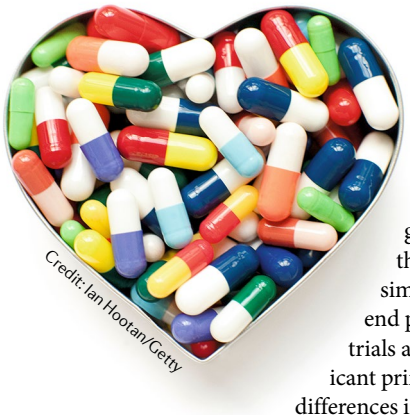

Credit: Ian Hootan/Getty

and dapagliflozin, respectively) to treat HFrEF in addition to guideline-directed therapy and had similar primary end points. "All three trials achieved significant primary end point differences in favour of the intervention; however, the hazard ratios differed," comment the investigators. "While the hazard ratio may suggest the largest treatment effect in DAPA-HF followed by PARADIGM-HF and then VICTORIA, a comparison of annualized or 12-month event rates for the primary end point suggests that the outcome benefits are comparable across trials."

Karina Huynh

ORIGINAL ARTICLES Armstrong, P. W. et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1915928 (2020) | Butler, J. et al. Comparing the benefit of novel therapies across clinical trials: insights from the VICTORIA trial. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.120.047086 (2020)

> The relative difference between treatment groups translated into an absolute event rate reduction of 4.2 events per 100 patient-years

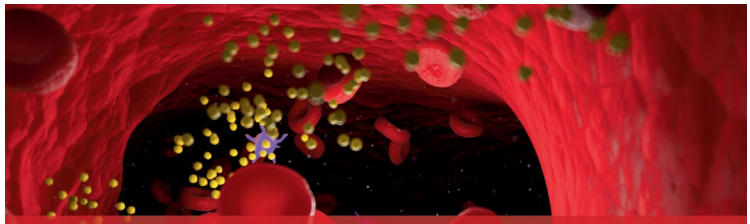
After a median of 2.2 years of follow-up, the rate of myocardial infarction or death from any cause (the primary outcome) was similar with the two strategies (estimated 3-year event rate 36.4% versus 36.7%; adjusted HR 1.01, 95% CI 0.79–1.29, $P = 0.95$). However, the risks of stroke (HR 3.76, 95% CI 1.52–9.32, $P = 0.004$) and death or initiation of dialysis (HR 1.48, 95% CI 1.04–2.11, $P = 0.03$) were higher with the invasive strategy. Finally, patients in the invasive-strategy group did not have substantial or sustained improvements in angina-related health status, assessed with the Seattle Angina Questionnaire, compared with those in the conservative-strategy group.

Taken together, these findings suggest that patients with CAD and advanced CKD should be treated with an initial conservative strategy.

Irene Fernández-Ruiz

ORIGINAL ARTICLES Bangalore, S. et al. Management of coronary disease in patients with advanced kidney disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1915925 (2020) | Spertus, J. A. et al. Health status after invasive or conservative care in coronary and advanced kidney disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1916374 (2020)

> these findings suggest that patients with CAD and advanced CKD should be treated with an initial conservative strategy


Credit: Sebastian Kaulitzki/Science Photo Library/Getty

DYSLIPIDAEMIA

Twice-yearly inclisiran injections halve LDL-cholesterol levels

The safety and durability of the LDL-cholesterol (LDL-C)-lowering effects of inclisiran, a small interfering RNA that inhibits the synthesis of PCSK9 in the liver, have now been confirmed in three phase III clinical trials. The ORION-10 and ORION-11 trials show that inclisiran therapy administered every 6 months reduces LDL-C levels by 50% in patients with atherosclerotic cardiovascular disease who had elevated LDL-C levels despite receiving maximally tolerated statin therapy. A similar LDL-C-lowering effect with inclisiran was seen in the ORION-9 trial in patients with familial hypercholesterolaemia (FH). "Importantly, compliance is guaranteed given that, with only two injections of inclisiran per year, the LDL-C level can be halved," says Frederick Raal, lead investigator of ORION-9. "This should reduce the risk of premature atherosclerotic cardiovascular disease."

"The phase II ORION-1 trial suggested that after dosing on day 1 and day 90, the interval could be extended to 6-monthly doses," says Kausik Ray, lead investigator of ORION-10 and ORION-11. Therefore, the ORION programme investigators conducted three trials to assess the efficacy and safety of inclisiran over 18 months. Two trials included patients who had high LDL-C levels despite receiving statin therapy at the maximum tolerated dose and either atherosclerotic cardiovascular disease (ORION-10; $n = 1{,}561$) or atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (ORION-11; $n = 1{,}617$). The ORION-9 trial included 482 adult patients with heterozygous FH.

In all three trials, patients were randomly assigned to receive either inclisiran 284 mg or placebo by subcutaneous injection on day 1, day 90 and every 6 months thereafter over 540 days. At day 510, the between-group difference in the change in LDL-C level from baseline with inclisiran therapy versus placebo was −52.3 percentage points in the ORION-10 trial, −49.9 percentage points in the ORION-11 trial and −47.9 percentage points in the ORION-9 trial (all $P < 0.001$). Of note, the large reductions in LDL-C levels occurred regardless of FH genotype. In all three trials, the adverse event profile of inclisiran was similar to that of placebo, except for a higher frequency of injection-site adverse events with inclisiran.

In addition to the advantages of this therapy to overcome non-adherence and non-compliance issues, Raal and Ray highlight the potential of inclisiran in early prevention approaches. "We could offer treatments earlier, and these might be more acceptable than taking 365 tablets a year," comments Ray. "This approach lends itself to population-level reductions in exposure to LDL-C at a scale that current therapies cannot achieve," he adds. Raal and Ray explain that several ORION trials are ongoing, including ORION-8 (involving participants with FH from ORION-9) to evaluate the longer-term efficacy and safety of inclisiran in this patient population, the cardiovascular outcomes trial ORION-4 and the primary prevention trial ORION-17.

Irene Fernández-Ruiz

ORIGINAL ARTICLES Ray, K. K. et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1912387 (2020) | Raal, F. J. et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1913805 (2020)
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