Article 1

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

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Abstract

**Background:** Inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin-kexin type 9. Previous studies suggest that inclisiran might provide sustained reductions in low-density lipoprotein (LDL) cholesterol levels with infrequent dosing.

**Materials and Methods:** We enrolled patients with atherosclerotic cardiovascular disease (ORION-10 trial) and patients with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (ORION-11 trial) who had elevated LDL cholesterol levels despite receiving statin therapy at the maximum tolerated dose. Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The coprimary end points in each trial were the placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 and the time-adjusted percentage change in LDL cholesterol level from baseline after day 90 and up to day 540.

**Results:** A total of 1,561 and 1,617 patients underwent randomization in the ORION-10 and ORION-11 trials, respectively. Mean (±SD) LDL cholesterol levels at baseline were 104.7 ± 38.3 mg per deciliter (2.71 ± 0.99 mmol per liter) and 105.5 ± 39.1 mg per deciliter (2.73 ± 1.01 mmol per liter), respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% (95% confidence interval [CI], 48.8-55.7) in the ORION-10 trial and by 49.9% (95% CI, 46.6-53.1) in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% (95% CI, 51.3-56.2) and 49.2% (95% CI, 46.8-51.6) (*P* < .001 for all comparisons vs. placebo). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent.

**Conclusion:** Reductions in LDL cholesterol levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months. More injection-site adverse events occurred with inclisiran than with placebo.

Comments

LDL pathway is a major target for lipid therapies, PCSK-9 being the predominant one. Statins are the mainstay of therapy, with many not achieving target LDL because of poor adherence. Monoclonal antibodies like Evolocumab directed against PCSK9 reduced LDL and improved cardiovascular outcomes when added to statin therapy. However, these drugs require injections every few weeks. Inclisiran, a small interfering RNA that blocks hepatic PCSK9 synthesis, can be administered over longer dosing intervals.

This study included patients with maximum tolerable doses of statins and achieved an impressive near 50% reduction in LDL cholesterol. This is not an outcomes study, the data on which is awaited. A comfortable dosing regimen with few adverse events makes inclisiran a promising drug in lipid management, mainly in those with inadequate response to statins.

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Article 2

Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM): A Randomized, Double-Blind, Placebo-controlled, Phase 3 Trial

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Abstract

**Background:** Cardiac muscle hypercontractility is a key pathophysiological abnormality in hypertrophic cardiomyopathy, and a major determinant of dynamic left ventricular outflow tract (LVOT) obstruction. Available pharmacological options for hypertrophic cardiomyopathy are inadequate or poorly tolerated and are not disease-specific. We aimed to assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic obstructive hypertrophic cardiomyopathy.

**Methods:** In this phase 3, randomized, double-blind, placebo-controlled trial (EXPLORER-HCM) in 68 clinical cardiovascular centers in 13 countries, patients with hypertrophic cardiomyopathy with an LVOT gradient of 50 mm Hg or greater, and New York Heart Association (NYHA) class II to III symptoms were assigned (1:1) to receive mavacamten (starting at 5 mg) or placebo for 30 weeks. Visits for assessment of patient status occurred every 2 to 4 weeks. Serial evaluations included echocardiogram, electrocardiogram, and blood collection for laboratory tests and mavacamten plasma concentration. The primary endpoint was a 1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO₂) and at least 1 NYHA class reduction or a 3.0 mL/kg per min or greater pVO₂ increase without NYHA class worsening. Secondary endpoints assessed changes in post-exercise LVOT gradient, pVO₂, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CS), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). This study is registered with ClinicalTrials.gov, NCT03470545.

**Findings:** Between May 30, 2018 and July 12, 2019, 429 adults were assessed for eligibility, of whom 251 (59%) were enrolled and randomly assigned to mavacamten (n = 123 [49%]) or placebo (n = 128 [51%]). Forty-five (37%) of 123 patients on mavacamten versus 22 (17%) of 128 on placebo met the primary endpoint (difference +19.4%, 95% CI 8.7 to 30.1; *P* = .0005). Patients on mavacamten had greater reductions than those on placebo in post-exercise LVOT gradient (~36 mm Hg, 95% CI −43.2 to −28.1; *P* < .0001), greater increase in pVO₂ (+1.4 mL/kg per min, 0.6 to 2.1; *P* = 0·0006), and improved symptom scores (KCCQ-CS +9·1, 5.5 to 12.7; HCMSQ-SoB −1.8, −2.4 to −1·2; *P* < .0001). A total of 34% more patients in the mavacamten group improved by at least 1 NYHA class (80 of 123 patients in the mavacamten group vs. 40 of 128 patients in the placebo group; 95% CI 22.2 to 45.4; *P* < .0001). Safety and tolerability were similar to placebo. Treatment-emergent adverse events were generally mild. One patient died by sudden death in the placebo group.

**Interpretation:** Treatment with mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with obstructive hypertrophic cardiomyopathy. The results of this pivotal trial highlight the benefits of disease-specific treatment for this condition.

**Comments**

Pharmacological therapy of HCM is a huge unmet need with a dearth of disease-specific therapies. There are no approved drugs except propranolol that too is based on weak evidence. The treatment of symptoms and alleviation of LVOT obstruction can be challenging. Mavacamten, a selective myosin ATPase inhibitor, showed promise in PIONEER-HF, a small, open-label phase 2 trial. EXPLORER-HCM was funded to prove this drug’s benefit on the symptoms and LVOT gradient in a phase 3 trial.

Mavacamten improved symptoms, quality of life significantly in patients with obstructive HCM. This is the first targeted drug that addresses the pathophysiological mechanism of obstructive hypertrophic cardiomyopathy. This study excluded patients already on disopyramide. We need more data on the long-term safety of the drug.

Article 3

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

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Abstract

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

Materials and Methods: In this double-blind trial, we randomly assigned 3,730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

Results: During a median of 16 months, a primary outcome event occurred in 361 of 1,863 patients (19.4%) in the empagliflozin group and in 462 of 1,867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65-0.86; P < .001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58-0.85; P < .001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (−0.55 vs. −2.28 mL per minute per 1.73 m² of body-surface area per year; P < .001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genitourinary infections, mostly uncomplicated, is a concern with this class of drugs.

SGLT2 inhibitors are a new revelation in the management of heart failure patients with improved cardiovascular and renal outcomes, irrespective of their diabetes status. This study provided additional evidence in a different subset of patients with advanced LV dysfunction. They are a strongly recommended class of drugs in heart failure patients, cost being the only prohibiting factor.

Article 4

Aspirin With or Without Clopidogrel After Transcatheter Aortic-Valve Implantation

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Abstract

Background: The effect of single as compared with dual antiplatelet treatment on bleeding and thromboembolic events after transcatheter aortic-valve implantation (TAVI) in patients who do not have an indication for long-term anticoagulation has not been well studied.

Methods: In a randomized, controlled trial, we assigned a subgroup of patients who were undergoing TAVI and did not have an indication for long-term anticoagulation, in a 1:1 ratio, to receive aspirin alone or aspirin plus clopidogrel for 3 months. The 2 primary outcomes were all bleeding (including minor, major, and life-threatening or disabling bleeding) and nonprocedure-related bleeding over a period of 12 months. Most bleeding at the TAVI puncture site was counted as nonprocedure-related. The 2 secondary outcomes were a composite of death from cardiovascular causes,
nonprocedure-related bleeding, stroke, or myocardial infarction (secondary composite 1) and a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction (secondary composite 2) at 1 year, with both outcomes tested sequentially for noninferiority (noninferiority margin, 7.5 percentage points) and superiority.

**Results:** A total of 331 patients were assigned to receive aspirin alone and 334 were assigned to receive aspirin plus clopidogrel. A bleeding event occurred in 50 patients (15.1%) receiving aspirin alone and in 89 (26.6%) receiving aspirin plus clopidogrel (risk ratio, 0.57; 95% confidence interval [CI], 0.42 to 0.77; *P* = .001). Nonprocedure-related bleeding occurred in 50 patients (15.1%) and 83 patients (24.9%), respectively (risk ratio, 0.61; 95% CI, 0.44-0.83; *P* = .005). A secondary composite 1 event occurred in 76 patients (23.0%) receiving aspirin alone and in 104 (31.1%) receiving aspirin plus clopidogrel (risk ratio, 0.98; 95% CI, 0.74 to 1.3; *P* = .214). A secondary composite 2 event occurred in 32 patients (9.7%) and 33 patients (9.9%), respectively (risk ratio, 0.69; 95% CI, 0.49 to 0.97; *P* = .035). A secondary composite event occurred in 32 patients (9.7%) and 33 patients (9.9%), respectively (risk ratio, 0.69; 95% CI, 0.49 to 0.97; *P* = .035). A total of 44 patients (13.3%) and 32 (9.6%), respectively, received oral anticoagulation during the trial.

**Conclusions:** Among patients undergoing TAVI who did not have an indication for oral anticoagulation, the incidence of bleeding and the composite of bleeding or thromboembolic events at 1 year were significantly less frequent with aspirin than with aspirin plus clopidogrel administered for 3 months.

**Comments**

The implanted prosthetic valve needs time to endothelize and has increased thromboembolic events before that period. Present guidelines recommend dual antiplatelet therapy for 3 to 6 months after TAVI in patients who are not on anticoagulation, based on weak evidence. Dual antiplatelet therapy has increased bleeding risk, which may mitigate the benefit. POPULAR-TAVI trial was conducted with 2 cohorts, first comparing aspirin vs. aspirin and clopidogrel in patients, not on anticoagulation. The second cohort comprised of patients who had an indication for long-term anticoagulation. This abstract presented the data of the first cohort.

This was an open-label trial but without any involvement of the industry. Aspirin alone was as effective as the combination with clopidogrel in the prevention of stroke with substantially low-bleeding events.

**Article 5**

**Colchicine in Patients with Chronic Coronary Disease**

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**Abstract**

**Background:** Evidence from a recent trial has shown that the anti-inflammatory effects of colchicine reduce the risk of cardiovascular events in patients with recent myocardial infarction, but evidence of such a risk reduction in patients with chronic coronary disease is limited.

**Materials and Methods:** In a randomized, controlled, double-blind trial, we assigned patients with chronic coronary disease to receive 0.5 mg of Colchicine once daily or matching placebo. The primary end-point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization.

The key secondary end point was a composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke.

**Results:** A total of 5,522 patients underwent randomization; 2,762 were assigned to the colchicine group and 2,760 to the placebo group. The median duration of follow-up was 28.6 months. A primary end-point event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence, 2.5 vs. 3.6 events per 100 person-years; hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; *P* < .001). A key secondary end-point event occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group. The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization (composite end point), cardiovascular death or spontaneous myocardial infarction (composite end point), ischemia-driven coronary revascularization, and spontaneous myocardial infarction were also significantly lower with colchicine than with placebo. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31).

**Conclusions:** In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo.

**Comments**

Inflammation is a primary culprit in coronary artery disease, and many anti-inflammatory agents are being tried. The CANTOS trial showed favorable results with canakinumab,
and the initial trial with colchicine in acute myocardial infarction was positive. With this background, colchicine was tested in patients with stable ischemic heart disease.

The trial was of low quality because of the nonblinded design. Patient compliance with the drug was lower, gastrointestinal intolerance being the primary adverse effect. The population recruited was lacking in diversity, which has implications for the generalizability of results. Increased noncardiovascular deaths, a phenomenon observed even in the previous colchicine trial, are of concern.

The results are promising, with a significant reduction in endpoints. As the drug is cheap and freely available, it will be an important tool in the pharmacological armamentarium. Further studies are needed before it can be recommended routinely.

Article 6

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

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Abstract

Background: The effects of rivaroxaban in patients with atrial fibrillation (AF) and a bioprosthetic mitral valve remain uncertain.

Materials and Methods: In this randomized trial, we compared rivaroxaban (20 mg once daily) with dose-adjusted warfarin (target international normalized ratio, 2.0–3.0) in patients with AF and a bioprosthetic mitral valve. The primary outcome was a composite of death, major cardiovascular events (stroke, transient ischemic attack, systemic embolism, valve thrombosis, or hospitalization for heart failure), or major bleeding at 12 months.

Results: A total of 1,005 patients were enrolled at 49 sites in Brazil. A primary-outcome event occurred at a mean of 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (difference calculated as restricted mean survival time, 7.4 days; 95% confidence interval [CI], −1.4 to 16.3; \( P < .001 \) for noninferiority). Death from cardiovascular causes or thromboembolic events occurred in 17 patients (3.4%) in the rivaroxaban group and in 26 (5.1%) in the warfarin group (hazard ratio, 0.65; 95% CI, 0.35 to 1.20). The incidence of stroke was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio, 0.25; 95% CI, 0.07 to 0.88). Major bleeding occurred in 7 patients (1.4%) in the rivaroxaban group and in 13 (2.6%) in the warfarin group (hazard ratio, 0.54; 95% CI, 0.21 to 1.35). The frequency of other serious adverse events was similar in the 2 groups.

Conclusions: In patients with AF and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to the mean time until the primary outcome of death, major cardiovascular events, or major bleeding at 12 months.

Comments

Patients with AF and bioprosthetic valve need long-term anticoagulation. At present, vitamin K antagonists are used, albeit with limited evidence. The usage of direct oral anticoagulants in this scenario is not studied except for a couple of small subgroup analyses. This study was the first major randomized trial comparing warfarin and rivaroxaban in patients with AF and a bioprosthetic valve.

This open-label, noninferiority trial was conducted in Brazil with industry funding. The primary outcome was a composite of death, major cardiovascular events, or major bleeding at 12 months, including hospitalization for heart failure. A time in the therapeutic range (TTR) of 65.5% was achieved for warfarin recipients, an ideal comparison arm.

This trial clearly showed that rivaroxaban is noninferior to warfarin in patients with bioprosthetic valves. Warfarin is effective when a high TTR is achieved, a difficult task in developing countries, with a higher risk of complications. More indications are being sought for direct oral anticoagulants, and this trial clears the way for their usage in a subset of patients with prosthetic valves. However, the results cannot be extrapolated to other valves, mainly metallic or valves in other locations.

Article 7

Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease

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Abstract

Background: Coronary calcification hinders stent delivery and expansion and is associated with adverse outcomes. Intravascular lithotripsy (IVL) delivers acoustic pressure waves to modify calcium, enhancing vessel compliance and optimizing stent deployment.

Objectives: The purpose of this study was to assess the safety and effectiveness of IVL in severely calcified de novo coronary lesions.

Methods: Disrupt CAD III (NCT03595176) was a prospective, single-arm multicenter study designed for regulatory approval of coronary IVL. The primary safety endpoint was freedom from major adverse cardiovascular events (cardiac death, myocardial infarction, or target vessel revascularization) at 30 days. The primary effectiveness endpoint was procedural success. Both endpoints were compared with a prespecified performance goal (PG). The mechanism of calcium modification was assessed in an optical coherence tomography (OCT) substudy.

Results: Patients (n = 431) were enrolled at 47 sites in 4 countries. The primary safety endpoint of the 30-day freedom from major adverse cardiovascular events was 92.2%; the lower bound of the 95% confidence interval was 89.9%, which exceeded the PG of 84.4% (P < .0001). The primary effectiveness endpoint of procedural success was 92.4%; the lower bound of the 95% confidence interval was 90.2%, which exceeded the PG of 83.4% (P < .0001). Mean calcified segment length was 47.9 ± 18.8 mm, calcium angle was 292.5 ± 76.5, and calcium thickness was 0.96 ± 0.25 mm at the site of maximum calcification. OCT demonstrated multiplane and longitudinal calcium fractures after IVL in 67.4% of lesions. Minimum stent area was 6.5 ± 2.1 mm² and was similar regardless of demonstrable fractures on OCT.

Conclusions: Coronary IVL safely and effectively facilitated stent implantation in severely calcified lesions.

Comments

Percutaneous coronary intervention of calcific lesions is associated with early and delayed complications. The rotational atherectomy system has a steep learning curve and a higher incidence of procedural complications. There is a need for effective adjunctive devices to address this subset of lesions.

This nonrandomized study excluded acute myocardial infarction and specific complex lesions like bifurcation, left main, and ostial lesions. An interesting finding noted was the frequent occurrence of IVL-induced ventricular capture, the significance of which is not known. The long-term results of the efficacy of this device are awaited.

This study demonstrated the safety and utility of IVL. Most of the operators were new to the device and used it without difficulty after a single roll-in patient, proving the minimal learning curve. IVL may become the standard of care in managing calcific lesions and may be utilized ahead of other modalities for the interventions on calcific vessels.

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