudinal and circumferential strains were similar, the trabeculated and papillary muscle mass was higher, and the apical circumferential strains were found to be significantly lower in LVNC. These minor alterations might be due to the morphological characteristics of LVNC with a trabeculated apical region.

**SARS-CoV-2 and heart failure**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the global coronavirus disease 2019 (COVID-19) pandemic, resulting in millions of deaths worldwide and impacting our everyday life. The pathophysiological drivers of the heart changes induced by SARS-CoV-2 infection need to be understood to guide therapy development and for prognostication. Fagyas M, et al. aimed to detect anti-cardiac autoantibodies in severe COVID-19 patients during hospitalization (16). For this purpose, 104 COVID-19 patients were recruited, while 40 heart failure patients with dilated cardiomyopathy and 20 patients with severe aortic stenosis served as controls. Anti-cardiac autoanti-bodies were detected in 68% (71 out of 104) of severe COVID-19 patients. Surprisingly, the presence of these anti-cardiac autoantibodies did not affect the clinical outcome but may have promoted autoimmune reactions, which could complicate post-COVID recuperation, contributing to post-acute sequelae of COVID-19 (long COVID). Rác Z, et al. aimed to investigate subclinical cardiac alterations characterized by parameters provided by advanced echocardiographic techniques following mild SARS-CoV-2 viral infection. A total of 86 patients were assessed 59±33 days after mild SARS-CoV-2 viral infection (requiring no hospital or <5 days in-hospital treatment) by advanced echocardiographic examination. With these special techniques (speckle-tracking echocardiography, myocardial work) they found cardiac alterations following even mild SARS-CoV-2 viral infection (17).

Increasing evidence links coronavirus disease 2019 (COVID-19) vaccination to rare cases of myocarditis and myopericarditis. The purpose of the study of Vágó H. and co-workers aimed to describe the clinical, CMR imaging and immunological features of different types of myocarditis after COVID-19 immunization in the acute phase and during follow-up (18). 16 CMR-confirmed cases of myocarditis were reported, mainly on young male patients (22±7 years) 4±2 days after administration of the anti-SARS-CoV-2 vaccine (75% received mRNA vaccines, and 25% received vector vaccines), frequently with predisposing factors such as immune-mediated disease and previous myocarditis. An amplified cellular immune response was found in acute myocarditis cases occurring 4 days after COVID-19 vaccination. Upon follow-up, the myocardial injury had healed.

Long COVID is an often debilitating illness that occurs in at least 10% of SARS-CoV-2 infections. More than 200 symptoms have been identified with impacts on multiple organ systems. A joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial & Pericardial Diseases was published about the effect of Long COVID on the cardiovascular system – elucidating causes and cellular mechanisms to develop targeted diagnostic and therapeutic strategies. In this work Ferdinandy P. and co-workers was also actively involved (19).

**Other noteworthy publications**

Several other original articles and case reports have been published. It is worth mentioning two papers about SGLT2 inhibitors. Drobi Zs. was involved in a retrospective cohort study testing the cardiac efficacy and overall safety of SGLT2 inhibitors in patients treated with anthracyclines. They found, that SGLT2 inhibitors were associated with lower rate of cardiac events...
among patients with cancer and DM who were treated with anthracyclines (20). Tornyos D. and co-workers published a network meta-analysis of randomized trials about the cardiovascular outcomes in patients treated with SGLT2 inhibitors. The meta-analysis supports a group effect of gliflozins, beneficial in a wide spectrum of patients with a risk of heart failure development. In addition to the improvement of HF-related outcomes, the risk of major adverse events is also reduced with SGLT2 inhibition (21).

Anemia is one of the most frequent comorbidities in heart failure; however, its prevalence in HfPEF patients varies widely. The aim of the work of Pintér A. and co-workers was to describe the characterization of patients with HfPEF or HFmrEF and to assess their outcome by the presence of anemia using their single-center retrospective database. They found, that in HfPEF-HFmrEF, anemia was an independent mortality predictor. Its presence multiplied the mortality risk in those with EF more than 40%, regardless of HF etiology (22).

Finally, Urbansek R. and co-workers published an interesting study about the feasibility of baroreflex sensitivity measurements in heart failure subjects. They conclude that similar to cardiovagal indices, the calculability of muscle sympathetic nerve activity (MSNA) burst incidence-based baroreflex index (BRSsymp) in HF is limited. Incalculability is associated with a higher level of sympathetic activation, which indicates a more severe disease stage (23).

**Focus issue of Cardiologia Hungarica on heart failure and cardiomyopathies**

Being true to our traditions, a focused issue of the Cardiologia Hungarica was published in 2022, presenting an interesting original article by Csósza Gy. And co-workers about the pulmonary vascular remodeling and right ventricular adaptation in precapillary pulmonary hypertension (24). Moreover, eight reviews provided insights into the actualities out of which three about the diagnosis and therapy cardiac amyloidosis (25–27), one about SGLT2 inhibitors (28), two about the new 2021 ESC Heart failure Guideline (29, 30), Adherence and psychosocial factors in heart failure (31) and genetic testing in hereditary cardiovascular diseases (32) was also discussed. Furthermore, two interesting case studies were reported, covering the topics of chloroquine induced cardiomyopathy (33), and arrhythmogenic cardiomyopathy (34).

**Conclusions**

As we proudly presented in the current review, Hungarian researchers collaborated in several valuable scientific papers from the field of heart failure and cardiomyopathies in the year 2022. The present review summarized a total of 12 international original publications, and 10 randomized controlled clinical trials, published in highly ranked journals. Topics covered novel drug therapy in heart failure, effect of SARS-CoV-2 on the cardiovascular system, genetics, and new therapeutical strategies of HCM and diagnostic issues in CA, DCM and LVNC. The presented publications prove the international recognition of Hungarian scientific work related to heart failure and heart muscle disease.

**Declaration of interest**

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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