IN BRIEF

CORONARY ARTERY DISEASE

Cardiovascular MRI versus FFR in stable angina

Revascularization in patients with stable angina is often guided by either myocardial-perfusion cardiovascular MRI or invasive angiography to measure fractional flow reserve (FFR). The unblinded, multicentre MR-INFORM trial was designed to compare these two approaches. A total of 918 patients with typical angina and cardiovascular risk factors were randomly assigned to cardiovascular MRI or measurement of FFR. In the cardiovascular MRI group, 40.5% of patients met the criteria to undergo revascularization (ischaemia in ≥6% of the myocardium), whereas 45.9% of patients in the FFR group met the revascularization criteria (FFR ≤0.8). Fewer patients in the cardiovascular MRI group than in the FFR group underwent index revascularization (35.7% versus 45.0%; $P = 0.005$). The primary composite outcome (death, nonfatal myocardial infarction or target-vessel revascularization within 1 year) occurred in 3.6% of patients in the cardiovascular MRI group and 3.7% of patients in the FFR group, which met the threshold for noninferiority of cardiovascular MRI compared with FFR.

ORIGINAL ARTICLE Nagel, E. et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N. Engl. J. Med.* **380**, 2418–2428 (2019)

INTERVENTIONAL CARDIOLOGY

Drug-coated balloons for high-bleeding-risk PCI

In the single-blind DEBUT trial, the use of balloons coated with paclitaxel and iopromide was compared with the use of bare-metal stents for percutaneous coronary intervention (PCI) in patients at high risk of bleeding. After successful predilatation of the target lesion, a total of 208 patients were randomly assigned to PCI with a drug-coated balloon or bare-metal stent. The primary outcome (major adverse cardiac event at 9 months) occurred in 1% and 14% of patients in each group, respectively (risk ratio 0.07, 95% CI 0.01–0.52, $P < 0.00001$ for noninferiority, $P = 0.00034$ for superiority). Two definite stent thrombosis events occurred with bare-metal stents, whereas no acute vessel closures occurred with drug-coated balloons. In future studies, drug-coated balloons should be compared with drug-eluting stents in patients at high risk of bleeding.

ORIGINAL ARTICLE Rissanen, T. T. et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet* https://doi.org/10.1016/S0140-6736(19)31126-2 (2019)

RISK FACTORS

Vitamin D supplementation and CVD

In a meta-analysis of 21 randomized clinical trials including a total of 83,291 patients, vitamin D supplementation was not associated with a reduction in cardiovascular events or death. Only four of the trials included in the meta-analysis had cardiovascular disease (CVD) as a prespecified primary end point. The rate of major adverse cardiovascular events (the primary end point of the meta-analysis) was not reduced with vitamin D supplementation compared with placebo (risk ratio (RR) 1.00). Furthermore, vitamin D was not associated with significant reductions in any of the secondary end points: myocardial infarction (RR 1.00), stroke (RR 1.06), CVD mortality (RR 0.98) or all-cause mortality (RR 0.97). "The findings suggest that vitamin D supplementation does not confer cardiovascular protection and is not indicated for this purpose," conclude the researchers.

ORIGINAL ARTICLE Barbarawi, M. et al. Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA Cardiol.* https://doi.org/10.1001/jamacardio.2019.1870 (2019)

Credit: Jennie Vallis/Springer Nature Limited

ATHEROSCLEROSIS

Longevity-associated gene variant halts progression of atherosclerosis

Atherosclerosis-prone mice transfected with the longevity-associated variant (LAV) of *BPIFB4* show reduced endothelial dysfunction and slowed atherogenic plaque progression compared with wild-type controls. These findings, published in the *European Heart Journal*, indicate that the favourable phenotype associated with long-living individuals and characterized by delayed or absent age-linked, atherosclerosis-related cardiovascular disease can be transferred to animal models via LAV-*BPIFB4* gene therapy.

Age is a major risk factor for the development of atherosclerosis. The LAV in BPI fold-containing family B member 4 (BPIFB4) is enriched in long-living individuals and has previously been shown to improve endothelial function when transferred to old mice via gene therapy. In addition, LAV-*BPIFB4* is thought to exert immunomodulatory activity, potentially via a CXC-chemokine receptor 4 (CXCR4)-dependent mechanism. "Thus, we adopted a model of atherosclerosis (a potential target of CXCR4 modulators) to evaluate the therapeutic effects of LAV-BPIFB4 in this setting and to determine if this effect was mediated by CXCR4," comment Carmine Vecchione and Annibale Puca, lead investigators of the study.

LAV-*BPIFB4*, wild-type-*BPIFB4* or an empty vector were delivered via adeno-associated viral transfer into *Apoe*$^{-/-}$ mice fed a high-fat diet. Mesenteric and femoral arteries taken from *Apoe*$^{-/-}$ mice overexpressing LAV-*BPIFB4* showed diminished endothelial dysfunction compared with wild-type mice. This protective effect was completely abolished by treatment with AMD3100, a non-peptide antagonist of CXCR4. Furthermore, LAV-*BPIFB4* gene therapy halted the formation of vascular plaques and reduced macrophage infiltration. These atheroprotective effects were again abolished by co-treatment with AMD3100.

At the immunological level, when autologous macrophages from patients with atherosclerosis were conditioned in vitro with a human recombinant LAV-BPIFB4 protein, the macrophages were polarized towards an anti-inflammatory M2 phenotype in a CXCR4-dependent manner. LAV-BPIFB4 reduced the inflammatory milieu within the vessels and improved endothelial-mediated vasorelaxation.

Taken together, these findings demonstrate the efficacy of LAV-*BPIFB4* gene therapy in reducing the atherogenic process. "Changes in immunological profile observed after gene therapy with LAV-*BPIFB4* makes this approach a potential cure for a broad range of cardiovascular diseases," concludes Vecchione.

Karina Huynh

ORIGINAL ARTICLE Puca, A. A. et al. Single systemic transfer of a human gene associated with exceptional longevity halts the progression of atherosclerosis and inflammation in ApoE knockout mice through a CXCR4-mediated mechanism. *Eur. Heart J.* https://doi.org/10.1093/eurheartj/ehz459 (2019)

FURTHER READING Ferrucci, L. & Fabbri, E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat. Rev. Cardiol.* **15**, 505–522 (2018)