

**ALBERICO**

There's always been this argument in the science field of cholesterol, whether we can have an LDL going down to almost 0 without any harm. Many of the people have been skeptical for two reasons. One, the two other main risk factors-- that is glycemia and hypertension-- they do have a J-shaped curve because of physiological reasons. With very low glucose, you die. With very low blood pressure, you die, because there is no blood flowing through the heart to the brains.

**CATAPANO:**

LDL is a different story. The biology is telling us you can have a very, very, very low LDL without any problem, provided you synthesize ApoB in the intestines, the B48, which will trigger [INAUDIBLE] production. And in that way, you can absorb vitamins, that are fat soluble vitamins, and other components of the diet that are essential for the growth, for the well-being of people. But you might not have ApoB 100 around, and then you still have no major problems with your health, as far as we know, from the genetics.

In terms of ultra-low LDL, by taking them very low with a drug, we have learned, both from the IMPROVE-IT and the two most recent trials-- the ODYSSEY and FOURIER with PCSK9 inhibitors-- that you can go as low as 10 million per deciliter-- the sub-analysis from the FOURIER for instance-- and still the incidence of side effects is exactly the same as for those who on trial at an LDL above 100 milligrams per deciliter.

What does that mean, there are no side effects? Well, this is not the point, because there may be side effects. But it stays that side effects are not related to the level of LDL achieved. In other words, every drug has some side effects, no exception for the drugs that use for lipid lowering. However, this is not linked to the level of LDL that has been achieved.