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PEER-REVIEWED CONFERENCE REPORT

Late-Breaking Trials
The IRON-CRT trial suggests that repletion with the injectable iron preparation ferric carboxymaltose improves cardiac performance in iron-deficient patients with progressive HFrEF.

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COVID-19 and the Heart
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MEDICOM MEDICAL PUBLISHERS

Editor Prof. Marc P. Bonaca, University of Colorado, USA

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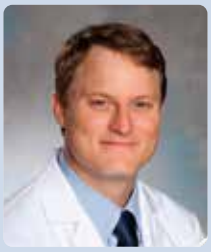
Letter from the Editor



Prof. Marc P. Bonaca

Dear colleagues,

Thank you for reading this edition of Medicom's Conference Report focused on HFA 2021. In the following pages you will see a broad summary of this rich and high-quality scientific meeting.

Several late-breaking trials were presented including data for Omecamtiv, Vericiguat, Dapagliflozin, and Iron. There are focused sections on COVID-19, cardio-oncology, and quality of life. A special focused section covers several exciting analyses of SGLT2 inhibitors and their effects on biomarkers as well as observed effects in real-world datasets.

As always, we have strived to provide balanced, concise, and informative summaries of these analyses. Thank you again for your readership and we hope you find these materials engaging and informative.

Sincerely,

Marc Bonaca

Biography

Marc P. Bonaca, MD, MPH, is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health at the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research.

Dr Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. After completion of his training he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group.

Dr Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events.

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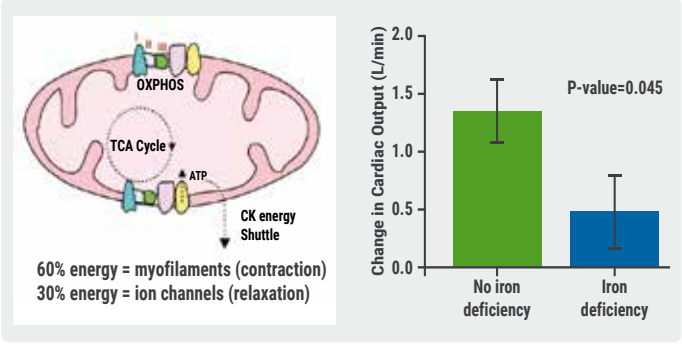
Late-Breaking Trials

Iron substitution improves LVEF in intensively treated CRT patients with iron deficiency

Therapy with ferric carboxymaltose (FCM) improved cardiac performance in intensively treated cardiac resynchronisation therapy (CRT) patients with persistently reduced left ventricular ejection fraction (LVEF). This was demonstrated in the randomised, multicentre, phase 4 IRON-CRT trial.

Iron deficiency is a frequent comorbidity in heart failure with reduced ejection fraction (HFrEF), affecting approximately 50% of patients. Iron deficiency aggravates both functional status and clinical outcomes of patients with heart failure [1]. Progression of iron deficiency parallels an increased risk of worsening heart failure. FCM has been shown to reduce the risk for heart failure admission. Yet, the cardiac effects are relatively unknown. From a cardiac perspective, iron deficiency is associated with progressive cardiac remodelling, diminished cardiac/cardiomyocyte contractility, and reduced cardiac energy reserve. "The myocardium requires a lot of energy, for which you need iron," Dr Pieter Martens (Hospital Oost-Limburg, Belgium) explained (see Figure) [2]. One of the operating mechanisms is the force-frequency relationship. In contrast to healthy controls, a reduced contractility is seen in HFrEF patients with increasing heart rate. "This energetic deficit worsens with iron deficiency," Dr Martens added.

Figure: Iron deficiency and energy/contractility. Modified from [3,4]



CK, creatine kinase; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle.

The rationale of the multicentre, randomised, double-blind, phase 4 IRON-CRT trial (NCT03380520) was to determine whether FCM induces incremental reverse remodelling in patients undergoing CRT with a persistently reduced LVEF and iron deficiency [2,5]. Moreover, the study assessed whether FCM could improve the force-frequency relationship in HFrEF. CRT patients were chosen specifically to perform a validated force-frequency pacing protocol.

The trial included adult patients with stable HFrEF and a CRT implant more than 6 months (n=75). All patients had a persistently reduced LVEF (<45%) and iron deficiency (ferritin <100 ng/mL or between 100-300 ng/mL if transferrin saturation was <20%). "Our patients were intensively treated: 50% of them received an angiotensin receptor neprilysin inhibitor on top of device therapy," Dr Martens said. They were treated with either standard of care (n=37) or FCM (n=38). The primary endpoint was change in LVEF from baseline to 3 months. Change in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were assessed as secondary endpoints.

Significant improvement in primary and secondary endpoints

After 3 months, LVEF in the FCM group improved significantly compared with the standard-of-care group (P<0.001). LVEF increased in the FCM group by 4.22% (95% CI 3.05–5.38) compared with a decrease of 0.23% (95% CI -1.44 to 0.97) in the standard-of-care group. "We noticed an absolute improvement of about 4%," Dr Martens said. The positive treatment effect of FCM was also noted in the secondary endpoints. LVESV was significantly decreased in the FCM group with 9.72 mL (95% CI -13.5 to -5.93) compared with a 1.83 mL decrease (95% CI -5.7 to 2.1) in the standard-of-care group (P=0.001). In addition, the force-frequency relationship changed from negative to positive. Therapy with FCM also improved maximal exercise capacity as measured by Peak VO2. A predefined subgroup analysis revealed that patients had a consistent beneficial treatment effect independent of their LVEF, haemoglobin, or transferrin saturation at baseline.

"We did not observe more adverse events in the FCM groups compared with placebo," Dr Martens said. Therefore, he concluded that therapy with FCM in HF patients with persistently reduced LVEF despite optimal medical therapy and CRT over 3 months resulted in cardiac reverse remodelling (documented by a change in LVEF and LVESV)

and an improvement in cardiac performance. Thus, the IRON-CRT trial further expands knowledge on the mode-of-action of FCM in HFrEF.

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2. Martens P, et al. The effect of intravenous ferric-carboxymaltose on cardiac reverse remodeling following cardiac resynchronization therapy – The IRON CRT trial. LBT 1, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.
3. Martens P, et al. Eur J Heart Fail 2018;20(5):920-2.
4. Martens P, et al. Eur J Heart Fail 2018;20(4):806-8.
5. Martens P, et al. Eur. Heart J. 2021. DOI: 1093/eurheartj/ehab411.

Novel mineralocorticoid receptor antagonist effective irrespective of HF history

A subgroup analysis of the FIDELIO-DKD trial revealed that the investigative mineralocorticoid receptor antagonist finerenone improved cardiovascular and kidney outcomes irrespective of a pre-existing heart failure status. In addition, finerenone had a reassuring safety profile.

Chronic kidney disease (CKD) and type 2 diabetes (T2D) are highly prevalent among patients with heart failure (HF), and patients suffering from all 3 conditions have an unfavourable prognosis [1–4]. In patients with HF with reduced ejection fraction (HFrEF), guidelines recommend therapy with a steroidal mineralocorticoid receptor antagonist (MRA). However, up to now, a treatment benefit has not been demonstrated in patients with HF and preserved ejection fraction (HFpEF).

Finerenone is a novel, selective, non-steroidal MRA that blocks overactivation of the mineralocorticoid receptor. The latter contributes to inflammation and fibrosis, which are both key drivers of CKD in T2D progression [5]. Finerenone has a balanced distribution between the heart and kidney compared with spironolactone, which is preferentially concentrated in the kidneys. In experimental models, the agent has shown potent anti-inflammatory and anti-fibrotic effects.

"In the FIDELIO-DKD trial (NCT02540993), finerenone demonstrated both kidney and cardiovascular (CV) benefits," Prof. Gerasimos Filippatos (Attikon University Hospital, Greece) said [6,7]. CKD progression was lowered by 18%, CV morbidity and mortality by 14%. "Our subgroup analysis aimed to evaluate the effect of finerenone on kidney and CV outcomes in CKD and T2D patients with versus without a history of HF. Because we excluded patients with symptomatic HF, we expected patients to have only a mild reduction of ejection fraction or HFpEF," Prof. Filippatos explained. Of the FIDELIO-DKD trial population, 436 patients (7.7%) had a history of HF at baseline. Compared with those without a history of HF (n=5,238), patients with a history of HF had a lower glomerular filtration rate, a higher BMI, and a larger waist circumference.

The subgroup analysis showed that finerenone reduced the risk of composite CV outcome (i.e. time to CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for HF) irrespective of history of HF. In patients with a history of HF, the relative risk of the composite CV outcome was lowered by 27% (RR 0.73; 95% CI 0.50–1.06). In patients without a history of HF, it was reduced by 10% (RR 0.90; 95% CI 0.77–1.04). The effect of finerenone on the single components of the composite CV outcome was also consistent across the subgroups. Likewise, finerenone slowed CKD progression in patients with HF history (HR 0.79; 95% CI 0.52–1.20) as well as in patients without HF history (HR 0.83; 95% CI 0.73–0.94). A history of HF did not modify the effect of the novel MRA on all-cause, CV, and non-CV hospitalisation.

"One other very important aspect is safety," Prof. Filippatos continued. The incidence of overall treatment-emergent side effects was similar between treatment arms, irrespective of HF history. In both subgroups, hyperkalaemia was more frequent in finerenone but did not lead to treatment discontinuation.

1. Anker SD, et al. Eur Heart J 2020;22:2383-92.
2. Solomon SD, et al. Circ Heart Fail 2018:11:e004962.
3. Seferovic PM, et al. Eur J Heart Fail 2018:20:853-72.
4. Filippatos G, et al. Eur Heart J 2014;35:416-8.
5. Agarwal R, et al. Eur Heart J 2021;42:152-61.
6. Bakris GL, et al. New Engl J Med 2020;383:2219-9.
7. Filippatos G, et al. Finerenone in patients with chronic kidney disease and type 2 diabetes, with and without a history of heart failure: a secondary analysis of the FIDELIO-DKD trial. LBT 1, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.

Iron substitution in iron-deficient HF patients is highly cost-effective

A cost-effectiveness analysis using data from the AFFIRM-AHF trial revealed that therapy with ferric carboxymaltose for iron deficiency in heart failure (HF) is highly cost-effective, despite the acquisition costs. This effect was evident across different healthcare systems in the USA, UK, Italy, and Switzerland.

In the AFFIRM-AHF study (NCT02937454), treatment with ferric carboxymaltose (FCM) significantly lowered total HF hospitalisations and cardiovascular death. An analysis presented by Prof. Phil McEwan (Swansea University, UK) estimated the cost-effectiveness of FCM compared with

placebo for the treatment of iron deficiency in patients with HF from the payer's perspective in the USA, UK, Italy and Switzerland [1,2]. "These 4 countries were chosen because they have different systems of healthcare," Prof. McEwan explained. A lifetime Markov model was built to characterise outcomes in patients according to the AFFIRM-AHF trial. In this model, disease status was defined by quartiles in the Kansas City Cardiomyopathy Questionnaire – clinical summary score (KCCQ-CSS), an established tool to assess symptom frequency, physical limitations, social limitations, and quality of life.

FCM treatment in patients admitted for acute HF was estimated to be cost-saving with additional health gains relative to placebo in the USA, UK, and Switzerland and highly cost-effective in Italy. Cost offsets were largely attributable to a reduction in hospitalisations due to HF. Over a lifetime, FCM was associated with an estimated 199 fewer hospitalisations due to HF events per 1,000 patients.

Modest quality-adjusted life years (QALYs) gains of 0.43–0.44 were attributable to increased time in higher KCCQ states. Moreover, sensitivity analyses demonstrated that FCM was cost-effective (i.e. cost per QALY under the current willingness-to-pay threshold) in all subgroups. The greatest cost savings relative to the overall population were seen in patients with a left ventricular ejection fraction of <25%. Patients with a non-ischaemic HF aetiology achieved the greatest increase in QALYs of all the subgroups. FCM also remained dominant or highly cost-effective in patients receiving triple therapy. De novo HF patients had the greatest cost increase per QALY relative to the overall population due to an increase in life expectancy leading to higher HF maintenance costs. This was dominant in the USA and Switzerland, and cost-effective in the UK and Italy.

Prof. McEwan concluded that from a payer's perspective, "the relative cost offset by avoiding hospitalisation is sufficiently high to justify the acquisition cost of the drug."

1 McEwan P. Ferric carboxymaltose for the treatment of iron deficiency in heart failure: a multinational cost-effectiveness analysis using AFFIRM-AHF. LBT 2, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.
2 McEwan P, et al. Eur J Heart Fail 2021. Doi 10.1002/ejhf.2270.

Omecamtiv mecarbil might be less effective in patients with atrial fibrillation or flutter

Heart failure (HF) patients with atrial fibrillation or flutter (AFF) at baseline had less treatment benefit from therapy with omecamtiv mecarbil than patients without AFF at baseline. According to post-hoc analyses of the GALACTIC-HF trial, this effect was significantly more pronounced in patients treated with digoxin.

"The myosin activator omecamtiv mecarbil augments cardiac sarcomere function by facilitating the actin-myosin interaction, resulting in an increased contractile force," said Prof. Scott Solomon (Brigham and Women's Hospital, MA, USA) [1]. In the GALACTIC-HF trial (NCT02929329), omecamtiv mecarbil reduced the risk of a composite of cardiovascular death or first HF event in patients with HF and reduced ejection fraction [2]. Prof. Solomon explained that "AF is very common in patients with HF and contributes to morbidity and mortality. This has not modified the treatment effect of renin-angiotensin-aldosterone inhibitors but may modify the treatment effect of β-blockers. It was one of 2 factors that modified the efficacy of omecamtiv mecarbil. In a subgroup analysis of GALACTIC-HF, it was less effective in patients with AF at baseline."

Thus, the objective of the current analysis was to assess whether the effectiveness of omecamtiv mecarbil is modified by baseline AFF. Patients included in the GALACTIC-HF trial had chronic HF (NYHA II-IV), left ventricular ejection fraction ≤35%, elevated B-type natriuretic peptide(BNP)/N-terminal pro B-type natriuretic peptide (NT-proBNP) and were managed with standard HF therapies.

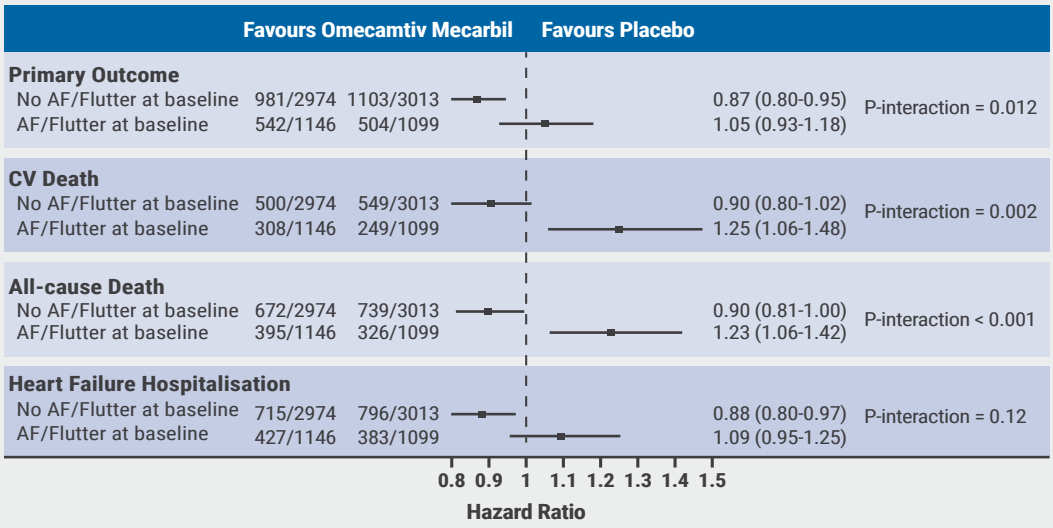
Of the GALACTIC-HF participants, 2,245 patients had AFF at baseline. Compared with patients without AFF (n=5,987), they were older, were more likely to have a history of hypertension or stroke, more likely to be in a higher NYHA class, and have a higher NT-proBNP concentration. Both groups were similarly well treated, but substantially more patients with AFF at baseline were treated with digoxin.

Greater treatment effect in patients without AFF

AFF modified the treatment effect of omecamtiv mecarbil in both the primary composite endpoint ($P_{interaction}$=0.012) as well as in secondary endpoints such as CV death ($P_{interaction}$=0.002), all-cause death ($P_{interaction}$<0.001), and HF hospitalisation ($P_{interaction}$=0.12; see Figure on the next page). "Treatment effect of omecamtiv mecarbil was greater in patients without AFF," Prof. Solomon explained. This effect remained after multivariable adjustment.

Because of notable differences in pharmacology background therapy, post-hoc analyses were performed to find possible

Figure: Atrial fibrillation/flutter modifies treatment effect of omecamtiv mecarbil [1]



explanations for this difference. "We found that the treatment effect modification for the primary outcome by AFF was significantly more pronounced in patients using digoxin compared with non-users," Prof. Solomon said. Plasma concentrations of omecamtiv mecarbil at 6 weeks were similar in those taking and those not taking digoxin (median 286 vs 280 mg/mL; P=0.78). In patients in whom digoxin doses were known, they were similar in both treatment arms. In patients without AFF and in healthy volunteers, there was no interaction with digoxin.

"So far, we do not have a smoking gun, we do not know what is responsible for this interaction," Prof. Solomon said in the discussion. While the presence of AFF at baseline was a prespecified subgroup, the use of digoxin was not. These additional analyses were data-driven and should be considered hypothesis generating. Despite this limitation, he concluded that these findings suggest caution when treating patients with AFF with both digoxin and omecamtiv mecarbil.

1. Solomon S, et al. Influence of Atrial Fibrillation on Efficacy of Omecamtiv Mecarbil in Heart Failure: The GALACTIC-HF Trial. LBT 1, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.
2. Teerlink JR, et al. JACC Heart Fail 2020;8:329-40.

Vericiguat effective irrespective of atrial fibrillation status

Heart failure (HF) patients in the VICTORIA trial were assessed for potential new-onset atrial fibrillation (AF). This new analysis demonstrated that new onset of AF led to worse outcomes, but the beneficial effect of vericiguat was present in all groups.

Vericiguat is an oral soluble guanylate cyclase (sGC) stimulator for HF treatment with a dual mode-of-action: it enhances the sensitivity of sGC to nitric oxide while also independently stimulating sGC [1,2]. In early studies, it has thus demonstrated vasodilative and anti-inflammatory effects in addition to improving haemodynamics. In clinical evaluation, vericiguat has been investigated as add-on treatment for HF in patients with reduced left ventricular ejection fraction (LVEF) within the VICTORIA trial (NCT02861534) [1,3]. Prof. Piotr Ponikowski (Wrocław Medical University, Poland) explained that the new analysis aimed to determine the relationship between clinical outcomes and presence of AF at baseline, the occurrence of new-onset of AF post-randomisation, as well as the effect of newly developing AF on the clinical outcome [1,4].

The VICTORIA population included 5,050 patients with HF, who had an LVEF <45%, an elevated natriuretic peptide level within 30 days prior to randomisation, and were recently hospitalised due to HF decompensation or had to be treated with intravenous diuretic therapy [1]. Information on AF status at baseline was available for 5,010 subjects of the VICTORIA cohort. Those were categorised into: not known AF, presence of AF on the ECG at randomisation, and intermittent AF. The latter category indicated a positive history of AF, but no AF on the randomisation ECG. At baseline, 53% of patients did not have known AF, 27% showed AF presence on the ECG at randomisation, and 20% were classified as intermittent.

The analysis found no association between AF status at randomisation and study outcomes, apart from an elevated

Table: Effect of vericiguat on the primary outcome by AF status. Modified from [4]

Outcome	Adjusted HR	HR (95% CI)	Event rate/100 per-yrs. Vericiguat	Placebo	P for interaction
Primary Outcome					0.45
No AF	0.84		31.2	36.2	
Intermittent AF	0.90		36.6	40.6	
AF on ECG	0.97		36.7	37.8	
Any AF	0.94		36.6	39.0	
HF hospitalisation					0.44
No AF	0.83		23.3	27.6	
Intermittent AF	0.98		30.3	30.8	
AF on ECG	0.93		27.9	29.9	
Any AF	0.95		28.9	30.3	
CV death					0.18
No AF	0.86		11.2	13.2	
Intermittent AF	0.83		13.8	17.0	
AF on ECG	1.14		15.3	12.6	
Any AF	0.99		14.6	14.5	

AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; HF, heart failure; HR, hazard ratio.

risk of CV death in the adjusted analysis (HR 1.21; 95% CI 1.01–1.47). "Vericiguat was effective across the whole spectrum of patients, irrespective of AF status at baseline," Prof. Ponikowski revealed (see Table).

Within the median follow-up time of 10.8 months, new onset of AF occurred in 9.4% of patients. Of note, the rate of appearance was 6.1% in the group without prior AF and 18.3% with baseline intermittent AF. Post-randomisation onset of AF was associated with a higher risk of primary and secondary outcomes. For the primary composite of CV death and hospitalisation for HF, the risk was more than 2-fold (HR 2.16; 95% CI 1.76–2.67) for all patients who developed new AF during the trial period. "Importantly, the incidence of post-randomisation AF did not differ according to the treatment arm," emphasised Prof. Ponikowski.

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2. Armstrong PW, et al. JACC Heart Fail. 2018;6(2):96-104.
3. Armstrong PW, et al. New Engl J Med 2020;382(20):1883-93.
4. Ponikowski P, et al. Eur J Heart Fail. 2021;June 30. DOI: 10.1002/ejhf.2285.

Baroreflex activation: a novel option to improve heart failure symptoms

A new patient-level meta-analysis of phase 2 and 3 data on Barostim therapy for heart failure (HF) patients with reduced ejection fraction confirmed significant improvements in 6-minute walking distance and quality of life across different classes of patients.

The Barostim™ system successfully reduced muscle sympathetic nerve activity while demonstrating safety in a proof-of-concept phase 1 study on baroreflex stimulation in HF patients [1,2]. In the phase 2 HOPE4HF trial (NCT01720160), the Barostim™ system also appeared to be safe and effective. Recently, the baroreflex activation with Barostim™ resulted in significant improvements in exercise capacity and quality of life in the pivotal BEAT-HF study (NCT02627196) [3]. "We decided to do a meta-analysis of individual patient data of these 2 randomised trials," stated Prof. Andrew Coats (University of Warwick, UK) [2].

Most of the inclusion criteria in the 2 studies were similar: ejection fraction ≤35%, mainly NYHA III, 6-minute hall walking distance (6MWD) between 150–400 metres, and a stable and guideline-conform therapy for 4 weeks. In BEAT-HF, participants also had a prior hospitalisation for HF, and an N-terminal pro B-type natriuretic peptide (NT-proBNP) of ≥400 pg/mL. Excluded were those with a class 1 indication for cardiac resynchronisation therapy (CRT). The demographic data of both trials were fairly similar, as were the comorbidities. For example, overall drug use was 80-84% renin-angiotensin system inhibitors and 86-95% of β-blockers.

The results of this new meta-analysis revealed significant improvements in the 6MWD by 48.5 metres as well as health status in terms of a reduction in the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score by 13.4 points. Furthermore, the odds ratio for an NYHA class amelioration was 3.4. As for the relative change in NT-proBNP, a trend was observed but no significance was reached. The investigation also looked at results in 4 different cohorts: A) all patients; B) only patients without CRT indication (no CRT); C) no CRT and an NT-proBNP <1,600 pg/mL; and D) NT-proBNP <1,600 pg/mL.

In general, the differences in effectiveness were not very extensive. Though in, for example, the 6MWD test, cohorts C and D had a higher improvement (63.0 and 61.2 metres, respectively) than cohorts A and B (48.5 and 50.2 metres, respectively). Looking also at subgroups by gender, Prof. Coats pointed out that the effect on 6MWD and health status was slightly better in women. "We believe Barostim™ may be a new option to improve HF symptoms and we look forward to longer term follow-up in terms of looking at more significant major clinical outcomes," said Prof. Coats in his conclusion.

1 Gronda E, et al. Eur J Heart Fail. 2014;16(9):977-83.
2 Coats A. BAROSTIM therapy in patients with HFrEF: A patient level meta-analysis of randomized trials. LBT 3, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.
3 Zile MR, et al. J Am Coll Cardiol. 2020;76(1):1-13.

Beta-blocker withdrawal to enhance exercise capacity in heart failure?

Spanish researchers assessed the effect of β-blocker discontinuation in patients with heart failure with preserved ejection fraction (HFpEF) on functional capacity in the phase 4 PRESERVE-HR study. They found a significant short-term amelioration of peak oxygen consumption (peak VO_2).

Prof. Julio Nuñez Villota (University Clinical Hospital of Valencia, Spain) explained that within the multiple pathophysiological mechanisms that are implicated in the heterogeneous syndrome of HFpEF, chronotropic incompetence plays a crucial role in some patients [1]. "Despite the lack of robust evidence, most HFpEF patients are currently treated with renin-angiotensin-aldosterone system (RAAS) inhibitors or β-blockers," he stated. In recent large HFpEF trials, 70–80% of patients received β-blocker medication [2]. With this in mind, the aim of the PRESERVE-HR trial (NCT03871803) was to assess whether β-blocker withdrawal would lead to a short-term improvement in functional capacity in patients with HFpEF [1].

The crossover, investigator-blinded, randomised PRESERVE-HR trial included 52 patients with a left ventricular ejection fraction (LVEF) ≥50% and an N-terminal pro B-type natriuretic peptide (NT-proBNP) of >125 pg/mL. Furthermore, all subjects had had a previous hospital admission for acute heart failure, were stable on β-blockers for ≥3 months, and had established chronotropic incompetence with an index of <0.62. Exclusion criteria included a resting heart rate of over 75 at screening. Baseline characteristics showed a mean age of 74.5 years, 59.6% women, 88.5% patients with hypertension, 34.6% in NYHA class III or IV, mean LVEF was 64.7%, and median NT-proBNP 400 pg/mL [1]. "Regarding the exercise test parameters, the mean peak VO_2 was 12.5 mL/kg/min, percentage of predicted peak VO_2 was approximately 72%, and the chronotropic index was 0.41, reflecting chronotropic incompetence. Importantly, there were no significant differences between both treatment arms," commented Prof. Nuñez.

All participants underwent cardiopulmonary exercise testing (CPET) with cycle-ergometry at days 0, 15, and 30 of the trial. Study arm A started with β-blocker withdrawal and crossed over to a re-introduction of β-blocker therapy after 15 days, while arm B stayed on β-blockers for the first part of the study and withdrew β-blockers in the second part. The primary endpoint was defined as change from baseline peak VO_2 and percentage of predicted peak VO_2. Among the secondary endpoints were differences in biomarkers, health status assessment, cognitive function, and specific echocardiographic measures [1,3].

The results demonstrated a significant rise in heart rate at peak exercise (30 beats per minute; P<0.001). Prof. Nuñez underlined that this was reflected by an increase of peak VO_2 of 2.1 mL/kg/min and 12.1% increase of percentage of predicted peak VO2. Looking at the secondary endpoints, significant changes with β-blocker withdrawal were only detected in an increase in quality of life in the Minnesota Living with Heart Failure Questionnaire (MLWHFQ; P=0.0236) and a decrease in the echocardiographic septal *E/e'* ratio (P=0.027). "Further studies should confirm the current findings and evaluate the mid- and long-term clinical safety and efficacy of this strategy in patients with HFpEF," concluded Prof. Nuñez.

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Inconclusive results for dapagliflozin treatment in heart failure

Two trials on the efficacy of dapagliflozin in heart failure patients with preserved (HFpEF) and reduced (HFrEF) left ventricular function showed only partially significant results. Symptom improvement, for example, was found in HFrEF but not in HFpEF.

"In patients with HFrEF, SGLT2 inhibitors have been shown to improve symptoms, to reduce HF hospitalisations, and even to improve survival, but we don't know their effect on walking distance," said Prof. John McMurray (University of Glasgow, UK) [1]. Prof. McMurray presented the results of the DETERMINE trials, which investigated the effect of dapagliflozin on symptoms and exercise capacity in HF patients.

DETERMINE-Reduced (D-R; NCT03877237) enrolled 313 patients with HFrEF and DETERMINE-Preserved (D-P; NCT03877237) 504 patients with HFpEF. All patients had to be on stable treatment, demonstrated an initial performance of ≥100 metres and ≤425 metres in 6-minute walking distance (6MWD) testing, and also had an estimated glomerular filtration rate of ≥25 mL/min/1.73m^2. The participants

differed in left ventricular ejection fraction (≤40% in D-R and >40% in D-P) and the trials used different inclusion cut-offs for N-terminal pro B-type natriuretic peptide (NT-proBNP; ≥400 pg/mL in D-R and ≥250 pg/mL in D-P). In both trials, patients were randomised 1:1 to receive a daily dose of 10 mg dapagliflozin or placebo over 16 weeks. The primary endpoint consisted of 3 components: reduction in patient-reported HF symptoms, reduction in patient-reported physical limitations, and improvement of walking distance.

In D-R, the baseline characteristics in the dapagliflozin and the placebo arm were balanced. The mean age was 68.4 and 67.3 years, 71.2% and 77.7% were men, and 83.3% and 79.6% were in NYHA class II, respectively. Baseline Kansas City Cardiomyopathy Questionnaire (KCCQ)-total symptom scores (TSS) were 79.2 in the dapagliflozin versus 80.2 in the placebo arm with correspondent values of 70.8 versus 75.0 in the KCCQ-physical limitation score (PLS) and 327.5 versus 344.0 metres in 6MWD. The results showed an average significant mean difference of 4.23 points in TSS (P=0.022) between dapagliflozin and placebo. Also, more patients reported a moderate or large improvement of ≥15 points in TSS, translating into a significant odds ratio (OR) of 1.6 (95% CI 1.0–2.7). The results in PLS (OR 1.6; 95% CI 0.9–2.6) and 6MWD (OR 1.1; 95% CI 0.7–1.8) failed to demonstrate a significant disparity between the study groups.

In the D-P trial, the overall mean patient age was 72 years, 63.5% were men, over 40% suffered from type 2 diabetes, and over 80% were NYHA class II. Median scores for TSS were between 77.1 and 78.1 and for PLS between 70.8 and 75.0. Median 6MWD was 320 metres. Interestingly, the assessment of possible treatment effects revealed no significantly different results in TSS, PLS, and 6MWD in the dapagliflozin versus the placebo arm.

Of note, the evaluation of exploratory outcomes in both trials showed a clear reduction in NT-proBNP with nominal P-values of 0.013 in D-R and 0.024 in D-P in favour of dapagliflozin therapy.

"At the moment, the therapeutic role of SGLT inhibition in HEpEF remains uncertain, although we are going to hear the results of a large trial in the next few weeks," Prof. McMurray added.

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Computerised cognitive training improves cognitive function in HF patients

The results of the CogTrain-HF study showed that twice-weekly cognitive training was able to improve cognitive flexibility and working memory in patients with chronic heart failure (HF).

Previous studies have revealed cognitive impairment in 25–75% of patients with HF [1]. Cognitive impairment has been associated with less disease-specific knowledge, poor self-care, higher hospitalisation rate, and higher mortality [2–4]. Therefore, guidelines suggest that cognitive impairment should be addressed as a relevant comorbidity that may influence the retention of information [5]. Cognitive impairment also leads to a decrease in executive functions that are crucial for goal-directed thinking and behaviour, and adaption to changing circumstances. Further deficits are reduced attention span, processing speed, and short-term memory [6].

In healthy adults, computerised cognitive training leads to higher cognitive plasticity [7]. In the CogTrain-HF study (NCT02415517), psychologist Sonja Wedegärtner (Saarland University Hospital, Germany) and colleagues tried to elucidate whether patients with HF benefit from a computerised training of executive functions. The primary outcome was an improvement in cognitive flexibility and working memory. Transfer effects, defined as an improvement of trained as well as untrained cognitive abilities, were assessed as a co-primary endpoint. In addition, the researchers documented the durability of transfer effects after 3 and 6 months without training.

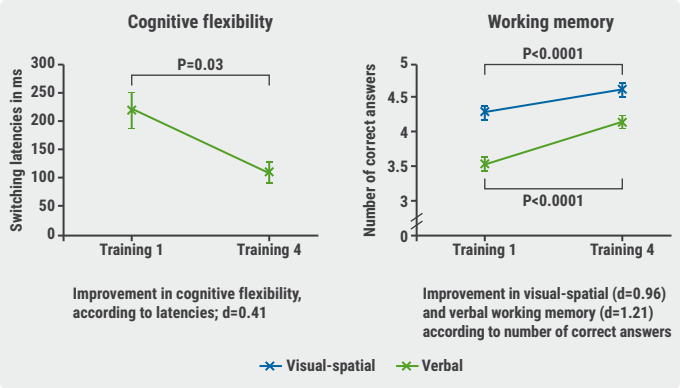
Patients were included who had symptomatic chronic HF (NYHA II-III), an ejection fraction of <45%, and 90% received β-blockers. Patients with depression and dementia were excluded from the study. "Patients in both groups were well balanced, there was no difference in their characteristics," Ms Wedegärtner said.

At baseline, an assessment of cognitive ability was performed. The intervention group was compared with a sham group that received a general-knowledge training. Both the cognitive training intervention and the sham intervention were performed twice a week with 2 tasks at each visit. After 3 weeks, the first and last training sessions were compared for the primary outcome.

The intervention group showed significant improvements in cognitive flexibility (P=0.03) and working memory (P<0.0001), assessed as induced cognitive gains (Cohen´s d >0.20 indicating a small effect size and >0.50 a medium effect size). "Improvement in working memory had a higher effect size than cognitive flexibility," Ms Wedegärtner said (see Figure). In addition, a significant transfer effect on untrained abilities was noticed in the single domains short-term memory (Cohen's d 0.60; 95% CI 0.16–1.04), prose recall (Cohen´s d 0.51; 95% CI 0.07–0.94), and processing speed (Cohen´s d 0.40; 95% CI -0.03 to 0.83). After 3 months without training, a medium effect size was still prevalent, but this faded after 6 months.

According to these positive results, cognitive training could potentially be a new, non-invasive HF intervention. "Perhaps there was a bias because HF patients with higher mobility are performing better. In the next trial, we plan a home-based intervention to also reach patients with restricted mobility," Ms Wedegärtner added.

Figure: Primary study outcome cognitive flexibility and working memory at 3 weeks [7]



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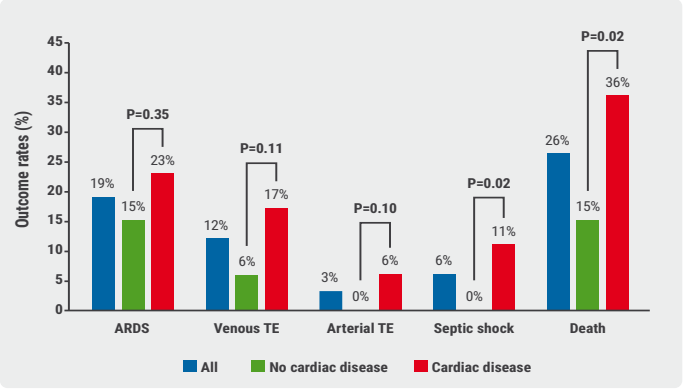
COVID-19 and the Heart

COVID-19-related HF: from systemic infection to cardiac inflammation

The heart is affected by COVID-19 infection through different mechanisms. Most relevant from a pathological point of view is myocardial damage due to generalised inflammatory reactions and cytokine storms.

"We found that cardiac patients are at increased risk for complications [of a COVID-19 infection] and mortality," said Prof. Marco Metra (University of Brescia, Italy) on his early experiences during the COVID-19 pandemic in Northern Italy [1]. Prof. Metra and his colleagues published a study including 99 patients with COVID-19 pneumonia. They compared 53 patients with a history of cardiac disease with 46 patients without this comorbidity. Mortality was dramatically higher in patients with cardiac disease compared with the others (36% vs 15%, log-rank P=0.019; relative risk 2.35; 95% CI 1.08–5.09). In addition, cardiac patients had a significantly higher rate of thromboembolic events and septic shock during hospitalisation (23% vs 6% and 11% vs 0%, respectively; see Figure) [2].

Figure Major complications and deaths at 14 days. Modified from [2]



ARDS, acute respiratory distress syndrome; TE, thromboembolism

Elevated troponin: a negative prognostic factor

Prof. Metra also pointed out that elevated high-sensitive troponin T levels have been associated with a worse outcome. This finding was corroborated in a multicentre study including 614 patients with laboratory-confirmed COVID-19 who were hospitalised in 13 cardiology units in Italy [3]. In this study,

elevated troponin was an independent variable associated with in-hospital mortality and a greater risk of cardiovascular and non-cardiovascular hospitalisation. "If a patient has low troponin and low B-type natriuretic peptide levels, they have a good prognosis," Prof. Metra said.

In an imaging study, patterns of myocardial injury in recovered troponin-positive COVID-19 patients were assessed by cardiovascular magnetic resonance (CMR) [4]. All participants (n=148) had suffered from severe COVID-19 infections requiring hospital admission. CMR imaging was performed at a median of 68 days. Normal cardiac imaging findings were found for 54% of patients. In 32%, a scar pattern was detected consistent with inflammatory myocardial damage. In 28% of patients, an ischaemic pattern was noted, of which two-thirds had no previous history. Other studies have also revealed that a substantial percentage of patients show abnormal CMR findings after acute COVID-19 – even after mild disease. "We have patients with pathologic CMR findings but normal left ventricular function," Prof. Metra said. Abnormalities of myocardial tissue characterised by MRI are common during COVID-19 recovery, but causal relationships of these tissue changes to symptoms and future cardiac events are not yet known [5]. Symptomatic COVID-19 infections can result in acute and chronic sequelae for the heart.

Prof. Metra pointed out that there are 2 main mechanisms of injury in COVID-19: myocardial ischaemia and myocardial inflammation. The latter is caused mainly by systemic inflammation but also by direct viral injury. Myocardial ischaemia is accompanied by increased myocardial oxygen demand, systemic hypoxia, endotheliitis, plaque rupture, and thrombosis.

Microthrombi: a major cause of cardiac injury in COVID-19

"We know that COVID-19 is specifically associated with endothelial and vascular thrombosis," Prof. Metra explained. A pathological analysis of 40 hearts from hospitalised patients who died of COVID-19 in Bergamo, Italy, showed that micro-thrombi were the most common pathological cause of myocyte necrosis [6]. Microthrombi had significantly greater fibrin and terminal complement C5b-9 immunostaining compared with intramyocardial thromboemboli from COVID-19-negative subjects. Non-occlusive fibrin microthrombi without universal acute ischaemic injury were also found in a pathological case series of patients who died from COVID-19 [7].

Prof. Metra also indicated that the virus itself only attacks the heart in rare cases, although this has been observed in a patient with cardiogenic shock [8]. More often, an adverse effect is mediated by macrophages, as was shown in an international, multicentre study, where cardiac tissues from the autopsies of 21 COVID-19 patients were assessed by cardiovascular pathologists [9]. The inflammatory cell composition by immunohistochemistry was assessed. Increased interstitial macrophage infiltration was present in 86% of the cases and multifocal lymphocytic myocarditis in a small fraction of the cases.

Taken together, inflammation-induced cardiac damage and necrosis are histologic hallmarks of cardiac involvement in COVID-19. Perivascular or vascular inflammation and/or macrophages are often present. In some cases, mild or absent inflammatory infiltrate with lymphopaenia is seen. "The most frequent scenario is myocardial damage due to generalised inflammatory reactions and cytokine storms," Prof. Metra concluded.

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Increased COVID-19 mortality in patients with cardiorenal comorbidity

A large Swedish registry study evaluated the likelihood of all-cause death after hospitalisation with a COVID-19 infection in patients with pre-existing cardiorenal disease. In comparison to controls, the death rate was significantly increased in this population.

Elderly patients and those with comorbidities are known to be more seriously affected by COVID-19 infections. "One particularly vulnerable patient group is those with cardiorenal disease defined as heart failure (HF), chronic kidney disease (CKD), or cardiorenal syndrome (CRS); the latter being a combination of chronic HF and CKD," informed Dr Johan Bodegård (epidemiologist, AstraZeneca, Norway) [1]. CRS is characterised by haemodynamic interorgan crosstalk between heart and kidney but also encompasses neurohormonal changes [2].

The nationwide, observational registry study investigated the risk for all-cause mortality by comparing patients with cardiorenal disease to matched controls [1]. The 39,146 participants were divided into 4 groups: HF, CKD, CRS, and controls, and were followed for 12 months or until death after their admission to the hospital due to a COVID-19 infection. At baseline, the participants had a mean age of 80 years, 43% were women, and the median in-patient stay was 6 days (25% of patients were hospitalised for over 9 days). Many suffered from comorbidities: 40% had ischaemic heart disease, 29% diabetes, and 32% had a history of prior pneumonia. As for medication, 59% received inhibitors of the renin-angiotensin system and 26% systemic corticosteroids.

"We had 6,570 deaths, which is about 17% of the population studied, and very high event rates between 200 to 300 per 100 person-years," Dr Bodegård stated. The highest risk for all-cause death was found in the CRS group, which was 60% higher than in the control group (HR 1.60; 95% CI 1.51–1.70; P<0.001). The hazard ratio for death was also significantly higher in the CKD and the HF groups versus control with an HR of 1.32 (95% CI 1.23–1.41; P<0.001) and 1.27 (1.21–1.33; P<0.001), respectively. Significances found for other variables within the multivariate analysis were in line with those shown in previous studies. A special assessment of all study subjects younger than 70 years exhibited similar patterns to the entire study cohort. Compared with controls, it resulted in HR values for CRS of 2.32 (95% CI 1.74–3.10; P<0.001), for CKD this was 1.83 (95% CI 1.41–2.37; P<0.001), and for HF 1.79 (95% CI 1.41–2.26; P<0.001).

"These results stress the fact that cardiorenal patients hospitalised with COVID-19 are at early high risks and should be prioritised for acute clinical awareness, improved disease management, and infection protection," Dr Bodegård suggested in his conclusion.

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Myocardial infarction outcomes were significantly affected by the pandemic

During the COVID-19 pandemic, patients with symptoms of a myocardial infarction waited longer before seeking medical attention. This resulted not only in delayed revascularisations but also in worse acute outcomes and rehospitalisation due to heart failure (HF) after 6 months.

A retrospective, multicentre study with a cohort of patients from Lithuania aimed to assess whether the pandemic-provoked lockdowns affected the use of emergency healthcare in patients with ST-elevation myocardial infarction (STEMI) and non-STEMI [1]. Evaluated were COVID-19 negative patients treated for STEMI or non-STEMI between 11 March and 20 April 2020 and during the same period in 2019. "In total, we enrolled 269 individuals; 107 individuals or about 40% presented in 2020, during the pandemic, and 162 individuals or about 60% presented in 2019, prior to the pandemic. They were well matched in terms of gender and other comorbidities," explained Dr Ayman Haq (Baylor University Medical Center, TX, USA). The study measured in-hospital outcomes and major adverse cardiovascular events (MACE), as well as the individual components of MACE at 6 months.

"One of the most significant findings was how much longer patients were waiting to seek medical attention," said Dr Haq. The overall pain-to-door time more than doubled from 385 minutes pre-pandemic to 858 minutes during the pandemic (P<0.0001). In the non-STEMI group, the difference was more pronounced with pain-to-door times of 558 and 2,021 minutes, respectively (P<0.0001). In the STEMI groups, the difference was also significant with pain-to-door times of 262 and 582 minutes, respectively (P=0.0003). Door-to-wire times were comparable for STEMI patients in 2019 and 2020, but numerically prolonged in 2020 for non-STEMI.

Also, the overall initial troponin I values were worse in 2020, with 7.8 mg/L versus 4.5 mg/L before the pandemic. Furthermore, post-interventional left ventricular ejection fraction was decreased during the pandemic. Overall, the incidence of MACE at 6 months was greater in 2020 (30.8% vs 13.6%; P=0.0006). This difference was again more pronounced in the non-STEMI group. "On examining the individual components of MACE, we saw that there were no statistical significances in the rates of stroke, non-fatal myocardial infarction, cardiovascular death, or target vessel revascularisation at 6 months. However, rates of hospitalisation for decompensated heart failure had increased dramatically," stated Dr Haq. Hospitalisation for decompensated heart failure was identified as a major driver of the rise in MACE events in 2020 by the researchers. For example, in patients with non-STEMI, a 20-fold increase of decompensated heart failure was observed during the pandemic (1.3% vs 30%; P<0.0001).

Causality for these findings cannot be provided by the present study, but Dr Haq suggested that it is nonetheless important

to emphasise that individuals should seek emergency medical attention during lockdowns and not delay or postpone care.

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TAPSE effective biomarker associated with high-risk of severe COVID-19

In a retrospective study, tricuspid annular plane systolic excursion (TAPSE) was associated with ICU admission or death in hospitalised patients with COVID-19.

The clinical course of COVID-19 is highly variable. Thus, the identification of biomarkers associated with severe disease might enable an effective risk stratification. Respiratory complications during the infection may lead to right ventricular (RV) failure. RV failure remains a major cause of mortality during acute pulmonary embolism. TAPSE has emerged as a simple RV longitudinal strain measure and a validated global RV function parameter [1]. Owing to its complex geometry, the RV is difficult to measure. Yet, it is still important to quantify the RV with echo. The basal diameter is a reproducible measure of RV size. In a retrospective, observational study, Dr Neil Bodagh (King´s College Hospital NHS Foundation Trust, UK) and colleagues assessed whether RV size and/or function were associated with worse outcomes in hospitalised patients with COVID-19 [2].

Enrolled were 119 patients (38% women and median age of 73 years), who were admitted to Princess Royal University Hospital between March and June 2020. RV basal diameter >41 mm was considered abnormal. TAPSE was used to assess RV function (abnormal values <17 mm). The primary outcome was ICU admission and/or death after 3 months of follow-up. Chi-squared tests were performed to assess associations between echocardiographic parameters and outcomes.

The association between RV size according to RV base diameter and admission to ICU and/or death was not statistically significant. In contrast, a significant association was found between abnormal TAPSE and either admission to ICU and/or death (chi-square 4.33; P<0.05). Thus, reduced TAPSE appears to correlate with admission to ICU and/or mortality in hospitalised patients with COVID-19. These results confirm a meta-analysis including 641 patients from 7 studies published this year [3]. In this analysis, every 1 mm decrease in TAPSE was associated with an increase in mortality of approximately 20%.

Although RV dilation was noticed in 27% of patients, it did not correlate with worse outcomes. Dr Bodagh pointed out that the retrospective design poses a limitation of the study. Interobserver variability in measurements cannot be excluded. However, these findings are in line with published data. An advantage of TAPSE is that it is simple to perform and easy to measure in a wide range of settings. Dr Bodagh concluded that TAPSE could be used to identify patients with severe disease.

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COVID-19 in AF patients with HF: no higher mortality but longer hospital stay

The results of a retrospective study suggest that the presence of atrial fibrillation (AF) is associated with a longer stay in ICU and hospital in patients with heart failure (HF). However, it did not affect other clinical outcomes such as cardiogenic shock or death.

"Recent studies reported a high prevalence of comorbidities, especially cardiovascular disease, and their association with severity of COVID-19 and increased mortality," said Prof. Bektaş Murat (Eskisehir Osmangazi University, Turkey) [1]. Patients with HF have shown to be a particularly vulnerable population regarding complications during a COVID-19 infection. In contrast, little is known about the effects of AF on clinical outcomes in HF patients with COVID-19. Thus, Prof. Murat and his team aimed to evaluate the effect of concomitant AF on clinical outcomes in patients with HF who were hospitalised for COVID-19. They identified 240 patients with HF hospitalised for a COVID-19 infection in electronic medical records. The patients' clinical features, laboratory findings, and in-hospital outcomes were compared according to the presence or absence of AF.

"Important biomarkers that have shown to be predictors of severity of COVID-19 infections are C-reactive protein (CRP) and procalcitonin," Prof. Murat explained. Both biomarkers were elevated in HF patients with AF compared with those without AF, whereas other lab findings such as D-dimer or fibrinogen concentrations were similar between groups. Patients with AF had longer stays in hospital (13.7 vs 11 days; P=0.024) and in ICU (7 vs 4.3 days; P=0.038) compared with those without AF. However, no difference between groups was

seen in the percentage of patients that required mechanical ventilation. "Presence of cardiogenic shock and death was also similar between groups," Prof. Murat said. Thus, the presence of AF seems to indicate prolonged hospital and ICU stay, although it does not affect other clinical outcomes.

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Cancer and the Heart

Heart failure patients might be at an increased risk for head and neck cancer

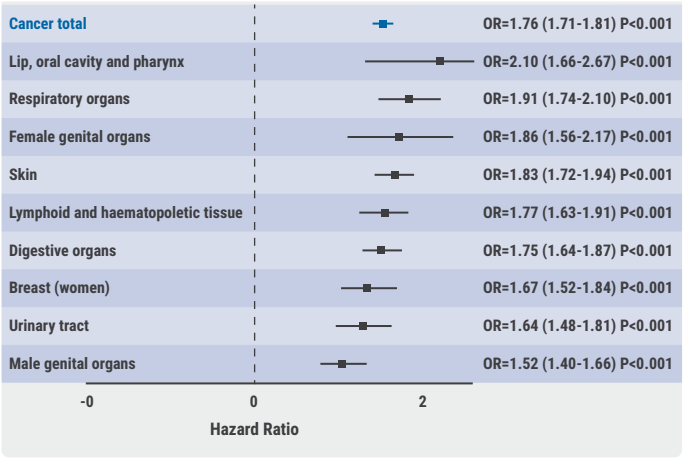
A retrospective cohort study including over 200,000 individuals from general practices in Germany showed heart failure patients to be at elevated risk of developing cancer. The risk varied according to cancer site with the strongest association for cancer of the lip, oral cavity, and pharynx.

Not only do some patients with cancer develop heart failure as a consequence of cancer treatment, but recent evidence has shown that heart failure may be associated with elevated cancer risk [1,2]. Hence, an observational study, presented by Dr Mark Luedde (Christians-Albrechts-University of Kiel, Germany) and published in the ESC Heart Failure Journal, aimed to explore a possible association between heart failure and incidence of cancer in a large collective of outpatients with heart failure [3,4].

Data was obtained from the nationally representative Disease Analyser Database, which covers 1,274 general practices in Germany. This database contains information on drug prescriptions, diagnoses, and basic medical and demographic data. Hazard regression models were conducted to study the association between heart failure and the incidence of different types of cancers. The incidence of cancer was assessed between January 2000 and December 2018. Included in the analysis were 100,124 patients with heart failure and 100,124 individuals without heart failure. The participants were individually matched by sex, age, obesity, diabetes, and consultation frequency. No participants had cancer at the start of the study.

During the observation period, the incidence of cancer was significantly higher among heart failure patients compared with those without heart failure (25.7% vs 16.2%; P<0.001). These proportions were 28.6% versus 18.8% in women and 23.2% versus 13.8% in men, respectively. In regression analyses, heart failure was significantly associated with the incidence of cancer at all assessed sites in both men and women (HR 1.76, P<0.001 in total; HR 1.85, P<0.001 in women; HR 1.69, P<0.001 in men). The strongest association was observed for cancer of the lip, oral cavity, and pharynx, followed by cancer of the respiratory organs (see Figure). Patients with heart failure had a 2-fold elevated relative risk for these cancers compared with individuals without heart failure (P<0.001).

Figure: Association between heart failure and the incidence of cancer at different sites (Cox regression models) [1]



Due to the study design, a causal relationship cannot be proven. "Our results allow us to speculate that there may be a causal relationship between heart failure and an increased rate of cancer. This is biologically plausible, as there is experimental evidence that factors secreted by the failing heart may stimulate tumour growth," Dr Luedde commented

on the results. Heart failure and cancer share common risk factors such as obesity and diabetes, but these were accounted for in the analysis by matching.

"It is common practice for cancer patients who have received heart-damaging drugs to be monitored for heart failure. Conversely, evidence is accumulating to indicate that heart failure patients could benefit from intensive monitoring for cancer development – for example, through screening. Considering the high incidence of both diseases and their impact on the lives of those affected, these patients deserve the maximum joint efforts of cardiologists and oncologists," Dr Luedde concluded.

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Trastuzumab associated with cardiotoxicity in breast cancer

According to a retrospective study in breast cancer patients, lower BMI and treatment with trastuzumab alone or in combination were predictors of cardiotoxicity. This might warrant closer monitoring of breast cancer patients with lower BMI.

Breast cancer therapy with anthracyclines and trastuzumab has been associated with cardiotoxicity. Reports from clinical practice have suggested that cardiotoxicity can result in a long-term impairment of left ventricular systolic function with increased long-term risk of heart failure in patients who survive breast cancer [1]. In a retrospective study of breast cancer patients treated with anthracyclines and trastuzumab, Dr Ana Filipa Cardoso (Hospital Senhora da Oliveira - Guimarães, Portugal) and colleagues explored the frequency of cardiotoxicity with these agents and its clinical impact on breast cancer patients [2].

All patients underwent an ECG exam at baseline. The assessment of global longitudinal strain (GLS) by speckle-tracking ECG has shown to be more sensitive for the early detection of cardiac contractility before a decline in ejection fraction (EF) can be discovered. Cardiotoxicity was defined as a reduction of EF >10% to a value of <40% or a relative reduction of GLS ≥15%. The researchers were able to include 69 women (mean age 55 years) with a mean BMI of 28 kg/m^2 in a single centre in 2017. Patients with baseline left ventricular EF <50% were excluded. Of the participants, 37 (54%) were treated with anthracyclines, 13 (19%) with trastuzumab, and 19 patients (28%) received both drugs (anthracyclines followed by trastuzumab).

The criteria of cardiotoxicity were met by 15 patients (22%), including 2 under anthracyclines, 6 under trastuzumab, and 7 under anthracyclines + trastuzumab. The GLS criteria were met by 12 patients (2 of them had been treated with anthracyclines and 5 with trastuzumab), and 3 patients met the EF criteria (1 woman treated with trastuzumab and 2 with both therapies). Analysed according to regimen, cardiotoxicity was more frequent in patients treated with trastuzumab (46%) and those treated with anthracyclines followed by trastuzumab (37%) compared with anthracyclines alone (5%).

On a regression model, therapy with trastuzumab (odds ratio [OR] 17.81; 95% CI 1.99–158.4; P=0.010), anthracyclines + trastuzumab (OR 31.11; 95% CI 3.25–298.18; P=0.003), and a lower BMI (BMI >25 kg/m^2 OR 0.06; 95% CI 0.01–0.38; P=0.003) were all associated with cardiotoxicity.

Among patients with cardiotoxicity, 2 developed heart failure (1 woman treated with trastuzumab and 1 receiving first anthracyclines and then trastuzumab) and 3 had to suspend treatment (1 treated with trastuzumab and 2 receiving first anthracyclines followed by trastuzumab).

Cardiotoxicity has a clinical impact leading to heart failure or suspension of chemotherapy in patients treated with trastuzumab or with anthracyclines and trastuzumab. "Perhaps we should monitor women with lower BMI more closely, but we should perform larger studies first to make the findings more robust," Dr Cardoso recommended.

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Prevention and HRQoL in the 21st century

Psychoactive substances put young people at risk of cardiovascular disease

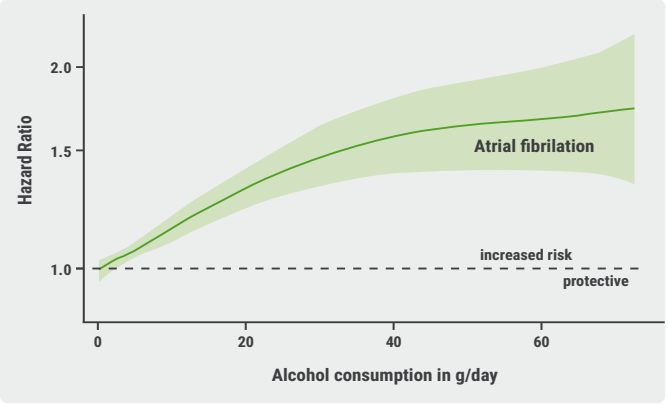
Recreational use of alcohol, vaping, and illicit drugs is on the rise globally; the latter especially in the younger population. This poses a substantial risk for cardiovascular health.

In recent years, tobacco use has increased largely by a rise in vaping in adolescents and young adults. "Industry claims that it is less harmful than smoking, but different studies have shown that most e-cigarette vapers will also use cigarettes," explained Dr Vijay Chopra (Max Super Speciality Hospital Saket, India) [1]. Similar to cigarettes, e-cigarettes cause cytotoxicity, oxidative stress, inflammation, DNA strand shrinkage, dysregulation of gene expression, and mitochondrial dysgenesis. According to a position paper of the European Association of Preventive Cardiology (EAPC), no direct randomised data is available on e-cigarettes in heart failure (HF) [2]. While the long-term direct cardiovascular effects of e-cigarettes remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product. E-cigarettes are likely to increase cardiovascular risk because they lead to an increased heart rate, increased arterial stiffness, and endothelial dysfunction. Moreover, they have been shown to increase blood pressure. Dr Chopra emphasised that "95% of all publications without a conflict of interest found a harmful effect of e-cigarettes compared with only 20% of sponsored publications by the vaping industry."

One drink a day elevates the risk of AF

A meta-analysis published in 2006 showed a J-shaped relationship between alcohol and total mortality in both men and women. Consumption of alcohol, up to 4 drinks per day in men and 2 drinks per day in women, was inversely associated with total mortality, maximum protection being 18% in women and 17% in men [3]. A study published this year showed detrimental effects of small amounts of alcohol intake [4]. In a community-based cohort, 107,845 individuals were followed for the association between drink consumption and drinking patterns, and the incident of atrial fibrillation (AF). The hazard ratio for only 1 drink (12 g) per day was 1.16 (95% CI 1.11–1.22; P<0.001; see Figure). Associations were similar across types of alcohol. Dr Chopra pointed out that small amounts of alcohol are protective for HF, but the risk of AF increases even with small amounts of alcohol, which needs to be considered in AF prevention.

Figure: Alcohol consumption and incident atrial fibrillation [4]



Methamphetamine use is another increasing problem worldwide. Its use results in an acute, rapid increase in both heart rate and blood pressure. Chronic methamphetamine exposure leads to vasoconstriction, cerebral hypoperfusion, and an imbalance of circulatory vasoregulatory substances. Methamphetamine use has been associated with a partially reversible, inflammatory, dilated cardiomyopathy with HF with reduced ejection fraction and can also present as takotsubo cardiomyopathy [5]. Improvement in left ventricular ejection fraction is often seen after abstinence. The extent of myocardial fibrosis seems to predict the recoverability of left ventricular function. Similarly, cocaine use stimulates the sympathetic nervous system and different cardiac and vascular complications can result from its use [6]. It can also cause takotsubo-like cardiomyopathy, aortic dissection, and acute myocarditis. "The abuse of psychoactive substances is a significant preventable cause of morbidity and mortality in HF," Dr Chopra concluded.

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The challenge of improving the quality of life of heart failure patients

Health-related Quality of life (HRQoL) is key to the patient and improving it is an important goal for the physician. However, evaluating the benefit of a certain treatment on HRQoL can be a challenging venture.

"The original definition of QoL is `the difference between what the patients perceive and what they actually have,' and it impacts physical, mental, and social well-being," explained Prof. Ileana L. Piña (Central Michigan University, MI, USA) [1]. HRQoL, which is often measured in trials, is a sub-entity of QoL that encompasses health perceptions, functional status, and psychosocial status. In terms of heart failure (HF), the patient's perspective of health status is based on symptoms like fatigue, dyspnoea, and oedema, which lead to functional limitations entailing physical, emotional, and social aspects.

Instruments widely used and accepted to measure HRQoL in HF are, for example, the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ). When using these instruments to evaluate HRQoL in a randomised controlled trial, much needs to be taken into consideration. "Both instruments have a large placebo component. So, if you do absolutely nothing, both of them get better in scoring," Prof. Piña elaborated. To illustrate, she pointed out a study in which, after 4 months of assessment of valsartan as add-on medication in HF, the placebo group had a greater improvement in MLWHFQ than the valsartan group. "If we looked at just objective worsening, more patients worsened who were on placebo, and fewer patients worsened on the drug, which is another way of looking at the scores," she commented on the same investigation. So, it is essential to always quantify the clinical changes to evaluate the benefits of a treatment.

Another consideration is the timing of measuring QoL. For example, in the PROVE-HF trial (NCT02887183), improvements in KCCQ scores occurred as early as week 2 [2]. Prof. Piña suggested that a plan for testing QoL at different times of a study could be appropriate. Furthermore, quantifying changes in QoL not only matters during trials, but also in monitoring patients over time for clinically important changes.

Focussing on QoL, different classes of HF drugs often present with pros and cons. For example, β-blockers decrease mortality but do not increase exercise capacity, and spironolactone reduces hospitalisations but induces only modest HRQoL improvement in HF patients with preserved ejection fraction. On the other hand, milrinone improves symptoms and thus makes patients feel better, yet mortality is high. Trials on inhibitors of the renin-angiotensin-aldosterone system have demonstrated clear and consistent results for benefits in mortality but have been inconsistent in QoL results.

Various outcomes in trials may be intertwined with QoL, but are nonetheless difficult to capture: for example, how can a decrease in hospitalised days be assessed by a questionnaire and will the patient sense this benefit? To illustrate, Prof. Piña drew attention to the DAPA-HF trial (NCT03036124) that showed clear improvements in hospitalisation already detectable within the first 3 months but, in contrast, only modest ameliorations in KCCQ scores [3].

"We have trade-offs: are we content to say 'no higher mortality' and do nothing else," she asked pointing to one of the remaining open questions [1]. Prof. Piña concluded that she implemented the evaluation of HRQoL with different instruments in her clinic at different times to get an impression of the impact the disease has on her patients and she underlined the benefit of engaging the patients in shared decision making.

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SGLT2 Inhibitors in Heart Failure

Empagliflozin linked to lower cardiovascular risk and renal events in real-world study

An analysis of patient information from large European and Israeli databases demonstrated that type 2 diabetes treatment with empagliflozin significantly reduced likelihoods for various undesirable cardiovascular and renal outcomes compared with a dipeptidyl peptidase-4 (DPP-4) inhibitor.

As there is a high prevalence of concomitant heart failure (HF) in diabetics, the impact of anti-diabetic medication on cardiovascular and renal outcomes may play a role in HF therapy [1]. A large, non-interventional study compared type 2 diabetes treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin with therapy with a DPP-4 inhibitor in terms of primary cardiovascular and secondary renal effectiveness outcomes [2].

Between 2014 and 2019, data was collected from large databases and registries in Sweden, Finland, Germany, Spain, and Isreal. Included were >75,000 adults who started diabetes treatment with either empagliflozin (n=38,203) or a DPP-4 inhibitor (n=38,203). The mean age was a little over 60 years, and most patients were men. Logistic regression was used for the analysis based on propensity score matching.

Prof. Leo Niskanen (University of Eastern Finland, Finland) presented the results as pooled incidence rates and hazard ratios for the comparison of empagliflozin versus DPP-4 inhibitor. The incidence rate of hospitalisation for HF was 7.36 per 1,000 patient-years with empagliflozin compared with 11.86 per 1,000 patient-years with DPP-4 inhibitor (HR 0.60; 95% CI 0.50–0.72; see Table). Likewise, an HR of 0.52 (95% CI 0.39–0.69) for all-cause mortality indicated

Table: Empagliflozin versus DPP-4 inhibitor reduced the risk of cardiovascular and renal events in the EMPRISE study [2]

Outcome	Country	EMPA (n=38,203)	DPP-4i (n=38,203)	Outcome	Country	EMPA (n=38,203)	DPP-4i (n=38,203)
Hospitalisation for Heart Failure	**Pooled HR (95% CI)**	**0.60 (0.50-0.72)**		**Composite outcome including Hospitalisation for Heart Failure and All-Cause Mortality**	**Pooled HR (95% CI)**	**0.60 (0.44-0.81)**	
	Mean FU (years)	0.67	0.83		Mean FU (years)	0.66	0.83
	Pooles N events (IR / 1,000 PY)	188 (7.36) (n=38,203)	378 (11.86) (n=38,203)		Pooles N events (IR / 1,000 PY)	414 (16.90) (n=37,364)	917 (29.17) (n=37,364)
	Finland	53 (6.84)	128 (12.41)		Finland	104 (13.42)	327 (31.69)
	Germany	18 (17.28)	35 (34.64)		Germany	N/A	N/A
	Spain	33 (6.04)	61 (12.20)		Spain	136 (24.90)	217 (43.39)
	Sweden	59 (6.94)	127 (9.87)		Sweden	131 (15.42)	331 (25.71)
	Israel	25 (8.97)	27 (10.09)		Israel	43 (15.43)	42 (15.69)
All-Cause Mortality	**Pooled HR (95% CI)**	**0.52 (0.39-0.69)**		**Composite outcome including Myocardial Infarction, Stroke and All-Cause Mortality**	**Pooled HR (95% CI)**	**0.64 (0.52-0.80)**	
	Mean FU (years)	0.66	0.83		Mean FU (years)	0.65	0.83
	Pooles N events (IR / 1,000 PY)	263 (10.70) (n=37,364)	643 (20.70) (n=37,364)		Pooles N events (IR / 1,000 PY)	474 (19.38) (n=37,364)	952 (30.87) (n=37,364)
	Finland	58 (7.45)	219 (21.08)		Finland	110 (14.18)	278 (26.86)
	Germany	N/A	N/A		Germany	N/A	N/A
	Spain	110 (20.08)	177 (35.18)		Spain	128 (23.44)	207 (41.34)
	Sweden	77 (9.04)	226 (17.46)		Sweden	192 (22.69)	424 (33.13)
	Israel	18 (6.43)	21 (7.79)		Israel	44 (15.80)	43 (16.04)

Shown are pooled incidence rates and pooled hazard ratios of events among empagliflozin versus DPP-4 inhibitor users in 1:1 propensity score-matched populations.
CI, confidence interval; DDP-4i, dipeptidyl peptidase-4 inhibitor; EMPA, empagliflozin; FU, follow-up; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PY, patient-years.Shown are pooled incidence rates and pooled hazard ratios of events among empagliflozin versus DPP-4 inhibitor users in 1:1 propensity score-matched populations.

significant superiority of empagliflozin. "If we then look at the composite outcome including hospitalisation for HF and all-cause mortality, we can see that this was clearly in favour of empagliflozin with a 40% lower risk, which was highly significant," Prof. Niskanen pointed out.

The second composite of myocardial infarction, stroke, and all-cause mortality, resulted in a 36% reduced likelihood for patients in the empagliflozin group (HR 0.64; 95% CI 0.52–0.80). The researchers also assessed myocardial infarction, stroke (pooled HR 0.71; 95% CI 0.56–0.90), and end-stage renal disease (pooled HR 0.40; 95% CI 0.17–0.95) for empagliflozin versus DPP-4 inhibitor. However, the individual outcome of myocardial infarction was non-significant (HR 0.95; 95% CI 0.74–1.22).

"These results complement the results from the clinical trial EMPA-REG OUTCOME (NCT01131676) and support changes recently made in the ADA and EASD consensus update," underlined Prof. Niskanen in his conclusion.

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2. Niskanen L, et al. Empagliflozin use versus dipeptidyl peptidase 4 inhibitors reduces risk of cardiovascular. Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.

Efficacy of dapagliflozin and empagliflozin not influenced by diabetes status

A pooled meta-analysis of 2 large studies on sodium-glucose cotransporter-2 (SGLT2) inhibition in heart failure (HF) treatment evaluated subgroups results. Adding an SGLT2 inhibitor to treatment was advantageous in cardiovascular (CV) outcomes irrespective of diabetic status.

EMPEROR-Reduced (NCT03057977) and DAPA-HF (NCT03036124) investigated the effects of adding SGLT2 inhibition with empagliflozin or dapagliflozin to recommended therapy in HF patients with reduced ejection fraction (HFrEF), including both subjects with and without diabetes. The 2 studies were similar in design and demonstrated positive results on CV death and hospitalisation for HF [1,2]. "The only difference was the higher event rate in EMPEROR-Reduced because we enriched it with more history about HF hospitalisation and higher levels of NT-proBNP as entry criteria," Prof. Faiez Zannad (University of Lorraine, France) pointed out. He presented a pre-specified meta-analysis of the 2 trials that was powered to assess CV and renal outcomes in subgroups of special interest [1].

The pooled hazard ratio for the primary outcome of first hospitalisation for HF or CV death for both trials was 0.74 (95% CI 0.68–0.82), with HR 0.75 (95% CI 0.65–0.86) for EMPEROR-Reduced and HR 0.74 (95% CI 0.65–0.85) for DAPA-HF. A test for heterogeneity of the effect was non-significant (P=0.89). "Because we had a wealth of data, we could look deeper into subgroups," Prof. Zannad introduced further results. When stratifying according to diabetes status, the treatment benefit was very similar in patients with and without diabetes: with diabetes the HR was 0.74 (95% CI 0.65–0.84) and without 0.75 (95% CI 0.65–0.87) for both trials.

Also of interest were the results for renal outcomes. Assessing the first renal composite, defined as ≥50% sustained decline in estimated glomerular filtration rate (eGFR), end-stage renal disease, or renal death, revealed a decrease of about 40% in those with SGLT2 inhibitor treatment (HR 0.62; 95% CI 0.43–0.90). This benefit was consistent in patients with and without diabetes. "Contrary to the conventional therapy group, there was a slowing of the decline in eGFR in patients with and without diabetes," said Prof. Zannad.

Further evidence on renal outcomes is provided by DAPA-CKD (NCT03036150), a study that enrolled only patients with an eGFR between 25–75 mL/minute/1.73 m^2 of body surface area and a urinary albumin-to-creatinine ratio between 200 and 5,000 mg/g [1,3]. The primary composite outcome was a lasting deterioration in eGFR of ≥50%, end-stage kidney disease, or death (renal or CV). Focusing on subgroups with and without diabetes, the hazard ratio for patients with diabetes was 0.64 (95% CI 0.52–0.79) and 0.50 (95% CI 0.35- 0.72) for non-diabetic patients. EMPA-Kidney (NCT03594110), a similar trial to DAPA-CKD but evaluating empagliflozin, is currently underway [1].

In view of these results for SGLT2 inhibition in HF, Prof. Zannad stressed that "benefits are not related to glucose-lowering. Patients with HFrEF and/or chronic kidney disease should be given an SGLT2 inhibitor whether they have or do not have type 2 diabetes." However, as trial-based evidence is only available for these 2 agents at present, he considered it premature to talk about a class effect.

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3. Heerspink HJL, et al. New Engl J Med. 2020;383(15):1436–46.

Biomarker panel predicts SGLT2 inhibitor response

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to lower cardiovascular (CV) risk in both patients with and without diabetes. An analysis of the CANVAS trial suggested that a biomarker assay can identify patients that benefit most from therapy.

Circulating biomarkers reflecting different mechanistic pathways may offer insights into how SGLT2 inhibitors reduce CV risk. "We undertook a secondary analysis of the CANVAS trial to understand whether the use of a multimarker panel may not only identify those at highest risk but also identify patients that may benefit from SGLT2 inhibitors," explained Dr Muthiah Vaduganathan (Brigham and Women´s Hospital, MA, USA) [1].

The CANVAS study (NCT01032629) evaluated the effect of canagliflozin compared with placebo on CV events, including CV death, heart attack, and stroke, in patients with type 2 diabetes whose diabetes was poorly controlled and who had a history of CV events or a high risk of CV events [2]. The biomarker panel used in the current analysis was designed based on 3,040 CANVAS participants. Measured were concentrations of cardiac troponin T by high-sensitivity assay (hs-cTnT), soluble suppression of tumorigenesis-2 (sST2), and insulin-like growth factor-binding protein 7 (IGFBP7). These biomarkers represent myocardial injury (hs-cTNT), vascular congestion (sST2), or acute kidney injury (IGFBP7). Patients were assigned 1 point for every elevated biomarker.

Overall, 36% of the participants had no elevated biomarkers, 35% had 1 elevated biomarker, 27% had 2, and 2% had 3 elevated biomarkers. The higher the biomarker level, the poorer the patients' prognosis. "We found that while the benefit [of SGLT2 inhibitor treatment] with regard to heart failure and kidney events were consistent irrespective of the biomarker score, benefits with regard to major adverse CV events appeared to be greatest in those with multiple abnormal biomarkers," Dr Vaduganathan said. He concluded that this hypothesis should be tested further in ongoing and completed trials with SGLT2 inhibitors.

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Best of the Posters

Real-world study suggests sacubitril/valsartan benefits elderly patients with HF

Preliminary real-world data demonstrated consistent benefits of sacubitril/valsartan for elderly patients with heart failure and reduced left ventricular function (HFrEF), even in those patients who were not fully titrated.

"Although post-hoc analysis of the PARADIGM-HF trial showed an optimal efficacy and safety profile of sacubitril/valsartan in elderly patients with HFrEF, real-world unselected data is needed to better define tolerability and safety in this population," postulated Dr Andrea Herbst (Azienda Ospedaliero-Universitaria Careggi, Italy) [1]. Thus, Dr Herbst and colleagues analysed registry data of 70 elderly patients with heart failure, enrolled between 2016 and 2020.

The participants had a mean age of 77.3 years, 18.6% were women, the mean ejection fraction was 31.7%, and 28.5% of participants were NYHA class III or IV. Further baseline characteristics were a high burden of cardiovascular and non-cardiovascular comorbidities, e.g. 34.3% had diabetes, 61.4% had hypertension, 51.4% had atrial fibrillation, and 50% had chronic kidney disease. Sacubitril/valsartan treatment was started at a minimum and intermediate dosage for 93% and 7% of patients, respectively. At baseline, around 90% received β-blockers and just under 80% received mineralocorticoid receptor antagonists.

After 12 months, 66 patients remained alive in the study. Of them, 88% were still on sacubitril/valsartan therapy. These patients demonstrated an improvement in function with

only 6.9% still in NYHA class III or IV. Also, the mean values for N-terminal pro B-type natriuretic peptide (NT-proBNP) dropped from 3,583 to 2,467 pg/mL, while mean values for systolic blood pressure, serum creatinine, and potassium hardly differed from baseline. Allergic reactions, hypotension, and worsening of renal function were identified as the main causes for suspending sacubitril/valsartan. "Among patients still on treatment, only 11 reached the target dose, while 17 reached the intermediate dosage. Hypotension, worsening of renal function, and hyperkalaemia were principal causes of non-titration," stated Dr Herbst, who also stressed that a clinical reason for lack of titration could not be uncovered in 17% of cases.

"After 1 year, we found a reduction in percentage of loop diuretic prescription and mineralocorticoid receptor antagonists, a stability in the percentage of prescription of β-blockers, and an increase in the sodium-glucose cotransporter-2 inhibitors rate," he stated.

The researchers concluded that sacubitril/valsartan was mostly well tolerated in their elderly patients and that those patients who tolerated sacubitril/valsartan were less symptomatic and had an improved bio-humoral profile after 1 year.

1 Herbst A, et al. Is sacubitril/valsartan well tolerated in elderly heart failure patients with reduced ejection fraction? Preliminary data from a real-word registry. P60565, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.

Proenkephalin: A useful biomarker for new-onset heart failure?

An analysis of the PREVEND cohort found an association between high concentrations of proenkephalin and a higher likelihood of new-onset heart failure (HF). However, this association was mainly driven by glomerular filtration rate.

Endogenous opioids such as enkephalins are activated in response to stress, are implicated in pain control, and mediate systemic and organ-specific responses to injury and adaption [1]. In cardiac hypertrophy and failure, the cardiac opioid system is activated. Enkephalins of the opioid system are known to exert several cardiorenal effects. Dr Lisa Emmens (University Medical Center Groningen, the Netherlands) pointed out that proenkephalin is a stable surrogate for enkephalins [2]. It is associated with HF development after myocardial infarction and worse cardiorenal function and prognosis in patients with HF. In studies with HF patients, proenkephalin levels were elevated and associated with the severity of HF and adverse clinical outcomes. However, the association between plasma proenkephalin concentrations and new-onset HF in the general population remained unknown. Thus, Dr Emmens and colleagues analysed 6,677 participants from the PREVEND study to evaluate an association of proenkephalin concentrations and new-onset HF, both with reduced and preserved ejection fractions.

Median proenkephalin concentrations were 52.7 pmol/L (IQR 45.1–61.9). Higher proenkephalin concentrations were associated with poorer renal function and higher N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations. "Main determinants of higher concentrations of proenkephalins were lower estimated glomerular filtration rate (eGFR), lower urinary creatinine excretion, and lower BMI," Dr Emmens explained (P<0.001 for all comparisons).

After a median follow-up of 8.3 years, 221 participants developed new-onset heart failure (127 with HFrEF and 94 with HFpEF). Higher proenkephalin concentrations were found in subjects who developed HF compared with those who did not. Patients with higher proenkephalin concentrations had a more than 2-fold elevated relative risk to develop new-onset HF (HR 2.09; P<0.001). An elevated risk was noticed both for HFrEF (HR 2.31; P<0.001) and HFpEF (HR 1.74; P=0.042). These associations were lost after adjustment for GFR. "High proenkephalin concentrations were univariately associated with HF, but this was mainly confounded by a low GFR," Dr Emmens concluded.

1. Bozkurt B. Circ Heart Fail 2019;12:e005851.
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Weight loss associated with increased mortality risk in heart failure patients

A retrospective study examined the impact of changes in weight on all-cause mortality of patients with heart failure (HF). More than 5% body weight loss over 1 year was associated with an increased likelihood of mortality in initially normal or overweight but not in obese patients.

Although obesity increases the development of HF, being overweight or obese compared with normal weight is associated with survival advantages in chronic HF patients [1]. This phenomenon is known as the obesity paradox. With this in mind, Dr Nuno Melo (Centro Hospitalar e Universitário de São João, Portugal) and his colleagues were interested in the impact of weight changes in HF patients [2]. They

conducted a retrospective cohort study including 589 adult patients who were all treated in an HF clinic between January 2012 and May 2018. The study assessed their mortality risk in association with body weight trajectories.

The study participants had a reduced ejection fraction of <40% and they were followed over a median of 49 months. Study subjects were stratified according to BMI into low/normal weight (BMI <25.0 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). Subgroups were formed based on the weight variations during the first year of observation: group 1 had gained over 5% body weight, group 2 lost more than 5%, and group 3 remained stable.

The mean age of the study cohort was 69 years, 30.2% of the patients were women, and 41.8% of the cohort suffered from ischaemic heart disease. The low/normal weight category comprised 37% of included patients, 37.7% were overweight, and 25.3% were obese. Most patients were NYHA class I (40.1%) or II (45.5%). The vast majority (88.6%) received treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. Over half of the patients remained stable in their weight, but 25.1% gained >5% and 16.5% lost over 5% body weight in the first 12 months. During follow-up time, 248 deaths occurred.

"Patients who lost more than 5% of their weight presented a higher death risk than those with weight gain or weight stability. An association between weight loss over 5% and worse survival persisted in overweight and low/normal-weight patients but not in the obese subgroup," Dr Melo explained the results. A Cox regression that adjusted for factors like age, sex, and comorbidities, revealed a significantly increased hazard ratio for mortality in case of >5% weight loss only for the low/normal (HR 1.63) and overweight group (HR 1.86). "However, in the initial subgroup of obese, a weight loss of over 5% was not prognostically associated," Dr Melo stressed. According to his conclusion, weight loss in obese HF patients should not be discouraged.

1. Horwich TB, et al. Prog Cardiovasc Dis. 2018;61(2):151–56.
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Echocardiographic parameters linked to dementia diagnosis

A correlation has been demonstrated between relative wall thickness in the ECG and screening diagnosis of dementia (SDD) in a study that evaluated ECG parameters of older patients with and without an SDD who were hospitalised for heart failure decompensation.

"The term 'cardiogenic dementia' was coined based mainly on studies that documented lower left ventricular ejection fraction (LVEF) in patients suffering from cardiovascular diseases and dementia. However, some studies provide data that LVEF is not a marker of dementia in some groups of patients," said Dr Karol Nowak (Jagiellonian University Medical College, Poland) [1]. Thus, Dr Nowak and colleagues performed detailed ECG assessments in patients following decompensated heart failure with and without SDD.

Included were 139 patients aged ≥65 years who were hospitalised for decompensated heart failure, and enrolled between 2008 and 2017. During their in-patient stay, clinical and laboratory, as well as detailed ECG measures were obtained. After their release, the patients were followed up with extensive questionnaires including the Adult Lifestyles and Function Interview-Mini-Mental State Examination (ALFI-MMSE) to evaluate for an SDD. Based on the presence of an ALFI-MMSE score <17 points that stood for SDD, 2 subgroups were investigated.

"The baseline characteristics of our study revealed older age, higher prevalence of renal failure, higher level of creatinine, lower glomerular filtration rate, lower haemoglobin, and lower haematocrit in patients with SDD," said Dr Nowak. Within the ECG measures, there were significant inter-group differences for interventricular septal diastolic diameter (P=0.021), aortic valve peak gradient (P=0.013), posterior wall diastolic diameter (P=0.005), and relative wall thickness (P=0.004), all with higher values in the SDD group.

Using a multivariate model, the study also assessed independent predictors of patients' ALFI-MMSE scores. The results revealed an independent correlation between older age as well as relative wall thickness and SDD. "The predictive value of relative wall thickness was the highest among all ECG parameters," underlined Dr Nowak. The authors concluded that this is the first research providing ECG data in this unique SDD group of patients following heart failure decompensation.

1. Nowak K, et al. Acute exacerbation of chronic congestive heart failure and cognitive impairment coexistency in elderly patients-the first echocardiographic measurements. P60749, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.

Telemedicine: Every light has its shadow

Especially during the pandemic, digital health may enable a more focused assessment of heart failure (HF) patients. However, experience has shown that healthcare providers often feel difficulties in establishing a connection, especially with new patients.

Prior to the COVID-19 pandemic, there were very few telemedicine clinics for HF. "Social distancing measures and increased demands on health services resulted in a shift to 'remote by default' clinic appointments in many organisations across Europe," explained Dr Arvind Singhal (Royal Brompton Hospital, UK) [1]. Digital health, focusing on teleconsultation, remote monitoring, and apps and wearables, can be used to support HF care and improve outcomes [2].

Dr Singhal presented clinician experiences of telemedicine from 16 March 2020 to 15 March 2021 at the Royal Brompton Hospital. During this time, there were 2,725 HF clinic appointments, and 99% of them were by telemedicine. The investigators interviewed 8 clinicians: 4 HF consultants, 3 HF specialist nurses, and 1 training-grade doctor. In these interviews, 4 key themes emerged:

1. time management,
2. information gathering,
3. rapport and relationships, and
4. choice and flexibility.

"Teleconsultations resulted in a more focused assessment and less time between appointments," Dr Singhal explained. Clinicians also felt less guilty to keep consultations brief as patients had not travelled to their appointments. On the other hand, this advantage was offset by the longer preparation time.

The second theme that emerged was information gathering. Without physical examinations, clinicians relied more on history and objective data such as test results or imaging. Video consultations were perceived as superior to telephone consultations for assessing patients due to the ability to pick up visual clues. "Examination of oedema was possible with video but more difficult and less reliable than in-person assessment," Dr Singhal said.

Telemedicine also changed the relationship between clinicians and patients. Clinicians experienced difficulty establishing rapport with new patients by telephone. Video was better than telephone, but clinicians still felt the lack of human connection that one experiences when meeting people face-to-face. Regarding choice and flexibility, clinicians expressed fear of a 'one-size-fits-all' approach for future delivery of care.

Finally, all clinicians felt that telemedicine consultation will continue to play a major role as they are more convenient for patients but patient´s choice is essential. Taken together, telemedicine HF consultations were acceptable for healthcare providers, but changed the workflow, consultation dynamics, and how clinicians establish a relationship with the patient.

1 Singhal A, et al. Clinician experiences of telemedicine heart failure clinics: The VIDEO-HF study. P61068, Heart Failure and World Congress on Acute Heart Failure 2021, 29 June–1 July.
2 Singhal A, Cowie MR. Card Fail Rev 2021;7:e08.