European Heart Journal Supplements (2024) **26** (Supplement 1), i99–i101
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae010

Eliminate LDL cholesterol after heart attack … but only for a while

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KEYWORDS
LDL cholesterol;
Secondary prevention;
Cardiovascular risk

There is a clear demonstration of the inverse linear correlation between LDL cholesterol levels and clinical benefit. However, the timing of the action of lipid-lowering drugs is not clear. According to animal studies with recombinant lipoprotein A-1, the composition of atherosclerosis changes within 40 h (with variations in lipid and inflammatory contents). Progression-regression studies of atherosclerosis in humans confirm the data, highlighting a rapid change in the plaque over 5 weeks. The data are also in line with what emerges from the survival curves of the old study comparing atorvastatin 80 mg vs. placebo (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering). The spacing of the curves occurs after only 4 weeks, indicating the precociousness of the favourable effects of powerful statins. Finally, a recent Odyssey *post hoc* analysis compared the risk of cardiac death and coronary revascularization between a group in which alirocumab lowered LDL cholesterol to below 15 mg (Group 1 and in which the drug was therefore stopped) against the subjects in the placebo group (Group 2), applying a propensity score matching. The primary endpoint occurred in a lower percentage of patients in Group 1 (6.4 vs. 8.4%). Furthermore, patients in Group 1 had a significantly lower hazard ratio (HR) for major adverse cardiovascular events [0.72; 95% confidence interval (CI) 0.51–0.997; $P = 0.047$] compared with the entire alirocumab group vs. placebo (HR 0.85; 95% CI 0.78–0.93; $P < 0.001$). According to these preliminary observations, aggressive and early treatment of hypercholesterolaemia in subjects with acute coronary syndrome translates into improved clinical results compared with a strategy that provides for more gradual control. These data will need to be confirmed through further prospective clinical studies and ideally with early conducted atherosclerosis regression studies.

Introduction

There is a clear demonstration of the inverse linear correlation between LDL cholesterol levels and clinical benefit.[1,2] The Fourier (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) and Odyssey (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) studies[3,4] have shown that the use of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors in subjects at high cardiovascular risk allows LDL cholesterol levels to reach below 40 mg/dL and significantly reduces cardiovascular events. The threshold value of LDL cholesterol in secondary prevention has therefore been lowered over the years, which the guidelines now establish at 55 mg/dL.[5]

However, the timing of the action of lipid-lowering drugs is not clear. A study recently published by Schwartz *et al.*[6] as a *post hoc* analysis of the Odyssey study has shown that dropping LDL cholesterol to very low values immediately

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(first weeks after starting therapy) is able to improve further the prognosis in subjects with recent acute coronary syndrome (ACS).

Effect of lipid-lowering drugs on atherosclerosis

The effects of lowering cholesterol on atherosclerosis are known.[7] The extensive work performed with intracoronary imaging modalities contributed to broaden our knowledge in the field.[8-14] Regression studies conducted with the intravascular ultrasound (IVUS) technique have demonstrated how it is possible to reduce the volume of atherosclerotic plaque.[8] More recently, randomized trials on the use of PCSK9 inhibitors[11,12] and conducted with optical coherence tomography (OCT) and near-infrared spectroscopy-IVUS techniques[12] have provided further explanations, highlighting the reduction of the lipid component, the thickening of the fibrous capsule, and finally the reduction of local inflammation following the marked lowering of LDL cholesterol.

However, the question remains: how long it takes for these drugs to have a stabilizing effect on atherosclerosis? Is it a phenomenon that is measured in months or are the changes in cholesterol levels such as to suggest a change in the plaque from the first weeks? The effects of lowering cholesterol on atherosclerosis are known.[6] The extensive work performed with intracoronary imaging modalities contributed to broaden our knowledge in the field.[7-11]

Early stabilization of atherosclerosis: animal studies

Animal studies conducted 20 years ago have shown that the use of lipid-lowering drugs such as lipoprotein A-1 is able to very quickly mobilize tissue cholesterol and reduce the inflammatory cell content of atherosclerotic plaques.[13] Recombinant lipoprotein apo A-1 acts as an acceptor of the phospholipid component of HDL and can therefore mobilize cholesterol from atherosclerotic plaque. Shah *et al.*[13] studied 34 mice maintained on a high-cholesterol diet: 16 received an intravenous injection of placebo, while another 18 received 400 mg per kilo of recombinant lipoprotein A-1. Blood samples were taken 1 and 48 h after administration of the drug or placebo. At 48 h, the mice were sacrificed to evaluate the lipid content of the aortic root as well as the macrophage content.

Free cholesterol, an index of tissue cholesterol mobilization, increased 1.6-fold 1 h after injection of recombinant lipoprotein A-1 and remained stably elevated at 48 h ($P < 0.01$). The mice treated with placebo had a lipid content (expressed as a percentage of atherosclerotic plaque) of $19.6 \pm 6.3\%$, while in the subgroup with recombinant lipoprotein A-1, the lipid content was $10.1 \pm 4.2\%$. The percentage of atherosclerotic plaque was therefore 50% lower in the treatment group ($P < 0.01$). The macrophage content at 48 h was $10.4 \pm 3.4\%$ in the placebo group vs. $6.4 \pm 2.0\%$ in the treatment group (36% reduction, $P < 0.05$).

Early stabilization of atherosclerosis: human studies

This observation in animals was confirmed a few years later by Nissen *et al.*[14] The authors carried out a progression-regression study of atherosclerosis on 123 patients, comparing the action of lipoprotein A-1 Milano vs. placebo in patients with ACS. As an element of originality of the study, the IVUS was repeated just 5 weeks after the start of the treatment. Surprisingly, lipoprotein A-1 Milano was able to reduce the volume of the atherosclerotic plaque by 15% in such a short time compared with 1% in the comparison group. At the time, the study raised a certain level of enthusiasm because the carriers of the genetic variant responsible for the lipoprotein A-1 Milano (Limone del Garda) were protected from atherosclerosis. However, in the following years, drugs capable of increasing HDL cholesterolaemia and therefore promoting the transport of cholesterol from atherosclerotic plaques to the blood did not prove clinically useful.

In my opinion, the study remains an important contribution; in fact, it shows what the dynamics of formation and reduction of the components of atherosclerosis could be. The apparently surprising data of the regression of atherosclerotic plaque in a few weeks are, moreover, in line with those of old clinical studies on the use of statins in subjects with ischaemic heart disease.[15]

Rationale for cholesterol reduction in the early stages of acute coronary syndrome

How long does it take for a lipid-lowering drug to produce clinical benefit?

The Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering study[15] conceived in the 1990s involved a comparison between atorvastatin 80 mg and placebo in subjects with ACS. Treatment with atorvastatin had to start within a week of the myocardial infarction event, and the main endpoint involved a very short follow-up (FU) of just 4 months. The combined incidence of death and non-fatal infarction, resuscitated cardiac arrest, and readmission for recurrent myocardial ischaemia was significantly lower in patients treated with atorvastatin.

It is important to note that the clinical benefit was obtained by lowering the cholesterol levels to 62 mg/dL, a very low value for the time of the study but much higher than what could be achieved with PCSK9 inhibitors.[11,12] Furthermore, the separation of the survival curves occurred after only 4 weeks, indicating the precociousness of the favourable effects of the administration of a potent statin. The data are certainly in line with those in the literature on regression studies in animals and humans.[13,14]

Clinical efficacy of early and transient reduction of LDL cholesterol

A recent study on the clinical efficacy of early and transient reduction of LDL cholesterol in ACS fits into this line of thought.[6] The authors evaluated the results of the Odyssey trial conducted on 18 924 patients with recent ACS in a *post hoc* study. The study design allowed the identification of two subgroups.

The authors compared the risk of cardiac death and coronary revascularization between Group 1 (760 subjects with 2 consecutive LDL cholesterol levels below 15 mg/dL and subsequent treatment with placebo instead of alirocumab, as foreseen by the study design) and Group 2 (1460 subjects from the placebo group, applying a propensity score matching with a ratio of 1:2). The

matching was based on the following parameters: age, sex, geographical region, history of diabetes, smoking, previous bypass, previous percutaneous transluminal coronary angioplasty, peripheral vascular disease, cerebrovascular disease, heart failure, chronic lung disease, neoplasms, revascularization during ACS, intensity of statin therapy, systolic blood pressure, glomerular filtration rate, and baseline LDL cholesterol concentrations.

The median LDL cholesterol value at FU was 49.1 mg/dL (37.1, −61.1) in Group 1 vs. 79.2 mg/dL (66.1, 93.2) in the placebo group. At a median FU of 2.8 years, major adverse cardiovascular events (MACEs) occurred in 47 subjects (6.4%) of Group 1 vs. 122 patients (8.4%) of the placebo group [treatment hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.51–0.997; $P = 0.047$].

As might be expected, patients in the alirocumab group who achieved consecutive baseline LDL cholesterol values below 15 mg/dL had lower baseline LDL cholesterol values than patients in the entire study cohort. Furthermore, patients who had an LDL cholesterol level below 15 mg/dL were more often male, had diabetes, received high-intensity statins, and had better adherence to therapy.

The primary endpoint occurred in 6.4% of patients in Group 1 (with LDL cholesterol <15 mg/dL and subsequently placebo instead of alirocumab). The difference was statistically significant compared with the placebo group, which had an event rate of 8.4% ($P < 0.01$). Furthermore, patients in Group 1 (with two consecutive LDL cholesterol levels <15 mg/dL and suspension of alirocumab) presented a significantly lower HR for MACEs [0.72; 95% CI 0.51–0.997; $P = 0.047$] compared with the entire alirocumab group vs. placebo (HR 0.85; 95% CI 0.78–0.93; $P < 0.001$).

Final considerations

According to these preliminary observations, aggressive and early treatment of hypercholesterolaemia in subjects with ACS translates into improved clinical results compared with a strategy that provides for more gradual control.

It cannot be ruled out that, reasoning in terms of stabilization of atherosclerosis, the reduction of cholesterol to very low levels is able to modify the plaques significantly from the first weeks, modifying those characteristics related to vulnerability.[16] We have seen from regression studies such as Hugyne[11] and PACMAN-AMI (Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction)[12] that PCSK9 inhibitors thicken the fibrous capsule and reduce the lipid component of atherosclerosis in an observation period of 9 and 12 months, respectively. We do not have regression studies with OCT conducted at 1 month, but it is not unlikely that what has been observed in the past, using molecules such as apolipoprotein A-1 Milano, can be replicated with PCSK9 inhibitors when cholesterol levels drop below 15 mg/dL, as demonstrated by the *post hoc* analysis of the Odyssey study. It is also possible that the effectiveness of the drugs is also expressed through a marked and early reduction of the inflammatory component, which we know is much more evident in subjects with ACS.

These preliminary observations, and in particular, the thesis that sees in ACS a great benefit from the early and transient reduction of LDL cholesterol are of great interest. They must be confirmed through further prospective clinical studies and ideally with early conducted atherosclerosis regression studies.

Funding

None declared.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. De Backer G, Jankowski P, Kotseva K, Mirrakhimov E, Reiner Ž, Rydén L *et al*. Management of dyslipidaemia in patients with coronary heart disease: results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* 2019;**285**:135–146.
2. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J *et al*. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: vytorin Efficacy International Trial). *Circulation* 2018;**137**:1571–1582.
3. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**76**:1713–1722.
4. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R *et al*. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2107.
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L *et al*. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
6. Schwartz GG, Szarek M, Bhatt DL, Bittner VA, Bujas-Bobanovic M, Diaz R *et al*. Transiently achieved very low low-density lipoprotein cholesterol levels by statin and alirocumab after acute coronary syndrome are associated with cardiovascular risk reduction: the ODYSSEY OUTCOMES trial. *Eur Heart J* 2023;**44**:1408–1417.
7. Arbustini E, Morbini P, Dal Bello B *et al*. From plaque biology to clinical setting. *Am Heart J* 1999;**138**:S55–S60.
8. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM *et al*. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;**295**:1556–1565.
9. Bruining N, Von Birgelen C, Di Mario C *et al*. Dynamic three-dimensional reconstruction of ICUS images based on an EGG-gated pull-back device. *Comput Cardiol* 1995;633–663.
10. Zimarino M, Prati F, Stabile E *et al*. Optical coherence tomography accurately identifies intermediate atherosclerotic lesions—an in vivo evaluation in the rabbit carotid artery. *Atherosclerosis* 2007;**193**:94–101.
11. Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R *et al*. Coronary atheroma regression with evolocumab in stable and unstable coronary syndromes. *JACC Cardiovasc Imaging* 2023;**16**:130–132.
12. Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J *et al*. Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA* 2022;**327**:1771–1781.
13. Shah PK, Yano J, Reyes O, Chyu K-Y, Kaul S, Bisgaier CL *et al*. High-dose recombinant apolipoprotein A-I(Milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein E-deficient mice. Potential implications for acute plaque stabilization. *Circulation* 2001;**103**:3047–3050.
14. Nissen S, Tsunoda T, Tuzcu M, Schoenhagen P, Cooper CJ, Yasin M *et al*. Effect of recombinant Apo A-1 Milano on coronary atherosclerosis in patients with acute coronary syndromes. *JAMA* 2003;**290**:292–300.
15. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D *et al*. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–1718.
16. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y *et al*. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;**41**:383–391.