Statin Cuts Cardiovascular Risk for People With HIV

REPRIEVE trial finds pitavastatin reduced the risk for heart attack, stroke and other major cardiovascular events by 35%.

July 24, 2023 By Liz Highleyman

People with HIV who are at low to moderate risk for cardiovascular disease can reduce their risk even further by taking a daily statin medication, according to a large international study presented at the International AIDS Society Conference on HIV Science (#IAS2023) in Brisbane, Australia.

As previously reported, the REPRIEVE trial was halted ahead of schedule in April after an interim analysis found that pitavastatin already showed a significant benefit. Detailed results were presented by Steven Grinspoon, MD, of Massachusetts General Hospital, and published simultaneously in The New England Journal of Medicine.

Based on these findings, "We would highly recommend that guidelines be changed," Grinspoon said. "Pitavastatin is effective, prevents major adverse cardiovascular events and will save lives."

> Statin therapy with lifestyle counselling should be considered for people living with #HIV, even for those with low-moderate risk, to reduce major cardiovascular events and death. - @MassGeneralNews Steven Grinspoon ???????? #IAS2023 #REPRIEVE pic.twitter.com/viPwNqK0VL
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> — IAS - the International AIDS Society (@iasociety) July 24, 2023

As people with HIV live longer thanks to effective antiretroviral treatment, cardiovascular disease (CVD) has become a leading cause of illness and death. A growing body of research shows that HIV-positive people are at greater risk for CVD than their HIV-negative peers. “Many large epidemiological studies have suggested up to a twofold increase,” according to Grinspoon. What’s more, people with HIV have excess plaque buildup in their arteries and experience ensuing complications at a younger age. Reasons for the disparity may include chronic inflammation, adverse effects of antiretroviral drugs and higher rates of traditional risk factors, such as smoking. “Residual immune activation persists even with good viral suppression, and antiretroviral therapy alone is not sufficient to prevent cardiovascular disease,” he said.

In addition to bringing down low-density lipoprotein (LDL, or “bad cholesterol”) levels, statins have other effects, including reducing inflammation and thrombosis, improving blood vessel function and stabilizing plaque. Thus, they could potentially address both traditional and nontraditional CVD risk factors. While these medications have been shown to lower the risk for cardiovascular events and death in the general population, their benefits for people living with HIV have been unclear until now.

“People with HIV are twice as likely to develop cardiovascular disease, and therefore [the REPRIEVE findings] could have very significant real-world impact,” said IAS president and conference cochair Sharon Lewin, MD, PhD, of the University of Melbourne at an advance media briefing.

REPRIEVE Results

REPRIEVE (NCT02344290), sponsored by the National Institutes of Health, began enrollment in 2015. The Phase III study was conducted at more than 100 sites in 12 countries in North and South America, Europe, Africa and Asia. It enrolled 7,769 HIV-positive people ages 40 to 75; the median age was 50. Nearly one third were women, 41% were Black, 35% were white and 15% were Asian.

In an editorial accompanying the REPRIEVE report, Matthew Freiberg, MD, of Vanderbilt University Medical Center, praised the study team for attempting to enroll participants who have often been excluded from clinical trials, such as those with hepatitis C or mental health conditions and those who use alcohol or drugs.

The study participants were on stable antiretroviral therapy, and most (88%) had an undetectable viral load; half had been on antiretrovirals for 10 years or longer. The median CD4 T-cell count at baseline was 621, but about half had previously fallen below 200, the threshold for an AIDS diagnosis.

The participants had no prior history of atherosclerotic cardiovascular disease and had not previously taken statins. They had demographics, comorbidities and laboratory values reflecting low to moderate cardiovascular risk, with a median 10-year CVD risk score of 4.5%. The median baseline LDL level was 108 milligrams/deciliter, or slightly elevated.

“We targeted a group that would not ordinarily have been prescribed a statin, or any therapy, who

would have been simply told to go home," Grinspoon said at the briefing. The U.S. Preventive Service Task Force recommends statins for HIV-negative adults with one or more cardiovascular risk factors and a 10-year CVD risk score of 10% or greater. But scoring systems developed for the general population tend to underestimate the risk for people living with HIV.

REPRIEVE participants were randomly assigned to receive oral pitavastatin (brand name Livalo) at a dose of 4 mg once daily or a placebo. Pitavastatin was chosen because it is a moderate-intensity statin with anti-inflammatory properties that is well tolerated and has few interactions with antiretrovirals.

The trial's composite primary endpoint was major adverse cardiovascular events, including myocardial infarction (heart attack), stroke and transient ischemic attack, unstable angina (chest pains), peripheral artery disease, revascularization procedures (such as stents or coronary bypass surgery), CVD-related death and death from an undetermined cause.

Over about five years of follow-up, adherence was very good to excellent, Grinspoon reported. LDL cholesterol levels, which were similar at baseline, decreased by 30% in the pitavastatin arm while remaining the same in the placebo arm; this effect was durable over time.

Major CVD event rates were 4.8 and 7.3 per 1,000 person-years, respectively, in the pitavastatin and placebo groups. That is, the rate of major cardiovascular events was 35% lower in the pitavastatin arm. The risk reduction was similar for heart attacks and strokes. Furthermore, the risk for CVD events or death from any cause was 21% lower with pitavastatin (9.2 versus 11.6 per 1,000 person-years, respectively). The risk reduction was similar for heart attacks and strokes.

In comparison, CVD risk fell by 44% in the JUPITER trial, a primary prevention study of rosuvastatin (Crestor) that enrolled an older, higher-risk HIV-negative population. Grinspoon said that the REPRIEVE team had expected about a 30% reduction for lower-risk people with HIV, which the study exceeded. Lowering LDL alone would have been expected to reduce CVD risk by 17%, he said.

The overall number needed to treat (NNT), or the number of people who would have to take pitavastatin for five years to prevent one major cardiovascular event, was 106. But for people with low to moderate CVD risk, the NNT was 53—similar to that seen in JUPITER. For those with a higher risk score (greater than 10%), the NNT fell to 35.

The size of the effect was "very consistent" for men and women across racial/ethnic groups and across most regions, Grinspoon noted. It was also comparable across CD4 counts and for the small proportion of people with a detectable viral load. What's more, the effect was similar for people with high or low LDL at baseline, indicating that the benefits of pitavastatin go beyond just lowering cholesterol.

"Ongoing research about how statin therapy may affect inflammation and increased immune activation among people with HIV may help us better understand the additional benefits we're seeing with this treatment approach," Grinspoon said in an NIH press release.

Pitavastatin was generally safe and well tolerated with no unanticipated safety concerns. Serious adverse events were uncommon and occurred with similar frequency (about 4%) in the pitavastatin and placebo groups; 2% and 1%, respectively, withdrew due to adverse events. There were more cases of diabetes in the pitavastatin group—as seen in most statin studies—but the rates were low (about 5% versus 4%), and glucose levels remained stable in both groups. Muscle-related side effects were also uncommon (about 2% versus 1%) and mostly mild. Only three people taking pitavastatin and four in the placebo group developed rhabdomyolysis, or severe muscle damage.

Study Implications

"This research suggests that statins may provide an accessible, cost-effective measure to improve the cardiovascular health and quality of life for people living with HIV," Gary Gibbons, MD, director of the National Heart, Lung, and Blood Institute, said in the NIH press release. "Additional research can further expand on this effect, while providing a road map to rapidly translate research findings into clinical practice."

In addition to assessing major cardiovascular events, REPRIEVE also included a variety of substudies and smaller cohorts established to shed more light on CVD manifestations and progression among people living with HIV. Prior to the main results, for example, the study found that participants had high rates of atherosclerosis and inflammation and were more likely than HIV-negative people to have abnormal heart rhythms. The researchers continue to analyze biomarkers and other outcomes in an effort to better understand the primary results.

At the same conference session, a panel of experts discussed unique aspects of CVD among women living with HIV, how the REPRIEVE findings might influence clinical practice and whether a single prevention strategy would be appropriate in high- and low-income countries.

Markella Zanni, MD, of Massachusetts General Hospital, noted that among women living with HIV, traditional metabolic factors, immune factors and accelerated reproductive aging all likely contribute to increased CVD risk. In a subset of REPRIEVE participants in the United States, women had higher levels of inflammatory biomarkers but less coronary artery plaque than men. What's more, standard CVD risk scores appear to underestimate risk to a greater extent for HIV-positive women compared with men.

In a global overview, Gerald Bloomfield, MD, MPH, of Duke University, noted that the burden of CVD and related disability attributable to HIV is increasing worldwide, but "is not experienced equitably," with a faster rise in low- and middle-income countries.

In sub-Saharan Africa, the region with the highest burden of HIV, noncommunicable disease (NCD) prevalence is rising rapidly, and in other regions, cardiovascular disease accounts for the majority of NCD deaths, according to Rosie Mngqibisa, MD, of the Enhancing Care Foundation in South Africa. "Let's go back to the drawing board and see how best we can incorporate [the REPRIEVE findings] into a bag of preventative strategies that are already there," she said. "We have to decide whether…to scale up the addition of statins onto what we have, or we wait until later when

we have to treat people with cardiovascular disease."

Beatriz Grinsztejn, MD, PhD, of Fundação Oswaldo Cruz in Rio de Janeiro, raised a concern about CVD and statin use among transgender women who take hormone therapy. REPRIEVE enrolled 127 participants (2%) who identify as transgender, but this number was too small to draw meaningful conclusions.

Although HIV is a known risk factor for CVD, doctors haven't known what to do with that information, and some were hesitant to prescribe statins for HIV-positive people with low to moderate CVD risk because there were no data showing they would be effective, according to Grinspoon. But now, he said, "our data in low to moderate risk groups suggest that the guidelines should be amended to recommend that HIV patients, because they have this excess risk, [should] be offered statin therapy."

Pitavastatin is now available in many countries and will be more broadly available once it goes off patent, likely in early 2024. Statins "are not fancy drugs," Grinspoon said. "These drugs are really cheap when off patent," which will potentially make them equitably accessible. Grinspoon and Anton Pozniak, MD, of Chelsea and Westminster Hospital, agreed that if pitavastatin is not available, it would be reasonable to offer another safe statin.

The panelists also raised questions about who will manage CVD prevention and statin prescribing, as leaving it to HIV and infectious disease specialists rather than primary care providers could limit access. "It would be great if it could be included in the primary care package," Grinsztejn said.

Statin use should be part of a broader CVD prevention plan that emphasizes a heart-healthy lifestyle, according to Grinspoon. "Patients get older every year, and prevention is cheaper than treatment," he said.

The REPRIEVE findings underscore the need for better risk-prediction tools specific to people living with HIV. "Predicting cardiovascular disease risk accurately is the first step to initiating appropriate primary prevention for those at elevated risk," Bloomfield said.

In conclusion, said Laura Waters, MD, of Mortimer Market Centre in London, "I think we'll look back on Brisbane 2023 as the conference at which we saw some truly guideline-changing data."

"We have to grasp this moment," Pozniak added. "We have to change the way we practice hand in hand with the community and get that message out there so that we can improve the lives of persons living with HIV."

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