IN BRIEF

LIPIDS

Sphingolipids are biomarkers of coronary disease

Ceramides, which are a category of sphingolipid, are cholesterol-independent biomarkers of coronary artery disease (CAD). This finding comes from a study published in *The Journal of Clinical Investigation*. Researchers performed lipidomics on serum samples from 462 patients with familial CAD and 212 population-based controls. An unbiased machine learning approach was used to identify sphingolipid species that were positively associated with CAD. Of the 32 sphingolipids measured, the levels of 30 were significantly elevated in patients with CAD compared with controls. Moreover, a novel sphingolipid-inclusive CAD risk score identified patients with CAD independently and more effectively than traditional clinical biomarkers of cardiovascular disease, such as serum levels of LDL cholesterol and triglycerides. "This study validates serum ceramides as candidate biomarkers of cardiovascular disease," summarize the researchers.

ORIGINAL ARTICLE Poss, A. M. et al. Machine learning reveals serum sphingolipids as cholesterol-independent biomarkers of coronary artery disease. *J. Clin. Invest.* https://doi.org/10.1172/JCI131838 (2020)

DIETARY FACTORS

Coconut oil raises LDL-cholesterol levels

Consumption of coconut oil, which is high in saturated fat, results in higher LDL-cholesterol levels than consumption of non-tropical vegetable oils. This finding comes from a meta-analysis of 16 studies in which consumption of coconut oil was compared with that of other fats over the course of ≥2 weeks. Consumption of coconut oil increased LDL-cholesterol levels by 10.47 mg/dl and HDL-cholesterol levels by 4.00 mg/dl compared with non-tropical vegetable oils. By contrast, markers of glycaemia, inflammation and adiposity were not significantly affected by consumption of coconut oil compared with non-tropical vegetable oils. "Coconut oil should not be viewed as healthy oil for cardiovascular disease risk reduction, and limiting coconut oil consumption because of its high saturated fat content is warranted," conclude the investigators.

ORIGINAL ARTICLE Neelakantan, N. et al. The effect of coconut oil consumption on cardiovascular risk factors: a systematic review and meta-analysis of clinical trials. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.119.043052 (2020)

VALVULAR DISEASE

5-year safety of TAVI in intermediate-risk patients

The incidence of death or disabling stroke is not significantly different at 5 years after transcatheter aortic valve implantation (TAVI) or surgery in patients with severe aortic stenosis and at intermediate surgical risk. A total of 2,032 patients were enrolled in the PARTNER 2 trial and randomly assigned to TAVI or surgical aortic valve replacement. At 5 years, the incidence of death or disabling stroke was not significantly different between the TAVI and surgery groups (47.9% versus 43.4%; HR 1.09). Results were similar in the transfemoral-access cohort (44.5% versus 42.0%; HR 1.02); however, the incidence of death or disabling stroke was higher after TAVI than after surgery in the transthoracic-access cohort (59.3% versus 48.3%; HR 1.32). Moreover, compared with surgery, TAVI was associated with higher rates of at least mild paravalvular aortic regurgitation (33.3% versus 6.3%), repeat hospitalizations (33.3% versus 25.2%) and aortic valve reinterventions (3.2% versus 0.8%). Longer-term data on bioprosthetic valve function and clinical outcomes after TAVI versus surgery are required.

ORIGINAL ARTICLE Makkar, R. R. et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1910555 (2020)

GENOME EDITING

New developments in gene editing for Duchenne muscular dystrophy

A somatic gene editing therapy for Duchenne muscular dystrophy (DMD) has shown promising results in a large-animal model of DMD and in an in vitro model of human DMD. DMD is caused by frameshift mutations in the *DMD* gene, which encodes dystrophin, leading to progressive muscle degeneration and premature death as a result of respiratory and cardiac failure. Kupatt and colleagues used a Cas9-mediated exon-excision approach to restore the *DMD* reading frame, which resulted in the expression of a shortened but functional dystrophin and ameliorated skeletal and cardiac muscle failure in pigs with DMD. Moreover, this approach prevented a vulnerability of DMD cardiomyocytes for arrhythmias.

In a pig model of DMD lacking exon 52 of *DMD*, intramuscular injection of adeno-associated virus 9 (AAV9) carrying an intein-split Cas9 and a pair of guide RNAs targeting exon 51 (AAV9-Cas9-gE51) yielded high local rates of gene editing with elimination of exon 51 and restoration of the *DMD* reading frame, resulting in the expression of a shortened form of dystrophin. This shortened dystrophin was only partially functional but was sufficient to improve skeletal muscle structure and function. However, this approach did not affect the diaphragm or the heart, which are the main muscles contributing to mortality in patients with DMD. To target these muscles, the investigators administered the AAV9-Cas9-gE51 via intravenous injection. This systemic application induced widespread dystrophin expression in a wide range of muscles, including the diaphragm and the heart, leading to improved muscle function, reduced cardiac arrhythmogenic susceptibility and prolonged survival. In vitro in

ARRHYTHMIAS

Reappraisal of LQTS-causing genes

Long QT syndrome (LQTS) is the most common inherited cardiac arrhythmia (affecting 1 in 2,000 individuals) and has been associated with mutations in 17 different genes. However, according to a new assessment, the evidence that many of these genes are actually causative for LQTS is limited or disputed. This finding has important implications for genetic testing, diagnosis and treatment.

The International, Multicentered LQTS ClinGen Working Group identified 17 genes reported to cause LQTS. In the context of a contemporary understanding of natural variation in the human genome, the group found that only three genes (*KCNQ1*, *KCNH2* and *SCN5A*) had definitive evidence for causing typical LQTS. These genes are traditionally classified as causing LQTS types 1–3, respectively. A further four genes (*CALM1*, *CALM2*, *CALM3* and *TRDN*) were found to have strong or definitive evidence for causing atypical LQTS, including neonatal atrioventricular block. One gene (*CACNA1C*) had moderate evidence for causing LQTS.

By contrast, three genes (*CAV3*, *KCNE1* and *KCNJ2*) had limited evidence and six genes (*AKAP9*, *ANK2*, *KCNE2*, *KCNJ5*, *SCN4B* and *SNTA1*) had disputed evidence for causing LQTS. Two of these genes (*KCNE1* and *KCNE2*) had a strong level of evidence for causing acquired LQTS.

"Genes with disputed or limited evidence for causation of LQTS should not be routinely tested for diagnostic purposes in patients with suspected LQTS," says Michael Gollob, who designed and led the study. "Testing genes that lack scientific evidence for disease causation creates a risk of misinterpretation of the genetic information, and potentially an