2024 SGK Congress – Satellite Symposium

Strike early and strike strong after MI: lowering LDL-C to target and below

Based on the growing clinical evidence on the benefit of very low LDL-C levels in combination with the availability of highly effective lipid-lowering therapy (LLT) options, official cardiovascular (CV) guideline recommendations continue to lower the LDL-C target with each new update [1–3]. Nevertheless, as real-world-data suggests, the vast majority of the medical community has not yet picked up speed when it comes to putting those recommendations into practice [4–6]. At this years' Joint Annual Meeting of the Swiss Societies of Cardiology and Cardiac Surgery, four lipid experts discussed the challenges of LDL-C lowering in Switzerland.

Acceleration post MI – LDL-C goal achievement

PD Dr. Stéphane Fournier kicked off the symposium with some rather defeating numbers: only 33% of European patients with established ASCVD reach the 2019 ESC LDL-C target of 1.4 mmol/L, revealing a suboptimal management of dyslipidemia in patients at very high CV risk [5]. The EU-wide DA VINCI study further revealed treatment inertia and poor adherence to guidelines, since only 82% of very-high risk patients were treated with a statin monotherapy, and half of them not even at high intensity [5]. In Switzerland, patients that have been hospitalized for an ACS showed an average LDL-C level of 2.2 mmol/L one year after the incident (baseline 3.3 mmol/L) [6]. To reach the recommended 1.4 mmol/L, a reduction of 50–60% from baseline would be needed, which might not be attainable with statins alone or in combination with ezetimibe [3]. PD Dr. Fournier stressed that an optimized LLT is key to increasing the number of patients that reach their LDL-C goal within a reasonable timeframe. This means escalation of LLT with addition of PCSK9i within 12 weeks after an event if target LDL-C levels are not reached, as recommended by the ESC guidelines and the Swiss Atherosclerosis Society (AGLA/GSLA) recommendations [2, 7].

Strike early

The CV benefit of lowering LDL-C levels has been associated with reduced atheroma volume as well as improved atherosclerotic plaque physiology, i.e. regression and stabilization, in ACS patients after successful LLT [8, 9]. Time is of essence when it comes to preventing a recurring CV event, which happens in one of five patients within one year after MI. Prof. Baris Gencer explained that delayed LLT intensification is observable in practice for most of the patients eligible for PCSK9i more than 12 months after the index event. A subanalysis of the FOURIER study focusing on patients with recent MI (within 12 months) demonstrated that early and strong lipid lowering through the PCSK9i Evolocumab (Repatha®) resulted in a significant risk reduction for the primary endpoint (19% relative risk reduction and 3.7% absolute risk reduction) with a number needed to treat of 27 over 3 years [10]. In contrast, the number needed to treat in those who started PCSK9i after 12 months was 95 over 3 years. Furthermore, the long-term open-label extension in the overall FOURIER study population suggested a legacy effect of Evolocumab with a persisting reduction in CV risk over a follow-up period of 8 years, with a signal for CV death reduction as well [11].†

Strike strong

In the FOURIER open-label extension study, patients treated with Evolocumab had an average LDL-C level of 0.8 mmol/L over the course of the study with a good tolerance and safety [11]. Accordingly, Dr. Jan Vontobel emphasized that there should be no fear of very low LDL-C values and gave the example of people with genetically determined low LDL-C levels (notably due to PCSK9 gene mutation) who display an intrinsically low life-time risk for CV events [12]. The same significant relationship was demonstrated in patients under LLT: the lower the achieved LDL-C level after randomization, the lower the event probability for the risk of CV endpoints [13]. After an acute event, strike strong and go as low as possible! Make sure that both patient and their GP know the importance of keeping LDL-C low, preferably below target.

Intensity of lipid lowering therapy

Treatment	Average LDL-C reduction
Statin (moderate intensity)	≈ 30%
Statin (high intensity)	≈ 50%
High intensity statin + ezetimibe	≈ 65%
PCSK9i	≈ 60%
PCSK9i + high intensity statin	≈ 75%
PCSK9i + high intensity statin + ezetimibe	≈ 85%

adapted from Mach et al, 2020 [3]

Getting patients to their LDL-C target and below

Prof. Isabella Sudano agreed and pointed out that even if the target is reached, many patients are "lost" and their LDL-C increases after some time due to changes in medication or non-adherence. Prof. Sudano acknowledged that the implementation of the ESC 2019 targets in Switzerland will require a practice change. To date, the available medication is underused and utilization of combination therapies should be increased especially in patients at very high risk. She identified the key problem to be twofold: first, the therapy sequence chain set by reimbursement regulations limits the therapeutic mobility; second, LLT intensification is not happening at the most efficient speed. Moving forward, it will be essential to adhere to the lowest time spans framed by PCSK9i reimbursement regulations* [14]. As suggested by the 2023 ACS guidelines, LDL-C levels should be monitored within 4 weeks after treatment initiation [2].

This allows an early switch to a different/more potent statin as well as further intensification of the LLT with ezetimibe and/or PCSK9i within 3 months in case of failure to achieve the LDL-C target.

Expert interview with
Prof. Dr. med. Baris Gencer
Centre Hospitalier Universitaire Vaudoise (CHUV)

How are we doing in Switzerland? Do you think that today – 4 years after publication of the presented real-world data – there are more patients who reach their LDL-C target?

Prof. Gencer: A lot has happened since 2020. The facilitation of PCSK9i reimbursement through lowering the LDL-C level criteria from 2.6 to 1.8 mmol/L could have improved the achievement of LDL-C targets in patients at very high risk of CV events, although we do not have strong data yet to support this hypothesis. Also, awareness about the benefits and safety of low LDL-C levels has increased, and the experts are involved in communicating recent guideline recommendations to their peers. But we still have a long way ahead of us for an optimal dissemination of guidelines.

In your experience, how many of your MI patients have already received an optimized (oral) LLT before their CV event?

Prof. Gencer: Less than half of the patients are treated with statin before hospitalization for MI suggesting that we still have to improve identification of patients at high risk of complications. In a recent publication we also found some gender differences: women with familial hypercholesterolemia were less likely to be treated with statin compared to men before MI [15]. In general, the combination of statin with ezetimibe or PCSK9i remains uncommon in patients without preexisting CV events.

Abiding by regulations, we are first toned to maximize oral treatment by changing to a second statin and/or adding ezetimibe after a recent CV event, before we can move to more efficient PCSK9i if LDL-C levels are not reaching the target. A significant number of recurring CV events could be prevented by early intensification of LLT with a structured clinical pathway following hospitalization for a recent CV event. The barriers for reimbursement are now less stringent with the possibility of starting therapy without a prior approval.

Do you think that patient education on the risk of elevated LDL-C is sufficient? What could be improved?

Prof. Gencer: It is true that not only doctors have to be convinced of the benefit of a pricey therapy. Most patients know that high LDL-C is “not good” for them. Still, they do not realize how high their individual risk actually is. Risk communication is key [16]: Doctors need to determine the LDL-C target specific to their patients’ CV risk and explain how the prescribed medication will help them achieve these or even lower LDL-C levels. Patients need to understand that their personal risk after an MI is higher compared to the norm. We also need to acknowledge the issues of polypharmacy and multimorbidity which impact the long-term adherence to therapy. High LDL-C is a chronic and asymptomatic condition. Patients do not see or feel the benefit of the treatment, which is another challenging aspect of LLT. It is essential to emphasize the “why” of the therapy: the goal is not to reach an arbitrary number in a blood test – the goal is to prevent a (recurring) CV event.

Footnotes

† Prespecified exploratory analysis of FOURIER-OLE. During FOURIER-OLE all patients were treated open-label with Evolocumab resulting in no concurrent placebo arm during this period [11]. Evolocumab is indicated for the reduction of the risk for cardiovascular events (MI, stroke and coronary revascularization). For effects on cardiovascular mortality, see Properties/Effects in the professional information (www.swissmedicinfo.ch).
* Evolocumab (Repatha®) is reimbursed for secondary prevention in patients with manifested ASCVD and an LDL-C level > 1.8 mmol/L, and for primary prevention in patients with familial hypercholesterolemia and an LDL-C level > 2.6 mmol/L. To qualify for reimbursement, patients must have undergone a pre-treatment for at least 3 months with either two different statins or ezetimibe, in the case of statin intolerance, while still exceeding the mentioned LDL-C thresholds [14].

Abbreviations

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; PCSK9i = proproteinkovertase subtilisin kexin type 9 inhibitor.

Further information

Text: Dr. sc. Tanja Blumenschein
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Abbreviated professional information of Repatha® (Evolocumab) see cover page 2.

Literature

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Healthcare professionals can request corresponding references from Amgen Switzerland AG.

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