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### Triglyceride-Lowering Therapies: Addressing Gaps in the Guidelines

Dr. Brown:

You're listening to ReachMD and this is Lipid Luminations sponsored by the National Lipid Association. I am your host, Dr. Alan Brown, and with me today is Dr. Dave Dixon. He is a clinical pharmacist and Associate Professor of Pharmacotherapy of Virginia Commonwealth University School of Pharmacy. Dave is also a board certified pharmacotherapy specialist, a clinical lipid specialist and, most importantly, a fellow of the National Lipid Association. He serves as a regional representative for the Southeast Chapter of the NLA and serves on the Editorial Board of the Journal of Clinical Lipidology. So, Dave, great to see all of your efforts within the Lipid Association and I am particularly grateful that you took time today during a busy meeting to come and talk to us.

Dr. Dixon:

Sure. Thank you Alan, it is a pleasure to be here. I enjoy the podcast all the time.

Dr. Brown:

Thank you. So, today our focus is going to be on triglyceride-lowering therapies and this is a very interesting topic because, in terms of looking at clinical outcome trials, reducing cardiovascular events by treating triglycerides to date is pretty obtuse and, as I know you have pointed out, the guidelines kind of recommended previous literature but gave no specific recommendations except to avoid pancreatitis when they are over 500. Why don't you tell us a little bit about what are the current recommendations and where the gaps are, and share your wisdom with us.

Dr. Dixon:

Sure, If you go back really in terms of guidance, you would have to go back to the 2011 American Heart Association scientific statement on triglycerides and it was a really important document. I think it really brought together excellent thought leaders in that topic area and really highlighted and emphasized the importance of diet, lifestyle change. And in that guideline, drug therapy was sort of withheld or recommended to be withheld until the triglycerides exceeded 500. We fast-forward to 2016 and essentially it's pretty much the same. If we look at our 2013 ACC and AHA guideline, they essentially punted the concept of going into triglycerides and referred back to that statement. So, fortunately, I think our NLA recommendations at least provide a little bit of context for practicing clinicians as to when to really consider triglyceride-lowering therapies.

Dr. Brown:

They focus on non-HDL for those so, over 500, avoiding pancreatitis is a no-brainer, right?

Dr. Dixon:

Absolutely.

Dr. Brown:

But then in the higher risk individuals, particularly those with established atherosclerosis, the non-HDL has been a concept that really was not delved into by the ACC/AHA guideline.

Dr. Dixon:

Right.

Dr. Brown:

Probably because there have not been any randomized trials of using non-HDL as a targeted therapy, but they did bring the concept up in the NLA recommendations. Do you want to talk to us a little bit about non-HDL and how we might look at that?

Dr. Dixon:

Sure. So, it is quite clear that in patients with high triglycerides that non-HDL is really a better predictor of risk in those patients. And so, we are dealing with an obesity epidemic as well as the increase in cases of diabetes. And so, in clinic, particularly in my practice, I see a lot of those patients who have that moderately elevated triglyceride, high levels of non-HDL cholesterol, and that is really where there seems to be some opportunity for some of the non-statin drugs that lower triglycerides to really offer some benefit in terms of reducing the overall atherogenic burden. The NLA recommendations for those patients that have triglycerides between the 200-250 mark on up to 500 is still statin first and then clearly looking at the non-HDL as a target of therapy and really trying to identify those patients that the statins fall short and then trying to add something like a fibrate or possibly omega-3 fatty acids, but really looking at therapies to further reduce non-HDL cholesterol. You can also through ezetimibe in there, of course, obviously not a potent triglyceride-lowering drug. Then, for those patients where triglycerides are between 500 but below 1,000, the NLA recommendations suggest that in patients without a prior history of pancreatitis that it would be reasonable to start high intensity statins. We have to remember that statins can lower triglycerides by as much as up to 30% at a high dose. In those patients, however, that have a history of pancreatitis, our fibrates and omega-3 fatty acids remain sort of a first line therapy and then obviously those folks over 1,000 it is definitely a no-brainer to go with a fibrate or omega-3 fatty acid first.

Dr. Brown:

So you gave actually several pearls that I hope our audience heard. Number one, that all patients for risk for cardiovascular disease, in particular the low HDL, high triglyceride patients who are at the highest risk, they respond with statins and they get a reduction in risk. That has been proven and, in fact, that drove many of the statin trials. A lot of people don't realize that. But then the second piece was if there's modest triglyceride elevation between 200 and 500 that once you have put them on a statin and saw what the numbers look like, lifestyle would be the next attempt, and you made that point, I just want to reemphasize that because I think that is a hugely important point that triglycerides are much more responsive to lifestyle modification than LDL, for example, right?

Dr. Dixon:

Absolutely. Triglycerides fluctuate throughout the day and they responded very well to lifestyle change; reducing carbohydrates, in particular, simple sugars, and just simply moving your body and that is something that we push our patients a lot to do. They get hung up on the triglyceride number being elevated and we encourage them that that is something they can do something about.

Dr. Brown:

Sure. In the 2013 guideline writing group they struggled because we had a couple of recent studies adding niacin or adding fibrates to a statin, and then when a patient is already on a statin with a very low LDL, we are unable to show whether that be study design or lack of efficacy.

Dr. Dixon:

Right.

Dr. Brown:

We were just unable to show any incremental benefit. So, that again would push it towards lifestyle. I was harkening to the days when we used to put everybody on procainamide for a PVC in my younger years and we found out that actually increased the risk of people so now we are more thoughtful and this may be a situation where thoughtfulness is valuable. Correct?

Dr. Dixon:

I agree.

Dr. Brown:

If you are just tuning in, this is ReachMD. I am Dr. Alan Brown and with me today is Dr. Dave Dixon, clinical pharmacist and Associate Professor of Pharmacotherapy at Virginia Commonwealth University School of Pharmacy. We are talking about treatment of hypertriglyceridemia. So for the people that we would be thinking of pharmacotherapy, which would be people either over 500, or people, as you eloquently pointed out, who had been started on a statin and despite their best efforts, their non-HDL remained elevated according to our NLA recommendations, then you would be thinking about therapy. How do you make a decision which therapy to start; fenofibrate versus omega-3 fatty acids. Give us your insights on that.

Dr. Dixon:

Looking at this from a pharmacist's perspective, you know, right away we are looking at – typically of course we are recommending fenofibrate over gemfibrozil in most cases clearly. With fenofibrate we have got a once daily medication. It is very easy to take and, for most patients, it is quite tolerable compared to the omega-3 fatty acid products, even if you are using the prescription product, you are looking at two to four capsules a day, very large capsules. There are some common side effects; dyspepsia, belching, and things that patients can experience that sometimes can limit their use. As far as data showing that these drugs reduce the risk of pancreatitis, I think also separates it a little bit. So, with fenofibrate we do have at least a little bit of data suggesting a reduction in the outcome we are trying to achieve. Whereas, with the omega-3 fatty acids, that data is fairly sparse.

Dr. Brown:

And probably depends on the cause of the hypertriglyceridemia.

Dr. Dixon:

Exactly, and alcohol seems to be number one and so trying to figure out how do you study those patients can be challenging.

Dr. Brown:

On the topic of omega-3 fatty acids, my patients always ask me is it okay to take over-the-counter or should I take prescription brand. My theory, my philosophy the reason the FDA approved the prescription brand is because the results are fairly predictable and also that they are distilled so they do not get the fishy smell, the fishy belching, and everything else. But even with the generic forms, they can

still be fairly expensive. So, now that I have told you my thoughts, let's hear yours. How do you deal with that over-the-counter versus prescription brand?

Dr. Dixon:

Sure. That question comes up quite frequently in practice. Fish oil is not the same as omega-3 fatty acids and that is usually the starting point from educating our patients and other providers. Fish oil is a dietary supplement. If you look at those tablets and capsules available over-the-counter, very limited actual amount of EPA and DHA, which are the real ingredients that drive the reduction in triglycerides and offer some potential benefit. You can find some over-the-counter products that have a higher amount of EPA and DHA but these patients will often have to take 6, 8, sometimes even 12 capsules. So, clearly that actually becomes quite expensive for patients. The other thing that I hear a lot is the new fad now is krill oil. If you actually look at the bottle of krill oil, you are looking at less than 100 mg in most cases of EPA and DHA and then, of course, because of that fishy smell, gummies, the fish gummies, are now quite popular. I usually advise patients it is more likely to cause cavities than actually help lower the triglycerides.

Dr. Brown:

Because of the miniscule amount of EPA and DHA.

Dr. Dixon:

Correct.

Dr. Brown:

So you are a proponent of sticking with prescription brand if you can.

Dr. Dixon:

I am. Reliable, and if you have a patient where cost is an absolute issue, there are some products over-the-counter that have a decent amount of EPA and DHA. Look for that USP sticker, United States Pharmacopeia; you at least know that there is a little bit of certainty that the product is more pure and accurately reflected on the label.

Dr. Brown:

I am hopeful since now at least one of the prescription brands has been generic for many months that we are going to see the price go down pretty significantly in the near term.

Dr. Dixon:

Exactly.

Dr. Brown:

Well, I wish we had more time to talk about this. I think you have really helped our audience, many of whom are not lipidologists, to figure out how to approach hypertriglyceridemia, one of those elusive things that people commonly ask about. I cannot thank you enough for joining us.

Dr. Dixon:

Absolutely. Thank you, Alan.

Dr. Brown:

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