

ACC: PCSK9 Inhibitors May Halve Heart Event Risk

— Novel lipid-lowering drugs suggest big benefit in exploratory trial analyses.

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SAN DIEGO -- The dramatic LDL cholesterol-lowering impact of the novel PCSK9 inhibitors appeared to pay out in a big cardiovascular risk reduction, according to post hoc analyses, which offered an early look at what the big outcomes trials will show.

Both evolocumab (Repatha) and alirocumab (Praluent) showed about 50% relative reductions in composite cardiovascular events at 12 to 18 months versus controls in a range of patient populations.

For evolocumab, pooled analysis of the open-label OSLER-1 and -2 long-term

extension studies, pulling patients from 12 phase II and III clinical trials, showed a 0.95% 1-year rate of adjudicated cardiovascular events compared with 2.18% on standard therapy, [Marc S. Sabatine, MD, MPH](#), of Brigham and Women's Hospital in Boston, and colleagues found.

That translated to a hazard ratio of 0.47 (95% CI 0.28-0.78) in favor of the anti-PCSK9 monoclonal antibody for the composite of death, myocardial infarction (MI), unstable angina, coronary revascularization, stroke, transient ischemic attack, or heart failure.

For alirocumab, post hoc data from the ODYSSEY LONG TERM randomized trial showed a 1.7% rate of cardiovascular events compared with 3.3% on placebo over 78 weeks.

That translated to an HR of 0.52 (95% CI 0.31-0.90) favoring the PCSK9-targeted agent for coronary heart disease-related mortality, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

Both trials were reported online in the *New England Journal of Medicine*, simultaneous with presentation here at the [American College of Cardiology \(ACC\) annual meeting](#) for OSLER-1 and -2, but following [earlier presentation at the European Society of Cardiology meeting](#) for ODYSSEY LONG TERM.

Implications

The two analyses "whet our appetites for further results," [Neil J. Stone, MD](#), and [Donald M. Lloyd-Jones, MD](#), both of Northwestern University in Chicago, wrote in an accompanying editorial.

"With the potential for improved adherence and a greater reduction in LDL cholesterol levels, the data from larger, longer studies of PCSK9 inhibitors could be compelling; such trials are now ongoing," they noted.

"The data are very impressive," meeting cochair [Jeffrey T. Kuvin, MD](#), a general cardiologist at Tufts Medical Center in Boston, agreed in an interview.

He predicted that the findings would be replicated in the large outcomes trials: [FOURIER](#) adding evolocumab to statins for people with preexisting heart disease, and [ODYSSEY Outcomes](#) comparing alirocumab to placebo atop medical and lifestyle management after a recent acute coronary syndrome.

While it could be years before even preliminary outcomes are released from the trials, an FDA approval decision is expected by late July for alirocumab and late August for evolocumab, likely based on the available post-hoc data along with cholesterol and safety findings.

"What we see here this weekend puts these drugs on a solid footing for early approval," [Steven Nissen, MD](#), told *MedPage Today*. "[As tough a guy as I am](#), I wouldn't wait....This is probably the most important class of drugs we've seen in a decade."

The FDA would be taking little risk with early approval based on this promising but preliminary data because they at the very least rule out harm, said Nissen, chair of cardiovascular medicine at the Cleveland Clinic and past president of the ACC.

The benefits might even increase, based on greater relative reductions in subsequent years in prior statin trials, the editorialists noted.

"However, it would be premature to endorse these drugs for widespread use before the ongoing randomized trials, appropriately powered for primary endpoint analysis and safety assessment, are available," Stone and Lloyd-Jones cautioned.

The field has been burned before by reliance on surrogate endpoints that didn't turn out in outcomes trials, for example with niacin and torcetrapib, they

pointed out.

The PCSK9 monoclonal antibodies cut LDL levels by an average of roughly 61% to 62% compared with placebo or standard therapy, but guidelines emphasize "that while lower is better, it matters how you get there and whether the benefits outweigh the risks for that patient," the editorialists noted.

The Risks

ODYSSEY LONG TERM included 2,341 patients at high risk for cardiovascular events already on maximum-tolerated doses of statins who were randomized to double-blind treatment with alirocumab (150 mg administered subcutaneously every 2 weeks) or placebo for 78 weeks.

OSLER-1 and -2 included 4,465 patients at various degrees of cardiovascular risk randomized to open-label treatment with evolocumab (140 mg subcutaneously every 2 weeks or 420 mg monthly) added to standard therapy versus standard therapy alone over about 1 year of treatment.

Sabatine, chair of the Thrombolysis in Myocardial Infarction (TIMI) Study Group, noted the consistency of effects across the mortality, coronary, and cerebrovascular events and across major patient subgroups.

Much like the statins, a class effect is anticipated for the anti-PCSK9 drugs.

Though Sabatine cautioned that his group's analysis was exploratory with relatively few events, it "appeared to be safe and well-tolerated."

No adverse events increased in incidence the lower the LDL levels achieved, even at less than 25 mg/dL, he noted.

The FDA, though, has signaled that it will be [paying close attention to neurocognitive events](#) with the PCSK9 inhibitors.

In OSLER-1 and -2, the neurocognitive adverse event rate was 0.9% on evolocumab compared with 0.3% on standard care alone. There was no clear upward trend with lower and lower achieved LDL.

In ODYSSEY LONG TERM, the neurocognitive adverse event rate was 1.2% with alirocumab versus 0.5% in the control arm.

Neurocognitive effects have been anecdotally associated with statins, although meta-analyses have not confirmed any significant signal, said [Anthony DeMaria, MD](#), of the University of California San Diego.

"If I'm going to have an adverse event, a neurocognitive event is the last one I want to have," he said in an interview monitored by ACC media relations.

However, he predicted that the rate was low enough not to block approval or to turn physicians or younger patients away from the drug.

"We badly need something for people who are statin intolerant," DeMaria said. "Given these data we have right now, if I have someone in the 40- to 60-age group with a high LDL who is statin intolerant, yes, I would use this drug."

"It's pretty rare," Nissen agreed. "It shouldn't be trivialized, but it's not a show stopper."

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Sabatine disclosed relevant relationships with Abbott Laboratories, Accumetrics, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, Nanosphere, Roche Diagnostics, Takeda, Gilead, Amgen, AstraZeneca.

Bristol-Myers Squibb, GlaxoSmithKline, Intarcia, Merck, sanofi-aventis, Cubist, MyoKardia, Pfizer, Quest Diagnostics, Vertex, Zeus Scientific, and CVS Caremark.

Robinson disclosed relevant relationships with Sanofi, Amarin, AstraZeneca, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Takeda/Zinfandel, Amgen, Merck, Regeneron/Sanofi, and Genentech/Roche.

Kuvin, Stone, and Lloyd-Jones disclosed no relevant relationships with industry.

Reviewed by [Robert Jasmer, MD Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner](#)

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New England Journal of Medicine

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New England Journal of Medicine

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New England Journal of Medicine

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