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What Comes Next: Building the Future Lipid Toolbox

Announcer:

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Dr. Ballantyne:

Hi, I'm Christy Ballantyne from Baylor College of Medicine. Here with me today is Dr. Erin Michos. In this episode, we'll look at the potential impact of emerging data on the current landscape in ASCVD.

So Erin, where do you think we're headed in terms of how we might be treating patients with ASCVD?

Dr. Michos:

Well, thank you. So as you know, we have numerous landmark randomized clinical trials and major meta-analysis that clearly establish the cardiovascular benefits of statins across primary and secondary prevention populations. But we also have studies showing that adding non-statin therapies, which we currently have ezetimibe, bempedoic acid, PCSK9 inhibitors, when you add these to background statin therapy, this further reduces risk. Now, the problem with what has typically done in clinical practice, this stepwise approach where you start a statin and then bring them back, and then maybe you add ezetimibe, and maybe you bring them back, and then maybe you PCSK9 inhibitor, is that when you do this stepwise approach, what you lose is time, and there's a real urgency to get to goals quickly. And delaying lipid-lowering intensification translates to worse outcomes than early intense lipid-lowering therapy. And so there's been this push with trying to use combination therapy more early and upfront in high-risk patients. For example, in the SWEDHEART Registry, we see that patients after an MI, if they get early upfront ezetimibe with the statin, they had significantly lower risk than people who got delayed ezetimibe adding or no ezetimibe at all. So we know that therapies provide the same risk reduction in ASCVD per degree of LDL lowering and are now embraced by our guidelines. We have PCSK9 inhibitors that are being increasingly used in high-risk patients and can be used in combination with other lipid lowering.

And we have actually, you know, new oral options in PCSK9 in addition to the injectables. PCSK9 inhibitors lower LDL by about 60%, and have some modest LPA lowering around 25%. But as we talked about in other episodes, we have this emerging new tool, a new CETP inhibitor, obeticholic acid, that has shown benefit in LDL lowering around 35%, across a background of lipid-lowering therapy.

So it has, similar efficacy on top of a statin, on top of ezetimibe, on top of PCSK9 inhibitor. Background therapy doesn't mitigate its efficacy, with similar lowering in ApoB and non-HDL, as well as we see some, Lp(a) reduction and good safety signals. So not only was there no increase in treatment-emergent adverse events, but there's actually some intriguing favorable reductions that we see in the phase 3 trials with reduction in risk for new-onset diabetes and reduction in renal dysfunction. So what we're really waiting for, though, is the sort of the landmark, cardiovascular outcome trial of obeticholic acid. This is called the PREVAIL Trial. It enrolled over 9,000 patients

with established cardiovascular disease who remains with elevated LDL despite maximally tolerated lipid-lowering therapy. Patients are randomized obeticholic acid 10 mg versus placebo. It's an event-driven trial with the primary outcome being 4-point MACE, but there's also going to be some really important secondary analyses, including, you know, the new-onset diabetes endpoint. So very excited to see those results.

I think we have an evolving therapeutic landscape across both oral and injectable lipid-lowering options, and I think obicetrapib is well-situated, within our broadening armamentarium of tools. and the ongoing PREVAIL outcome trial is sort of posed to define the clinical role of obicetrapib. but I think, you know, this is in terms of patients and that I would choose for therapies, I think, depends on, you know, their baseline risk, their baseline LDL value, our LDL target, their underlying comorbidities, and trying to match patient preferences as well in terms of choosing which lipid-lowering tool for which patient. So Christy, what are your thoughts on this?

Dr. Ballantyne:

The new guidelines, it goes with the same concept, lower is better. I think less than 55, they're saying a high risk, but I think it's going to be all secondary prevention and probably in high-risk primary prevention from what we saw, with the recent VESALIUS-CV study. And as you mentioned, we can do it now.

And a lot of times you could just be a statin, and then you could add PCSK9. Now the combination tablet of obeticholic acid and ezetimibe also gives you about a 50% reduction. So there's going to be easy ways when we've got an oral PCSK9. So there's going to be easy ways to go straight to boom, getting someone down below 55, probably 40 or 30 is optimal.

And, it's very exciting. It's going to be great for our patients.

Dr. Michos:

Great. So I think we'll, you know, be thinking about precision lipid care, maybe combining genetic risk profiling, some functional biomarkers, but really we have an expanding therapeutic toolkit to move beyond, LDL towards comprehensive ASCVD risk modification. again, in terms of patient selection, I'd be thinking about things like metabolic risks such as pre-diabetes. Maybe an agent like obeticholic acid that might have favorable glycemic benefits may be, you know, preferred potentially in a patient that has a cardiometabolic background, maybe patients with high Lp(a) or kidney dysfunction, and as well as patients' preferences, whether they want to be an oral versus an injectable medicine.

So it's good to have tools to choose from.

Dr. Ballantyne:

Yeah, basically in summary, the toolbox is going to be full of some very effective tools, so stay tuned. It's looking like it'll be great opportunities for our patients and also making it a little easier as a, as healthcare providers to get them to their targets. Thank you very much for joining us.

Announcer:

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