

Critical appraisal of laropiprant and extended-release niacin combination in the management of mixed dyslipidemias and primary hypercholesterolemia

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Abstract: Niacin is a B-complex vitamin which has been used for decades for the management of mixed dyslipidemias and primary hypercholesterolemia. It decreases the risk of cardiovascular events either when used as a monotherapy or in combination with other lipid lowering medications. However, a major limitation to its use is niacin-induced flushing occurring even with the extended-release formulations. Laropiprant, a selective prostaglandin-2 receptor inhibitor, specifically targets the cascade of events causing the flushing. It has been recently used in combination with extended-release niacin. This article will review the early experience with this combination with focus on efficacy, safety, tolerability and current place in therapy. Early data are promising and suggest that more patients in clinical practice will benefit from niacin combined with laropiprant. Ongoing clinical trials will provide a better insight on the long-term safety of the drug and its efficacy for reducing cardiovascular events.

Keywords: niacin, laropiprant, dyslipidemias, hypercholesterolemia

Introduction

The management of mixed dyslipidemias and primary hypercholesterolemia is a cornerstone in the management of patients with coronary artery disease (CAD).¹ It is well known that elevated levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG) are risk factors for the formation and progression of coronary plaques (2, 3). Among lipid-altering therapies, lowering LDL-C cholesterol with statins remains the most commonly used strategy in clinical practice.⁴⁻⁶ It has been shown to decrease the incidence of major cardiovascular events by 25% to 35%. While intensive LDL-C lowering may result in further benefit, it is likely that even greater prevention of cardiovascular events will be achieved by also aiming to raise HDL-C and lower TG.

Considerable evidence suggests that even minor improvements in HDL-C levels may have a benefit on CAD risk. A meta-analysis by Gordon et al⁷ demonstrated that an increase of 1 mg/dL in HDL-C levels is associated with reduction in CAD risk by 2% in men and 3% in women. This potentially beneficial effect of HDL-C on reduction of CAD risk relates to its major role in cholesterol transport from tissues to the liver, as well as potential anti-inflammatory, antithrombotic and antioxidative effects.⁸

Lowering TG levels may also reduce CAD risk.⁹⁻¹² In an analysis of the Copenhagen Male Study,⁹ 2906 men free of cardiovascular disease were followed for 8 years.

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An elevated fasting TG level was found to be a strong risk factor for ischemic heart disease, independent of known major cardiovascular risk factors, including low HDL-C. Similar observations were also reported from the Prospective Cardiovascular Munster (PROCAM) study,¹⁰ which followed 4849 men for up to 8 years. The association between high TG levels and CAD risk may be related to the presence of atherogenic TG-rich particles in the plasma or associated prothrombotic state.^{8,10,11} Conservative measures such as lifestyle changes may lower TG levels but medical therapy is to be considered when these measures fail to achieve recommended therapeutic targets. Lipid-lowering guidelines currently recommend specific targeting of LDL-C with mild hypertriglyceridemia, with a greater focus on TG-lowering therapies when levels are more severely elevated.

A strategy targeting multiple lipid parameters will potentially have the greatest benefit on CAD. This supports a joint statement from the American Diabetes Association (ADA) and American College of Cardiology (ACC) recommending multiple risk factor modifications in the management of CAD.¹ This management often requires the prescription of multiple drugs and relies to a major degree on patient's adherence. The best treatment is one that is efficacious, safe, simple to use and is well tolerated by patients. This has led to an increased use of combination products in clinical practice to achieve better therapeutic outcomes.

Niacin is a water soluble vitamin which has been used for decades for the management of dyslipidemias,¹³ either alone or in combination with other agents. It has been shown to be efficacious for the reduction of cardiovascular events in clinical trials.^{14–21} At therapeutic doses of 1500 to 2000 mg/day, niacin is efficacious for reducing LDL-C, TG and non-HDL-C cholesterol, while increasing HDL-C.²² Accordingly, niacin has the most potent HDL-C raising therapy among currently used lipid-modifying therapies. Furthermore, niacin is the only lipid-modifying therapy with a beneficial effect on levels of lipoprotein (a). However, given that flushing is commonly experienced at such doses, compliance is limited with traditional preparations. As a result, there has been considerable interest in developing niacin preparations that limit flushing, and therefore enable more patients to tolerate therapeutically effective doses. Laropiprant, is a prostaglandin receptor inhibitor, has been used to reduce niacin-induced flushing and recently has been used in a combination pill with extended-release niacin (ERN).

In this article, we will review the early experience with laropiprant and ERN, rationale for combination, efficacy and

safety studies, patient's adherence and the current place in therapy of this novel agent.

Niacin for the management of coronary disease

Pharmacology, mode of action, lipid and nonlipid effects of niacin

Niacin is an essential component of coenzymes required for tissue respiration. As a lipid-altering therapy, its main effect is thought to involve inhibition of hepatic synthesis of VLDL-C and its metabolite LDL-C.²³ It is likely to raise HDL-C levels by reducing lipid transfer of cholesterol from HDL-C to VLDL-C and by delaying HDL-C clearance,^{23,24} although its effects on apolipoprotein A-I metabolism remains to be completely elucidated. The HDL-C raising properties of niacin are usually seen with doses as low as 1000 to 1500 mg/day,²⁵ however, at doses of 1500–2000 mg/day, it also has additional improvements in lipid profiles,^{23,24} reducing LDL-C, VLDL-C, non-HDL-C, TG, and lipoprotein (a).²⁶

The favorable effects of niacin on coronary plaques may be also exerted through its effects on nonlipid parameters as it reduces plasma fibrinogen levels,²⁷ plasminogen activator inhibitor-1, monocyte chemotactic protein-1, vascular cell adhesion molecule-1, and increases adiponectin and has antioxidative and anti-inflammatory vascular effects.^{26,28} It may also reduce blood pressure contributing to the overall risk reduction in CAD.^{29,30}

It is therefore not surprising that combination regimens including niacin have consistently been found to have a beneficial impact on progression of carotid intima-media thickness^{31,32} and coronary plaques.³³

Efficacy studies: niacin and cardiovascular risk

The role of niacin in reduction of cardiovascular risk is well established.^{14,15,20} The Coronary Drug Project was among the first trials to assess the cardiovascular benefits of niacin. This 1960s' trial was placebo-controlled in which the use of niacin was associated with reduction in nonfatal myocardial infarction and death²¹ on both short-term and long-term follow-ups.¹⁶ The Cholesterol-Lowering Atherosclerosis Studies (CLAS I and II) and Familial Atherosclerosis Treatment Study (FATS) showed either angiographic regression or slow progression of coronary plaques on high dose (4300 mg/day) niacin co-administered with colestipol.^{17,34} The observation that there is typically substantial plaque regression underlying the finding of regression on an angiogram further highlights

the benefits of niacin on arterial wall pathology. Similar observations were also made in the Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) study, in which the addition of ERN on an ongoing statin treatment slowed the progression of atherosclerosis at 12 and 24 months.^{31,32} Most recently, this benefit was further demonstrated in ARBITER-6, in which niacin had a favorable impact on carotid intima-media thickness progression compared with ezetimibe in statin-treated patients.³⁵ In addition to coronary stenosis regression, the HDL-C Atherosclerosis Treatment Study (HATS)³³ showed that, compared to placebo, simvastatin plus niacin therapy significantly reduced cardiovascular events including coronary death, stroke, revascularization, myocardial infarction and worsening ischemia. Reduction of ischemic heart disease mortality and overall mortality by combined treatment with niacin and clofibrate was also achieved in the Stockholm Ischemic Heart Disease Secondary Prevention Study.¹⁸

Two major clinical trials on niacin effects on cardiovascular events are ongoing. The atherothrombosis intervention in metabolic syndrome with low HDL/high TG and impact on global health outcomes trial (AIM-HIGH) enrolled 3300 patients with low HDL-C (≤ 40 mg/dL in men and ≤ 50 mg/dL in women) and high TG (≥ 150 mg/dL), not on statin therapy. Patients were randomized to ERN plus simvastatin or simvastatin therapy to test the value of ERN as an add-on to statin therapy for the reduction of major cardiovascular events. The completion date is expected to be in late 2010. Another major ongoing niacin trial is the Heart Protection Study – Treatment of HDL-C to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial which is evaluating 25,000 patients randomized to laropiprant 40 mg and ERN 2000 mg with simvastatin 40 mg and ezetimibe 10 mg or to placebo with simvastatin 40 mg and ezetimibe 10 mg. This is a 4 year trial with a primary objective to assess major cardiovascular events. The expected completion date is in 2012. In all, there is strong evidence that niacin is beneficial for the reduction of cardiovascular risk, either alone or in combination with other lipid-altering agents.

Niacin-induced flushing

Poor tolerability at doses producing significant lipid profile changes has limited the use of niacin in clinical practice. Flushing is frequent but other side effects such as pruritis, paresthesia, and nausea can occur in up to 20% of patients.^{14,24} The flushing is most severe with the immediate-release formulations, while less common when released slowly. However, the slow-release formulations are associated with

increased risk of hepatotoxicity at clinically significant doses.³⁶ This has led to the development of an ERN with an 8 to 12 hours absorption time (time to peak serum levels is 4 to 5 hours), aiming to reduce the flushing and hepatotoxicity observed with the immediate and slow release preparations respectively. ERN is administered once daily, usually at bed time with a snack to reduce flushing. It is uptitrated starting at doses of 500 mg per day for 4 weeks, followed by increasing the dose to 1000 mg for 4 weeks and to 2000 mg 4 weeks later if well tolerated. Despite its better tolerability and less flushing, the long-term adherence on ERN is low.^{14,37,38} This is particularly true for patients on 2000 mg/day, with flushing occurring in up to 90% of patients in some observational studies.¹⁴ In a recent study using telephone encounters to assess compliance on niacin, a large proportion of patients (60%) prescribed ERN discontinued the drug or changed their doses to 500 mg/day or less after 3 months of initiation of treatment, whereas only 8% of the patients in the study continued ERN at doses of 1500 mg/day or higher.³⁷ The findings in some centers of much higher long-term compliance rates (as high as 85% in our own experience on doses higher than 1500 mg/day) underscore the importance of patient education for maintenance of compliance. In fact, dedicated preventive cardiology nurses are in charge of patient education and long-term follow-up at our institution, whereas in the report by Kamal-Bahl³⁷ only 50% of patients treated with ERN reported receiving appropriate education on the flushing and ways to avoid it. However, the time resources, intensive follow-ups with dedicated preventive cardiology nurses and the currently used 4-step titration regimen of ERN make the whole situation even more complex in daily practice.

Laropiprant pharmacology and rationale for combination with ERN

Niacin-induced flushing has been demonstrated to be mediated by activation of prostaglandin-2 (PGD2) subtype receptor-1 (DP1 receptors) in vascular smooth muscle cells of dermal arterioles resulting in dilation, increased blood flow and subsequently flushing. Niacin appears to activate this cascade of events by stimulation of PG2 release from Langerhans cells.

Laropiprant is a highly selective DP1-receptor antagonist that was initially introduced as an anti-allergy agent.³⁹ It is rapidly absorbed ($T_{max/4}$ 0.8 to 2.0 hours) with a half-life of 12 to 18 hours.⁴⁰ It was noted in early trials of laropiprant that the drug reduces niacin induced flushing without affecting its therapeutic effects,⁴¹ suggesting that lipid-lowering and

flushing are mediated by two independent pathways. Also, it seemed that the blood pressure-lowering effect of niacin is independent from DP1-mediated vasodilatation.²⁹ These observations stimulated interest in combining laropiprant and ERN. In early clinical trials, laropiprant was co-administered with ERN to dyslipidemic patients⁴² and significantly reduced flushing supporting its effectiveness in blocking PG2 subclass receptor D1. Subsequently, a combination pill with laropiprant and ERN (LERN) was developed, aiming to improve lipid profiles with the same efficacy of ERN while reducing side effects by use of laropiprant. A single tablet with fewer side effects would improve compliance and optimize outcomes. A major benefit of the improved tolerability is to eliminate the need for titration by replacing the 4-step titration strategy with a one-step increase in the dose from 1000 mg to 2000 mg/day of ERN. This concept of dose escalation was emphasized in early efficacy trials of LERN.

Early experience with laropiprant and ERN

Early efficacy studies

Data from early trials combining laropiprant and ERN was encouraging. In an initial phase II trial,⁴² patients were randomized to ERN 1000 mg/day alone or with laropiprant. The first part (A) of the study randomized 154 dyslipidemic patients randomized to laropiprant 150 mg/day or placebo in a 9-week crossover study. After a 2-week washout, all 122 patients who completed part A of the study entered part B, in addition to 290 patients who entered part B directly. In this second part of the trial, patients were randomized to placebo, ERN 1000 mg/day, or ERN 1000 mg/day with laropiprant 18.75, 37.5, 75, or 150 mg for 4 weeks and then doses were doubled for the remaining 4 weeks of the study. In this study, the co-administration of laropiprant with ERN significantly reduced niacin-induced flushing without affecting the niacin effects on lipid parameters. Also, in this study, it was found that doses of 20 mg or 40 mg of laropiprant provide maximum protection against flushing associated with chronic use of niacin at doses of 1000 mg and 2000 mg respectively. Based on these initial findings, pharmacodynamics and pharmacokinetics studies led to the development of a LERN tablet containing 20 mg of laropiprant and 1000 mg of niacin. Subsequent studies used a 2-step escalation of the dose from LERN 1000 mg/20 mg to 2000 mg/40 mg, aiming to overcome the limitations of the 4-step uptitration regimen of ERN with a starting dose of 1000 mg/day in light of data suggesting that almost 1 in

every 3 patients never titrate up beyond a starting dose of 500 mg/day in the current ERN uptitration strategies.⁴³

The early phase III trials focused on tolerability, safety and efficacy of LERN for lipid management. The major endpoints of these trials were the lipid effects and reduction in niacin-induced flushing at initiation and chronic treatment regimens, as well as safety and tolerability of the new 1000 mg to 2000 mg dose escalation strategy. In an early phase III pivotal trial, LERN (40 mg of laropiprant/2000 mg of niacin) significantly improved lipid parameters compared to placebo, and resulted in 18.4% reduction in LDL-C, 20% increase in HDL-C, 25.8% reduction in TG, 19.8% decrease in non-HDL-C cholesterol, 18.8% decrease in ApoB and 6.9% increase in ApoA-1.⁴¹ In this study, two-thirds of patients were on a statin at enrollment and were randomized to LERN, ERN or placebo. The 1000 mg starting dose was escalated to 2000 mg at 4 weeks and maintained for 20 more weeks. The efficacy of LERN for lowering LDL-C as monotherapy or as a combination with a statin was the same, despite the lower LDL-C levels in the statin group at enrollment. The addition of laropiprant did not interfere with the efficacy of ERN and similar effects on lipid profiles were observed in the LERN and ERN groups.

Subsequently, a second phase III trial⁴⁴ randomized 1398 patients to LERN (20 mg/1000 mg), simvastatin or LERN plus simvastatin after a 6 to 8 weeks washout and 4 weeks diet-placebo run in. Simvastatin was given at 10, 20 or 40 mg. Four weeks after enrollment, all doses were doubled at the exception of simvastatin 40 mg. In this trial, the improvements seen in lipid profiles were more significant with LERN/simvastatin combination compared to simvastatin alone. In fact, the combination was more efficacious for reducing LDL-C (48% vs 37%, $P < 0.001$), reducing TG (33% vs 15%, $P < 0.001$) and increasing HDL-C (28% vs 6%, $P < 0.001$). In both studies, the effects of LERN on lipid profiles were independent of LDL-C, HDL-C and TG levels at enrollment, and consistent across age, gender, diabetes and concomitantly used types of statins subgroups.

These early studies supported the efficacy of LERN. It was necessary, however, to compare the tolerability of the 2 steps uptitration strategy of LERN to the ERN 4 steps titration in a head-to-head comparison. The clinical relevance is to assess the value of adding laropiprant with focus on patient acceptability, adherence and long-term compliance.

Patient-focused perspectives: assessing flushing, tolerability and adherence to treatment The early trials implemented the use of a niacin flushing scale in order to objectively assess the flushing. The scale was developed initially and then

validated. It assesses flushing using an 11-question Flushing Symptom Questionnaire (FSQ). The degree of flushing is graded 1 to 10 based on frequency, duration, severity and bother of symptoms including warmth, paresthesia, itching and redness.⁴⁵ This questionnaire was validated⁴⁶ in an 8-week randomized, double-blinded, placebo-controlled trial. The FSQ items and specifically the Global Flushing Severity Score (GFSS) were found reliable and valid measures for objective assessment of flushing. Subsequently, the GFSS was used in clinical trials and became the surrogate of the FSQ.

Phase III studies evaluated the flushing profile of LERN during initiation of therapy where flushing symptoms are the most severe and during chronic maintenance of treatment where symptoms can be intermittent but unpredictable and bothersome. The flushing at initiation of therapy was evaluated in the first phase III trial.⁴¹ Patients receiving LERN experienced less flushing symptoms than those receiving ERN with only 31% of patients experienced more than moderate flushing during the first week in the laropiprant group versus 56% in the ERN group. Similarly fewer patients experienced severe and extreme symptoms (14% vs 33%). At week 6, the symptoms experienced at initiation in patients in the LERN group decreased to a level similar to that in the placebo group, however patients in the ERN group continued to have symptoms. These findings persisted until the completion of the trial (24 weeks), with overall reduction of moderate to severe duration of symptoms to 1 day per month in the laropiprant group compared to 1 day per week in the ERN group,⁴⁵ suggesting that adding laropiprant did not only result in reduction of symptoms during induction of treatment but also in chronic maintenance. Also, the persistence of symptoms over a 24 weeks period in the ERN group suggested that most of the patients do not develop tolerance and explains the high discontinuation rates in the first year in clinical practice.³⁸

The third phase III trial¹⁴ compared the new 2-step dose escalation regimen of LERN to the currently used 4-step ERN uptitration strategy. In this study, patients were permitted to take aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) with niacin, which was taken with a meal. Patients on LERN escalation regimen had less moderate to severe flushing than those on ERN uptitration (GFSS equal or greater than 4). In the first 4 weeks, the addition of laropiprant reduced the flushing of ERN 1000 mg to less than the flushing experienced with ERN at the dose of 500 mg. In real world, this may correlate with more compliance on the starting dose of 1000 mg of niacin when laropiprant is added, which is clinically significant as most of the benefits on lipid profiles

are seen with doses equal or higher to 1000 mg. Also, in this trial, symptoms in the laropiprant group decrease after week 5 but persisted in the ERN group, which were consistent with findings from earlier phase III trials. The differences between the groups were even larger with time. At week 16, only 7% of patients on LERN reported more than moderate symptoms compared to 21% in the ERN group. Overall, starting at week 5, patients on LERN were experiencing fewer symptoms whereas patients in the ERN group were having more symptoms with every uptitration step. Importantly, therapeutic doses of 2000 mg were reached by week 8 in the LERN group with only few patients experiencing more than moderate symptoms (GFSS ≥ 4). These differences were seen despite that patients were permitted aspirin or NSAIDs to alleviate symptoms. These drugs would have more effects in the ERN group, as they do not provide any additional benefits in terms of flushing beyond the effect of laropiprant.⁴⁷ More patients in the ERN used aspirin or NSAIDs, suggesting that laropiprant provided a strong protection against flushing. Overall, the new regimen with laropiprant was more tolerated than the 4-step ERN uptitration regimen. Also, it is simple and would increase long-term compliance. In fact, the discontinuation of niacin because of flushing were 10% in the LERN group compared to 22% in the ERN group over a 24-week period. These findings suggest superiority but do not necessarily reflect a real world situation. The discrepancy between discontinuation in the real world and clinical trials is underscored by the findings that ERN discontinuation in clinical trials was not as high as in observational studies.⁴⁵ In fact, dropout rates due to flushing in clinical trials were only modest (22, 38, 41, 42, 48–55), but observational studies suggest dropouts as high as 75%.³⁸ In the niacin development program, early LERN trials were designed to assess flushing severity but not dropouts secondary to flushing. Also, patients were encouraged to stay in the trials. Patients in clinical trials may have more compliance than those in clinical practice, because of motivation, more education on side effects before enrollment as they go through informed consent process, exclusion of patients with history of flushing, close follow-up and short duration of trials. The exact discontinuation rates of LERN in clinical practice have yet to be determined. The data from early trials, however, are encouraging. One would expect more compliance and less discontinuation rates with more tolerability.

Safety

In a pooled analysis¹⁴ of 3 active phase III trials and 3 phase II 1-year safety extensions, 1268 patients on ERN and 2548 patients on LERN patients were evaluated for safety and

occurrence of adverse events. The overall drug-related adverse events were the same in both ERN and LERN groups. The incidence of increase in liver enzymes to concentrations equal or 3 times the upper limit of normal were low, similar in both groups, reversible and not associated with clinical hepatotoxicity. However, the occurrence of hepatotoxicity is not predictable and serial monitoring of liver enzymes is needed in clinical practice to screen for niacin-induced liver injury. The data from phase II and III trials showed that the addition of laropiprant did not have any clinically observable effect on muscle, in terms of either significant enzyme elevations or reports of myalgia. While one case of myopathy was documented in each of the ERN and LERN groups, these were associated with excessive physical activity.

Both groups demonstrated an increase of 4 mg/dL in fasting glucose levels, with only very few patients diagnosed with new-onset diabetes. While it is known that niacin may increase insulin resistance in susceptible patients,³⁶ the clinical significance of this is unknown. However, the benefits of niacin for reduction of cardiovascular events are likely to outweigh the risks associated with a small rise in fasting plasma glucose levels. This is supported by data suggesting that niacin has clear benefits on cardiovascular events in patients with hyperglycemia,⁵⁶ as a result of its beneficial effects on lipid profile abnormalities that usually accompany diabetes. In addition to these side effects, niacin can increase uric acid levels and should be used cautiously in patients with gout. Moreover, it can cause hypotension and precipitate angina in patients treated with vasodilators.⁵⁷

Overall, the data from preliminary trials suggest that the combination LERN is as safe as ERN. However, the endpoints from these trials were primarily the efficacy of laropiprant for the reduction of niacin-induced flushing. Also, there was a focus on ERN adverse events and there were no long-term safety data. Data from animal studies on long-term toxicity as well as early clinical human studies suggest that there are no safety concerns with the laropiprant component,^{14,40} but long-term safety has yet to be determined.

The concerns about long-term safety of LERN are not unreasonable. Given that prostanoid receptors are ubiquitously expressed in the human body, it is possible that adverse effects may occur. Laropiprant is a selective PG2 DP-1 receptor inhibitor, but it is unknown to what extent its selectivity for skin arterioles precludes any mechanism of action in other tissues. This may have implications in terms of currently unknown untoward adverse effects, in addition to blocking potential homeostatic pathways. The ongoing HPS2-THRIVE trial will likely address these safety concerns.

When long-term safety data are available and raise no concerns, the likelihood of LERN approval will be enhanced. Given that the safety of the preparation requires ongoing definition, in addition to relatively modest effects on lipid profiles, the Food and Drug Administration (FDA) rejected an early application for registration for the preparation. This highlights the ongoing need to understand more about its effects in humans before approval will be granted.

Conclusion: place in therapy

For decades, the only ways to prevent niacin-induced flushing were either conservative measures or nonselective medications such as aspirin or NSAIDs. For the first time, we have the option of targeting the specific cascade of events causing the flushing. With the introduction of laropiprant, more patients in clinical practice will be able to benefit from the effects of niacin on lipid profiles and reduction in cardiovascular events. The early experience with LERN is encouraging and shows that the drug is well tolerated and represents a new option for the management of dyslipidemias either as monotherapy or as a combination with other lipid-altering medications especially statins. In fact, the best effects on lipid profiles were seen in patients treated with a combination of LERN and a statin. The addition of laropiprant did not affect the lipid-modifying effects of niacin. However, it is still unknown whether the addition of laropiprant will affect the niacin effects on cardiovascular events.

Given the early data on its safety and efficacy, the LERN combination was approved by the European Union and other countries, but rejected by the FDA. Two major clinical endpoints have yet to be identified: the long-term safety and efficacy for reduction of cardiovascular events. The initial trials had short duration follow-up and were not powered to assess cardiovascular outcomes. While we await the HPS2-THRIVE trial results, data on safety and efficacy may emerge from countries that have approved the drug. If HPS2-THRIVE demonstrate that LERN is efficacious for the reduction of cardiovascular events and raises no safety concerns, it will be likely then that the FDA will approve the drug.

Disclosures

The authors report no conflicts of interest.

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