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# NATIONAL PBM BULLETIN

August 29, 2014

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DEPARTMENT OF VETERANS AFFAIRS  
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),  
VISN PHARMACIST EXECUTIVES (VPES), OFFICE OF NATIONAL PROGRAM DIRECTOR FOR  
CARDIOLOGY, AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

**UPDATE**

**NIACIN: AIM-HIGH AND HPS2-THRIVE: STUDY RESULTS AND IMPLICATIONS**

## I. ISSUE

Two large, long-term studies conducted to examine the incremental benefit of adding niacin to statins in patients with known atherosclerotic cardiovascular disease (ASCVD) have been published. Results from these studies demonstrates that the addition of niacin does not improve cardiovascular outcomes and may be harmful when added to statins in patients whose low-density lipoprotein cholesterol (LDL-C) is well controlled on statins alone.

## II. BACKGROUND

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) was published in 2011. Investigators examined whether the addition of niacin would further reduce adverse cardiovascular events in patients with established ASCVD and atherogenic dyslipidemia (*HDL-C <40 men, <50 women and triglycerides 150-400 mg/dL and LDL-C <180 mg/dL off statins*) and who were well controlled on statin based therapy (*LDL-C 48-80 mg/dL*). In AIM-HIGH, 3,414 patients were randomized to receive niacin 1500-2000 mg or placebo daily for a mean follow up of three years. All patients received simvastatin 40-80 mg daily to maintain a LDL-C of 40-80 mg/d. Ezetimibe was added if the LDL-C target was not achieved with simvastatin alone. Despite improvements in lipid values in the combination group, the trial was stopped early because of a lack of incremental benefit over statins alone and a numerically higher rate of ischemic strokes, which was later found not to be statistically different between groups.<sup>1</sup> More recently, investigators reported a significantly higher rate of infections in patients in the niacin treatment arm.<sup>2</sup>

The recently published Heart Protection Study-2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) adds further information on use of niacin. HPS2-THRIVE sought to determine whether the addition of niacin/laropiprant (a medication to prevent flushing) provided an incremental reduction in adverse cardiovascular events in patients with ASCVD who were well controlled on statin based therapy. In HPS2-THRIVE, 25,673 adults were randomized to receive niacin 2000 mg/laropiprant 40 mg or placebo in addition to simvastatin 40 mg daily and were followed for a median of 3.9 years. All patients entered a simvastatin run-in phase for four weeks and if their LDL-C was higher than 135 mg/dL or if their prior cholesterol regimen was more effective, ezetimibe 10 mg daily was added. Although improvements were noted in LDL-C, HDL-C and triglycerides in the combination group, there was no incremental benefit on cardiovascular outcomes when niacin/laropiprant was added to statins. Prespecified subgroup analyses, including patients with low HDL/high triglycerides, likewise showed no benefit although the authors reported a nominally statistically significant difference observed in the primary endpoint in a subgroup of patients with higher baseline LDL-C ( $p=0.02$ ). The combination of niacin/laropiprant plus statins was associated with statistically significant increase in serious adverse events compared to statins +/- ezetimibe.<sup>3-4</sup> The contribution of the anti-flushing drug laropiprant to the increase in adverse events, separate from niacin, is unknown.

## III. DISCUSSION

Two large, well performed clinical trials evaluating the addition of niacin in patients with established ASCVD and baseline statin therapy failed to demonstrate a decrease in cardiovascular events, but showed a significant increase in adverse



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(continued from page 1)

events. These studies call into question the use of niacin to reduce adverse cardiovascular events in patients when their LDL is well controlled on a statin alone. However, several patient groups were not addressed in these studies. Although HPS2-THRIVE was touted as including all types of patients with ASCVD, the mean LDL-C prior to randomization was 63 mg/dL, HDL-C 44 mg/dL and the vast majority of patients had baseline triglycerides of  $\leq 150$  mg/dL. As a result, the findings from HPS2-THRIVE and AIM-HIGH may not be easily extrapolated to other populations where evidence is lacking, including: high risk patients with elevated LDL-C despite treatment with maximum dose or maximally tolerated statin doses; those with recent acute myocardial infarction (AMI) or acute coronary syndrome (ACS); those patients who may be intolerant of statin therapy; or patients that are on statin therapy and have severely elevated triglyceride levels ( $>500$  mg/dL) who may be on niacin to mitigate the risk of developing pancreatitis. In light of the available evidence of no reduction in cardiovascular events with statin-niacin combinations and an increase in adverse events, niacin should not be routinely used or combined with statins as statin monotherapy represents the best evidence for cardiovascular risk reduction. Providers should strongly consider the risks (*HPS2-THRIVE: statistically significant excess of serious adverse events including gastrointestinal, skin, infection, bleeding, musculoskeletal and new diabetes or disturbances in glucose control in the study population*) and benefits (*no benefit in the populations studied, unknown benefit in other groups of patients*) of niacin therapy in their individual patients if the decision is made to initiate or to continue niacin therapy.

#### IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

1. Review and discuss the use of niacin with your patients who are currently receiving niacin or being considered for niacin at their next visit.
  - a. Niacin should not be routinely used or combined with statins. Evidence supports statin monotherapy as the having the best evidence for cardiovascular risk reduction.
  - b. If niacin was added solely for the purpose of increasing HDL-C in a patient receiving at least a moderate dose statin, PBM recommends discontinuing the niacin. A recent meta-analysis of lipid therapies (niacin, fibrates or cholesterol ester transfer protein [CETP] inhibitors) added to statins to increase HDL-C were not shown to improve cardiovascular outcomes.<sup>5</sup>
  - c. Niacin may be recommended for initiation or continued as monotherapy in selected patients not able to tolerate statins, as clinically appropriate. However, providers should discuss the risks (*as observed in HPS2-THRIVE*) of niacin therapy (including the use of over the counter niacin products) with their patients if the decision is made to initiate or to continue niacin therapy.
2. Assess statin choice and dosage at the time of discontinuation of niacin. If appropriate, consider increasing the dose of the particular statin and/or changing to a higher potency statin at recommended dosing for the underlying condition or cardiac risk profile.
  - a. If the patient is not receiving at least a moderate dose statin, increase the dose of statin as tolerated to moderate



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(continued from page 2)

- (reduces baseline LDL-C 30 to <50%) or high dose (reduces baseline LDL-C  $\geq$ 50%), as clinically indicated and discontinue niacin.
- b. If the statin dose has been maximized but the desired percent reduction in baseline LDL-C has not been achieved (30 to >50%), consider switching to an alternate high potency statin (e.g., atorvastatin or rosuvastatin).
  3. If, despite the potential risks and lack of outcomes evidence with statin combination therapy, a clinician and patient choose combination therapy for further reducing LDL-C, consider continuation of niacin or alternatively, replacement of niacin with ezetimibe or bile acid sequestrants (e.g., colestipol, cholestyramine). However, it is important to recognize, and for patients to be aware, that the addition of other lipid lowering drugs (e.g., niacin, fibrates, ezetimibe, bile acid sequestrants) to statin based therapy for the purpose of lowering LDL-C levels has not been proven to reduce cardiovascular events and therefore, these combinations should not be routinely used.
  4. In patients who are on statins and have severely elevated triglyceride levels (>500 mg/dL), despite life-style modification and management of secondary causes of hypertriglyceridemia, a formulary fish oil should be used rather than niacin. If fish oils inadequately reduced triglycerides or if the patient cannot tolerate fish oils, the best option for combination therapy is unclear given the potential for interaction/harm and the lack of evidence for benefit in reducing cardiovascular events or for preventing pancreatitis when a statin is combined with either a fibrate or niacin for reducing triglyceride levels. Therefore, caution should be used when considering combining a statin with either a fibrate or niacin in these patients.

## V. REFERENCES

1. AIM-HIGH Investigators. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. *N Engl J Med* 2011;365:2255-2267.
2. Anderson RJ, Boden WE, Desvigne-Nickens P, et. al. Safety Profile of Extended-Release Niacin in the AIM-HIGH Trial. *N Engl J Med* 2014;371: 288-290.
3. HPS2-THRIVE Collaborative Group. Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. *N Engl J Med* 2014;371:203-212.
4. HPS2-THRIVE Collaborative Group. HPS2-THRIVE Randomized, Placebo-Controlled Trial in 25,673 High-Risk Patients of ER Niacin/Laropiprant: Trial Design, Pre-Specified Muscle and Liver Outcomes, and Reasons for Stopping Study Treatment. *Eur Heart J* 2013;34:1279-1291.
5. Keene D, Prince C, Shun-Shin MJ, Francis DP. Effect on Cardiovascular Risk of High Density Lipoprotein Targeted Drug Treatments Niacin, Fibrates and CETP Inhibitors: Meta-Analysis of Randomized Controlled Trials Including 117,411 Patients. *BMJ* 2014;349:g4379 doi:10.1136/bmj.g4379. <http://www.bmj.com/content/bmj/349/bmj.g4379.full.pdf> (Accessed 7-30-14)

### ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives**: Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, and cardiologists, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D**: Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).