IN BRIEF

HEART FAILURE

HDACs as a therapeutic target in HFpEF

New research suggests that histone deacetylase (HDAC) inhibition might improve cardiopulmonary structure and function in heart failure with preserved ejection fraction (HFpEF). In a cat model of slow-progressive, pressure overload-induced diastolic dysfunction, which recapitulates features of human HFpEF, daily treatment with the pan-HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) for 2 months reduced left ventricular (LV) hypertrophy and left atrial size, increased myofibril relaxation ex vivo and LV relaxation in vivo, and improved LV systolic and diastolic function and pulmonary structure and function compared with vehicle-treated cats. Mechanistically, SAHA treatment reduced the acetylation of mitochondrial metabolic enzymes, leading to increased mitochondrial respiration. These results suggest that HDAC inhibition with SAHA, which has FDA approval for the treatment of cutaneous T cell lymphoma, might be beneficial for improving adverse cardiopulmonary remodelling in HFpEF.

ORIGINAL ARTICLE Wallner, M. et al. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. *Sci. Transl Med.* **12**, eaay7205 (2020)

DYSLIPIDAEMIA

AKCEA-APO(a)-L_{Rx} lowers Lp(a) levels in patients

AKCEA-APO(a)-L_{Rx} therapy reduces lipoprotein(a) (Lp(a)) levels in a dose-dependent manner in patients with established cardiovascular disease, according to a phase II trial. AKCEA-APO(a)-L_{Rx} is an antisense oligonucleotide targeting *LPA* mRNA (which encodes the main Lp(a) constituent, apolipoprotein(a)) conjugated with triantennary *N*-acetylgalactosamine to direct the therapy specifically to hepatocytes. A total of 286 patients with high levels of Lp(a) (≥60 mg/dl) and pre-existing cardiovascular disease were randomly assigned to receive AKCEA-APO(a)-L_{Rx} at different doses or placebo for 6–12 months. All doses induced significant reductions in Lp(a) levels compared with placebo, with the highest dose (20 mg weekly) inducing a mean 80% reduction. At the highest cumulative dose regimen (equivalent to 80 mg monthly), 98% of patients achieved Lp(a) levels ≤50 mg/dl.

ORIGINAL ARTICLE Tsimikas, S. et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1905239 (2020)

RISK FACTORS

Alcohol abstinence reduces AF recurrence

A substantial reduction in alcohol consumption by individuals who are regular drinkers and have symptomatic atrial fibrillation (AF) reduces the recurrence of AF and the proportion of time spent in AF, according to a study conducted in six hospitals in Australia. The study included 140 patients with AF and an average intake of approximately 17 drinks per week at baseline. Patients randomly assigned to the abstinence group reduced their alcohol intake from 16.8 to 2.1 drinks per week, whereas patients in the control group reduced their alcohol intake from 16.4 to 13.2 drinks per week. After a 2-week blanking period, the abstinence group had a lower risk of AF recurrence during the 6 months of follow-up (53% versus 73%) and lower AF burden than the control group (median percentage of time in AF 0.5% versus 1.2%). These findings add to the body of evidence demonstrating that excessive consumption of alcohol is associated with incident AF and adverse atrial remodelling.

ORIGINAL ARTICLE Voskoboinik, A. et al. Alcohol abstinence in drinkers with atrial fibrillation. *N. Engl. J. Med.* **382**, 20–28 (2020)

LIPIDS

Non-HDL cholesterol levels linked with long-term risk of CVD

The concentrations of non-HDL cholesterol in the blood are strongly linked to the long-term risk of cardiovascular disease (CVD), according to a risk evaluation study published in *The Lancet*. On the basis of this finding, the study investigators established a model to assess the potential benefit of an early lipid-lowering strategy for primary prevention of CVD.

Although the efficacy of lipid-lowering therapy for secondary prevention of CVD is well established, the use of such a strategy for primary prevention is contentious, given the lack of data on the link between lipid concentrations and very long-term cardiovascular outcomes in the general population. Using individual-level data from the Multinational Cardiovascular Risk Consortium, Brunner and colleagues sought to evaluate the relationship between long-term risk of CVD and blood non-HDL-cholesterol levels in individuals without prevalent CVD.

In total, 38 cohorts comprising 398,846 individuals were included in the analysis. During a maximum follow-up of 43.6 years (median 13.5 years), 54,542 CVD end points were reported. A stepwise increase in reported CVD events was observed across increasing concentrations of non-HDL cholesterol. Notably, the 30-year CVD event rates in both women and men at the highest non-HDL cholesterol category (≥5.7 mmol/l) were approximately threefold to fourfold higher than those in the lowest category (<2.6 mmol/l).

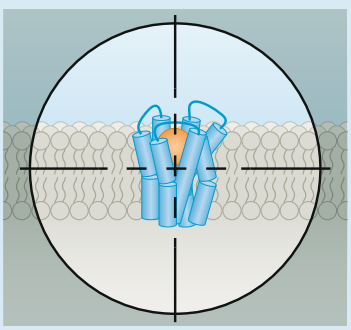
Using this data, the investigators established a risk prediction tool that incorporated age, sex and CVD risk factors to estimate the long-term

DYSLIPIDAEMIA

GPR146 is a potential new therapeutic target for lipid lowering

Deficiency in the orphan G protein-coupled receptor 146 (GPR146) decreases blood lipid levels and protects against atherosclerosis in mice independently of LDL receptor (LDLR) activity, according to a new study. "Considering that GPR146 is a druggable target, developing small molecules to inhibit GPR146 is potentially an effective strategy to treat hypercholesterolaemia and atherosclerosis," say study investigators Haojie Yu and Chad Cowan.

In agreement with previous human genetic studies that identified GPR146 as a potential regulator of plasma LDL-cholesterol (LDL-C) levels, Yu et al. found that *GPR146* depletion in mice substantially reduced plasma LDL-C and triglyceride levels, mediated by decreased hepatic sterol regulatory element binding protein 2 (SREBP2) activity and VLDL secretion rate. Mechanistically, GPR146 regulated plasma lipid levels in mice though activation of extracellular signal-regulated kinase (ERK) signalling in hepatocytes upon feeding or after a short period of fasting. Activation of ERK signalling increased hepatic SREBP2 activity and VLDL secretion, which in turn increased circulating LDL-C and triglyceride levels. Importantly, GPR146 deficiency decreased circulating LDL-C levels in both wild-type and *Ldlr*$^{-/-}$ mice and reduced aortic atherosclerotic lesion area by 90% and 70% in male and female *Ldlr*$^{-/-}$ mice, respectively, compared with *Gpr146*$^{+/+}$*Ldlr*$^{-/-}$ mice. These findings indicate that the benefits of



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