Medical News & Perspectives

Cardiovascular Corner—Stable Coronary Artery Disease, An LDL "Vaccine," and Anti-inflammatories

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A trial to answer an important clinical question, along with studies of novel and repurposed drugs, made news at the American Heart Association's flagship conference in Chicago late last year.

Medical Therapy First

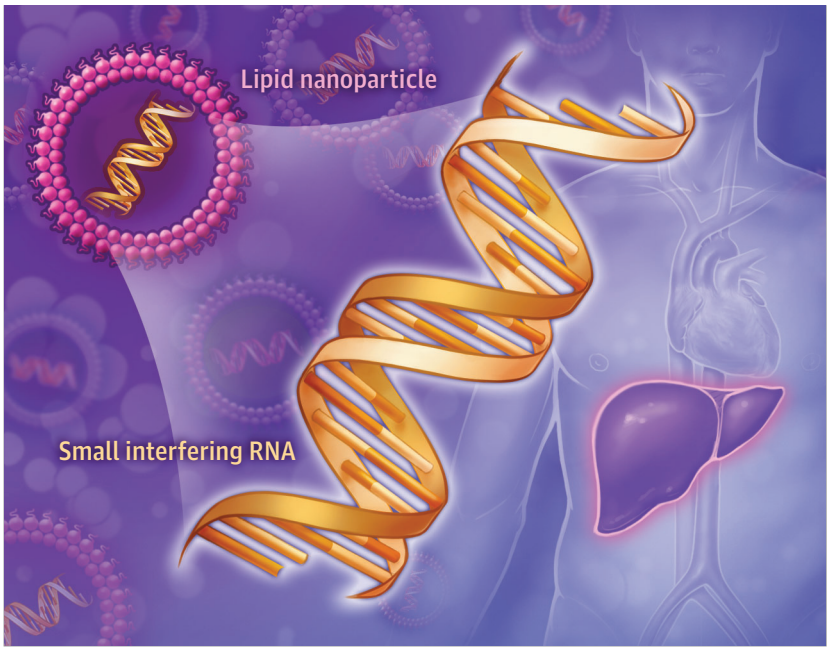
The hotly anticipated results from a major trial should help to resolve a common clinical question: should patients with significant but stable coronary artery disease begin treatment with medication and lifestyle changes alone or will undergoing an invasive procedure, like stent placement or bypass surgery, along with medical therapy produce better outcomes?

Starting with optimal medical therapy alone was just as effective as also undergoing cardiac catheterization and revascularization in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial. With 5179 participants in 37 countries, the National Heart, Lung, and Blood Institute–funded study is the largest head-to-head trial to compare an invasive or conservative strategy for patients with stable ischemic heart disease.

Over a median of 3.3 years, having an initial invasive procedure on top of optimal medical therapy did not reduce the risk of the primary end point—a composite of cardiovascular death, myocardial infarction (MI), resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure. The more aggressive approach also didn't cut down on a composite of cardiovascular deaths or MIs. The results were largely similar in a group of 777 patients with ischemia and advanced chronic kidney disease.

The procedures did, however, benefit patients with frequent angina. Those with daily, weekly, or monthly angina symptoms had significant, durable improvements in symptom control and quality of life not observed among those without the chest pain.

"Patients with angina have a choice," ISCHEMIA study chair Judith Hochman, MD, of NYU Langone Health, said in an email. "They can try more medication to see if their quality of life is as good as they want it to be. Or they can go right to an invasive procedure knowing that they will have a greater chance of having no angina a year out with the procedure."



Inclisiran is a small interfering RNA that blocks PCSK9 protein production in the liver, which decreases blood LDL-C levels.

The group randomized to conservative treatment underwent an invasive procedure if their symptoms worsened or if they had a heart attack. According to Hochman, about a fifth of this group ended up needing a stent implant or bypass surgery over the study period but waiting didn't affect their chance of survival.

"This was a blockbuster," conference chair Donald Lloyd-Jones, MD, ScM, a cardiologist at Northwestern Medicine in Chicago, said of the ISCHEMIA trial during an interview with *JAMA*. "Even though there was no clear winner, I think we're a lot smarter about how to present the options to our patients and help them understand what the pros and cons are."

A 5-year follow-up study will track patients' longer-term survival outcomes.

A Cholesterol-Lowering "Vaccine"

Most people with atherosclerotic cardiovascular disease (ASCVD) treated with statins don't achieve target low-density lipoprotein cholesterol (LDL-C) levels. To move the needle, expert groups now recommend the addition of daily ezetimibe or once- or twice-monthly injections of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for some patients. In addition, the US Food and Drug Administration in February approved the ATP-citrate lyase inhibitor bempedoic acid (Nexletol) as a daily pill to lower elevated LDL-C levels in those with maximally tolerated statin therapy.

The investigational agent inclisiran could soon be another option in the LDL-C–lowering toolkit, but one that's dosed much less frequently than these statin add-ons,

potentially boosting treatment adherence and outcomes.

At the conference, researchers announced results from the ORION-10 phase 3 trial testing twice-yearly clinician-administered inclisiran subcutaneous injections. The study included 1561 US patients with stable ASCVD and elevated LDL-C levels (110 mg/dL on average) despite maximally tolerated statin therapy. The participants received 300 mg of inclisiran sodium or placebo on days 1 and 90, and then at 6-month intervals over the next year.

At day 510, the drug had reduced LDL-C levels by 58% compared with placebo. Patients in both groups had comparable adverse events and similar elevations in serum creatinine and liver function tests.

Two other pivotal ORION studies also reported results last year. The international ORION-11 trial demonstrated similar results as ORION-10 among non-US patients. And ORION-9 showed inclisiran's LDL-C–lowering potential for people with familial hypercholesterolemia.

Inclisiran is the first investigational drug for cholesterol-lowering in a novel class of agents called small-interfering RNAs (siRNAs). The drug blocks PCSK9 protein production in the liver through RNA interference, which in turn tamps down LDL-C levels in the blood.

A follow-up of the ORION-1 phase 2 trial published last fall found that the drug's cholesterol reductions lasted at least a year for most patients. "In higher-risk patients, this may be a new arrow in the quiver to help lower LDL and reduce risk in the long-term," Lloyd-Jones said.

Many patients don't adhere to statin therapy, and a long-acting drug like inclisiran could help to address this. Lloyd-Jones cautioned that it's still an open question whether a drug that requires an office visit will increase adherence. "But it's fascinating that we can think about a 6-month vaccination, if you will, against LDL," he said.

The Medicines Company submitted inclisiran for US regulatory approval late last year. If approved, it could be the first siRNA on the market for a common condition and—depending on longer-term safety and effectiveness data—could open the door for more widely used gene-silencing therapies. Novartis, banking on the drug's success, acquired The Medicines Company in January for $9.7 billion.

A pooled analysis of ORION phase 3 studies showing potent and durable reductions in LDL-C levels was scheduled to be presented at the American College of Cardiology conference in March before the meeting was cancelled due to the coronavirus disease 2019 outbreak.

Meanwhile, siRNAs targeting other molecules in the lipid pathway, like apolipoprotein CIII and angiopoietin-like protein 3, are in early trials. "This is going to be a very hot area for therapeutics for the foreseeable future," Lloyd-Jones said.

Targeting Inflammation

Despite evidence that inflammation contributes to atherosclerosis, no medications targeting the process are approved for cardiovascular disease.

Investigators are therefore interested in repurposing existing drugs for the task. In the recent Colchicine Cardiovascular Outcomes Trial (COLCOT), the generic anti-inflammatory typically used for gout and pericarditis lowered the risk of ischemic cardiovascular events among patients with a recent heart attack.

The multicenter trial involved 4745 participants who had experienced an MI within the past 30 days and were randomized to receive daily low-dose (0.5 mg) oral colchicine or a placebo. Most of the patients underwent percutaneous coronary intervention after their heart attack and were taking dual antiplatelet therapy and statins.

Over a median follow-up of 22.6 months, 5.5% of patients in the colchicine group and 7.1% of patients in the placebo group met the criteria for the primary end point, a composite of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization. Although there were slightly more pneumonia cases in the intervention group, the drug was generally well-tolerated.

Reductions in angina hospitalizations and stroke—not MI or cardiovascular death—mainly drove the composite outcome. However, Lloyd-Jones said the study may have been too small to accurately capture the drug's effect on individual component end points.

In an editorial, L. Kristin Newby, MD, MHS, of the Duke University Medical Center in Durham, North Carolina, wrote that a modest benefit driven by hospitalization for angina "does not support the routine use of colchicine for secondary prevention without a better understanding of the absence of effect on death or myocardial infarction." Newby noted, however, that a recent meta-analysis of 4 randomized trials and 1 cohort study also suggested that colchicine may reduce stroke risks, which she said should be further investigated.

COLCOT is the latest trial to target inflammation in cardiovascular disease. In 2017, the Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) found a reduction in post-MI cardiovascular events among patients who received the drug. However, canakinumab, a costly monoclonal antibody for autoinflammatory conditions, also increased fatal infections in the study. A year later, in 2018, the generic anti-inflammatory methotrexate demonstrated no effect in the Cardiovascular Inflammation Reduction Trial (CIRT), leading researchers to stop the study early.

"At the end of the day, I think this is really intriguing," Lloyd-Jones said of the COLCOT results. "We've known inflammation is part of this process. We haven't really known how to treat that, or whether treating that above what we already have helps. This suggests it could help a little bit more with a drug that we're pretty comfortable using." He added that additional colchicine trials for cardiovascular disease are under way, which should flesh out the recent findings. ■

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