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Understanding the role of triglycerides in the assessment of residual risk

Dr. Zambon:
Today's topic is understanding the role of triglyceride-rich lipoproteins in the assessment of cardiovascular residual risk.

These are my disclosure slides.

These are the points that I will be briefly talking through in the next 10 minutes. Cardiovascular residual risk, it's a complex clinical challenge that recognizes multiple players, as you can see on the left-hand side of the slides. There are lipid components, LDL cholesterol not properly controlled, triglyceride-rich lipoprotein, LP(a), but also inflammation and procoagulant state.

Now, since we're focusing on lipids, what I'd like to show you is how relevant is cardiovascular residual risk in the context of optimally controlled LDL cholesterol. And to do so, I will use FOURIER trial. As you can see on the left-hand side panel, these are patients with diabetes, cardiovascular disease, who we treated and recruited in the FOURIER trial with evolocumab and high-intensity statin therapy with an LDL cholesterol of less than 1 mmol; it's a 0.8 mmol, 30 mg/dL. And as you can see here, the event rate is 10.2%, which is higher than the same patients in the same trial without diabetes, treated with placebo, at the blue line, which means only high-intensity statin, and an LDL cholesterol of 90 mg, not 30, 90 mg. Despite excessively nice LDL cholesterol control, patients with diabetes remain at significant risk of cardiovascular disease.

Now, let me show you how triglyceride plays a role in that. Evidence from over the past 10 years really suggested that triglyceride-rich lipoprotein are causally promoting initiation and progression of atherothrombotic process. Mendelian randomization analysis suggested one TG-rich lipoprotein is at least as atherogenic as one LDL particle. Patients with diabetes have an overproduction of TG-rich lipoprotein from the intestine, and particularly from the liver, and a slower catabolism of this lipoprotein. This lipoprotein accumulates in the blood. They're small enough they can cross the endothelial barrier, reaching the subendothelial space, the intima space. They accumulate in the macrophages. They're also associated with endothelial dysfunction and inflammation. So it's a quite nice and complex way of causing damages.

So if the question is, are triglyceride-rich lipoproteins star or second leads? Let me show you how I believe they're stars, rather than second leads. Looking at pathophysiology, inflammation, and triglyceride, and clinical evidence on cardiovascular events.

Triglyceride-rich lipoproteins, as I showed you, when they get hydrolyzed, they become smaller, so they cross the endothelium; they penetrate the intima. And once they enter the intima, they're taken up by macrophages, loading them with cholesterol, and transforming them into foam cells. But lipolytic product in the blood from triglyceride-rich lipoprotein are contributing to inflammation, endothelial dysfunction, and activation of platelets. So, again, procoagulant, proinflammatory, as well as inside the plaque, leading to foam cell formation.

Now, we knew from 1994 that triglyceride-rich lipoproteins were dangerous and were inside the atherosclerotic plaque. This is a paper published, again, in 1994, I called it evidence from the past, Dick Havel and John Kane from San Francisco. They look at the blood of patients undergoing coronary artery bypass graft. On the left-hand side, you see triglyceride-rich lipoprotein at the microscope picture,

slightly larger on the right-hand side, LDL. When they look inside the coronary plaques that were removed from these patients, of course, they found LDL particles, as you see on the bottom left- and right-hand side. But up to 36% of the mass of the lipoproteins were triglyceride-rich lipoproteins. So we knew 30 years ago that triglyceride-rich lipoproteins were inside the plaque where they should then not have been. We simply forgot this concept.

Now, inflammation. This is a more recent observation; 50,000 people, it's Copenhagen General Population Study. After adjustment by multiple confounding variable, they look at how much CRP increases by 1 mmol, or 40-mg increase in LDL cholesterol in this population, and that increases about 6%. Now, they look at the CRP increase for the same amount of increase, 1 mmol, or 40 mg, in the cholesterol now in the triglyceride-rich lipoprotein, and what they found is that increases 36%, not 6%, 36%, suggesting highly proinflammatory role of TG-rich lipoproteins.

Now, this is an old paper we published 10 years ago looking at carotid plaques and plaque composition, plaque phenotype. On the left-hand side are macrophages in the plaque. On the right-hand side smooth muscle cells. And what we showed is that concentration of macrophages is significantly associated with triglyceride-rich lipoprotein rather than LDL cholesterol levels as well as smooth muscle cells. In this case, poor and few smooth muscle cells are associated with the triglyceride-rich lipoprotein. A lot of macrophages, few smooth muscle cells, that's the recipe of unstable atherosclerotic plaque.

Now, no wonder that in 2019, Peter Libby, looking at some nontraditional risk factor drivers of arterial inflammation, recognized triglyceride-rich lipoprotein as the powerful component moving towards the inflammation. Now, clinically speaking, this is a primary prevention population. It's called TG-REAL. It's a retrospective cohort analysis, almost 160,000 individuals divided into 3 groups of triglycerides below 1.7 or 150, between 150 and 500, and above 150. They look at atherosclerotic cardiovascular events and overall mortality. Top part of the table, atherosclerotic cardiovascular event, those with high triglyceride, 150 to 500, as compared to the reference group, those with normal triglycerides, in the age- and gender-adjusted analysis, they had more than twice the risk of developing atherosclerotic cardiovascular disease. On the right-hand side column, after adjustment for multiple variables – as you can see, the list is on the lower right side of the slide – still, the risk remained higher by 60% as compared to normal triglyceride. Mortality rate was 50% to 60% higher in the multiple adjusted or age- and gender-adjusted model, suggesting that, indeed, in this moderate to low or intermediate-risk population, a moderate elevation of triglyceride-rich lipoprotein is significantly associated with increase of all-cause mortality in atherosclerotic cardiovascular disease. Clinical implication, we need to measure triglyceride, because that's part of a more accurate cardiovascular risk profiling.

Now, this is a population at a high risk. Atherosclerotic cardiovascular disease already there, Northern America, in fact, it's a Canadian population. It's about 200,000 people. About 25% of these patients, they have a mean LDL cholesterol of 68 mg, so 1.8, nicely controlled. The 25% had triglyceride level ranging between 135 and 500 mg/dL. So it's not a rare situation.

Now, if you move your attention to the right-hand side panel, you can see clearly that risk of recurrent event progressively goes higher as triglyceride increases. This is a nicely controlled LDL population with progressively higher triglyceride, the secondary prevention.

So really now we have evidence that triglyceride-rich lipoproteins are stars in the context of residual cardiovascular risk, and also there is a crosstalk between triglyceride inflammation, I showed you, macrophages in the plaque, higher CRP. In fact, hypertriglyceridemia, it's very common place and in a number of acute and chronic clinical settings, not only the atherogenic dyslipidemia, but insulin-resistant state, obesity, metabolic syndrome, type 2 diabetes, as suggested by the very nice recent paper by Gary Lewis and Bob Hegele. But it's also present in the subinflammatory states and also in the procoagulant state. So it's clinically very common in the number of what the authors call perfect clinical storms. So it's very relevant. So reducing triglyceride-rich lipoprotein atherogenicity, we need to look and tackle more than just decreasing triglyceride, but we need to modulate multiple steps. They need to decrease, actually, the number of atherogenic lipoprotein. This is something that happens with fenofibrate, one of the two approaches suggested by the guidelines. The other approach, using omega-3 fatty acid, and particularly icosapent ethyl, has more sophisticated ways of resulting in reduction of cardiovascular events. There is a small decrease in the number of triglyceride-rich lipoprotein, like in fenofibrate. Icosapent ethyl tackles the inflammatory component of dyslipidemia and also the procoagulant state. So I think we need to be more sophisticated in the approach when we look at triglyceride-rich protein atherogenicity.

And again, I hope I convinced that triglyceride-rich lipoprotein are highly proatherogenic and they are stars in the context of cardiovascular risk.