Research highlights

Dyslipidaemia

siRNA therapy markedly reduces Lp(a) levels

Olpasiran, a small interfering RNA (siRNA) that reduces lipoprotein(a) (Lp(a)) production in the liver, administered every 12 weeks induces a pronounced and sustained decrease in the plasma levels of Lp(a) in patients with established atherosclerotic cardiovascular disease. This finding from the OCEAN(a)-DOSE trial was presented at the AHA Scientific Sessions 2022.

This phase II study included 281 patients with established atherosclerotic cardiovascular disease and a plasma Lp(a) concentration of >150 nmol/l who were randomly assigned to receive subcutaneous injections of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks or 225 mg every 24 weeks) or placebo. Most of the patients were taking LDL-cholesterol-lowering therapy, including high-intensity statins and PCSK9 inhibitors.

At 36 weeks, Lp(a) levels had increased by a mean of 3.6% in the placebo group. By contrast, olpasiran therapy reduced Lp(a) levels in a dose-dependent manner, with ≥95% reductions compared with placebo in patients who received the 75-mg or 225-mg dose every 12 weeks. Moreover, at the higher doses, nearly all patients achieved an Lp(a) level of ≤125 nmol/l. The incidence of adverse events was similar in the olpasiran and placebo groups.

Longer and larger trials are needed to determine the effects of olpasiran therapy on atherosclerotic cardiovascular disease.

Irene Fernández-Ruiz

Original article: O'Donoghue, M. L. et al. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2211023 (2022)

Resuscitation

Alternative defibrillation strategies improve outcomes

Alternative strategies for defibrillation improve outcomes in patients with refractory ventricular fibrillation. This finding comes from the DOSE VF trial, which was presented at the AHA Resuscitation Science Symposium 2022 and published in *NEJM*.

In a cluster-randomized trial performed in Canada, six paramedic services were randomly assigned to treat patients with refractory ventricular fibrillation during out-of-hospital cardiac arrest with one of three defibrillation strategies: double sequential external defibrillation (DSED; rapid sequential shocks from two defibrillators), vector-change defibrillation (VCD; switching the defibrillation pads to an anterior–posterior position) or standard defibrillation.

The trial was stopped because of the COVID-19 pandemic after 405 patients had been enrolled. Survival to hospital discharge was higher in the DSED and VCD groups than in the standard group (30.4%, 21.7% and 13.3%, respectively). DSED, but not VCD, was associated with a higher likelihood of a good neurological outcome than standard defibrillation.

The results seem to favour DSED, but the requirement for a second defibrillator might be a limitation to widespread uptake of this strategy. In these settings, the use of VCD might be a suitable alternative strategy.

Gregory B. Lim

Original article: Cheskes, S. et al. Defibrillation strategies for refractory ventricular fibrillation. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2207304 (2022)

Surgery

Surgery safer than endovascular therapy for CLTI

In patients with chronic limb-threatening ischaemia (CLTI) who had an adequate conduit for vein bypass, bypass surgery is associated with fewer adverse events or deaths than an endovascular procedure. This finding from the BEST-CLI trial was presented at AHA 2022.

The BEST-CLI trial included 1,830 patients with CLTI and infrainguinal peripheral artery disease who were assigned to one of two parallel cohort studies. Cohort 1 included 1,434 patients who were deemed to be ideal candidates for surgical revascularization because they had an adequate great saphenous vein. Cohort 2 included 396 patients who required an alternative bypass conduit. All patients were randomly assigned to undergo bypass surgery or endovascular therapy.

In cohort 1, the primary outcome event (composite of a major adverse limb event or all-cause death) occurred in significantly fewer patients in the surgical group than in the endovascular group (42.6% versus 57.4%; $P < 0.001$). In cohort 2, the incidence of the primary outcome event did not differ significantly between treatment groups (42.8% versus 47.7%; $P = 0.12$).

"Overall, the findings from this large, international trial suggest that preprocedural planning of treatment in patients with CLTI should include a surgical risk assessment and a determination of saphenous-vein availability," say the investigators.

Karina Huynh

Original article: Farber, A. et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2207899 (2022)

Atrial fibrillation

Cryoballoon ablation reduces AF progression

In patients with untreated paroxysmal atrial fibrillation (AF), first-line cryoballoon ablation is associated with a lower incidence of persistent AF than antiarrhythmic drug therapy. This finding from the EARLY-AF trial, presented at AHA 2022, adds support to earlier observations that initial catheter ablation may be disease-modifying.

"As catheter-based interventions have become safer and more effective, there has been a shift to consider intervention earlier in the disease process," says Jason Andrade, a lead investigator of the trial. In 2021, the EARLY-AF trial demonstrated that first-line cryoballoon ablation resulted in fewer recurrent AF episodes and hospitalizations and improved quality of life in 303 patients with symptomatic paroxysmal AF as compared with rhythm-control drug therapy. Now, the 3-year follow-up data show that cryoballoon ablation is associated with a significant reduction in the progression of AF, as evidenced by a 75% reduction in the progression from paroxysmal to persistent AF. Furthermore, cryoballoon ablation was also associated with improved quality of life, less health-care utilization and a trend towards reduced rates of serious adverse events.

"Moving forward, we would want to evaluate whether the change in disease trajectory could translate into lower rates of heart failure, less thromboembolism and increased survival," comments Andrade.

Karina Huynh

Original article: Andrade, J. G. et al. Progression of atrial fibrillation after cryoablation or drug therapy. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2212540 (2022)