IN BRIEF

HYPERTROPHY

Dapagliflozin reduces left ventricular mass

Treatment with dapagliflozin, an inhibitor of sodium–glucose cotransporter 2, reduces left ventricular (LV) mass in patients with type 2 diabetes mellitus (T2DM) and LV hypertrophy. In the DAPA-LVH trial, 66 patients with T2DM and LV hypertrophy were randomly assigned to receive dapagliflozin (10 mg once daily) or placebo for 12 months. In the intention-to-treat analysis, dapagliflozin therapy significantly reduced MRI-assessed LV mass compared with placebo (absolute mean change: −2.82 g, 95% CI −5.13 g to −0.51 g; $P = 0.018$). Dapagliflozin therapy also reduced ambulatory 24 h systolic blood pressure, body mass, visceral and subcutaneous adipose tissue, and insulin resistance. The researchers suggest that dapagliflozin can initiate LV reverse remodelling and changes in LV structure that might partly contribute to the cardioprotective effects of the drug.

ORIGINAL ARTICLE Brown, A. J. M. et al. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. *Eur. Heart J.* https://doi.org/10.1093/eurheartj/ehaa419 (2020)

HEART FAILURE

Myosin activator improves cardiac function

Danicamtiv, a cardiac myosin activator, improves left ventricular (LV) and left atrial (LA) function in patients with heart failure with reduced ejection fraction (HFrEF). This finding was presented as part of the Heart Failure Association Discoveries webinars. Danicamtiv is a novel small molecule that selectively enhances cardiac actomyosin activity. In ex vivo animal studies, danicamtiv was associated with a dose-dependent increase in sarcomere activity in LV and LA myofibrils and an increase in calcium sensitivity in LV and LA skinned muscle fibres. In a dog model of heart failure, danicamtiv increased LV stroke volu me and LA emptying fraction. Finally, in a phase IIa study, patients with HFrEF were randomly assigned to danicamtiv (50–100 mg twice daily for 7 days; $n = 30$) or placebo ($n = 10$). Danicamtiv improved LV and LA volumes and function, without impairing relaxation. Adverse events, mostly mild, occurred in 57% and 40% of the patients in the danicamtiv and placebo groups, respectively.

ORIGINAL ARTICLE Voors, A. A. et al. Effects of danicamtiv, a novel cardiac myosin activator, in heart failure with reduced ejection fraction: experimental data and clinical results from a phase 2a trial. *Eur. J. Heart Fail.* https://doi.org/10.1002/ejhf.1933 (2020)

HEART FAILURE

Benefit of dapagliflozin is independent of LVEF

In patients with heart failure with reduced ejection fraction (HFrEF), the benefit of dapagliflozin therapy is independent of the degree to which left ventricular ejection fraction (LVEF) is reduced. This finding comes from a post-hoc analysis of the DAPA-HF trial. A total of 4,744 patients with HFrEF and a LVEF ≤40% were randomly assigned to dapagliflozin (10 mg once daily) or placebo. The extent of the reduction in LVEF was a significant predictor of hospitalization for heart failure and cardiovascular mortality. The reduction in the primary end point (worsening heart failure event or cardiovascular death) with dapagliflozin treatment was consistent regardless of LVEF (HR 0.75, 0.75, 0.67 and 0.83 for LVEF <26%, 26–30%, 31–35% and >35%, respectively; $P = 0.762$ for interaction). The efficacy of dapagliflozin was also independent of whether or not patients had diabetes mellitus.

ORIGINAL ARTICLE Dewan, P. et al. Efficacy and safety of sodium–glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF. *Eur. J. Heart Fail.* https://doi.org/10.1002/ejhf.1867 (2020)

EXERCISE

Exercise adaptations to milk confer benefits to offspring

Maternal exercise before and during pregnancy in animal models confers benefits to offspring, including improvements in glucose metabolism, adiposity and cardiac function, via uncertain mechanisms. A study in *Nature Metabolism* now shows that the benefits of exercise training are mediated by an oligosaccharide present in breast milk.

The researchers exposed wild-type female mice to running exercise before and during pregnancy. A second group of wild-type mice were sedentary, and all mice were fed a high-fat diet. "We took offspring from exercise-trained dams and had them drink milk from sedentary dams, and offspring from sedentary dams and had them drink milk from exercise-trained dams," explains corresponding author, Kristin Stanford. Strikingly, adult offspring that had consumed milk as neonates from exercise-trained dams had improved glucose metabolism, reduced adipose tissue mass and reduced body mass, compared with offspring that had drunk milk from sedentary dams.

Next, the researchers examined the activity levels of 139 pregnant women and the concentrations of oligosaccharides in human breast milk at 2 months postpartum. The levels of 3′-sialyllactose (3′-SL) correlated with activity levels and negatively correlated with BMI. Exercised female mice also had increased levels of 3′-SL in their milk.

Crucially, exercise training did not confer benefits to the offspring of mice with global knockout of *St3gal4*, which lack 3′-SL in their milk. Furthermore, cross-fostering experiments showed that milk from

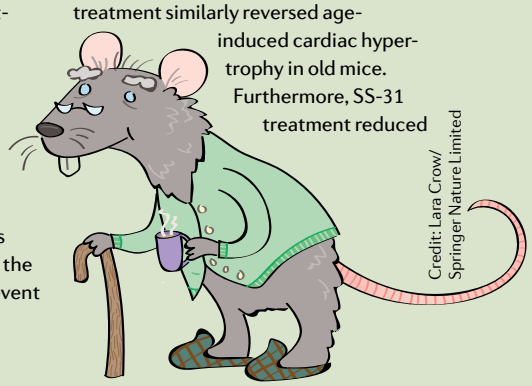
BASIC RESEARCH

Targeting the mitochondria to reverse ageing-induced cardiac dysfunction

SS-31 treatment and overexpression of mitochondria-targeted catalase (mCAT) can reverse age-related diastolic dysfunction in old mice through pathways downstream of mitochondrial reactive oxygen species (ROS) production, according to a new study published in *eLife* by Ying Ann Chiao and colleagues. This finding supports the therapeutic potential of targeting the mitochondria to suppress the hallmarks of cardiac ageing.

Mitochondrial dysfunction is thought to have a critical role in both ageing and the development of cardiovascular disease. "Previous studies showed that reducing mitochondrial ROS levels starting at a young age and before the onset of pressure overload can prevent cardiac dysfunction, but whether improving mitochondrial function at late-life can rescue pre-existing age-related cardiac dysfunction is unknown," remarks Chiao.

Old mice aged 24 months treated with the tetrapeptide SS-31, an inhibitor of mitochondrial ROS production, for 8 weeks showed a reversal in echocardiography-measured parameters of diastolic dysfunction compared with saline-treated control mice. SS-31 treatment similarly reversed age-induced cardiac hypertrophy in old mice. Furthermore, SS-31 treatment reduced



Credit: Lara Crow/ Springer Nature Limited