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FDA Expands Bempedoic Acid Label to Include Primary, Secondary CV Risk Reduction, With or Without Statins

By **Grace Halsey**

The FDA on March 22, 2024, approved broad label expansions for bempedoic acid (Nexletol) and bempedoic acid with ezetimibe (Nexlizet) tablets to include indications for expanded LDL-C lowering in primary and secondary prevention of cardiovascular (CV) risk, according to a news release from manufacturer Esperion Therapeutics. The expanded indications support the use of bempedoic acid alone or in combination with ezetimibe as monotherapy or with statin drugs; they include an indication for treatment of primary hyperlipidemia alone or in addition

to statin therapy.

With these expanded indications, the agents, taken orally and once daily, become the only LDL-C-lowering nonstatins indicated for primary CV disease (CVD) prevention, the company said. According to Esperion, the label expands the potential patient population for the nonstatin agents to approximately 70 million US adults with or at risk for CVD linked to hyperlipidemia.

“These approvals expand the accessibility of our highly effective drugs to primary prevention patients,” Sheldon Koenig, president and chief executive

officer of Esperion Therapeutics, said in a news release. “These approvals also eliminate the statin use requirement, allowing patients to take Nexletol or Nexlizet either with or without a statin, which significantly reduces previously existing prescribing limitations. We are confident these approvals position Nexletol and Nexlizet as the nonstatins of first choice within the cardiovascular risk reduction treatment paradigm.”

The widely anticipated—and expected—CV risk reduction indications are based on findings from the phase 3 CLEAR Outcomes clinical trial (NCT02993406) that

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assessed the effects of bempedoic acid on CV outcomes in a cohort of 14,000 participants with or at high risk of CVD who were statin intolerant or unwilling to take the medications. Participants were followed for a median of 3.4 years. Investigators reported in *The New England Journal of Medicine* that bempedoic acid–treated participants experienced relative risk reduction as follows:

- **15% for major adverse cardiovascular event (MACE)–3 (death from CV cause, nonfatal stroke, or nonfatal myocardial infarction [MI])**
- **27% for nonfatal MI**
- **19% for coronary revascularization**
- **39% for MACE-3 in primary prevention participants**

Researchers also reported 20% reductions in LDL-C and 22% reductions in high-sensitivity C-reactive protein; further, no elevation of glucose was observed in participants who received bempedoic acid compared to those who received placebo, Esperion stated.

Results of a prespecified analysis of CLEAR Outcomes published in January 2024 that assessed the impact of bempedoic acid vs placebo on the total incidence of CV events during the study

showed treatment with the drug was associated with relative risk reductions of 20% for 4-point MACE, 17% for 3-point MACE, 31% for MI, and 22% for coronary revascularization.

“Nexletol and Nexlizet are once-daily, accessible, oral medications that reduce LDL-C and cardiovascular risk, but without the

adverse effects most common to statins. Nexletol and Nexlizet are also the first oral nonstatin LDL-C-lowering drugs to be approved by the FDA to reduce the risk of CV events in both primary and secondary prevention patients. We believe this significantly differentiated profile is a game changer for patients and health care providers alike,” Koenig said.

Brief History

The FDA approved bempedoic acid in February 2020 as an add-on therapy to maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease. At the time, the label also stated that

the effect of bempedoic acid on CV morbidity and mortality had not been determined. The first label expansion in December 2023 updated the indication to include treatment of primary hyperlipi-



demia in eligible individuals as a qualifier for existing approved populations. Importantly, language was removed from the label that stipulated maximally tolerated statin therapy as prerequisite for treatment with bempedoic acid as was the limitation of use that stated the undetermined effect on CV morbidity and mortality.

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U.S. FDA approves broad new labels for Nexletol and Nexlizet to prevent heart attacks and cardiovascular procedures in both primary and secondary prevention patients, regardless of statin use. News release. Esperion Therapeutics. March 22, 2024. Accessed March 24, 2024. <https://www.esperion.com/news-releases/news-release-details/us-fda-approves-broad-new-labels-nexletolr-and-nexlizetr-prevent>

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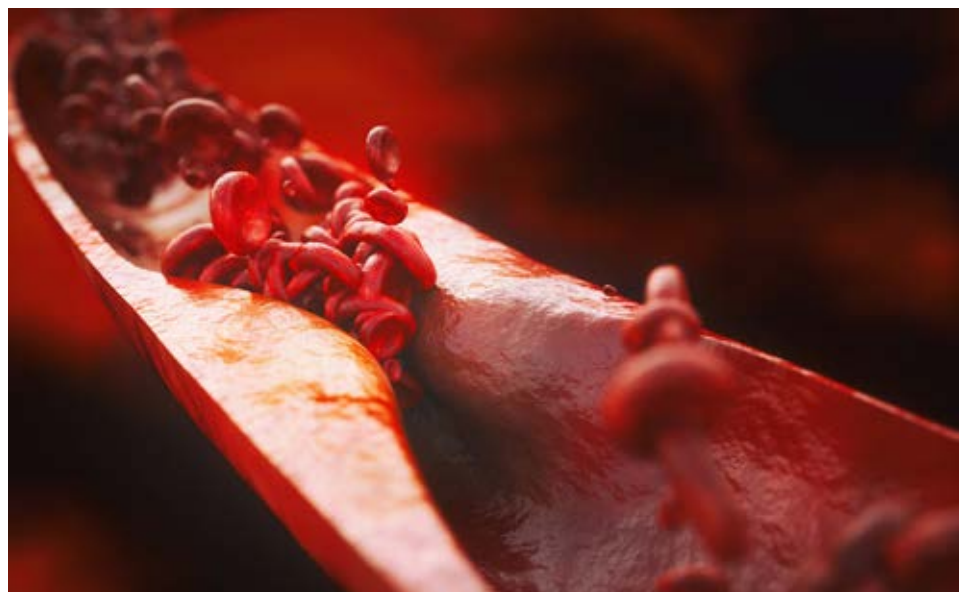
“Inclisiran First” Strategy Leads to 60% Reduction in LDL-C vs 7% for Usual Care: VICTORION-INITIATE Findings

By **Grace Halsey**

A pragmatic study that used an “inclisiran first” strategy for the treatment of adults with atherosclerotic cardiovascular disease (ASCVD) not at the low-density lipoprotein cholesterol (LDL-C) goal despite maximally tolerated statin therapy found that immediate addition of inclisiran led to a 60% reduction in LDL-C from study baseline to day 330 vs a reduction of 7% observed among study participants treated with usual care.

These findings from the phase 3 VICTORION-INITIATE randomized trial (NCT04929249) were announced at a late-breaking clinical trial session at the American College of Cardiology 73rd Annual Scientific Session and Expo on April 6, 2024, in Atlanta, Georgia. Lead and presenting author Michael Koren, MD, the CEO of ENCORE Research Group in Jacksonville, Florida, also reported that study participants in the inclisiran first group were 4 to 8 times more likely to reach guideline-recommended LDL-C targets at the end of the study than those treated with usual care.

“What we were asking in this study was how can we do better in treating cholesterol issues in people that have cardiovascular disease?” Koren said in an interview with *Patient Care*. “The sad reality



is that only 2% of our patients who have cardiovascular disease actually get to their LDL goals.” The reasons, according to Koren and colleagues, are many and include nonadherence to medication, clinical inertia, and poor access to therapy. Inclisiran, a small-interfering RNA molecule, is dosed twice yearly and has been shown to reduce LDL-C by approximately an additional 50% when added to background lipid-lowering therapy. The “simplified” semiannual treatment implementation may also support reaching LDL-C goals, the authors wrote in the study abstract.

VICTORION-INITIATE was a phase 3b prospective, randomized, open-label trial to evaluate the effect of treatment with twice-yearly inclisiran on lowering LDL-C in addition to usual care, compared to usual care alone—usual care being defined as any lipid-lowering therapy prescribed or titrated at a treating physician’s discretion. Participants had prior ASCVD and LDL-C of 70 mg/dL or greater on maximal statin therapy or were statin intolerant. They were randomly assigned 1:1 to inclisiran 284 mg on study days 0, 90, and 270 plus usual care or usual care alone. The study’s primary

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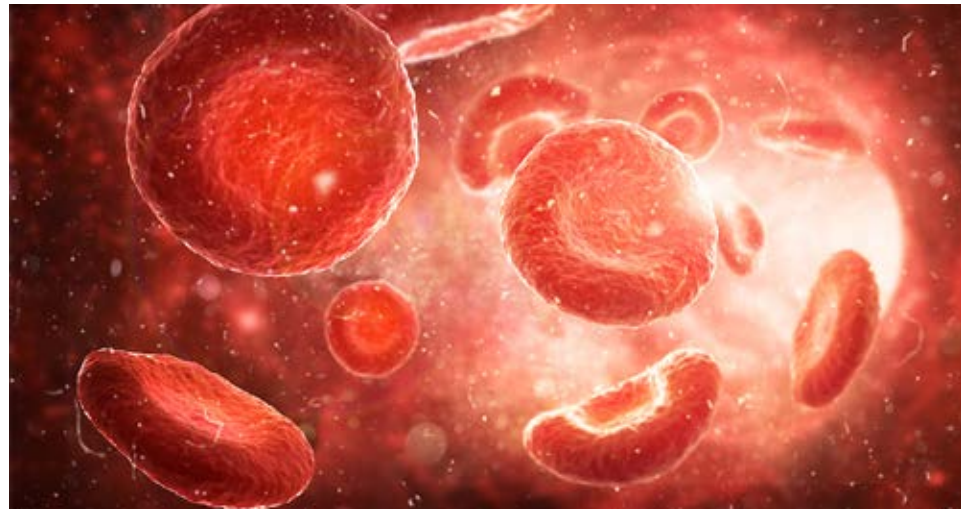
end points were change in LDL-C from baseline to day 330 and statin discontinuation, defined as no statin use for 30 days or more before the end of the study (noninferiority margin of 15%).

The study cohort numbered 450 participants with a median age of 67 years; 30.9% were women, 12.4% were Black, and 15.3% were Hispanic. Prior or current ASCVD included coronary heart disease reported by 91.8%, cerebrovascular disease by 18.2%, and peripheral artery disease by 14.7%.

Results

Koren and colleagues reported that the strategy of initiating inclisiran immediately when statin therapy alone is inadequate to reach LDL-C targets led to a significantly greater mean LDL-C reduction from baseline to day 330 than a usual care approach ($P < .001$). VICTORION-INITIATE was an open-label study, Koren said in the interview. “So even though we [randomly assigned] patients to reduce any selection biases, we actually wanted to observe the effect of bias in the system; we wanted to see whether or not this structured approach of implementing this product would make a difference in terms of people getting to their goals.” He added that when there is a plan “to get a very effective therapy to patients sooner in the pathway, it makes a huge difference in the first year.”

Speaking about the second primary end point—statin discontinuation—Koren said the findings were different than anticipated “but really fascinating.” Investigators had thought that if someone is taking a highly effective new drug, the inclination might be to stop taking their statin medication. What they found was an opposite effect. There was no statistical difference between the proportion of participants in either group that discontinued statin



“Even though we [randomly assigned] patients to reduce any selection biases, we actually wanted to observe the effect of bias in the system; we wanted to see whether or not this structured approach of implementing this product would make a difference in terms of people getting to their goals.”

therapy 30 days or more before the end of the study period. However, Koren explained, “numerically more people in the usual care arm stopped their statins than in the inclisiran group. The actual numbers were that in the usual care arm, 16.7% of all participants who were on statins at the start stopped them. In the inclisiran first arm, just 6% stopped their statins.” That was surprising, he said.

The effects of the clinical trial structure likely led to better adherence than is typically seen in the real world, Koren observed. “I think if it weren’t a clinical trial, the dropout rate would be more than 16.7% in the usual care group. I think [it is] just an unfortunate reality of what happens in our usual clinical care settings.”

According to the study abstract, treatment-emergent adverse event (TEAE) and serious TEAE rates

were similar for inclisiran first (62.8% and 11.5%, respectively) and usual care (53.7% and 13.4%). TEAEs leading to study drug withdrawal occurred in 6 (2.6%) and 0 patients for inclisiran first and usual care, respectively.

“What we’re finding here is that instead of just trusting ‘usual care,’ we should be putting systems in place that structure our approach” to lowering LDL-C, so people are treated more aggressively, earlier in the process,” Koren said. “And that’s the key take-home message for clinicians.”

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Comparison of an “inclisiran first” strategy with usual care in patients with atherosclerotic cardiovascular disease: results from the VICTORION-INITIATE randomized trial. Abstract presented at: American College of Cardiology 73rd Annual Scientific Session and Expo; April 6-8, 2024; Atlanta, GA.

CV Risk Prevention Profiles Significantly Worse Following Stroke vs MI in 2 Large National Cohorts

By **Grace Halsey**

Among individuals with prior stroke, new research identified significant deficiencies in risk factor control compared with individuals with previous myocardial infarction (MI). Those with prior stroke were far less likely to have met targets for low-density lipoprotein cholesterol (LDL-C) and blood pressure, among other vascular measures, and were less adherent to guideline-directed therapies, including statin and antiplatelet drugs. The analysis, which drew on data from large national databases in the US and the UK, found that race and ethnicity and neighborhood deprivation levels were significantly associated with the odds of having a favorable cardiovascular (CV) risk prevention score.

“There are significant public health implications for the inadequate management and control of vascular risk in stroke survivors and a missed opportunity for individual patients,” study authors wrote in the *Journal of the American Heart Association*. The findings underscore significant gaps in secondary prevention for stroke survivors, they continued. “Furthermore, we must understand the root causes that explain diminished use of secondary prevention strategies in stroke survivors compared with those with MI.”

Senior author Kevin N. Sheth, MD, and colleagues point to the

increasing prevalence of stroke and thus of survivors requiring effective secondary prevention strategies, but also to limited knowledge of how widely and consistently those interventions are in use, particularly compared with aftercare for “other large populations who carry similar vascular risk.” Given the similar CV risk profiles between individuals with a history of stroke and one of MI, the secondary preventive care should ideally be similar, they wrote.

Sheth, a professor of neurology and neurosurgery at Yale School of Medicine in New Haven, Connecticut, and director of the Yale Center for Brain and Mind Health, and fellow researchers set out to compare the quality of that care among participants in 2 large national cohorts—the UK Biobank and the US All of Us (AoU) Research Program. From the UK Biobank, they identified 14,760 adults (mean age, 61.2 years; 62% men) with a history of either stroke (5567) or MI (9193), and from the AoU, 7315 adults (mean age, 64.24 years; 49.2% men) with history of stroke (2948) or MI (4367).

For the study outcomes of interest, the researchers evaluated 4 variables related to adherence to CV risk prevention guidelines: LDL control (<100 mg/dL), blood pressure control (<140/90 mm Hg), statin use, and antiplatelet use. A fifth, an overall CV prevention score (CPS), was a composite of the 4 other variables. A binary metric, the CPS categorized individuals

who met standards for 3 or 4 CV risk prevention variables as having “good” CPS and those who met fewer than 3 as having “insufficient” prevention profiles. Sheth et al used tertiles of the Deprivation Index to create categories of neighborhood deprivation to assess the potential effect on CPS and separately analyzed the effects of age, sex, race, and ethnicity.

Findings: UK Biobank

Overall, after adjusting for covariates, UK Biobank participants with a history of stroke had 58% lower odds of having all risk factors at target control levels compared with those who had a history of MI (OR, 0.42; 95% CI, 0.39-0.45; $P < .001$). History of stroke was also consistently associated with reduced odds of meeting criteria for all 4 preventive variables. After adjustment for age, sex, and race/ethnicity differences, stroke history vs MI history was linked to the following:

27% lower odds of having LDL-C levels controlled (OR, 0.73; 95% CI, 0.68-0.78; $P < .001$)

37% lower odds of blood pressure control (OR, 0.63; 95% CI, 0.59-0.68; $P < .001$)

55% lower odds of being on a statin medication (OR, 0.45; 95% CI, 0.42-0.48; $P < .001$)

72% lower odds of being on an antiplatelet medication (when also considering anticoagulant use) (OR, 0.28; 95% CI, 0.26-0.31; $P < .001$)

“There are significant public health implications for the inadequate management and control of vascular risk in stroke survivors and a missed opportunity for individual patients. Furthermore, we must understand the root causes that explain diminished use of secondary prevention strategies in stroke survivors compared with those with MI.”

All of Us

Analysis of data from the AoU cohort returned similar patterns, with participants with a history of stroke being overall 43% less likely to have good control across all 4 CV risk prevention variables than peers with a history of MI after adjusting for covariates (OR, 0.57; 95% CI, 0.50-0.65; $P < .001$; $P < .05$ for all individual variables).

According to the results, subgroup analyses in the more diverse AoU cohort revealed significant racial and ethnic disparities in risk factor control. White participants with MI had higher rates of control vs Black participants with MI (65% vs 43%), but for those with stroke, the difference was much less, at 47% vs 45%, respectively.

The researchers also found a more pronounced difference in odds of achieving a favorable CV risk prevention score between White participants with stroke vs MI (49%; OR, 0.51; 95% CI, 0.45-0.58; $P < .001$) compared with Black participants with stroke vs MI (28%; OR, 0.72; 95% CI, 0.59-0.88; $P < .001$).

Using the Deprivation Index, the researchers compared composite CV risk prevention scores based on participants' neighborhood deprivation level, which was based on mean income and the prevalence of vacant housing, poverty, high school education, health insurance coverage, and assisted income.

Overall, researchers found that neighborhood deprivation “was suggestive of having an influence” on the likelihood of having good composite CPS for participants with stroke vs MI. Specifically, in privileged neighborhoods, those with a history of stroke had 56% (OR, 0.44; 95% CI, 0.36-0.53; $P < .001$) reduced odds of achieving favorable CPS vs those with MI, whereas in deprived neighborhoods the odds were reduced by 36% (OR, 0.64; 95% CI, 0.53-0.77; $P < .001$).

“In summary, our study, using 2 large and diverse data sets, highlights a clear discrepancy in care between patients with stroke and MI, observed consistently in populations from both the United Kingdom and the United States, across several races, ethnicities, and deprivation levels,” Sheth et al wrote. “This disparity in care, as evidenced by our findings, suggests fundamental differences in the care systems for these 2 conditions.”

“There may be opportunities to understand facilitating elements that are helpful for survivors of myocardial infarction that may not be present for stroke survivors,” they concluded.

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