

Expert Roundtable

Clinician Perspective on the Benefits of Niacin Therapy for the Treatment of Dyslipidemia and Strategies to Improve Long-Term Adherence to Therapy

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The following Expert Roundtable Discussion was held on November 23, 2011. Dr. Peter H. Jones from the Baylor College of Medicine moderated the topic "Clinician Perspective on the Benefits of Niacin Therapy for the Treatment of Dyslipidemia and Strategies to Improve Long-Term Adherence to Therapy" with Dr. Bradley Bale of the Grace Clinic and Texas Tech Health Science Center and Amy Doneen from the Heart Attack and Stroke Prevention Center, Spokane, WA and Texas Tech Health Science School of Nursing.

The discussion focused primarily on: (1) when and how to use niacin in clinical practice; (2) how to manage the expected flushing reaction that may interfere with compliance and adherence; (3) educating the patient on niacin's benefit and benign effect of flushing; and (4) a current trial that aims to answer the broader questions about the use of niacin above and beyond what was shown in the AIM-HIGH trial. (Med Roundtable Cardiovasc Ed. 2011;2(4):249–255) ©2011 FoxP2 Media, LLC

TRIAL DISCUSSED: ASTEROID, AIM-HIGH, ARBITER 6, INTERHEART, Framingham Heart Study, Women's Health Study, INTERSTROKE, HATS, HPS2-THRIVE, Helsinki Heart Study, VA-HIT

COMPOUNDS DISCUSSED: rosuvastatin, niacin, ezetimibe, laropiprant

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Dr. Jones: Welcome to an expert roundtable discussion on the clinical benefits of niacin for the treatment of dyslipidemia and on the strategies to improve adherence to long-term use. I'm Dr. Peter H. Jones, Associate Professor in the Section of Atherosclerosis and Lipid Research at Baylor College of Medicine and joining me are Dr. Bradley Bale, Medical Director of a heart health program, Grace Clinic, and Clinical Assistant Professor at Texas Tech Health Science Center in Lubbock, Texas; and Ms. Amy Doneen, a Nurse Practitioner and the Medical Director of the Heart Attack and Stroke Prevention Center in Spokane, Washington, and an Adjunct Professor at the Texas Tech Health Science School of Nursing.

The overwhelming and indisputable clinical outcomes benefit of reducing low-density lipoprotein cholesterol (LDL) in high-risk patients with statins has made this drug class first step treatment in all cardiovascular (CV) guidelines around the world. While relative CV risk reductions with statins have been between 25% and 40% in randomized clinical trials over five years, the total CV disease event rate still remain well over 20% for high-risk subjects during that same time.¹

This so-called residual risk most likely has many causes. One plausible contributor is persistently low high-density lipoprotein (HDL) cholesterol and/or high levels of triglyceride-rich lipoproteins. Niacin, which is vitamin B3, has been an effective lipid-lowering drug, and, in adequate doses, can increase HDL cholesterol, reduce triglyceride-rich lipoproteins, as well as reduce LDL cholesterol, non-HDL cholesterol, lipoprotein(a) and apolipoprotein (Apo)B.²

The important clinical question is when and how to use niacin in clinical practice, and how to manage the expected flushing reaction that may interfere with compliance and adherence.

Let me start with a question for Dr. Bale. There have been surrogate outcomes trials such as quantitative coronary angiography and carotid intima-media thickness (IMT), suggesting that combining niacin with statins reduces atherosclerosis progression and may actually induce regression of these measures. However, the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial³ was recently published showing that statin plus niacin versus statin monotherapy didn't provide incremental outcomes benefit. Brad, can you give us your analysis of this trial?

Dr. Bale: Yes. There are many issues that can be discussed here, but one that I really haven't heard discussed at this point that I think may be pertinent is that in the Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTERIOD) trial,⁴ where they showed regression of coronary disease, and the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6) trial,⁵ where they showed regression of carotid-intimal thickness with a statin plus niacin, at the end of study total cholesterol (TC):HDL ratio was 2.8 in ASTERIOD and 2.7 in the ARBITER 6.

There are a great deal of published data showing that the ApoB/ApoA1 ratio, or the "poor man's version," which is the TC:HDL ratio, is the most predictive lipid measurement over time for CV events. In the recent AIM-HIGH trial neither arm got down into the twos for a final TC:HDL ratio. The mean ratio in the niacin arm in AIM-HIGH ended up at 3.1 and in the statin arm it was 3.6. It may be that to have a bigger impact on event risk, the ratio needs to be driven into the twos. Both arms of AIM-HIGH

still carried very significant event risk of 16%, which would be considered extremely high-risk. Perhaps the AIM-HIGH study did not aim low enough.

So I think there is an issue trying to compare the ASTROID trial, the ARBITER 6 trial with the AIM-HIGH in terms of the endpoint lipids that were achieved and in particular the TC:HDL ratio. And I'm curious, Dr. Jones and Ms. Doneen, whether that thought went through your heads when you looked at the results of AIM-HIGH.

Dr. Jones: Yes, Amy, what do you think about the results of AIM-HIGH, and how does that impact your feelings about the combination of niacin and statin compared with statin monotherapy?

“Aspirin is said to minimize the flushing that occurs with the niacin products. Many of the patients we would consider candidates for niacin need to be on aspirin anyway because they're high-risk.”

~ Peter H. Jones, MD

Ms. Doneen: The most predictive ratio that we know of, as far as predicting events in men and women globally was published in the INTERHEART trial in 2004.⁶ Vascular disease is a multifactorial disease state and that's probably the most important point. Additionally, in 2007,⁷ the Framingham Health Study showed that ApoB/ApoA1 and TC/HDL was the most predictive of CV events over six years. Most recently, in 2010, the Women's Health Study was analyzed and TC/HDL was the most predictive lipid parameter for women. When we manipulate one variable such as lipids we want to be as inclusive in that application as possible. TC/HDL and ApoB/ApoA1 clearly provide the most value in regard to predictability of CV events in both men and women. In AIM-HIGH, the ratio did not get to a level that has historically proven CV disease stability, TC/HDL <3.0. The ending ratio in the niacin arm of AIM-HIGH was 3.1 and in the statin-only arm was 3.6.

Also in AIM-HIGH, reflecting back to the multifactorial element of this trial, we can learn about stroke predictability from the INTERSTROKE trial. The top cause of ischemic stroke was elevated blood pressure. Additionally, we have to question whether psychosocial factors were addressed adequately. When we deal with patients clinically on a one-on-one basis, we have the opportunity to assess the disease more carefully. And I believe that's where the clinical application of this knowledge from AIM-HIGH coupled with data that's been published historically can be taken into account.⁸ When we analyze the results from AIM-HIGH, which clinically weren't what we anticipated—we must examine it for its value, it's that it re-emphasizes the fact that to manipulate one variable only, such as lipids, along with the hypothesis that in either arm those lipids were not manipulated optimally, may not be enough to change events.

Dr. Jones: Yes, the intensive lowering of LDL-C and Apo B in both of the statin arms seems to be the basis of most guidelines. The answer to whether adding niacin on top of that intensive, targeted treatment could add any outcomes benefit was disappointing. It's just unfortunate we were not able to

see the benefits of what niacin does through increasing HDL-C when both randomized arms were targeted to such intensive reductions in LDL-C and ApoB.

In AIM-HIGH, they were using 2g/d of extended-release niacin in the niacin arm, compared with placebo, and that therapy did increase HDL 25%. Niacin also provided additional LDL-C lowering and Apo B reduction when combined with a statin, so, effects on lipids were seen. In light of the AIM-HIGH results, how do both of you now use, or how will you use niacin in CV disease prevention? Let's start with Dr. Bale.

Dr. Bale: I think before I get to that question it is important to point out that the actual difference in HDL between the statin arm and the niacin arm at the end of the trial turned out to be only 4 mg/dL. The actual difference in the LDL arm turned out to be only 6 mg/dL. This may have been influenced by confounding therapy with ezetimibe, which was used in 22% of the individuals in the statin arm and only 10% in the niacin arm. The difference in HDL and LDL would predict about a 10% reduction in events in favor of niacin. The trial, of course, was not powered to pick up that type of event benefit. They anticipated 25%, but that degree of benefit is unlikely with such a slight difference between the HDL and LDL values.

So I think it's unfortunate that they allowed therapy with ezetimibe. That medication may have changed some of the study end points. The bottom line is that it is important to point out the trial neither confirmed nor negated the hypothesis that niacin is a good agent. There are lots of reasons to use niacin. It may be excellent therapy for a high-risk population, such as individuals who just suffered an acute coronary event. The AIM-HIGH trial did not address that hypothesis. The AIM-HIGH patients were stable; they weren't acute or high-risk individuals.

There are practical matters to consider. Statins are marvelous agents and we believe they are the cornerstone of therapy in the reduction of CV risk. There are some patients who have trouble tolerating the statins. All of us run into the myalgia problems with statins. They are real and must be taken seriously. Biopsy studies have been performed demonstrating actual damage to the muscle fibers. When a patient is taking a statin and complains about muscle pain, it doesn't matter what the creatin kinase level is; those complaints need to be taken very seriously.

Some of these individuals cannot tolerate even moderate doses of statins. Many can tolerate lower doses. You can get very creative, of course, with rosuvastatin. With a 19-hour half-life it's not unusual for us to place a patient on half of 5 mg and have them take it every other day. It doesn't have to be dosed every day and many patients with statin myalgia can get by with that amount of rosuvastatin. Low-dose statins can provide significant benefit but will leave a lot of patients exposed to CV risk from lipids that are not ideally lowered. If the patient has the insulin-resistant condition, which is present in about 70% of people with atherosclerosis, they very likely will have complex lipid issues not only with the HDL but problems with LDL and HDL along with elevated triglycerides.⁹ They may be unlucky enough to also have inherited a lipoprotein(a) problem. Low dose statin treatment is not going to take care of all those issues. These patients would be excellent candidates for niacin therapy.

“We can usually find a way to keep our patient on the medication... it starts with the right education.”

~ Bradley Bale, MD

We certainly still plan to use niacin in patients. The AIM-HIGH trial did not conclude that niacin should not be used. It didn't say it was a bad agent or caused harm. The study was stopped for futility, not harm. I think there are many patients who will be candidates for niacin therapy, especially those with the statin myalgia issues.

Dr. Jones: Amy, what are you going to do in your practice?

Ms. Doneen: Yes, I agree. One thing I'd like to point out is that Dr. Philip Barter from the Heart Research Institute in Sydney, Australia really made a great statement in the AIM-HIGH evaluation. Brad mentioned it and I just want to highlight it, that this trial in no means challenges the hypothesis that HDL is an important element in the equation. It doesn't really challenge the hypothesis because the study lacked the power to tell us that either it did or it didn't. Nor does the AIM-HIGH trial mitigate what we've learned historically with Dr. Greg Brown's work, which showed beneficial effect of niacin/statin combination on disease stabilization. Additionally, Dr. Allen Taylor's work with cIMT and niacin/statin combination also demonstrates disease benefit.

The concept that we need regression or stability of lesions to halt vascular events is best documented clinically with inflammatory biomarkers coupled with study of structure. So what I'd like to see in trials moving forward and even with the Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE),¹⁰ is clinical structure analysis whether it is carotid IMT, intravascular ultrasound, something else to show us that the disease is halting and stopping its growth pattern. Intravascular ultrasound-derived radio frequency imaging can visualize necrotic core volume stabilize, coupled with biomarkers that are clinically useful. Clinical biomarkers that provide demonstration of arterial wall stability include high-sensitivity C-reactive protein, microalbumen, albumen/creatinine urine ratio, and lipoprotein-associated phospholipase A2.

So when we see a patient clinically, if I'm going to add to their statin therapy I look at what the comorbidity is and why they have disease in the first place? Also, is the disease driven by a problem that monostatin therapy can adequately treat? Monostatin therapy cannot adequately treat insulin-resistant dyslipidemia or an inherited lipoprotein(a) or a persistent ApoB problem. Additionally, as Brad mentioned, some people just can't get to doses of statin therapy that will mitigate even some of these lipid concerns, I always back it up by looking at clinical biomarkers for stabilization, such as high-sensitivity C-reactive protein, albumen/creatinine urine ratio, and lipoprotein-associated phospholipase A2. I want to see these stabilize.

My use of niacin therapy and statins and the doses I'm going to choose are dependent on the effect the treatment has on the inflammatory process. I would like to see inflammatory biomarkers and structural analysis added to AIM-HIGH. Perhaps a subgroup analysis will offer some of this valuable information.

Dr. Jones: Yes, there are going to be substudies from the AIM-HIGH trial that will look at the vascular wall. There is a subgroup of patients who had magnetic resonance imaging of their carotid arteries and the investigators will be examining plaque volume changes. They may be able to also look at the biological activity in the carotid wall. There will also be biomarker substudies, as well as measures of HDL function. It is possible that these evaluations will help us predict a subgroup of patients who may have gotten greater benefit from combination treatment than was shown in the overall population. So, do you still use a low HDL cholesterol level as a reason to use niacin over other options such as fibrates? I'll start with Dr. Bale.

Dr. Bale: It's more complicated than just low HDL. Certainly that would make me take a hard look at niacin, but as Amy just mentioned, one of the things that we monitor frequently in our patients with known disease is the amount of inflammation in the artery. So we pay a lot of attention to lipoprotein-associated phospholipase A2, and quite frankly I would be more likely to reach for niacin, assuming I already had them taking a statin at a good dose if lipoprotein-associated phospholipase A2 was still elevated. That would be a situation where I definitely would be looking at adding in niacin. We know it's synergistic with the statin to lower the level of that enzyme. We have a strong signal from a trial that used intravascular ultrasound radio frequency to monitor the necrotic core of coronary plaque that this enzyme not only marks arterial inflammation, but it appears to be a player in the disease process. Any time something is a player in the actual disease process it becomes a target of therapy.¹¹ So HDL would influence the decision to use niacin, but it wouldn't be the only thing I'd be looking at. I would be looking at inflammation as well. Niacin is an excellent agent for reducing arterial inflammation. We monitor inflammation frequently in our patients. We know if we can keep the artery cool we can keep the body warm.

Dr. Jones: Amy, do you still use low HDL-C level in a patient as a reason to use niacin over other options?

MS. Doneen: Well, if you find a patient with a low HDL level, and let's make an assumption that they have vascular disease, the next job is to find out why they have vascular disease, and the low HDL can be a huge clue. There's always a reason why disease is present and if you see a low HDL or even more specifically a TC:HDL ratio that's off, or a triglyceride to HDL ratio that is more than 3.5 in a Caucasian, or more than 2.0 in an African American, it definitely allows us to make an underlying diagnosis of why the plaque is sitting in those arteries. And if there is insulin-resistant dyslipidemia and the low HDL was our playing card to diagnosis it, we then know that monostatin therapy treatment, based on the data that's been published historically, is probably not going to be enough and they might be in the risk population where we want to gravitate towards adding niacin to the statin.

The question also is why use niacin perhaps instead of a fibrate. Brad mentioned PLAC2 quite a bit and I mentioned it previously as well. This enzyme lacks biovariability, but it is important to understand that clinically we've got to do something to know whether our patient has either inflamed or stable disease. We know that niacin added to statin therapy will result in a synergistic decrease in PLAC2. This is not something observed with a fibrate/statin combination.

We don't see that synergy when we use the fibrate. So fibrates have their place in a population that mimics what we saw historically with the Helsinki Heart Study and Veterans Affairs HDL Intervention

Trial (VA-HIT), but in the general population niacin has more widespread application. Clinically, I will be very interested to see the subgroup analysis with data on inflammatory factors.

Dr. Bale: Do you know, Dr. Jones, whether they are going to have lipoprotein-associated phospholipase A2 data from the AIM-HIGH trial?

Dr. Jones: They're going to measure several important biomarkers and one of them is lipoprotein-associated phospholipase. There is also the ongoing trial of maximal statin treatment with or without an extended release niacin/laropiprant product (HPS2-THRIVE), which has enrolled 25,000 patients. This trial includes a broader patient population not defined by low HDL-C. All participants are at high risk, that may help us understand more about some of these issues that you brought up on how to use niacin in the prevention of CV disease.

Another important issue for those of us who are going to continue to use niacin as an important lipid-altering drug is the well-known and expected cutaneous flushing response that can be a barrier to the initiation and persistence of treatment. This was a challenge in the AIM-HIGH trial, in which there were more dose reductions and more discontinuations in the niacin group compared with the placebo group. Amy, how do you introduce a niacin-naive patient to treatment?

MS. Doneen: Well, the first thing is education. Patients need to understand why they are being asked to take this drug. They also need to know that it is a natural product, vitamin B3, but it also has many clinical side effects of almost all other prescription medications for atherosclerosis and hyperlipidemia. It's probably the trickiest drug to place onboard for a patient because the side effects are so tangible and they may affect the patient's daily life. So educating the patient on why they need it and why it's important to take it is number one.

Once they understand the value and its effect on atherosclerotic inflammation and lipid and dyslipidemia management and they're onboard, then we move forward with the big three concerns which would be safety, efficacy, and tolerability. So when we're looking at tolerability issues it is a bit of a trick to buffer niacin safely with efficacy. If we use a prescription form of extended-release niacin we know we have the safety impact and we know that it's a fairly well-tolerated drug. There are some over-the-counter extended-release products that also have proven to be safe and we're learning of their efficacy and tolerability.

To put it simply, we start very low at 500 mg and prescribe it at night. If the patient is going to flush, hopefully they're going to sleep through it. We have them take it with some high-fiber snacks, even sugar-free Metamucil—everyone's got tricks up their sleeves. But we really spend time on education and move very, very slowly. And there is a safety issue as well. Vitamin B3 is metabolized through the hepatic system so we usually check liver function in a month and then have another point of contact with the patient. We then push up that dose to 1 g/day. The dose appropriate for that patient is based on their inflammatory marker responses to the treatment. We don't automatically push them up to 2 g or 3 g, or 1.5 g, even. We really just stick to where we're going to see inflammatory benefit and we move slowly. It's not a race. We move slowly and get them to a level that they're going to tolerate long-term.

If a patient is very hot when they first come in and perhaps they've even had a recent CV event, we often use high dose statin therapy to reduce the vascular inflammation quickly, and then we do our due diligence to treat any comorbidities, and this is when niacin comes into the picture. So we have the ability to take it slowly and take it easy, and then hopefully titrate down their statin dose just a bit and get them on a nice combination regimen that they can handle long-term.

It's a process of education, and that's the other thing. I just want to make one last point with AIM-HIGH. I know we're moving on from it but, this was an intent to treat trial with a drug that needs a lot of time and education and resources for the patients. There is a problem: Are people really going to take it if they get a flush reaction? Do they understand that clinically it may be beneficial and it's not harmful, et cetera? When we use a trial design such as that used in AIM-HIGH with this drug it's challenging for compliance and maintenance for even getting to the end of the trial.

Dr. Jones: Aspirin is said to minimize the flushing that occurs with niacin products. Many of the patients we would consider candidates for niacin need to be on aspirin anyway because they're high-risk. Dr. Bale, do you find that you need 325 mg at initiation of treatment, or is 81 mg low-dose aspirin adequate? What's your feeling about the dose of aspirin for both short-term initiation and then long-term therapy?

Dr. Bale: Great question. We really do not rely on aspirin to blunt the flushing effect with niacin because we want to just block the cyclooxygenase (COX)-1 pathway with aspirin. That is the pathway that can be harmful from an arterial standpoint. When you use adult aspirin 325 mg you can block the COX-2 pathway. You really don't want to block this pathway because it can actually have benefits for the artery. In order to block the prostaglandin effect, which is one of the main products that ends up stimulating the flushing, you have to block the COX2 pathway, which usually requires adult aspirin. In terms of aspirin to reduce the niacin flush, clinically we will tell patients, "Look, you may want to have some chewable baby aspirin by your bedside table, so if you wake up in the middle of the night flushing, you can chew a couple of baby aspirin to help reduce the flushing." We don't try to reduce the flushing by putting them on adult aspirin.

We put a positive spin on the flush. Amy made an excellent point that education is the key to good compliance. There are a lot of different potential aspects to that education. Just telling the patient they need niacin for a low HDL level is not a lot of education about the potential benefit of niacin. We anchor our work in identifying subclinical atherosclerosis. If the patient has just had a carotid IMT test, for example, and they are shown a plaque in the carotid artery, they will realize they have risk for a stroke. We then educate them on the potential benefit of niacin in reducing that risk. It's a much greater motivator to take the medicine and put up with some flushing.

And we also put a positive spin on the flush. We say, "Look, yes you're going to flush. That means your arteries are dilating. You may be getting blood flow through those arteries like you hadn't seen since you were a child. That's not all bad. And when you flush you need to know that chemically that's due to an increase in something we call prostaglandin D2, and the main byproduct of that is a substance that has a fancy name 15-deoxy-prostaglandin J2, which happens to turn on this thing we call PPAR-gamma." If they are insulin resistant, we let them know that turning on peroxisome proliferator-activated receptor gamma is great for that condition. Therefore, every time they flush they know it is a really a good thing. If you put a positive spin on the flush, it makes a difference.

There are other tricks to minimize flushing, such as taking niacin with some dried fruit. This can significantly reduce the flush and nobody knows exactly why. Some people theorize that maybe the niacin is absorbed slower, yielding lower peak concentrations. However, it may very well be due to flavonoids.

Another trick involves the important lifestyle element of exercise. If a patient persists with flushing, we tell them to take it 30 to 60 minutes prior to exercise. They will most likely flush while exercising. If they are at a gym, they will look like a hero as they get red, hot and sweaty. It is an excellent trick for some patients. The time of day to take niacin is not written in stone. Some people tolerate it much better in the morning with breakfast. We can usually find a way to keep our patient on the medication, but Amy's exactly right; it starts with the right education.

Dr. Jones: Amy, how do you deal with patient interruption of treatment? You know, sometimes patients forget to take their medications because, for instance, the prescription runs out and it's several days before they can resume. For most drugs, you can just pick right up and go forth without an issue. So a patient is taking 2 g/d and they want to resume after 5 days. What do you advise?

MS. Doneen: This is real life, so yes, things do happen. Niacin, a drug that has some dose dependency as far as the frequency of flushing. So if someone's on a 2 g/d dose and they've been stabilized for quite some time and they're off it for a week they may be able to tolerate going back on. To be safe and cautious and just allow them to kind of titrate back up slowly is a nice move to make because you want the long-term benefit.

The other thing that I always point out to patients is that sometimes a renegade flush occurs for no rhyme or reason. Perhaps they had a high-fat meal, a salad dressing they're not normally used to, or they had known triggers such as spicy foods or more alcohol than they normally have. It doesn't mean that from that point forward they're going to deal with this persistent flush that they've had when they started treatment.

Again, it's another opportunity to have contact with patients. In the world of clinical lipidology, you need every chance you can to educate that patient. So, yes, if they stop their medicine they should start slow and gradually increase the dosage.

Long-term usage of 325 mg or higher of aspirin, which you really need to block the prostaglandin flush, is not what we want, because we do not want persistent blockade of COX-2. If someone has a flush and they want to increase their aspirin dose to try to mitigate it, you have to discuss it. Perhaps they can take two baby aspirin as they migrate back on to their niacin dosage. There are lots of tricks that can be used.

Dr. BALE: Let me add just one thing, regarding tolerance. We all know there is a tolerance that develops with flushing. This is due to diminishing levels of prostaglandin D2 and prostacyclin. The longer you're taking niacin, the more the release of these substances decreases. This issue can stimulate calls to our office, as our patients are educated that flushing is expected and good for them. We actually have patients call us up if they haven't flushed for a month or so and say, "Wow, I'm a little worried about this. I haven't had any flushing for a month. I'm wondering if they gave me good

stuff.” Patients need to know they’re going to flush out of the chute, but as time goes on that’s going to decrease.

MS. Doneen: Can I say one quick thing, because I don’t want people to misread one point? There are people who cannot tolerate niacin. We talk about all these ways to tolerate the flush and take it, and most people can, but just like everything else, people do have allergies, so always listen to your patient. If they come in and they are miserable and have an itch or hives that won’t go away, the niacin should be stopped. Take every sort of call and complaint seriously, and don’t minimize them.

Dr. Jones: That’s a good point. A patient has the prescription form of extended-release niacin and they have a flush, and their next question is whether they can buy over-the-counter niacin such as a “flush-free” niacin or a sustain released niacin. What do you tell patients about that?

Dr. Bale: Well, obviously if they’ve been educated correctly they’re going to know that flush-free isn’t going to work. We want them to flush. There are two pathways for the metabolism of niacin. One yields byproducts that affect the lipids well. This pathway causes flushing. The other pathway produces metabolites, which do not affect the lipids. This pathway does not cause flushing. The University of Washington tested several no-flush niacin over-the-counter products. These agents did not produce any positive lipid effects.

Dr. Jones: The final question to both of you is what is your minimum dose of niacin for both lipid efficacy and other effects?

Dr. Bale: I have some patients taking 500 mg who have gotten significant benefit, not just with the lipids, but also inflammation. They tend to be older, thinner patients. We’ve actually analyzed our data and our average dose turns out to be 1250 mg, so it’s rather unusual that we go to 2000 mg. Most of our patients settle in at 1000 to 1500 mg.

MS. Doneen: I would like to emphasize that the target dose of niacin should be based on the anti-inflammatory response of the patient. Once the fire is out in those arteries, you can hold there usually and aim for a TC:HDL ratio less than three. Get ApoB to goal. Once the patient is stable and the inflammation is optimally controlled, the dose of all medications can be evaluated on a regular basis, based on the unique needs of the patient. This process allows for frequent contact with the patient.

Dr. Jones: In summary, we’ve reviewed the clinical utility of niacin in CV disease prevention, and I believe we all agree that lowering LDL cholesterol to target is of primary importance, and statins are first-line treatment. Our next point is that niacin has beneficial lipid effects that are useful in selected patients, particularly those who can’t tolerate maximum statin therapy to achieve LDL-C and/or apo B targets, in those with elevated lipoprotein(a) and those with elevated inflammatory biomarkers.

Importantly, there is an outcomes trial in progress that may help us answer some of the broader questions about the use of niacin above and beyond what we’ve been able to get out of the AIM-HIGH trial. Lastly, the expected cutaneous flushing reaction of niacin can be managed to enhance both compliance and adherence through several techniques that we outlined. Probably the most important is to educate the patient about the need for the use of this natural product, and that the short-term cutaneous flush is a benign but very important part of the niacin affect. Also, titrating the niacin dose

up over a short period of time may help with the tolerability of flushing, and that the flush does seem to get better over time. And lastly, the use of aspirin and ingesting certain types of food at the time of dosing may also help patients with the initiation of therapy to reduce the flush.

I want to thank both Dr. Bale and Ms. Doneen for their clinical insights.

Dr. Jones is a consultant to Abbott, has participated as a speaker, and has served as an investigator of clinical research at Baylor, which has received funding from Abbott. Both Dr. Bale and Ms. Doneen serve on a speakers' bureau for Berkeley Heart Lab and Cleveland HeartLab. Neither Dr. Bale or Ms. Doneen have any other conflicts to disclose.

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