Inclisiran in primary prevention: reality or fiction?

Accompanying editorial to "*Effect of inclisiran on lipids in a primary prevention cohort from the ORION-11 randomised trial*"

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Keyword: lipids, prevention, clinical trials

In the current version of the European Heart Journal, Ray and colleagues report the effect of inclisiran on lipids in a primary prevention cohort from the ORION-11 randomized trial. (X) Inclisiran was recently approved in several countries for the treatment of hypercholesterolemia. Inclisiran is a small interfering ribonucleic acid (siRNA)-based therapy that targets hepatic production of proprotein convertase subtilisin kexin 9 (PCSK9) and consequently lowers plasma low-density lipoprotein cholesterol (LDL-C).[1] In randomized controlled trials recruiting patients with heterozygous familial hypercholesterolemia or in patients with established atherosclerotic cardiovascular disease, inclisiran was shown to be effective to reduce LDL-C levels on top of maximally tolerated statin therapy.[2,3] However no data so far has reported the efficacy of inclisiran in the primary prevention population. This publication is a prespecified analysis focusing on the effect of inclisiran in the primary prevention cohort from the ORION-11 trial.[3]

ORION 11 randomized a total of 1617 patients. Of the 203 (12.6%) patients in the primary prevention cohort, 98 were assigned to receive inclisiran and 105 to placebo. (X) The included population had a high prevalence of diabetes mellitus (65.0%) and familial hypercholesterolemia (14.8%), and 56.2% were categorized as high-risk (10-year CV of ≥20%). Patients were requested to have an LDL-C of ≥2.6 mmol/L. Compared to the secondary prevention cohort, participants included in the primary prevention cohort were younger (63.2 vs 65 years old) and characterized by a higher proportion of women (53.2% vs 24.7%). Patients in the primary prevention were also less likely to receive concomitant lipid-lowering therapies (84.7% vs. 97.8%), especially high-intensity statin (61.6% vs. 80.3%). The mean LDL-C value was higher (3.6 mmol/L vs 2.6 mmol). Over the trial duration, four injections of inclisiran vs matched placebo were planned at days 1, 90, 270 and 450. Both co-primary endpoints were met, with similar effects compared with the secondary prevention cohort. In the primary prevention cohort, inclisiran significantly reduced mean placebo-adjusted LDL-C levels by 43.7% from baseline to day 510, corresponding to an absolute reduction of 1.5 mmol/L, and by 41.0% from day 90 to day 540, corresponding to an absolute reduction of 1.3

mmol/L. The proportion of patients who achieved the LDL-C targets in the primary vs secondary prevention cohort was also higher with inclisiran (77.6% vs. 30.5%, respectively for a target of less than 2.6 mmol/l mg/dL and 49.4% vs. 1.1%, respectively for a target of less than 1.8 mmol/l. Other key lipoproteins were also reduced, such as non-HDL-C (-39.5%), apoB (-35.8%) and lipoprotein(a) (-28.9%).

The level of completeness of lipid measurements over the duration of the trial was high in both groups, although numerically there were more patients in the inclisiran arm who had missing values (13 vs 10 at day 510 and 14 vs 5 at day 540). Imputation techniques were applied for sensitivity analysis, assuming that the missing data was a random effect and not linked to intervention, drug discontinuation or patient characteristics. In case of non-random missing values, there is the potential pitfall of overestimating the effect of the intervention since those patients lost over the trial duration are less likely to receive the intervention or be treated similarly. In this regard, reporting co-interventions after randomization (e.g. lifestyle habits, adherence to therapies) should systematically be required to exclude potential attrition bias.[4] Although the trial was blinded and the protocol did not encourage the measurement of lipids over the trial's duration, participants may have requested a measurement of LDL-C from their general practitioner or treating cardiologist. Although it is unlikely this occurred on a large scale, this might overestimate the effect of the intervention because of possible co-interventions potentially influencing the primary outcome. Such concerns are often overlooked when appraising results of trials with lipid-lowering therapies.

In terms of safety, the use of inclisiran was generally well tolerated. The proportion of patients with adverse events was higher with inclisiran (92.9% vs. 83.8%), including serious adverse events (20.4% vs. 12.4%), adverse events leading to drug discontinuation (5.1% vs. 2.9%), and mild treatment-emergent adverse events at the injection site (4.1% vs. 0%). However, the absolute numbers were low (4 vs. 0 for injection site) and given the small sample size of the study, the distribution of events was more likely to be unbalanced by chance. For instance, the proportion of new worsening or recurrent malignancy was 5/98 (5.1%) in the inclisiran group vs. 1/105 (1.9%) in the placebo group, although several previous trials with lipid-lowering therapies have not shown an increased risk of malignancy.[5,6] Post-marketing observational studies are now needed to better reflect real-world practice safety and efficacy and the potential impact on long-term adherence. As a rule, the safety threshold required to adopt a medical strategy is more stringent if the expected benefit is lower. Since the absolute risk reduction of cardiovascular events with lipid-lowering therapy is smaller in the primary compared to secondary prevention setting, safety considerations are particularly important for informed shared decision-making to be made. In contrast to currently available monoclonal antibodies against PCSK9 (alirocumab and evolocumab), inclisiran is administered by subcutaneous injections, but only once every 6 months.[7] The distinction in the mechanism and length of action between inclisiran and monoclonal antibodies may come to play a role when considering duration and persistence of any side-effect. Future observations reporting on intensity and duration of side effects observed with the different PCSK9 inhibitors will be needed for the day-to-day management.

The 2019 ESC/EAS guidelines on the management of dyslipidaemia recommend the use of PCSK9 inhibitors in high-risk or very-high risk patients to reach LDL-C targets on top of maximally tolerated

statin therapy and ezetimibe.[8] The recommendations were, however, based on the safety and efficacy of PCSK9 inhibitors observed in large cardiovascular trials in patients with already established cardiovascular disease and not for primary prevention, and only on results from the monoclonal antibodies directed against PCSK9 as those from inclisiran were not yet available.[9,10] For inclisiran, the ORION-4 trial is currently evaluating the efficacy and safety of inclisiran on major adverse cardiovascular events among 15'000 participants (males and females aged 40 and 55 years or more, respectively) with preexisting atherosclerotic cardiovascular disease (NCT03705234). Results are expected for 2026.

Studies with inclisiran do not provide any scientific novelty compared with other PCSK9 inhibitors in terms LDL-C lowering, however, adherence to inclisiran is expected to be higher compared with evolocumab or alirocumab as injections can only be performed by health care professionals rather than be entirely managed by the patients. Administrating inclisiran as a vaccine could, moreover, be an interesting alternative in patients for whom daily drug intake is not possible, or as an adjunct therapy. Health policies might also want to consider the vaccine approach that inclisiran provides for the prevention of cardiovascular risk at a larger scale in the population. Furthermore, therapeutic adherence reached at a widespread level might also increase and extend cardiovascular disease-free life expectancy.[11]

On the other side, independent experts from medical societies consider that non-statin agents have not yet demonstrated any benefit in the primary prevention of cardiovascular disease in terms of stroke or myocardial infarction risk reduction because the trials for these agents were not designed to answer this question appropriately.[12,13] In primary prevention, the risk of cardiovascular disease is also lower at baseline than in secondary prevention, and therefore clinical trials in this population require larger patient numbers, extensive resources and a longer follow up to show any morbi-mortality benefit. The injection of inclisiran has already shown to effectively reduce LDL-C levels in both settings, however, the translation of this reduction into clinical benefit in the real-world will depend on a large number additional of factors, such as baseline risk, tolerability of background therapy, side effects, patient motivation to continue the injections, long-term sustainability of LDL-C lowering, but also biological disturbances of other organs, multimorbidity, age and life expectancy, incidence of competitive risk events, such as cancer and so on and so forth (see Figure). The level of expertise of the medical team will also need to be taken into account, as will the reimbursement of the drug by the health care system. Several cost-effectiveness analyses have been undertaken for inclisiran in the secondary prevention setting and treatment was only found to be cost-effective if the cost of treatment was lowered. [14,15] Since cost-effectiveness depends on cardiovascular event rates in the population of interest, the incremental cost-effectiveness ratio of inclisiran will be even higher for patients in the primary prevention setting compared to the secondary prevention setting. Such medical economic considerations are inevitably likely to impact medical decisions and the choice of therapies, especially for chronic conditions such as hyperlipidemia. Treatments with no clear cost-effectiveness benefit are becoming increasingly targeted by health services, and actions have already been undertaken to prevent their reimbursement, such as statin therapy for people aged 75 or older without cardiovascular disease in Switzerland. In this light, it will be interesting to see how the results of the ongoing ORION studies will be able to position inclisiran as a game changer in the prevention of cardiovascular disease.

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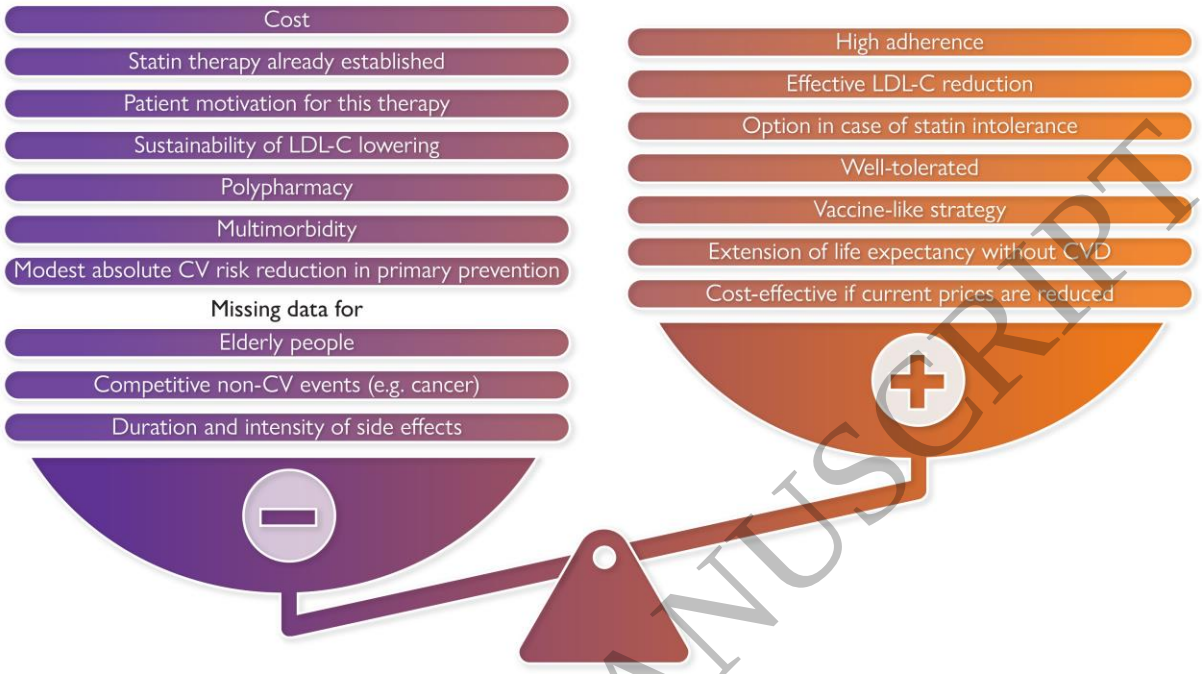

Graphical Abstract
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