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Reassessing the role of triglycerides in residual cardiovascular risk

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I'm Richard Hobbs, head of Oxford Primary Care, and I'm delighted to be talking about a topic in terms of reassessing the role of triglycerides in cardiovascular disease residual risk. You'll see my disclosures at the bottom of the slide.

In terms of summary of my presentation, I'm going to briefly talk about the global importance of CVD, touch on the main risk factors, in particular, then focus on the role of lipids, and in that context consider the continued residual risk in patients even on maximal therapies. Then at the end, we'll look at the evidence for the role of triglycerides in terms of cardiovascular residual risk.

Let's just look at the global importance. These are the most recent data from the WHO on the major causes of death globally. As you can see, the major manifestations of vascular disease, namely coronary heart disease and stroke are way out in front in terms of most important causes of death. By some margin, stroke is double the third most common cause of death. Ischemic heart disease is three times that third. As you can see, long-term conditions are by far and away now globally the most important drivers of mortality. Perhaps of even greater importance is that cardiovascular disease is the most important cause of premature death as well, and that's obviously what we are trying to reduce through prevention.

Now, if we look at disability-adjusted life years, then the pattern is the same. At the top there, you can see patients between 50 and 74, and then over 75 in the bottom table. Now, if we look at disability-adjusted life years, then we can see that actually, vascular disease are the principle drivers here of disability. That is important because it's disabilities that actually drive healthcare utilization costs. Again, ischemic heart disease and stroke resulting, in this instance, not death but in suffering significant events. We've got other vascular diseases actually significantly increasing in prominence such as CKD and diabetes.

Then if we look at the main risk factors for what is driving these disease states, then it's the vascular risk factors, not surprisingly, that dominate the global charts in terms of the importance of blood pressure, the importance of smoking cessation, of controlling lipids, and controlling risk factors such as sugar in diabetes. Now, there have been some successes though. If you look at the rate of change of these global risk factors, what you can see is that some, particularly smoking as a consequence of largely big public health policies has actually declined year on year, which is a really good sign. Other traditional risk factors are slowly increasing, including lipids, and factors such as obesity, unfortunately, are significantly increasing. We've got this backdrop of high-risk factor rates in the population and some risk factors actually accelerating globally.

Let's now just focus on lipids, and of course, this is one of the most evidence-based areas for clinical practice. It's been statin-dominated for the last 20 years, and here we have the CCT analysis showing what's significant, over 20% risk reduction you get. For every one millimole LDL reduction, you're going to achieve a 21% reduction in major vascular events, and it's all vascular events that are reduced.

If we look at cause-specific mortality, then again, more coronary deaths will be prevented through statins. In fact, you do get a significant reduction in all vascular events through the use of statins, and importantly, you get early treatment effects. Within a few months of commencing therapy, you're going to get improvements in outcomes.

If you look at the next large group of LDL-lowering drugs, the PCSK9 inhibitors, then you can see that on top of well-treated patients with

a statin, the additional LDL lowering you'll get with a PCSK9 inhibitor will constitute a similar additional benefit. You're getting, actually, additive beneficial effects through using both a statin and a PCSK9 inhibitor.

Not surprisingly therefore, international guidelines, in this instance, the European Society guidelines focused particularly on statin-based therapy and have increasingly tried to identify particular at-risk groups in the population so that you can triage treatment to more intensive therapies for people who have clusters of factors that put them at greater risk.

That's important because, despite the successes I showed you earlier in relation to statin therapy, as you can see on the right, all the statin trials demonstrate this significant residual risk because, obviously, if you get say a 25% reduction in vascular events by using a statin, you've still got 75% of events that aren't being averted.

Remember that these patients are in trials so they're maximally treated for other risk factors such as blood pressure and smoking. Even the addition of a PCSK9, which will add about an additional 15% risk reduction, you can see there continues to be this residual risk.

That, therefore, has been the topic of lots of discussions of what we can do to try and lower that gap is to actually have interventions that actually further reduce risk in the population.

There's a summary on the slide of the various mechanisms that may contribute to that, be they thrombotic or be they other lipid characteristics, or other factors such as generalized information.

What I'm now going to focus on is the potential for triglycerides potentially being a target for therapy, but if not, certainly being a marker for increased risk. If we look at large global cohort studies, on the left there, you'll see the Copenhagen large population studies showing this incremental risk with raised triglyceride levels. On the right there, you can see that even in patients where the dominant pathology is LDL cholesterol, these are patients basically who suffer FH, you've still got a gradient of risk in terms of triglycerides once they get above 150 milligram per deciliter.

Similar data come from the Framingham Offspring Study, again showing that above 150 and up to about 300 milligrams per deciliter, you're getting very rapidly accelerating risk. Then still increasing but at a slower rate and replicated there in the Copenhagen Heart study shown on the right.

Even in real world studies, the same observations come out, the increasing levels of triglyceride within this time, just a routinely screened population of people who are just routinely getting lipid measurements showing the same gradient effect above 150 milligrams per deciliter.

On the left there, you can see that within the population, this represents about a quarter of patients with some degree of coronary vascular disease. This is a particular potential new target group in terms of identifying people who need additional benefit.

Of course, the same was seen in the old fibrate trials, these were pre-statin trials largely, which were disappointing in terms of their effect on vascular risk reduction, but interestingly, did seem to have an effect in the subgroup of the population who had raised triglycerides and low HDL levels. Although, the recent PROMINENT study has effectively put fibrates to bed since there was no benefit seen in this large outcome trial on the background of good statin treatment.

I'll summarize by saying that CVD remains the most important cause of premature death and disability in the world, that traditional risk factors explain most disease, and that despite the large evidence base we've got for interventions, we continue to have a significant risk within the population, and what the future is going to hold is better phenotyping the subgroups of this treated population who have sufficient markers for residual risk to guide additional treatment.

Thank you.

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