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The case for early LDL-c lowering in patients at increased CV risk: When should we start?

**Dr. Perrone:**
Dear colleagues, it was a great opportunity to participate in this symposium at the 2024 ESC meeting this year. And the title I was assigned was a very challenging one. The case for an early LDL lowering in patient after increased cardiovascular risk. And it will be my pleasure to share with you my Italian experience that will be part of this presentation.

A little bit of a background why it's so important to start optimizing and reducing very intensively LDL-C in patients with acute coronary syndromes, that will be the topic of my presentation, comes from these very nice and elegant studies, 2 of them.

The first was the iGEN study that was investigating where bringing cholesterol very low with evolocumab as compared to placebo in a background of high-intensity statins in patients with a recent ACS was giving any good changes in the stability of non-culprit plaque. And therefore, patients were randomized to evolocumab 1 per monthly up to 420 mg administration versus placebo.

And the primary endpoint of this study was the minimum thickness of the fibrous gap, which is, as we know, a parameter of stability of plaque. And the magic number here as a threshold is 65 µm, meaning that patient plaques with higher than this are relatively more stable than having a lower FCP. And you see here how it was positively influenced at this endpoint by bringing LDL down to 30 mg/dL as it took hold in patients taking evolocumab. And on the right-hand side, you see holds another parameter that is describing the vulnerability of plaque, is the length of the lipid arch. The content of lipid is associated with the plaque instability. And the higher the lipids, the lower the stability of the plaque. And once again, on this secondary endpoint that were measured by OCT, evolocumab was providing a very nice difference compared to placebo in reducing the lipid arch.

A twin study was also reporting the changes in the plaques that were non-culprit in patients with ACS; that was the PACMAN-AMI study, with a different primary endpoint that was the change in percent atheroma volume. And once again, here, the patients were randomized to alirocumab versus placebo. And patients taking alirocumab were reaching the LDL value as a mean of 23 mg/dL, the lower value ever obtained in a randomized trial. And you see how this was influencing the percent atheroma change that was very significantly reduced in patients taking alirocumab.

And another important parameter is in the middle of this slide. That is the lipid content of the lipid present in the plaque that is measured by a new imaging technique, which is called near-infrared spectroscopy. And once again, when you bring LDL very low, you very nicely and substantially reduce the content of the lipid in the plaque. And once again, also, as you've seen in previous study, the minimum fibrous gap thickness was positively influenced by alirocumab.

So very consistent data that indicate that when you act very timely and very intensively in patients with ACS, you obtain, in a follow-up of 52 weeks, very good changes in terms of plaque stability. How does this translate into clinical events and into the clinical outcome of this patient? And these are very nicely hypothesis-generating results from the PACMAN-AMI. They took patients that were positively changing all the 3 parameters that we have seen in the previous slide and they compared these patients to patients who did not. And they observed the events at 52-week follow-up, and look how dramatically the event rate was reduced from above 18 to less than 9% in patients reaching all 3 favorable changes in the plaque, in the non-culprit plaque, as opposed to patients that did not. So very

encouraging data.

And of course, the feasibility of this approach being administering a PCSK9 in the context of acute coronary syndromes was tested in the EVOPACS study few years ago. Here, patients were randomized to evolocumab versus placebo, and the first lipid change were observed at 4 weeks. And you see here that the number of patients, the percent of patients that reached the LDL target for the US population, which is less than 1.8 mmol/L, was obtained in more than 99% of patients. So by doing this, you can be very effective in bringing patients to target and also very safe.

That was the background for our experimental observation that we reported from this Italian networking that was created in my country. It's called the AT-TARGET-IT investigator group. It's a group of 35 Italian centers that are working together to make observational, real-world data in our country. And from this group of patients, we took the subgroup of those who received a PCSK9 therapy during the hospital stay or immediately after discharge. And this can be done in Italy, because in Italy, we have very friendly regulatory rules for giving PCSK9, for facilitating PCSK9 initiation in patients with very high risk, including those with ACS. It's called the fast-track approach that we have in Italy.

So we focus our attention on this subgroup of patients belonging to the overall registry. And these were 771 patients, and we looked at the changes in lipid profile and also in the outcome. Looking at the lipid profile first, as we observed in other registries, including the European registry, that multicenter registry that was reported few years ago, we observed the same aspect; the patients are not very well treated. And in fact, the baseline level of these patients was 137 mg/dL. And by taking either alirocumab or evolocumab, that was reduced to 43 mg/dL, corresponding to about a 70% reduction. And this number was obtained at the first observation. The first lipid control after ACS death by clinical practice was done at 33 days from the index event.

Another important piece of information we obtained is that when you want to be successful in bringing patients to the target, you have to intensify the number of medications and use triple therapy, including a fixed-dose combination of a statin plus ezetimibe, and on top of that, the PCSK9 inhibitor. By doing so, 74% of patients reached the target, you see. You may also appreciate, though, that we have still a sizable number of patients where even triple therapy is not enough to bring them to the target.

And here is the most fascinating results we obtained in this real-world registry. We were looking at the event over a follow-up of 11 months. And we looked first at the 4-point MACE, nonfatal MI and stroke, ischemia-driven revascularization, and all-cause mortality. The same parameter for mortality was used on the ODYSSEY outcome trial. And you see here very nicely, by dividing patients into quartiles from the lower to the higher LDL level at the first observation at 33 days, you see very nicely differentiation in prognosis among those 4 quartiles. And you also see this for the 3-point MACE. In this case, the significant difference was observed between the higher versus the lower LDL quartiles. But most intriguingly, you see also a difference in the all-cause mortality, exactly as reported as in the randomized ODYSSEY outcome trial.

And when we also looked at the patients reaching or not reaching the 55 mg/dL target, which is our European target, you see also how this is nicely dividing patients with the different prognosis for the 4-point MACE, the 3-point MACE, and for all-cause mortality. That means, yes, we have to be very fast and we have to be very effective in reaching the target, because this is associated with much better prognosis. And also, if we go lower, and if you divide patients based on the median LDL level that we achieved at the first month, that was 43 mg/dL. And 43 is very close to the 40 mg/dL that is recommended by guidelines in the very-high-risk patient. You also see that you continue to accrue benefit, and the patients going lower than 43, they have a better prognosis for all the outcome parameters we select. So the lower, the better. And in addition, the earlier, the better. That's why we call this paper "strike early, strike strong" approach.

So these are my conclusions. The residual risk in patients suffering an ACS is still very high, and therefore we must be very timely and very aggressive in lowering LDL. Clinical trials and also the data you have seen from imaging intravascular studies do support this approach to be very timely and very strong. And now for the first time, the Italian real-world data that were obtained in a context of a public health system, where we are allowed to be very quick in administration of PCSK9, demonstrated that this strategy is very good also in a real-world scenario.

Thank you for your attention.