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## The Patient You Might Be Missing: Severe Hypertriglyceridemia in Clinical Practice

### Announcer:

This is *Heart Matters* on ReachMD. This program, titled “The Patient You Might Be Missing: Severe Hypertriglyceridemia in Clinical Practice,” is sponsored by Ionis Pharmaceuticals Medical Affairs. Here’s your host, Dr. Charles Turck.

### Dr. Turck:

Welcome to *Heart Matters* on ReachMD, I’m Dr. Charles Turck. And today, I’m joined by Dr. Erin Michos, to explore a condition that affects millions of patients, yet often flies under the clinical radar—severe hypertriglyceridemia, or sHTG.<sup>1-3</sup> We’re going to break down the definition, the metabolic drivers, the clinical risks, and where current management stands.

Dr. Erin Michos is a Professor of Medicine, Director of Women’s Cardiovascular Health, and Associate Director of Preventive Cardiology at Johns Hopkins University School of Medicine. Dr. Michos, it’s great to have you here today.

### Dr. Michos:

Thanks, Dr. Turck. It’s great to be here.

### Dr. Turck:

Well let’s start with the foundation, Dr. Michos. When we talk about sHTG, how is that typically defined in practice?

### Dr. Michos:

That’s a great place to begin. In practical terms, severe hypertriglyceridemia, or sHTG, generally refers to a fasting triglyceride level of 500 milligrams per deciliter or higher.<sup>1,4</sup> And in the United States, sHTG is estimated to affect more than three million people.<sup>1-3</sup>

Now, triglyceride levels that reach even higher levels have been associated with chylomicronemia and a substantially increased risk of acute pancreatitis.<sup>1,2,5</sup> But from a practical clinical standpoint, when we see triglycerides at or above 500 milligrams per deciliter threshold, that should really get our attention. Because at this point, we’re looking at a level of hypertriglyceridemia where the clinical implications change, shifting our attention towards acute pancreatitis risk and prompting a more careful evaluation for underlying causes and risk.<sup>5</sup>

### Dr. Turck:

And once triglycerides get into that range, what’s driving that from a pathophysiologic standpoint?

### Dr. Michos:

At its core, sHTG comes down to an imbalance between the production and clearance of large triglyceride-rich lipoproteins—mainly the very low-density lipoproteins, or VLDL, and chylomicrons.<sup>6</sup> In some patients, the liver is producing more VLDL than usual. But as triglyceride levels rise, the bigger issue is impaired clearance of these particles.<sup>1,6,7</sup> When everything is working as it should, it’s normal to see triglyceride-rich lipoproteins in the bloodstream after a meal, but not after an overnight fast.<sup>1</sup> And that’s because lipoprotein lipase, or LPL, helps hydrolyze triglycerides in circulating chylomicrons and VLDL.<sup>6</sup>

But in sHTG, that clearance pathway may no longer keep up with the lipoprotein load. And so triglyceride-rich particles continue to remain in the circulation.<sup>6,7</sup> Then, as levels continue to rise, we’ll even see circulating chylomicrons in the fasting state.<sup>7,8</sup> Chylomicrons are those largest triglyceride-rich lipoproteins and their accumulation in the bloodstream contributes to the increased risk of acute pancreatitis that we see in sHTG.<sup>1</sup>

**Dr. Turck:**

Now with all of that being said, how does sHTG typically present in clinical practice?

**Dr. Michos:**

Well, some of these patients will present with multifactorial chylomicronemia syndrome, or MCS. In patients with MCS, triglyceride levels are rising because there's an underlying genetic susceptibility, as well as secondary contributors. These might be poorly controlled diabetes, obesity, alcohol use, dietary patterns, or certain medications.<sup>1, 7</sup> Another clinical presentation, familial chylomicronemia syndrome, or FCS, is much rarer. FCS is an autosomal recessive disease that's caused by mutations in genes that are critical for LPL to function. And as a result, FCS leads to absent or near-absent lipolysis.<sup>1,8,9</sup>

In clinical practice, you're often seeing patients with sHTG as part of a broader metabolic picture that includes co-morbidities such as obesity, type two diabetes, insulin resistance, or metabolic syndrome. Other secondary factors can also influence triglyceride levels like diet, alcohol use, liver disease, and renal disease.<sup>4</sup> So for many patients, the picture isn't explained by a single syndrome alone. It reflects a mix of underlying predisposition, comorbid disease, and secondary drivers that together push triglycerides into the severe range and increase the risk of complications, including pancreatitis.<sup>7</sup>

**Dr. Turck:**

Let's shift gears now and talk about those clinical consequences. Acute pancreatitis is probably the complication clinicians worry about most in this context. What does the evidence tell us here?

**Dr. Michos:**

It's a critical relationship to understand. We know that hypertriglyceridemia is the third most common cause of acute pancreatitis, right behind gallstones and alcohol, and it accounts for roughly five to 22 percent of acute pancreatitis episodes.<sup>10</sup> As I mentioned, once triglycerides are in that 500 milligram per deciliter range and above, the risk of acute pancreatitis becomes much more clinically relevant.<sup>4</sup> And that risk continues to rise as triglyceride levels go even higher.<sup>2,5</sup>

One study reported that patients with very severe elevations—above 1,000 milligrams per deciliter—had an increased risk 17times higher than patients with triglycerides below 200 milligrams per deciliter, with a confidence interval ranging from 15 to 20.<sup>2</sup>

What's also important is that after a patient has had one episode of acute pancreatitis, the risk of another event becomes a real concern. In one analysis of patients who had an acute pancreatitis event in the prior 12 months, the incidence rate of another event was 23 percent in those with triglyceride concentrations greater than 880 milligrams per deciliter and 24 percent in those above 1,000 milligrams per deciliter.<sup>2</sup> The risk is even higher in patients with a history of multiple events. Among those who have had two or more acute pancreatitis episodes in the previous 12 months, the incidence of another event was 49 percent in both of the extreme hypertriglyceridemia groups.<sup>2</sup> So when we see a patient with triglycerides in that severe range, it's important to keep in mind that once acute pancreatitis occurs, recurrence becomes a very real concern—especially if triglycerides remain severely elevated.<sup>2</sup>

**Dr. Turck**

For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Erin Michos about severe hypertriglyceridemia, or sHTG—its disease burden, clinical risks, and recommended management approaches.

Now, Dr. Michos, beyond the risk of that first event, what else should clinicians understand about the burden and consequences of hypertriglyceridemia-associated acute pancreatitis?

**Dr. Michos:**

The burden on patients is substantial. When you compare acute pancreatitis events associated with sHTG to events from other causes, the severity profile is notably worse. In one analysis, sHTG-associated cases had higher rates of ICU admission, organ failure, pancreatic necrosis, and mortality compared to acute pancreatitis from other causes. Hospital stays are also longer, at a median length of stay of 17 days compared to seven days for patients with pancreatitis in the setting of normal triglyceride levels.<sup>11</sup> And then there's a meaningful healthcare-system impact. Recurrent episodes, prolonged hospitalizations, and the need for intensive care can also add substantially to the overall burden.<sup>12-14</sup>

**Dr. Turck:**

Now we've focused on pancreatitis, but there's also a dimension here of atherosclerotic cardiovascular disease, or ASCVD. How should clinicians think about elevated triglycerides in relation to cardiovascular risk?

**Dr. Michos:**

Well, that's a great question. We know that elevated triglycerides are associated with increased ASCVD risk,<sup>5</sup> but the relationship is definitely more nuanced than it may seem at first glance. In the Copenhagen studies, elevated triglycerides were associated with increased risk of myocardial infarction, ischemic heart disease, ischemic stroke, and all-cause mortality.<sup>15</sup> Part of that gets back to the biology we discussed earlier. Overproduction and inadequate lipolysis of VLDL and chylomicrons result in the formation of remnant particles.<sup>16</sup> These particles are relatively enriched in cholesterol, also known as remnant cholesterol, which appears to be an important link between elevated triglycerides and atherosclerotic risk.<sup>15,17</sup>

For example, one millimole per liter increase in remnant cholesterol, which is about 39 milligrams per deciliter, this was associated with a 2.8-fold causal increase in risk for ischemic heart disease.<sup>17</sup> Now, when triglyceride levels are very high, low-density lipoprotein, or LDL, particles become enriched with triglycerides and they carry less cholesterol. And that's part of the lipoprotein remodeling process. Hepatic lipase hydrolyzes these triglyceride-rich LDL particles to form small, dense LDL particles, which are proatherogenic.<sup>18-21</sup> As you bring triglycerides down with treatment, that remodeling starts to reverse. LDL particles shift back to carrying more cholesterol, so you may see LDL cholesterol, or LDL-C, levels go up.<sup>18,19,22</sup>

But let's pause there, because that rise in LDL-C doesn't necessarily mean there are more atherogenic particles circulating, but rather that each particle is carrying more cholesterol.<sup>5,19,22</sup> And at the same time, there is only limited evidence from randomized controlled trials that lowering triglycerides or triglyceride-rich lipoproteins reduce ASCVD risk.<sup>16</sup> And that's an important distinction, because elevated triglycerides may be serving, in part, as a marker of atherogenic remnant particles rather than acting as the sole direct driver themselves.<sup>17</sup>

Another clinical nuance is that once triglycerides move into that severe range, pancreatitis prevention often becomes a more immediate concern, even though cardiovascular risk remains elevated.<sup>5,10,15</sup>

**Dr. Turck:**

And beyond pancreatitis and cardiovascular risk, are there other ways sHTG affects patients that clinicians should be aware of?

**Dr. Michos:**

Yes, and I think this is an important part of the picture that sometimes gets overlooked.

From a physical standpoint, patients may experience symptoms like fatigue, abdominal discomfort, or more general aches and pains, and those symptoms can start to interfere with their day-to-day activities.<sup>1,23</sup> There's also an emotional and psychosocial component. Patients can report anxiety, irritability, or concerns about having another acute event, particularly if they've already experienced pancreatitis. And then over time, that can affect sleep, family life, and work.<sup>23</sup> Some patients also describe more subtle cognitive effects, things like difficulty concentrating or what they might describe as brain fog. While those symptoms can be multifactorial, they still contribute to overall disease burden.<sup>1,23</sup>

And beyond symptoms, we're also recognizing that sHTG often exists as part of a broader, multisystem metabolic condition. For example, many patients have metabolic dysfunction–associated steatotic liver disease, or MASLD.<sup>1</sup> So, when you put that all together, sHTG can affect multiple aspects of a patient's health and quality of life, which is another reason it's important to recognize and address it in clinical practice.

**Dr. Turck:**

Let's turn our attention now to management. What do current guidelines say about treating this patient population?

**Dr. Michos:**

Current guidelines really focus in on a few core priorities in these patients. First, they call for assessing ASCVD risk, identifying and managing any secondary causes of hypertriglyceridemia, and optimizing statin therapy and adherence when indicated.<sup>5</sup> From there, lifestyle intervention remains the foundation of management. That includes dietary changes, weight loss, regular physical activity, and for patients with diabetes, improving glycemic control is also a key part of treatment.<sup>5</sup>

From a nutrition standpoint, there's an emphasis on low-fat and low-carbohydrate diets. For patients with triglyceride levels above 1,000 milligrams per deciliter, the recommendations include a very low-fat diet, which typically is only around 10 to 15 percent of total calories from fat.<sup>5</sup> Now while they are the cornerstone of treatment, in practice, lifestyle measures alone often aren't enough. They require intense long-term adherence and rarely lead to normal triglyceride levels on their own.<sup>5</sup>

As a result, for triglycerides 150 to 499 milligrams per deciliter, guidelines recommend that therapies should focus on reducing ASCVD

risk. When triglycerides get above 500 milligrams per deciliter, pancreatitis risk increases, and at levels above 1000 milligrams per deciliter, management focus should shift to reducing the risk of pancreatitis.<sup>5</sup> Overall, while current standard approaches can lower triglycerides, their effect is often moderate.<sup>5</sup>

**Dr. Turck:**

And on that note, are there still patients who aren't able to get to goal with current approaches?

**Dr. Michos:**

Yes, unfortunately. In patients with more severe disease, standard-of-care approaches often don't achieve adequate triglyceride reductions, and some patients may have persistent sHTG despite guideline-recommended interventions.<sup>5</sup>

And for patients with FCS, standard therapies like fibrates and omega-three fatty acids aren't typically effective options because these therapies rely on functional LPL activity, which these patients fundamentally lack. So historically, management for FCS has relied on extreme dietary fat restriction and elimination of alcohol and added sugars, which can be extraordinarily difficult to maintain long term.<sup>5,23</sup> But the recently updated 2026 ACC/AHA/Multisociety Guideline for Dyslipidemia Management reflects an important change: this new guideline now recommends an apoC-III inhibitor as an adjunct to diet for adults with FCS and fasting triglycerides at or above 1,000 milligrams per deciliter.<sup>5</sup>

Now, among patients with MCS, response to fibrates and omega-three fatty acids can vary.<sup>5</sup> So the bottom line is that, even with the tools we have, we're still falling short for a meaningful number of patients with sHTG.

**Dr. Turck:**

And as we come to the end of our discussion, Dr. Michos, what's the main takeaway you'd want clinicians to leave with?

**Dr. Michos:**

You know, in a busy office practice, it's very easy for hypertriglyceridemia to fall to the bottom of the problem list. But given the serious risks we've talked about today, sHTG really does need to be a clinical priority. And that's the call to action here. It's on us to take a closer look of how we're evaluating and managing these patients in our practice.

**Dr. Turck:**

Well, as those final insights bring us to the end of today's program, I'd like to thank my guest, Dr. Erin Michos, for a thoughtful discussion on severe hypertriglyceridemia. Dr. Michos, thanks again for joining us.

**Dr. Michos:**

Thank you, Dr. Turck. It was a pleasure.

**Announcer:**

This program was sponsored by Ionis Pharmaceuticals Medical Affairs. If you missed any part of this discussion or to find others in this series, visit *Heart Matters* on ReachMD.com, where you can Be Part of the Knowledge.

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