Heart Failure Research Review™

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Issue 71 - 2022

In this issue:

Abbreviations used in this issue:

ACE/ARB/ARNI = angiotensin converting enzyme/receptor blocker/receptor neprilysin inhibitor; **CRP** = C-reactive protein; **CV** = cardiovascular; **EF/LVEF** = (left ventricular) ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **MRA** = mineralocorticoid receptor antagonist; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **NYHA** = New York Heart Association; **RCT** = randomised controlled trial.

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Welcome to issue 71 of Heart Failure Research Review.

This issue begins with the phase 3 DELIVER study reporting that dapagliflozin reduced the risk of worsening HF or CV-related death among patients with a mildly reduced or preserved EF. This is followed by the ADVOR study, one of the first positive RCTs in acute decompensated HF with volume overload, reporting better decongestion rates and shorter hospital stays with acetazolamide compared with placebo. There is also research that delves into the association between periodontal disease and HF risk in the ARIC (Atherosclerosis Risk In Communities) study cohort. We conclude the issue with research reporting that not only was hyperuricaemia common in participants with HF from the EMPEROR-Reduced trial of the SGLT-2 inhibitor empagliflozin, it was also an independent predictor of advanced disease severity and increased mortality.

We hope you enjoy the HF research selected. As always, we look forward to comments and feedback.

Kind Regards,

Dr Mark Nolan
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Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction

Authors: Solomon SD et al., for the DELIVER Trial Committees and Investigators

Summary: The DELIVER trial randomised patients with chronic HF and a high LVEF (>40%) to receive dapagliflozin (n=3131) or placebo (n=3132). Over a median of 2.3 years, the primary outcome (composite of worsening HF [unplanned hospitalisation for HF or urgent visit for HF] or CV-related death) occurred in 16.4% of dapagliflozin and 19.5% of placebo recipients (HR 0.82 [95% CI 0.73–0.92]); worsening HF occurred in 11.8% of dapagliflozin and 14.5% of placebo recipients (0.79 [0.69–0.91]) and CV-related death occurred in 7.4% and 8.3% (0.88 [0.74–1.05]). Total event rates and symptom burden were lower with dapagliflozin than with placebo. Results were similar for an LVEF of ≥60% vs. <60%, and in patients with versus without diabetes. Adverse event rates did not differ between the treatment groups.

Comment: The DELIVER study is the second large RCT to confirm clinical benefit of the SGLT-2 inhibitor class in the HFPEF subgroup. Conducted at 353 centres in 20 countries with median follow-up of 2.3 years, it demonstrated an 18% reduction in the primary outcome of HF hospitalisation or CV death (p<0.001). This finding was driven primarily by a reduction in HF admissions. CV death was numerically lower in the dapagliflozin arm (HR 0.88 [95% CI 0.74–1.05]) – in a recent meta-analysis of DELIVER and EMPEROR-Preserved (Vaduganathan M et al., Lancet 2022;400:757–67), there was a significant reduction seen in CV mortality (HR 0.88 [95% CI 0.77–1.00]). There was no significant adverse safety outcomes signal, and quality of life was significantly improved in the SGLT-2 inhibitor arm. Importantly, the benefit of dapagliflozin was consistent in subgroups with LVEF greater and less than 60%, which is different to results of the EMPEROR-Preserved group. This study further cements the role of SGLT-2 inhibitor agents as first-line therapies for HFPEF patients.

Reference: N Engl J Med 2022;387:1089–98
Abstract

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CHF patients aged ≥ 70 years deserve an age-proven β-blocker[1,2]

NEBILET reduced the risk of all-cause mortality or cardiovascular hospitalisation in a broad range of CHF patients aged ≥ 70 years*[1,2]

*vs placebo P = 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

NEBILET: Age proven in CHF patients aged ≥ 70 years[1,2]

CHF = Chronic Heart Failure

PBS Information: Restricted benefit. Moderate to severe heart failure. Refer to PBS Schedule for full restricted benefit information.

Please review full Product Information before prescribing. The Product Information can be accessed at www.menarini.com.au/pi

NEBILET (nebivolol hydrochloride) tablets 1.25mg, 5mg, 10mg. Indication(s): Essential hypertension. Stable chronic heart failure (CHF) as an adjunct to standard therapies in patients 70 years or older. **Dose and Method of Administration:** Once daily dosing, can be given with or without meals, consistent approach is recommended. Indication 1 - Hypertension: 5 mg daily. Renal insufficiency: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 65 years: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 75 years: caution must be exercised and these patients should be monitored closely. Indication 2 - CHF: The initial up titration should be done gradually at 1-2 weekly intervals based on patient tolerability, starting at 1.25 mg once daily, increased to 2.5 mg, then to 5 mg and then to 10 mg once daily. Initiation of therapy and every dose increase should be done under close medical supervision for at least 2 hours. No dose adjustment is required in patients with mild to moderate renal insufficiency. Use in patients with severe renal insufficiency (serum creatinine ≥ 250 micromol/L) is not recommended. **Contraindications:** Hypersensitivity to the active or any of the excipients; liver insufficiency or liver function impairment; acute heart failure; cardiogenic shock or episodes of heart failure decompensation requiring IV inotropic therapy; sick sinus syndrome, including sino-atrial block; second and third degree heart block (without a pacemaker); history of bronchospasm (e.g. including COPD) and/or asthma; untreated phaeochromocytoma; metabolic acidosis; bradycardia (HR < 60 bpm prior to starting therapy); hypotension (systolic BP < 100 mmHg); severe peripheral circulatory disturbances. **Precautions:** Avoid abrupt cessation unless clearly indicated – reduce dosage gradually over 1-2 weeks. If it must be withdrawn abruptly, close observation is required. Anaesthesia; untreated congestive heart failure, unless stabilised; bradycardia; peripheral circulatory disorders (e.g. Raynaud's disease, intermittent claudication); first degree heart block; Prinzmetal's or variant angina; lipid and carbohydrate metabolism – does not affect glucose levels in diabetic patients, but may mask symptoms of hypoglycaemia; hyperthyroidism; COPD; asthma; phaeochromocytoma; various skin rashes; conjunctival xerosis; oculomucocutaneous syndrome; psoriasis; increased sensitivity to allergens and severity of anaphylactic reactions; galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption; hepatic insufficiency or impaired liver functions; severe renal insufficiency; children and adolescents; pregnancy (Cat C); lactation; driving vehicles or operating machines. See approved PI. **Interactions:** Combination not recommended: Class I antiarrhythmics; calcium channel antagonists (verapamil/diltiazem); centrally-acting antihypertensives; other beta-blockers (incl. eye drops). Combination to be used with caution: Class III antiarrhythmics; anaesthetics (volatile); insulin and other oral diabetic medicines; calcium antagonists (dihydropyridine type); catecholamine depleting agents; baclofen; amifostine. For other combinations requiring careful consideration, see approved PI. **Adverse effects:** Headache, dizziness, tiredness, fatigue, paraesthesia, constipation, nausea, diarrhoea, cardiac failure aggravated, bradycardia, hypotension, hypertension, atrial fibrillation, angina pectoris, dyspnoea, oedema, slowed AV conduction/AV-block, bronchospasm. Post-marketing reports of hypersensitivity, angioneurotic oedema, abnormal hepatic function, acute pulmonary oedema, acute renal failure, myocardial infarction, Raynaud's phenomenon, thrombocytopenia. See approved PI. [mPI Version 8.0]

References: 1. NEBILET® Approved Product Information, 13 November 2020.
2. Flather MD *et al. Eur Heart J* 2005; 26: 215–25.

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Acetazolamide in acute decompensated heart failure with volume overload

Authors: Mullens W et al., for the ADVOR Study Group

Summary: Patients with acute decompensated HF were randomised to receive intravenous acetazolamide 500 mg/day (n=256) or placebo (n=259) added to standardised intravenous loop diuretics in the ADVOR trial. Compared with placebo, acetazolamide was associated with a greater proportion of participants achieving successful decongestion within 3 days of randomisation (primary outcome; 42.2% vs. 30.5%; risk ratio 1.46 [95% CI 1.174–1.82]) as well as greater cumulative urine output and natriuresis, with no significant between-group difference for the composite of all-cause mortality or rehospitalisation for HF (29.7% vs. 27.8%; HR 1.07 [0.78–1.48]), worsening kidney function, hypokalaemia, hypotension or adverse events.

Comment: ADVOR represents one of the first positive RCTs of a novel therapy in acute decompensated HF. Acetazolamide is a carbonic anhydrase inhibitor acting on the proximal convoluted tubule of the nephron. Patients treated with acetazolamide were 46% more likely to completely decongest at 72 hours compared with standard therapy (p<0.001), and had a significantly shorter inpatient hospital stay (p=0.02). There were no significant safety signals, and renal function and potassium levels were not significantly different. The primary outcome of successful decongestion is clinically important, and the finding that >50% of patients in both arms remained congested at 72 hours indicates further progress is urgently needed. No significant difference was seen in hospital readmission between arms; this may reflect that successful decongestion was eventually achieved in a great majority of patients in both arms, as evidenced by long inpatients stays (8.8 vs. 9.9 days). Acetazolamide represents an effective, safe and very cost-effective strategy to improve inpatient decongestion, and its use should be considered in all acute decompensated HF cases.

Reference: N Engl J Med 2022;387:1185–95
Abstract

Association of empagliflozin treatment with albuminuria levels in patients with heart failure

Authors: Ferreira JP et al.

Summary: This *post hoc* analysis of participants with HF from the EMPEROR-Reduced and EMPEROR-Preserved trials (EMPEROR-Pooled) explored the association of empagliflozin with study outcomes according to albuminuria across the EF spectrum. Compared with normoalbuminuric participants (n=5552), macroalbuminuria (n=1025) was associated with younger age, races other than White, obesity, male sex, site region other than Europe, higher NT-proBNP levels, higher high-sensitivity troponin-T levels, higher BP, more advanced NYHA class, greater HF duration, more frequent prior hospitalisations for HF, diabetes, hypertension, lower estimated GFR and less frequent use of ACE inhibitors, ARBs or MRAs. The association of empagliflozin with CV mortality or HF hospitalisation was similar for normoalbuminuric, microalbuminuric and macroalbuminuric participants (HRs 0.74–0.80 [p=0.71 for trend]). Empagliflozin treatment was associated with a significant reduction in the incidence of new macroalbuminuria (HR 0.81 [95% CI 0.70–0.94]) and increases in remission to sustained normoalbuminuria or microalbuminuria (1.31 [1.07–1.59]), but did not reduce urine albumin-to-creatinine ratio overall; however, there were reductions in this ratio in participants with diabetes, for whom it was significantly higher compared with nondiabetics.

Comment: Albuminuria presence indicates structural damage of renal glomerular filtration barrier and is associated with increased risk of HF admission and CV death. Agents that reduce albuminuria have the potential to improve clinical outcomes. This pooled *post hoc* analysis of EMPEROR-Reduced and EMPEROR-Preserved demonstrates that albuminuria is common in HF, with 32% having microalbuminuria and 11% having macroalbuminuria, and associated with a 2- to 3-fold increased risk of CV outcomes. Benefits of empagliflozin were consistent across all tertiles of albuminuria (p=0.71 for interaction). No significant reduction in urinary albumin-creatinine ratio was seen in the overall cohort; however, the incidence of new microalbuminuria was 19% lower (p=0.005) and the remission rate to normo-albuminuria was 31% higher (p=0.009) in the empagliflozin arm, with no difference seen across LVEF or diabetic status subgroups. These findings suggest that empagliflozin can protect and rebuild the glomerular filtration barrier, which may partially explain its renal benefits.

Reference: JAMA Cardiol; Published online Sept 21, 2022
Abstract

Hyperkalaemia as a cause of undertreatment with mineralocorticoid receptor antagonists in heart failure

Authors: Henrysson J et al.

Summary: This retrospective medical record review reported the incidence of hyperkalaemia during uptitration of guideline-directed medical therapy in 630 real-world patients admitted with new-onset HFREF to a Swedish hospital. After guideline-directed medical therapy uptitration, 48.4% of the patients received MRAs, and these patients were significantly older, had a significantly lower EF and estimated GFR, had a significantly higher NT-proBNP level, and were more often likely to be treated with an ACE inhibitor, ARB or ARNI. There was a significant increase in the incidence of hyperkalaemia from 5.9% to 24.4% at 6 months after uptitration of guideline-directed medical therapy, with significant increases from 6.8% to 54.5% in patients with an MRA dose reduction, from 8.8% to 50.9% in those who discontinued MRAs, from 5% to 10% in those on stable MRAs, and from 6% to 28% in those who were MRA-naïve. Among patients who were MRA-naïve, 87.5% had normokalaemia/hypokalaemia recorded at baseline, whereas 6 months after guideline-directed medical therapy up-titration, normokalaemia/hypokalaemia persisted in 47.8%, but 22.4%, 5.7% and 0.9% had progressed to mild, moderate and severe hyperkalaemia, respectively.

Comment: MRAs remain underutilised, with a recent HF registry showing that 67% of HFREF patients do not receive MRA therapies (Greene SJ et al., J Am Coll Cardiol 2018;72:351–66) despite a powerful 30% relative reduction in mortality with MRA in the RALES RCT. Reasons for MRA underutilisation are unclear, but concern amongst clinicians regarding precipitating hyperkalaemia may play a role. This observational analysis of 630 recently hospitalised Swedish patients with newly-diagnosed HFREF showed some interesting findings. Forty-three percent of patients were never commenced on an MRA at 13 months after HFREF discharge, and these patients were older with lower LVEF and higher NT-pro-BNP levels. Renal function was only moderately reduced in this never-MRA group (median estimated GFR 58 mL/min/m^2 [IQR 44–74]). The incidence of hypokalaemia was 28% in the no-MRA subgroup, 10% in the stable MRA group, and 51% in patients who had MRAs discontinued. These findings suggest that the majority of patients denied MRA therapy are eligible; also that the majority of patients that have MRAs discontinued do not have hyperkalaemia and that the incidence of hyperkalaemia may be similar in non-MRA and MRA-treated subgroups.

Reference: ESC Heart Fail; Published online Sept 25, 2022
Abstract

Riociguat in pulmonary hypertension and heart failure with preserved ejection fraction

Authors: Dachs TM et al.

Summary: Patients with pulmonary hypertension and HFPEF were randomised to receive thrice-daily oral riociguat starting at 0.5mg and increasing to 1.5mg (n=58) or placebo (n=56) in this phase 2b trial. Compared with placebo, riociguat recipients had achieved a significant improvement in cardiac output at 26 weeks (+0.37 vs. –0.11 L/min [p=0.0142]). Five riociguat recipients dropped out of the study due to adverse events, but there were no serious adverse events or deaths related to the agent.

Comment: HFPEF is the final endpoint of a variety of diverse pathophysiological pathways. One important pathway is endothelial dysfunction, which results in reduce nitric oxide local bioavailability and hence microvasculature vasoconstriction and also interstitial fibrosis. Riociguat is a soluble guanylate cyclase stimulator that increases nitric oxide production and has demonstrated efficacy in chronic thromboembolic pulmonary hypertension. This phase 2b study assessed 114 HFPEF patients with mean pulmonary artery pressures of >25mm Hg and mean left atrial pressures of >15mm Hg, and randomised them to riociguat or placebo. At 6 months, there was a net +0.54 L/min improvement in cardiac output in the riociguat arm compared with the placebo arm (p=0.01). This value suggests a potential benefit of riociguat in the HFPEF population, and phase 3 trials are indicated. The authors did not discuss whether riociguat has any advantages over vericiguat, which is also a soluble guanylate cyclase stimulator.

Reference: Eur Heart J 2022;43:3402–13
Abstract

Transvenous right greater splanchnic nerve ablation in heart failure and preserved ejection fraction

Authors: Fudim M et al.

Summary: Eleven patients with HFPEF (NYHA functional class II–III, EF ≥50% and elevated pulmonary capillary wedge pressure at rest or with exercise) underwent a novel catheter procedure of right-sided greater splanchnic nerve ablation in this first-in-human study. Follow-up through to 12 months revealed no device-related adverse cardiac events or clinical sequelae. There were significant improvements from baseline for: i) median Kansas City Cardiomyopathy Questionnaire score (from 48 to 65 points at 1 month and 80 points at 12 months); ii) 6-minute walk distance (from 292 to 341m at 1 month and 359m at 12 months); and iii) mean NT-proBNP level (from 1292 to 472 pg/mL at 6 months and 379 pg/mL at 12 months; the difference at 1 month was not significant).

Comment: It has been observed that less than 50% of acute decompensated HF patients will have an increase in their weight in months leading up to admission. It is possible that congestion in these patients results from 'auto-transfusion' of unstressed blood volume from the splanchnic circulation reservoir. Vasoconstriction of this reservoir is mediated by the greater splanchnic nerve, and it is possible that blocking this nerve may reduce congestion. This first-in-human, single-arm, open-label phase 1 trial of 11 HFPEF patients involved insertion of a catheter into the intercostal veins adjacent to the right-sided great splanchnic nerve and permanently ablating it with radiofrequency. Over 12 months of follow-up, these patients demonstrated a significant improvement in quality of life (p<0.05) and a 23% improvement in 6-minute walk test distance (p<0.05). There was no significant change in NT-proBNP level at 1 month. Causality cannot be proven due to the absence of a control arm. This study suggests that the procedure is feasible, and a larger phase 2 trial is currently recruiting.

Reference: JACC Heart Fail 2022;10:744–52
Abstract

Stem cell-derived extracellular vesicles reduce the expression of molecules involved in cardiac hypertrophy – in a model of human-induced pluripotent stem cell-derived cardiomyocytes

Authors: Constantin A et al.

Summary: These researchers sought to investigate the effects that mesenchymal stem cell-derived extracellular vesicles have on cardiac hypertrophy. Their experimental procedures culminated in the finding that in human-induced pluripotent stem cell-derived cardiomyocytes, stem cell-derived extracellular vesicles, via their cargo, reduced expression of hypertrophic specific markers, and also of molecules that are involved in inflammatory processes associated with cardiac hypertrophy.

Comment: Cardiac hypertrophy may develop via either physiological or pathological pathways depending on ongoing stimulus. Both pathways are initiated by cardiac fibroblasts secreting IGF-1 (insulin-growth-factor-1), which acts in cardiomyocyte IGF-1 receptors to stimulate phosphatidylinositol-triphosphate production, which in turn causes transcription of hypertrophy-related genes. Pathological hypertrophy is characterised by transcription of fetal genes that can impair contractility. This paper by Constantin et al. looked at cultures of stem-cell-derived human cardiomyocytes, and found that adding mesenchymal stem-cell-derived extracellular vesicles reduced protein expression of hypertrophic and inflammatory markers. If the beneficial messengers in the vesicles can be identified, then this could plausibly be a therapeutic strategy to prevent adverse cardiac hypertrophy.

Reference: Front Pharmacol; Published online Oct 10, 2022
Abstract

Periodontal status, C-reactive protein, NT-proBNP, and incident heart failure

Authors: Molinsky RL et al.

Summary: The association of periodontal disease with HF risk was explored in 6707 evaluable participants from the ARIC study, among whom there were 350 incident cases of HFPEF, 319 of HFREF and 509 of unknown type HF recorded over a median 13 years of follow-up. Among these HF cases, 59% had periodontal disease, whereas 18% were edentulous. Participants with versus without periodontal disease had a numerical increase in the risk of incident HFPEF (HR 1.35 [95% CI 0.98–1.86]) and a significantly increased risk of incident HFREF (1.69 [95% CI 1.18–2.43]). Participants with versus without edentulism had significant increases in the risks of both HFPEF and HFREF (respective HRs 2.00 [95% CI 1.37–2.93] and 2.19 [1.43–3.36]). Participants with edentulism were noted to have unfavourable changes in CRP and NT-proBNP levels, whereas those with periodontal disease had an unfavourable change only in CRP level.

Comment: The pathophysiology of HF includes prolonged systemic inflammation and venous congestion. It is possible that disruption of gut mucosal barriers may allow entry of microbial endotoxins and metabolites and contribute to HF incidence. This observational study followed 7514 patients in the ARIC cohort over 13 years. Patients were categorised as normal, periodontal disease or edentulous (i.e. no teeth). Periodontal disease was significantly associated with a 69% increased risk of HFREF and a 35% increased risk of HFPEF. Edentulism was associated with a 119% increased risk of HFREF and a 100% increased risk of HFPEF. A causal relationship cannot be inferred as this was an observational study and unmeasured confounders almost certainly influenced the results. These results are intriguing, and it is possible that preventative strategies aimed at reducing chronic inflammatory burden could reduce HF incidence.

Reference: JACC Heart Fail 2022;10:731–41
Abstract

Alerting clinicians to 1-year mortality risk in patients hospitalized with heart failure

Authors: Ahmad T et al.

Summary: Patients hospitalised for HF who had NT-proBNP levels of >500 pg/mL and who had received intravenous diuretics within 24 hours of admission were randomised to have their 1-year mortality risk calculated with an algorithm derived and validated using data from similar historical patients (n=1590) or usual care (n=1534) in the REVEAL-HF RCT; the groups were similar for demographics, NT-proBNP levels, ICU admissions and LVEF ≤40%. There was no significant difference between the intervention versus usual care group for the composite primary outcome of 30-day hospital re-admission or 1-year all-cause mortality (38.9% vs. 39.3% [p=0.89]), discharge HF medication prescriptions, implantable cardioverter-defibrillator placement or palliative care referral.

Comment: Management of contemporary HF remains suboptimal with well-documented undertreatment demonstrated in large cohort studies. It is possible that providing treating clinicians with an automated alert that calculates estimated 1-year mortality from data in electronic health records could improve intensity of treatment and clinical outcomes. Patients hospitalised for HF (n=3124) were randomised to the automated alert arm or the control arm. The mortality prediction model achieved an area under the curve value of 0.74 for the cohort, indicating reasonable prognostic accuracy. There was no significant difference for the composite of 30-day hospital re-admission or all-cause mortality at 12 months between the arms. There was also no evidence that provision of electronic alerts altered treatment patterns, such as HF medications at discharge or defibrillator insertion. Alternative strategies for improving the intensity of HF treatment should be investigated.

Reference: JAMA Cardiol 2022;7:905–12
Abstract

Independent commentary by Dr Mark Nolan

Mark Nolan is a Non-Invasive Cardiologist working at Western Health and the Peter Mac Cancer Centre in Melbourne, as well as a Post-Doctoral Researcher at the Baker Heart and Diabetes Institute. He has completed an Echocardiography Fellowship in Adelaide, Cardiac MRI and CT Fellowship in Toronto, and also a Cardio-Oncology Fellowship in Toronto. His PhD thesis examined the optimal use of cardiac imaging to guide treatment in cancer patients. He has first-author publications in Journal of American College of Cardiology: Cardiovascular Imaging, Journal of American College of Cardiology: CardioOncology and American Journal of Cardiology. His professional interests also include Cardio-Diabetology and Health Economics, and he has published in both of these fields. His recreational interests include bush walking in the Mornington Peninsula and reading about classical history. One of the things he likes most about medicine is the ability to both teach and learn.

Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction

Authors: Doehner W et al.

Summary: This analysis of EMPEROR-Reduced trial data explored the association between serum uric acid level and the trial's outcomes in 3676 participants, 53% of whom had hyperuricaemia. A serum uric acid level in the highest versus lowest tertile was associated with advanced HF severity and with a worse primary composite outcome of CV-related death or hospitalisation for worsening HF (adjusted HR 1.64 [95% CI 1.28–2.10]), CV-related mortality (1.98 [1.35–2.91]) and all-cause mortality (1.8 [1.29–2.49]). Empagliflozin treatment led to a 1.12 mg/dL lower serum uric acid level at 4 weeks compared with placebo (p<0.0001), with the decrease persisting throughout follow-up and similar reductions in prespecified subgroups. Empagliflozin was also associated with a reduction in the risk of clinically relevant hyperuricaemia (HR 0.68 [95% CI 0.52–0.89]). Neither baseline serum uric acid level nor change in serum uric acid level at 4 weeks had a significant impact on the beneficial effect of empagliflozin on the primary endpoint. The researchers also noted significant interactions between serum uric acid level and treatment effects that suggested a benefit of empagliflozin on CV and all-cause mortality in participants with an elevated serum uric acid level.

Comment: Elevated serum uric acid level is associated with increased risk of mortality and hospitalisation in HF patients. Uric acid is produced by xanthine oxidase, which is upregulated in HF due to increased inflammatory mediators, and in turn may generate dangerous oxygen radicals. This *post hoc* analysis of the EMPEROR-Reduced cohort found that an elevated serum uric acid level was present in 53% of the cohort at baseline. A rapid ~15% relative reduction in uric acid level was seen in the SGLT-2 inhibitor arm at 4 weeks with no change seen in the placebo arm. Increased renal excretion of uric acid did not appear to explain this finding and the mechanism remains speculative. Impressively, the number of clinical sequelae due to hyperuricemia (gout, initiation of uric-acid lowering medications) was 32% lower in the SGLT-2 inhibitor arm. These findings demonstrate yet another additional benefit of the SGLT-2 inhibitor class beyond their cardiac, renal and endocrine benefits, and once again the mechanism of action remains unclear. Further clinical studies of SGLT-2 inhibitor agents as long-term treatment for recurrent gout may even be indicated.

Reference: Eur Heart J 2022;43:3435–46
Abstract

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