STEFANO DEL PRATO: Type 2 diabetes is a condition which is still associated with a very high risk of cardiovascular disease. Very recent data have shown that over the years, the cardiovascular mortality in the diabetic population is dropping. So we have done quite a good job over the time. However, when we compare the cardiovascular mortality of diabetic people with those without diabetes, the rate of mortality is still at least twice as much. So something needs to be done.

The reason for the very high cardiovascular risk in type 2 diabetes is probably relying on the multiplicity of factors that increase such risk. And among these factors, one of the ones that's been identified very early on, actually, by the UKPDS already, is the level of LDL. And over the years, we have learned that reducing the LDL to a number of interventional trials is very important, is very fundamental, in reducing cardiovascular risk.

And even going lower levels, to lower levels of LDL cholesterol, is associated with a significant reduction to cardiovascular risk. For instance, in the improved combination of statin and ezetimibe the subgroup of the diabetic population was associated with a [INAUDIBLE] reduction in cardiovascular risk and the major cardiovascular events. However, in that particular study, the diabetic patients still had a 40% rate of mortality of cardiovascular events as compared to the 30% in a non-diabetic population. So suggesting that in the diabetic subject that there is an intrinsic residual cardiovascular risk that needs to be dealt with.

How to deal with that? One potential way is to reduce further down the level of LDL cholesterol. And maybe not just LDL cholesterol. Also taking into account other faction of of the lipid profile that may be of importance specifically in diabetic individuals. And I'm referring in particular to the triglyceride-rich lipoproteins which may be reflected to a better extent by the non-HDL cholesterol concentration or by the level of the ApoB. So it is important to try to reduce cholesterol in these individuals.

Now, we have a new potential option nowadays, because when a patient does not achieve the target levels for LDL cholesterol using the statin, or if they are intolerant to statins and do not reach the level even in the presence of the ezetimibe, now we have the option of using the PCSK9 inhibitors. The PCSK9 inhibitors have been initially approved by the FDA in 2015 for reduction of cholesterol levels. And later on, after two years, in 2017, it has been also approved for preventing cardiovascular events in people at high cardiovascular risk.

And we have now a number of data suggesting that, indeed, the further reduction of LDL cholesterol can result in a major improvement or another significant improvement in the reduction of cardiovascular risk. For instance, the FOURIER study using evolcumab has shown in something like 11,000 diabetic individuals out of the 37,000 subjects that had been recruited into the study, that the reduction with of cholesterol with the PCSK9 was associated with a further 27% reduction in the risk of cardiovascular events, in particular a cardiac attack, a stroke, and so on and so forth.

Now, the point is-- and based on this data, what has been suggested by guidelines-- I'm from Europe. I'm from Italy. And for instance, the European Society of Cardiology has been suggesting that PCSK9 should be considered to reduce their LDL cholesterol to a level lower than 50 milligram per deciliter-- 55 milligram per deciliter in very high risk individuals-- that means diabetic individuals with prior cardiovascular events-- or those who do not achieve the target LDL cholesterol in spite of the use of statin and ezetimibe. So in those patients, there is a recommendation for using a PCSK9 inhibitor.

PCSK9 inhibitor is administered by injection. Usually it's every one or two weeks, depending on the formulation. And this has been associated with quite a powerful reduction LDL cholesterol levels and in non-HDL cholesterol levels concentration. In average, what has been shown in studies, there is something like between 50% and 60% reduction in LDL cholesterol and around 40% to 50% reduction in non-HDL cholesterol. There is a little bit less effect on triglycerides. So the main effect of the PCSK9 is on LDL cholesterol.

And what is even more interesting and important, or something that we need to take into consideration, is that statin have been associated with an increased risk of developing diabetes. So one question about the PCSK9 inhibitor was whether this injection-- this antibody could impact into the glycemic control of diabetic individuals. And specific studies have been done with respect to that.

For instance, using alirocumab, the study has been looking at the effect of alirocumab in type 2 diabetic individuals as well as in a small group of type 1 diabetic individuals in term of reduction of LDL cholesterol and non-HDL cholesterol. And it's showing very interesting-- and confirming other data also as shown by the evolocumab-- that the LDL reduction that can be obtained in normal subjects is the same reduction can be also obtained in type 2 diabetic individuals with a very safe profile in terms of the side effects.

So the current guidelines suggest that we need to be more aggressive in reducing LDL cholesterol. The current recommendation suggests that we have to go below 70 milligram, and according to some of the organization even lower, to 55 milligram per deciliter of LDL cholesterol, and potentially to reduce non-HDL cholesterol at least below 100 milligram per deciliter. And this may be particularly true in diabetic individuals for the very simple reason that type 2 diabetes subjects are associated with a very high residual cardiovascular risk.