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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

New Insights in the Control of Low-Density Lipoprotein Cholesterol to Prevent Cardiovascular Disease

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Abstract

Purpose of Review Low-density lipoprotein cholesterol (LDL-C) is one major cause of cardiovascular disease (CVD). In this review, we discuss current developments in the understanding of LDL-C as lifelong risk factor, treatment targets, and emerging approaches to reduce cardiovascular risk by lowering LDL-C.

Recent Findings Recent evidence underscores the importance of LDL-C lowering in CVD prevention by mechanisms that increase the hepatic clearance of apolipoprotein B-containing lipoproteins from the plasma. Mendelian randomization studies provided evidence on both safety and efficacy of lower LDL-C in the long term. For young individuals, metrics other than 10-year CVD risk are required. Despite this evidence, LDL-C treatment target attainment is poor. Novel approaches are therefore needed. These include individualized strategies and new LDL-C-lowering pharmaceuticals.

Summary Early, long-term treatment with LDL-C-lowering therapies has the potential to markedly reduce CVD incidence and progression. Future research should aim to identify patient characteristics that enable physicians to tailor therapy to each individual patient.

Keywords Low density · Lipoprotein · Cholesterol · Prevention · Cardiovascular disease · Coronary artery disease · Mendelian randomization · Statin

Introduction

The development of cardiovascular diseases (CVD) is a multifactorial process, which is driven by genetic predisposition and interacting cardiovascular risk factors. In CVD prevention, attempts to minimize exposure to these risk factors are crucial to reduce cardiovascular morbidity and mortality.

One major CVD risk factor is low-density lipoprotein cholesterol (LDL-C). The causal role of LDL-C in the development and progression of CVD is well established. While in the majority of studies on LDL-C lowering, patients with established CVD were included, the importance and the potential of LDL-C-lowering strategies in individuals without symptomatic CVD are increasingly recognized.

The first part of this review provides an overview of current evidence of LDL-C lowering in the prevention of CVD. Second, LDL-C treatment targets and their implementation in clinical practice are discussed. Finally, current evidence on individualized medicine and emerging pharmacological approaches is reviewed.

This article is part of the Topical Collection on *Lipid Abnormalities and Cardiovascular Prevention*

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Prevention of CVD by Lowering LDL-C

Prevention in the CVD Continuum

LDL-C is one of the most extensively investigated risk factors for the development and progression of CVD. The evidence from genetic, observational, and randomized studies consistently demonstrates a causal, log-linear association between exposure to LDL-C and CVD risk. This evidence relies on data of more than 2 million participants and over 20 million

person-years of follow-up [1•]. Therefore, control of LDL-C represents one cornerstone in the prevention of CVD.

The development of atherosclerosis is a slowly progressing process as result of genetic predisposition and acquired cardiovascular risk factors. Frequently, atherosclerosis does not cause any symptoms until a certain threshold of atherosclerotic burden is exceeded, and cardiovascular events like myocardial infarction occur [2]. The distinction in primary vs secondary prevention—prevent CVD from occurring at all vs prevent CVD from progression—does not reflect pathophysiology, as atherosclerosis develops over the course of decades as continuum [3]. The assessment of risk factors allows to categorize patients into individual risk categories that provide the basis for treatment decisions.

Usually, the initial studies on one drug class include patients with established CVD. This is reasonable because of different reasons: patients are at high short-term risk after the first cardiovascular event, which indicates that the threshold from asymptomatic to clinical CVD has been exceeded; therefore, this population has the highest short-term need for effective treatment. As the absolute risk is comparably high, the potential absolute risk reduction is also high, and in turn, the number needed to treat is low, which translates in lower numbers of participants and shorter follow-up in a randomized study to show a discernible effect.

By contrast, in patients without clinically manifest CVD, the absolute risk is comparably low. Individuals might already have atherosclerosis, but some may never exceed the threshold to clinical CVD. In these patients, in order to show any treatment effect, the intervention needs to markedly reduce the risk factor, a large cohort of apparently healthy individuals needs to be included, and the follow-up ideally encompasses decades. As consequence, some questions are unlikely to ever be answered by a randomized trial, especially for interventions in young individuals with corresponding low short-term risk and need for extensive follow-up.

In meta-analyses of randomized statin trials—the most of them including patients with established CVD—the reduction in CVD risk is comparable among different risk categories, among men and women, and younger and older individuals [4, 5, 6•]. However, while the benefit of statins over the course of some years is certain, follow-up in randomized trials does not represent lifelong treatment. To overcome this hurdle, registries, long-term follow-up of randomized trials, and Mendelian randomization studies can provide insights [7].

Lowering LDL-C in the Long Term: Evidence from Clinical and Genetic Studies

Results of the longest follow-up of all randomized statin trials were reported from the West of Scotland Coronary Prevention Study (WOSCOPS) [8]. The original study included 6595 men between 45 and 64 years of age (mean 55 years) with hypercholesterolemia and no history of myocardial infarction. The participants were randomly allocated to receive pravastatin 40 mg or placebo. Pravastatin treatment resulted in 31% relative reduction of the primary end point (nonfatal myocardial infarction, death from coronary heart disease). The 20-year follow-up results were reported in 2016 [9•]. The 5-year treatment in the primary study was followed by a legacy effect after 20 years, showing significant decreases in cardiovascular (21%) and all-cause mortality (13%). Non-cardiovascular or cancer deaths did not differ between pravastatin and placebo. Despite important caveats (e.g., no record about statin medication in the last 10 years of follow-up), these data impressively demonstrate continuous efficacy and safety of statin treatment in the long term.

However, one could speculate that many of the participants at mean age of 55 years and with hypercholesterolemia already had subclinical atherosclerosis, and lowering LDL-C earlier, e.g., at 35 years of age, could have prevented even more cardiovascular events. As to the complexity and costs of proving this in a randomized trial, the Mendelian randomization approach represents a viable alternative to provide insights on lifelong effects of lower LDL-C. Using Mendelian randomization, participants of epidemiologic studies can be randomized according to genetic polymorphisms. These polymorphisms are inherited at random due to the random reassortment of chromosomes during meiosis. If a polymorphism is associated only with the exposure of interest, i.e., LDL-C, and with the disease of interest, e.g., coronary heart disease, a causal association between exposure and disease can be assumed and quantified. The presence or absence of a polymorphism represents allocation to treatment or placebo in randomized clinical trials. The effect estimates are lifelong effects of the exposure on disease risk. In contrast to epidemiologic studies, Mendelian randomization studies are not prone to confounding or reverse causation [10].

In the recent years, several Mendelian randomization studies have improved our understanding of LDL-C as lifelong and cumulative risk factor for CVD: while the relative reduction of CVD risk as estimated from randomized statin trials is 21% for 1 mmol/L (38.67 mg/dL) lower LDL-C [4], the relative risk reduction for *lifelong* 1 mmol/L lower LDL-C is 55%, and thus, threefold greater [11]. This suggests cumulative effects of LDL-C and supports initiation of LDL-C-lowering strategies early in life. Mendelian randomization studies not only informed about the association of LDL-C and CVD in general, but also about specific pharmacological approaches to lower LDL-C by using polymorphisms in genes that encode proteins which are the targets of LDL-C-lowering drugs: similar associations of the absolute reduction in LDL-C and CVD risk have been shown for polymorphisms that mimic the effect of statins, ezetimibe, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors [12–15]. The

findings are consistent with the results of the corresponding clinical trials [16, 17••, 18••]. This supports benefits from LDL-C lowering regardless of the mechanism by which LDL-C is lowered [19] (with the exception of cholesteryl ester transfer protein [CETP] inhibitors [20]). Furthermore, and importantly, none of the studies showed any safety signal of lifelong lower LDL-C.

In summary, both the results of recent clinical and genetic studies suggest that early and long-term LDL-C lowering, independent of the mechanism by which LDL-C is lowered, is effective and safe.

LDL-C Control: Treatment Targets and Current Status

LDL-C Treatment Targets

LDL-C represents the amount of cholesterol carried by LDL particles and has been used as primary diagnostic and therapeutic target for decades. However, it has been suggested that apolipoprotein B (apoB) might be a superior diagnostic and therapeutic target than LDL-C [21, 22]. All atherogenic lipoproteins, namely LDL-C, triglyceride-rich lipoproteins, and lipoprotein(a), contain one single apoB molecule. Therefore, apoB reflects the number of atherogenic particles rather than the content of cholesterol or triglycerides carried by these lipoproteins, which is described by LDL-C and triglyceride levels. In a recent Mendelian randomization study, the authors showed that the effect of lowering lipoproteins on CVD risk stratified by the decrease in apoB was nearly identical independent of how much LDL-C and triglycerides were lowered correspondingly [23•]. This implies that any benefit from lowering LDL-C or triglycerides should be proportional to the absolute change in apoB. As consequence, it seems reasonable to power future studies on lowering lipoproteins on the expected change in apoB. This notion also explains why CETP inhibitors in combination with statins did not lower CVD risk as expected: although LDL-C was lowered, apoB was not lowered proportionally. The achieved risk reduction corresponded with the attenuated lowering of apoB [20]. However, because all randomized trials are primarily based on LDL-C and in the most cases, LDL-C and apoB are lowered proportionally, LDL-C remains the primary diagnostic and treatment target to date. In patients with elevated triglycerides, diabetes, obesity, or low LDL-C values, apoB or non-HDL cholesterol, which is a proxy for apoB, should be preferentially used to estimate risk and guide treatment.

Although LDL-C treatment targets have never been investigated in randomized trials, both the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guideline from 2016 [24••], which is currently under revision, and the recently published American Heart Association (AHA)/American College of Cardiology (ACC) guideline [25••] suggest using treatment targets. The fact that the AHA/ACC guideline reintroduced treatment targets instead of statin intensities reflects the current understanding of CVD risk reduction by LDL-C lowering independent from the mechanism by which LDL-C is lowered. Treatment targets provide a useful tool for treatment decisions and for patient communication. The targets are based on the individual CVD risk. In particular, the lowest recommended LDL-C target is <1.8 mmol/L (70 mg/dL) for patients at the highest risk. However, in 2017, for the first time a category of patients at extreme risk was introduced by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [26•]. These patients are characterized by progressive CVD despite statin therapy or established CVD in combination with multiple risk factors. An LDL-C treatment target of <1.4 mmol/L (55 mg/dL) was recommended.

This lower treatment goal is supported by randomized trials published within the last years, suggesting that the beneficial effects of lowering LDL-C extends to LDL-C levels lower than currently recommended. In particular, in IMPROVE-IT, by adding ezetimibe to simvastatin, LDL-C levels of 1.4 mmol/L were achieved [16]. In FOURIER [17] and ODYSSEY Outcomes [18], treatment with the PCSK9 monoclonal antibodies (PCSK9 inhibitors) evolocumab and alirocumab resulted in LDL-C values of 0.8 mmol/L and targeted values of 0.6–1.3 mmol/L, respectively. All three studies showed a significant reduction of cardiovascular events. The relative reduction in risk was proportional to the absolute decrease in LDL-C and comparable to the effects of statins per mmol/L change in LDL-C [19]. Importantly, none of the studies showed any safety signal for the lowest LDL-C levels ever achieved, including no signs of cognitive impairment [27–29]. This implies that there is no J-curve effect with a lower limit for LDL-C which should not be undercut. However, potential adverse effects beyond the follow-up of 7 years for ezetimibe and less than 3 years for the PCSK9 inhibitors are unknown.

In the most studies on LDL-C lowering—including the studies mentioned above—patients with established CVD were investigated. Therefore, the results are not necessarily valid for individuals without clinical apparent CVD. The 10-year risk estimation as recommended by the ESC/EAS and AHA/ACC guidelines to assign individuals to risk categories might, especially in young people, result in low 10-year risk despite markedly elevated lifetime risk. This is underscored by a recent observational study, in which individuals at low 10-year risk had a 50–80% increased CVD mortality after 27 years of follow-up when LDL-C was > 4.1 mmol/L [30]; importantly, the finding of increased mortality did not reach statistical significance after 10 years of follow-up. To assess

the need of LDL-C lowering in young individuals, other metrics that focus on disease trajectory rather than 10-year risk are needed [31]. Current recommendations regarding timing of LDL-C intervention and treatment targets in young individuals are based on epidemiology, genetics, and basic science. Noteworthy, the process of atherosclerosis begins early in life: 1 out of 6 teenagers has atherosclerotic lesions as detected by intravascular ultrasound [32], and LDL-C levels above 1.8 mmol/L during young childhood are associated with increased coronary calcium scores two decades later [33]. Furthermore, cumulative exposure to only moderately elevated non-HDL-C has been associated with increased CVD risk later in life [34]. These findings favor early LDL-C-lowering interventions.

In conclusion, major guidelines on LDL-C lowering for CVD prevention recommend treating patients to 10-year risk-based targets. Recent evidence suggests that LDL-C targets lower than currently recommended are beneficial. In young individuals, 10-year risk is no adequate measure for risk assessment.

LDL-C Control: Current Status

The following section provides a brief overview on the recommended strategy to attain LDL-C control and on the status quo of LDL-C control.

Both the ESC/EAS and the AHA/ACC guidelines recommend lifestyle modification to improve the lipid profile in all disease stages. For pharmacologic reduction of LDL-C, statins are the cornerstone of treatment. Ezetimibe and, especially for patients with established CVD, PCSK9 inhibitors can be added successively. In rare cases, lipoprotein apheresis might be indicated. The ESC/EAS guideline is complemented by a recent position paper on the use of PCSK9 inhibitors [24••, 25••, 35•].

Despite extensive evidence on the benefits of lowering LDL-C, treatment targets are achieved only in a minority of patients [36, 37]. In the EUROASPIRE IV survey, conducted in 24 European countries, LDL-C was controlled in only 19.5% of the participants who had established CVD [38]. In its successor, EUROASPIRE V, LDL-C was controlled in no more than 32% of patients. Eighty-four percent of the patients were treated with LDL-C-lowering drugs, mainly statins [39]. High-intensity statin therapy was used more frequently than in the previous survey (50% vs 33%), but the included cohorts were different, i.e., the seemingly increased rate of LDL-C control does not necessarily reflect improvement [38–40]. The situation is similar in the USA [41]. It can be speculated that the expected adherence in patients at risk but without established CVD, i.e., treatment over decades in healthy individuals, might be even worse.

Reasons for these disappointing results are diverse. Potential side effects of statins are among the reasons why physicians do not prescribe them. However, the beneficial effects of statins outweigh potential adverse effects, which include new-onset diabetes mellitus among patients with prediabetes and statin-associated muscle symptoms. Nevertheless, statin therapy is among the best investigated drug therapies at all, and remarkably safe [42•, 43•]. Other reasons might include a lack of awareness regarding guideline recommendations and/or clinical inertia, underpinned by the fact that up-titration of statins is rare in the outpatient setting [37].

The discrepancy between a comparably high proportion of patients treated with statins in EUROASPIRE V, but a small proportion attaining the LDL-C target, suggests that not only prescribing patterns of physicians explain the unsatisfying situation, but also low medication adherence contributes to it. Low adherence accounts for a considerable proportion of potentially avoidable cardiovascular events [44]. Adherence to statin therapy is associated with improved survival [45]. In a recent cross-sectional study from Germany, medication adherence to lipid-lowering medication was associated with lower blood pressure, lower LDL-C, and a higher proportion of patients achieving the recommended blood pressure and LDL-C targets. Depression and low adherence were strongly associated [46]. Although low medication adherence is not solely responsible for low rates of treatment target attainment, it is still an important missed opportunity. Strategies to improve adherence include fixed-dose combination treatment, which reduces blood pressure to a greater extent than single pill treatment does [47, 48]. These results can probably be translated to the situation in LDL-C lowering, as adherence to blood pressure- and lipid-lowering medication strongly correlates [46].

Emerging Approaches to Control LDL-C

Patient Selection: Individualized Medicine

As consequence of lower LDL-C treatment targets and lower risk thresholds that indicate treatment recommendations, in future, more people are likely to be treated with LDL-C-lowering agents. As this is accompanied from increasing costs for the health care system (neglecting prevented events at this moment) and potential side effects in the long term, selection of patients who are most likely to benefit from a certain treatment becomes increasingly important.

Promising developments towards individualized medicine take place in the field of genetics. Genetic information can potentially be used in different ways to tailor treatment to an individual patient. First, genetic risk scores can improve cardiovascular risk prediction. The usefulness of those risk scores has been a matter of debate [49]; however, with increasing numbers of participants in respective studies and the use of

millions of genetic polymorphisms, risk prediction with genetic risk scores is superior compared to conventional risk factors [50] and monogenic mutations [51]. As clinical consequence, patients with higher genetic risk score might preferably be treated more intensively. Healthy lifestyle has been demonstrated to be associated with marked reductions of genetic risk [52•]. For statin therapy, an increasing relative risk reduction from 13 to 48% in patients from low to high genetic risk categories has been reported [53, 54].

Second, genetic information can be used to assess treatment response to specific drugs. For example, in genome-wide association studies, genetic loci were identified which were associated with response to statin treatment [55]. Furthermore, genetic polymorphisms associated with higher LDL-C are also associated with decreased efficacy of statins [56]. The effect sizes are comparably small; thus, this does not necessarily imply clinical relevance, but warrants further investigation.

Apart from genetic variation due to sequence changes in DNA, another emerging field is epigenetics. Here, changes in DNA methylation, histone modification, and non-coding RNAs that cause different gene expression are investigated. Epigenetic changes can be caused by environmental influences and have been linked to cardiovascular risk factors like cigarette smoking. Epigenetic changes are also associated with disease development and progression and are potential treatment targets. The current evidence is summarized in a recent review [57].

Using genetic and epigenetic information for clinical decision making is likely to become more important in future with dropping costs for genotyping.

Apart from genetic information, knowledge about differences in metabolism could potentially yield in more precise allocation to specific treatments. In particular, patients with high cholesterol absorption in relation to hepatic cholesterol synthesis appear to benefit less from statin therapy. For those patients, ezetimibe or a combination therapy of statin and ezetimibe could be superior. However, this hypothesis is derived from experimental data and post hoc analyses and has not been tested in a randomized trial yet [58].

Finally, specific characteristics of risk factors, in particular LDL-C, might be helpful to distinguish patients with regard to their cardiovascular risk. It has been shown that despite similar cholesterol content of LDL particles as measured by LDL-C, LDL particles may differ in atherogenicity depending on specific characteristics: LDL-C of increased density are better risk predictors than total LDL-C [59]. Furthermore, a recent study provided evidence that the susceptibility of LDL particles to aggregate predicts future cardiovascular events independently from conventional risk factors, and that this risk marker is both reliably measurable and modifiable [60]. This provides an opportunity both for risk assessment as well as for specific treatment.

In conclusion, individualized diagnostic and therapeutic approaches regarding LDL-C based on genetic, clinical, and laboratory data have the potential to inform about expected benefits of specific treatments in individual patients. However, clinical studies are needed for validation of this promising and important concept.

Emerging Pharmacological Approaches to Lower LDL-C

The most important achievements in the recent years in pharmacological treatment of elevated LDL-C are represented by the studies of ezetimibe and the PCSK9 inhibitors [16–18]. Based on this data, two drug classes with proven efficacy were added to the portfolio of LDL-C-lowering medication. Currently, one major caveat which limits the use of PCSK9 inhibitors is their cost, although it is dropping. To be affordable for the community, careful patient selection is required.

Apart from ezetimibe and the PCSK9 inhibitors, many promising pharmaceutical approaches to lower LDL-C are at different stages of evaluation for clinical use. Three of them are briefly introduced below.

Bempedoic acid is an inhibitor of ATP citrate lyase, an enzyme involved in cholesterol synthesis upstream of HMG-CoA reductase, the therapeutic target of statins. Bempedoic acid is administered orally once daily and, as prodrug, specifically activated in the liver, which is why muscle effects like for statins are not expected to occur. Bempedoic acid lowers LDL-C consistently as monotherapy and combined with statins and ezetimibe [61]. In the recent CLEAR Tranquility study of statin-intolerant patients treated with ezetimibe, bempedoic acid lowered LDL-C by 28.5% compared to placebo with no adverse effects [62]. Bempedoic acid is currently evaluated in the CLEAR Outcomes trial of statin-intolerant patients [63].

Several pharmacologic approaches targeting PCSK9 are currently evaluated. One is a small-interfering RNA (siRNA) molecule called inclisiran. In general, siRNA targets complementary messenger RNA (mRNA) and inhibits translation of the encoded protein. Inclisiran selectively targets hepatic mRNA encoding PCSK9. In the ORION-1 trial, administration of inclisiran resulted in LDL-C reductions comparable to those achieved by PCKS9 inhibitors. Importantly, in this dose regimen, inclisiran was administered in a 3-month interval, while effects of a single dose were still present after 6 months [64]. A phase III trial for assessing the effect of inclisiran on cardiovascular outcomes, ORION-4, is at the planning stage [65]. A major advantage of inclisiran is that, after an initial repeat dose after 3 months, it will be administered only every 6 months. This has the potential to markedly improve adherence.

The same is true for another approach that also addresses PCSK9: active vaccination. The principle of active vs passive

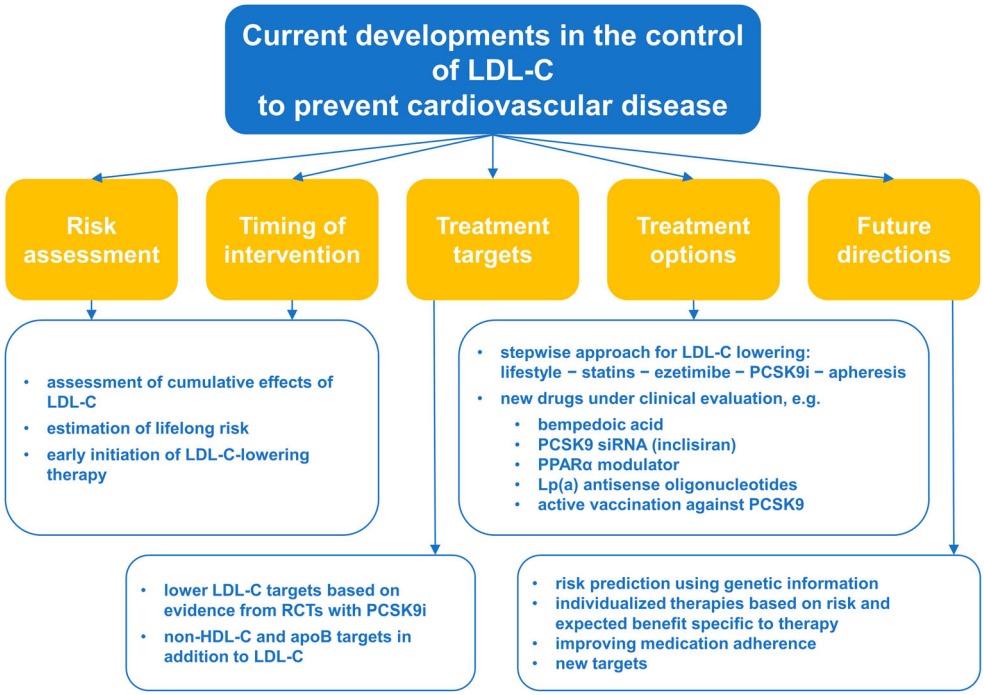

Fig. 1 Graphical overview on current developments in the control of LDL-C to prevent cardiovascular disease. LDL-C: low-density lipoprotein cholesterol, non-HDL-C: non-high-density lipoprotein cholesterol, PCSK9: proprotein convertase subtilisin-kexin type 9, siRNA: small-interfering RNA, RCT: randomized controlled trial, PCSK9(i): (inhibitor)

vaccination (as established with the PCSK9 inhibitors) has important advantages in terms of adherence and costs [66]. A vaccine directed against PCSK9 (AT04A) has been proven successful in mice [67]. Results of a phase I trial in humans have been presented recently: although LDL-C was reduced by only 9% after 90 weeks, the principle is promising [68].

Conclusions

In this review, we provided an overview of current evidence of the causal association of LDL-C and CVD (Fig. 1). LDL-C lowering reduces CVD risk proportionally to the absolute change in LDL-C and independently from the mechanism by which LDL-C is lowered. Mendelian randomization studies have expanded our understanding of LDL-C as lifelong and cumulative risk factor.

Current LDL-C treatment targets are based on 10-year risk. Especially in young individuals without CVD, lifetime risk estimation is more adequate, as low 10-year risk may conceal high lifetime risk. Due to cumulative effects of LDL-C, early initiation of LDL-C-lowering therapies has the potential to lower risk to a greater extent compared to treatment initiated later in life. In patients with established CVD, recent evidence shows beneficial effects of lower LDL-C levels than currently targeted. Importantly, in daily practice, even the current treatment targets are achieved in just a minority of patients. Strategies are required to improve implementation of guideline recommendations, overcome physicians' inertia, and enhance medication adherence.

With potentially more individuals being treated with LDL-C-lowering drugs in the future, individualized approaches to tailor therapy to the individual patient gain importance and should be focus of future research. Novel LDL-C-lowering pharmaceuticals with long dosing intervals are currently evaluated and may markedly improve adherence.

Compliance with Ethical Standards

Conflict of Interest Julius L. Katzmann declares that he has no conflict of interest.

Ulrich Laufs has received fees for lectures or consulting from Amgen and Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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