"Goal attainment for lipid-lowering therapies is very low....The single most important lifestyle-related factor for the effect of lipid-lowering therapy is medication adherence. Up to one-third of lipid (and blood pressure)-lowering tablets are not taken as intended by the prescribing physician. The importance of this problem is underscored by the observations that adherence to statin therapy is directly correlated with survival both in primary and secondary prevention."

Hypertension and dyslipidemia: where are we?

Part II: Update on dyslipidemia diagnosis and treatment

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Atherosclerotic cardiovascular disease (ASCVD) is the main cause of disability and death worldwide. The molecular pathogenesis of atherosclerosis is initiated and maintained by the retention of low-density-lipoprotein cholesterol (LDL-C) and other cholesterol-rich ApoB-containing lipoproteins within the arterial wall. The pathology correlates with the plasma concentration of and the duration of exposure to LDL-C. This is underscored by epidemiology as well as genetic evidence provided by the monogenetic causes of familial hypercholesterolemia and the human mendelian randomization studies. Randomized trials of LDL-C lowering with statins including over 20 million person-years of follow-up demonstrate a dose-dependent log-linear association between LDL-C and ASCVD risk. The addition of either ezetimibe or anti-PCSK9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibodies to statin therapy provides an additional risk reduction corresponding to the added cholesterol reduction. These recent trials indicate that the lower the achieved LDL-C values, the lower the risk of future CV events. There appears to be no lower limit for LDL-C values, or "J"-curve effect, with no report of adverse events even at very low LDL-C levels. In summary, LDL-C are causally related to ASCVD, and lowering of LDL-C and other ApoB-containing particles reduces CV events. Despite this evidence, lipid-lowering treatments in clinical practice are characterized by poor goal attainment. Especially medication adherence represents a large opportunity for improvements in care. On the basis of the current guidelines of the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and American Heart Association (AHA)/American College of Cardiology (ACC), this review summarizes the current evidence on the diagnosis and treatment of dyslipidemias.

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The 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias and the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guideline on the management of blood cholesterol focus on low-density-lipoprotein cholesterol (LDL-C) as the primary target for treatment.[1,2] Both guidelines agree on the concept of treatment goals based on individual risk assessment. If LDL-C goals cannot be reached with lifestyle modification and statins, which represent the basis of therapy, a stepwise approach adding ezetimibe and, in specified high-risk individuals, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is rec-

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Measures of atherogenic lipoproteins		
	Advantage	Disadvantage
LDL-C	Extensively studied Evidence for causality from basic science, epidemiology, genetics Proven as treatment target in RCT	Calculated LDL less reliable when TG very high Calculated LDL-C includes Lp(a)
Non-HDL = TC-HDL	Support from epidemiology	HDL analysis may be affected by high TG Not primary treatment target in RCT Not in most risk algorithms
ApoB	Includes all ApoB-containing lipoproteins Support from epidemiology Reliable even when TG very high	Not primary treatment target in RCT Not in most risk algorithms Analysis not universally available, extra cost

Table I. *Measures of atherogenic lipoproteins.*
Abbreviations: *ApoB, apolipoprotein B; HDL, high-density lipoprotein; LDL-C, low-density-lipoprotein cholesterol; Lp(a), lipoprotein(a); RCT, randomized controlled trial; TC, total cholesterol; TG, triglyceride.*

ommended.[1,2] The ESC/EAS guidelines are currently revised; it seems very likely that these principles will be confirmed taking into account new evidence that extends the correlation of achieved LDL-C with ASCVD reduction to lower levels.

LDL-cholesterol

Plasma LDL cholesterol levels (LDL-C) have emerged as the primary risk factor and treatment target for lipid-associated atherosclerotic cardiovascular disease (ASCVD).[3] This is based on the detailed cellular and molecular understanding of the pathology of atherogenesis, which cannot occur in the absence of LDL-C.[4] Genetic mutations, eg, in individuals with familial hypercholesterolemia (FH) that cause reduced LDL-receptor (LDLR) function, lead to markedly higher LDL-C and a dose-dependent increase in the risk of ASCVD, whereas genetic variants leading to lower LDL-C are associated with a correspondingly lower risk of ASCVD.[5,6] Very large and long-term cohort studies, population-based genetic analyses, randomized trials, and large registries with long follow-up demonstrate a consistent dose-dependent log-linear association between the absolute magnitude of exposure of the vasculature to LDL-C and the risk of ASCVD.[5] The risk of atherosclerosis is determined by the extent of exposure of the vascular endothelium to LDL-C, eg, the plasma concentration and the duration of exposure. Randomized trials with LDL-C–lowering medication (statins, ezetimibe, PCSK9 inhibitors) demonstrate that lowering of plasma LDL particle concentration reduces the risk of ASCVD proportional to the absolute reduction in LDL-C. In summary, this evidence establishes that LDL causes ASCVD.[5] The old term "LDL-hypothesis" is outdated. The absolute reduction in ASCVD risk by lowering LDL-C via an LDL-receptor (LDLR)-mediated mechanism, eg, with a statin, ezetimibe, or PCSK9-inhibitor, depends on the baseline individual risk of the patient, the absolute reduction in LDL-C—with each 1 mmol/L (about 40 mg/dL) reduction corresponding to a reduction of about one-fifth in ASCVD—and the duration of treatment.

Fasting is not routinely required for determination of a lipid profile.[7] Since LDL-C is typically not directly measured but calculated with the Friedewald formula, nonfasting measurements should be interpreted with caution in patients with elevated triglycerides (TGs), eg, for the metabolic syndrome or diabetes. Several parameters to quantitate pathogenic lipoproteins are available (see *Table I*).

Especially ApoB is a useful measure of an individual's exposure to atherosclerotic lipoproteins. Its use may be particularly helpful for risk assessment in people where measurement of LDL-C underestimates this burden, such as those with high TG levels, diabetes, obesity, or very low LDL-C. However, ApoB is not established as the primary treatment target in randomized controlled trials (RCTs); it is not reflected in most risk algorithms, the analysis not universally available and associated with extra cost. Therefore, LDL-C remains the primary parameter for risk assessment and treatment.

SELECTED ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
ApoA/ApoB	apolipoprotein A/apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
CKD	chronic kidney disease
FH	familial hypercholesterolemia
FOURIER	Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk
GFR	glomerular filtration rate
HDL-C	high-density-lipoprotein cholesterol
IMPROVE IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
LDL-C	low-density-lipoprotein cholesterol
LDLR	low-density-lipoprotein receptor
Lp(a)	lipoprotein(a)
ODYSSEY Outcomes	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
PCSK9	proprotein convertase subtilisin/kexin type 9
SAMS	statin-associated muscle symptoms
SCORE	Systemic Coronary Risk Estimation

HDL-cholesterol

High-density lipoproteins (HDLs) are still widely believed to exert atheroprotective effects. Previously, it was thought that high HDL-C would prevent or help reverse atherosclerosis by mediating transfer of cholesterol from the arterial wall to the liver for excretion. Hence, HDL-C is in general still considered as "good cholesterol." Recent research, however, has led to a fundamental reassessment of the clinical significance of HDL-C.[8] Low HDL-C is now considered a risk marker (not a causal factor) for ASCVD.

In individuals without a history of CV events, low concentrations of HDL-C are inversely associated with the risk of future CV events. This relationship may, however, not apply to patients with metabolic disorders or manifest CVD. The classical function of HDL is to mobilize cholesterol from extrahepatic tissues for delivery to the liver for excretion. These roles in cholesterol metabolism, and many other biological functions of HDL particles, are dependent on the number, as well as protein and lipid composition, of HDL particles. They are poorly reflected by the HDL-C concentration. HDL can even exert negative vascular effects if its composition is pathologically altered. High serum HDL-C therefore is no longer regarded protective. In line with this, recent pharmacological approaches to raise HDL-C concentration have not shown reductions in CV outcomes.

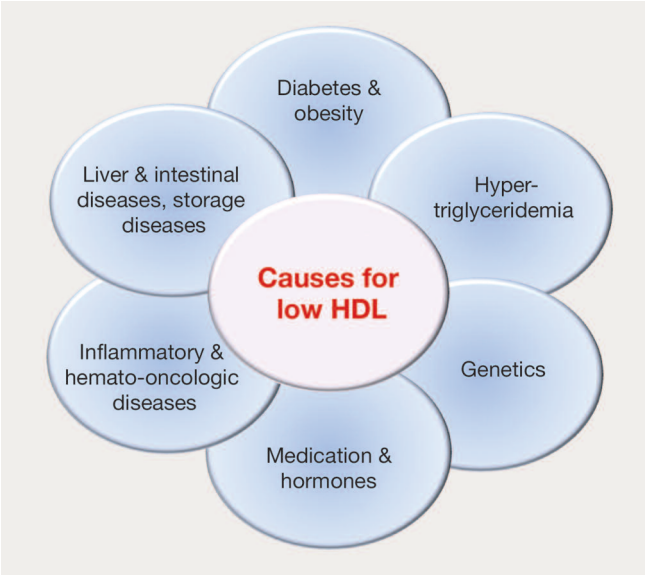

Figure 1. *Causes for low HDL-cholesterol.*

Abbreviation: *HDL, high-density lipoprotein.*
After reference 8: *März et al.* Clin Res Cardiol. *2017;106(9):663-675. © 2017, The Author(s).*

In contrast to LDL-C, HDL-C correlates with CV risk only in healthy individuals. The calculation of the ratio of LDL-C to HDL-C is not useful. The diagnosis of low HDL-C should prompt examination of additional metabolic and inflammatory pathologies that are depicted in *Figure 1*.[8] An increase in HDL-C through lifestyle change (smoking cessation, physical exercise) has positive effects and is recommended. However, HDL-C is currently not a valid target for drug therapy.[8]

Triglycerides

The majority of the circulating TGs are carried by TG-rich very-low-density lipoprotein (VLDL) particles and their remnants. Recent evidence strongly suggests that the effect of TGs on ASCVD risk is primarily mediated by the non-HDL-C, an estimate of the total concentration of all ApoB-containing lipoproteins. Elevated TG levels often occur in persons with a combination of multiple risk factors such as impaired glucose metabolism, obesity, and hypertension.

Primary goals for the management of hypertriglyceridemia are a reduction in CV risk and prevention of TG-associated complications, such as the chylomicronemia syndrome. Initially, patients should be counseled about therapeutic lifestyle changes (dietary intervention, alcohol avoidance, regular physical activity, weight loss, smoking cessation) to modify risk factors. If TG levels cannot be significantly reduced by lifestyle intervention, pharmacotherapy (fibrates and omega-3-acid ethyl esters) can be considered. Beyond reduction in TG levels, optimization of other lipoproteins, such as LDL-C, non-HDL-C, and HDL-C by statin treatment to reduce vascular risk is warranted.

Lipoprotein (a)

Lipoprotein(a), Lp(a), is an ApoB-containing particle similar to LDL that carries an apolipoprotein(a), Apo(a), moiety. Up to 90% of Lp(a) is autosomal-dominantly inherited. Epidemiologic and genetic evidence documents that Lp(a) is causally related to myocardial infarction, atherosclerosis, and aortic valve stenosis. Lp(a) levels do not correspond to lifestyle. A one-time measurement of Lp(a) should be considered to identify people with high inherited Lp(a) levels who have a substantial lifetime risk of ASCVD. A one-time measurement of Lp(a) is helpful for further risk stratification, in patients with a family history of premature CVD, and for determining treatment in people with estimated risk that is on the border of risk categories.

A recent mendelian randomization study suggests that large absolute changes in Lp(a) may be needed to produce a clinically meaningful reduction in the risk of ASCVD events, eg, the authors predict that an approximately 100 mg/dL change in Lp(a) concentration has the same association with coronary heart disease (CHD) risk as a 1 mmol/L (about 40 mg/dL) change in LDL-C.[9] The currently available oral therapies do not significantly lower Lp(a). PCSK9 inhibitors lower Lp(a); however, the clinical significance of this effect is undetermined. In Germany only, lipoprotein apheresis is approved for Lp(a) lowering in patients with progressive ASCVD. Novel treatments with Apo(a) antisense oligonucleotides targeting hepatic Apo(a) production are evaluated in ongoing clinical studies. At pres-

ent, effective ApoB-lowering with statins (and nonstatin drugs) is recommended to reduce the ASCVD risk of persons with high Lp(a).

Familial hypercholesterolemia

With an estimated prevalence of at least 1:300, FH is one of the most common genetic disorders in medical practice. FH is characterized by a pronounced increase in LDL and premature manifestation of CHD. It is underdiagnosed and undertreated in most countries.[10] The clinical diagnosis of FH is made in patients with an LDL-C over 90 mg/dL (about 5 mmol/L) if familial clustering of hypercholesterolemia or premature CHD or tendon xanthomas are present. Genetic analysis contributes to improved specificity in diagnostics. The therapeutic targets are LDL-C lowering to below 100 mg/dL (2.6 mmol/L) or at least a 50% reduction in LDL-C in adult patients with FH (children <135 mg/dL [3.5 mmol/L]) or below 70 mg/dL (1.8 mmol/L) in the presence of clinical manifestations of atherosclerosis. The basis of the treatment is lifestyle modification, statins, and the addition of ezetimibe and PCSK9 inhibitors to reach these goals. For treatment of severe cases, eg, the very rare heterozygotes, LDL apheresis is available. In light of its grave prognosis, early diagnosis is relevant, since the high ASCVD risk in FH—sufficiently early recognized—can be effectively treated.[11]

The new AHA/ACC guidelines recommend that all patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]) begin high-intensity statin therapy, with no calculation of 10-year ASCVD risk necessary because risk calculators are not valid for these patients.[2] If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), combination treatment with ezetimibe and PCSK9 inhibitors is suggested.[2]

Treatment

◆ *Risk estimation and treatment goals*

Both the European and the US-American guidelines on dyslipidemia recommend stratifying the decision for initiation of drug therapy and the intensity of treatment according to the individual risk of the patient. CV risk is a continuum without discrete thresholds. The cutoff points for risk categories are in part arbitrary and in part based on characteristics of populations included in the clinical trial. The purpose of risk categories is the communication of the principle that the achievable absolute risk reduction corresponds with the baseline individual risk. It is important that the highest-risk patients achieve the largest LDL-C reduction possible.

Risk factor screening including the lipid profile should be considered in men over 40 years of age and in women over 50 or who are post menopausal. The SCORE (Systemic Coronary Risk Estimation) system provides a helpful tool; calibrated country-specific versions can be found at http://www.heartscore.org. Adherence and the response to LDL-C–lowering medications and lifestyle changes should be assessed with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment and repeated every 3 to 12 months.[2]

Although specific treatment goals cannot be tested in a RCT, a goal-directed strategy provides important advantages for communication and patient-centered care. Based on the integrated evidence from basic science, clinical observations, genetics, epidemiology, RCTs, and registries, both the current ESC/EAS and AHA/ACC guidelines agree on recommending LDL-C treatment goals as part of a comprehensive CV risk reduction strategy.[1,2]

◆ *Very high risk*

Persons with a calculated SCORE ≥10% for 10-year risk of fatal CVD or with established CVD, type 1 or type 2 diabetes with a major risk factor, very high levels of individual risk factors (such as FH), or chronic kidney disease (CKD; glomerular filtration rate [GFR] <30 mL/min/1.73 m^2) are automatically considered at very high CV risk without needing risk scoring. They require immediate attention to all risk factors. Documented CVD includes previous acute coronary syndrome (ACS; myocardial infarction or unstable angina), stable angina, coronary revascularization (percutaneous coronary intervention, coronary artery bypass grafting, and other arterial revascularization procedures), stroke and transient ischemic attack, and polyvascular arterial disease. Documented CVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or computed tomography scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound.

The treatment goal for very-high-risk patients is at least a LDL-C reduction by 50% and a LDL-C level under 70 mg/dL (<1.8 mmol/L); however, recent evidence clearly suggests that additional LDL-C lowering will provide additional ASCVD reduction. Indeed, within the population of patients with established CVD, a subgroup of *extreme-risk* patients can be identified, such as those with recurrent events or symptomatic progression of atherosclerosis despite being on a statin, or patients with a prior event and two or more of the above conditions. Subgroup analyses of recent trials (eg, IMPROVE IT [IMProved Reduction of Outcomes: Vytorin Efficacy International Trial], FOURIER [Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk], ODYSSEY Outcomes [Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab]) report that these individuals significantly benefit from more intensive LDL-C lowering.

◆ *High risk*

High risk is determined by a calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD or one of the following factors: markedly elevated single risk factors, in particular total cholesterol (TC) >8 mmol/L (310 mg/dL) or blood pressure

(BP) ≥180/110 mm Hg; LDL-C >4.9 mmol/L (190 mg/dL) or with FH; diabetes mellitus without organ damage or major risk factors (at younger ages, such patients may be at low or moderate risk); and moderate CKD (estimated GFR, 30-59 mL/min/1.73 m^2). The recommended LDL-C goal for high risk is <2.6 mmol/L (100 mg/dL) at least, although lower LDL-C (50% absolute LDL-C reduction, <1.8 mmol/L [70 mg/dL]) will provide additional benefit.

◆ *Moderate risk*

Moderate risk corresponds to a calculated SCORE ≥1% and <5%; the LDL-C goal is <3.0 mmol/L (115 mg/dL).

◆ *Additional determinants of risk*

Low income, social deprivation, and psychosocial stress increase CV risk but are not integrated in the available risk scores. Additional risk enhancing factors include a positive family history, metabolic syndrome; CKD; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of TG ≥175 mg/dL (≥1.97 mmol/L); high-sensitivity C-reactive protein ≥2.0 mg/L; ankle-brachial index <0.9 and Lp(a) ≥50 mg/dL or 125 nmol/L.[2]

◆ *Vascular imaging*

Vascular imaging is recommended for borderline treatment decisions; the best reclassification ability is available for the coronary artery calcium (CAC) score. Assessment of carotid or femoral plaque burden with ultrasound can be helpful for patient communication and monitoring. Measurement of the carotid intima-media thickness is inferior to CAC scoring and carotid plaque detection. Of note, CAC score is increased following statin treatment and intensive physical exercise, maybe due to the reduction in the lipid content of the plaques, which is believed to correspond with increased plaque stability, and should be interpreted with caution in these patients.

◆ *Young patients*

In young people with high levels of risk factors, a low short-term absolute risk may conceal a very high relative risk and a very high lifelong risk. The concept of "risk age" or "vascular age" can be useful for communication. It calculates the age of a person with several CV risk factors corresponding to the age of a person with the same level of risk but with ideal levels of risk factors. Risk age calculation is provided as part of the latest revision of HeartScore (http://www.HeartScore.org). "Lifetime risk" is another approach to illustrate the longer-term impact of risk factors.

◆ *Elderly patients*

Elderly patients benefit from risk factor control with physical exercise, smoking cessation, and control of hypertension and hyperlipidemia; clinical judgment is warranted in order to avoid side effects from overmedication.

The current stepwise approach to LDL-C lowering is depicted in *Figure 2.*

◆ *Lifestyle*

A healthy lifestyle reduces ASCVD risk at all ages and therefore represents the basis of treatment for all patients.

The best evidence is available for stopping exposure to tobacco in any form and for physical activity. Moderately vigorous physical activity is recommended for 2.5 to 5 hours per week or 30 to 60 minutes most days. A diet low in trans fat and in saturated fat with a focus on whole grain products, vegetables, fruit, and fish may reduce ASCVD risk, although randomized studies on this subject are rare. Calorie intake

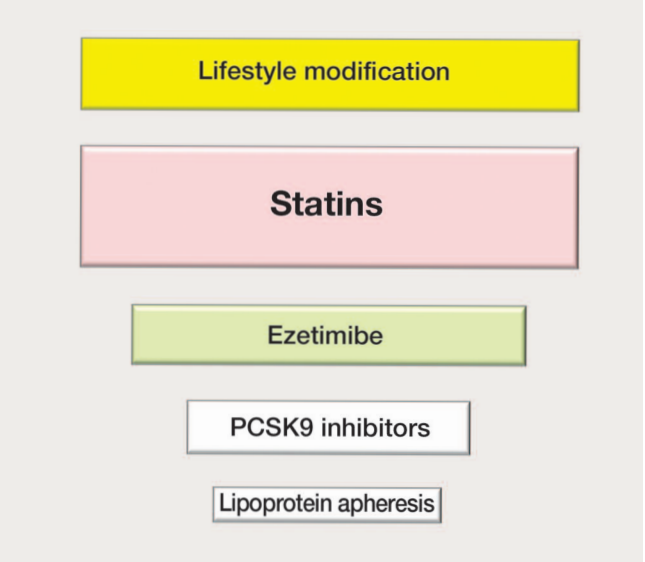

Figure 2. *Current concept of LDL-cholesterol lowering.*

Abbreviations: *LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.*

should correspond to energy expenditure; weight gain should be avoided. The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, especially for persons with hypertriglyceridemia, metabolic syndrome, or diabetes. No evidence for a reduction in ASCVD and no long-term safety data exist for nutraceuticals, such as phytosterols, "functional foods," or red yeast rice. Vitamins B_6, B_{12}, C, D, E, and folic acid have been tested in large RCTs, which have proven that they do not reduce ASCVD.

◆ *Statins*

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase [HMG-CoA] inhibitors) inhibit the rate-limiting step in cholesterol biosynthesis. This leads to increased expression of the hepatic LDLRs with enhanced clearance of LDL-C and other ApoB-containing lipoproteins from the plasma. The efficacy of statins in preventing both first and recurrent CV events and mortality is very well documented for individuals in all risk categories including "primary prevention." For example, the

Cholesterol Treatment Trialists' analysis of individual participant data from 170 000 participants in 26 RCTs showed that a 1 mmol/L (about 40 mg/dL) reduction in LDL-C with statin/more statin reduced major vascular events by 22%, major coronary events by 23%, coronary artery disease death by 20%, stroke by 17%, and total mortality by 10%.[12] Excellent safety and tolerability have been proven in large long-term trials and "real world" data. Because of the unequivocal positive evidence, statins are recommended by all guidelines as first-line treatment for lipid management.[1,2] For all patients with clinical ASCVD, high-intensity statin therapy or maximally tolerated statin therapy is indicated. The more LDL-C is reduced, the greater will be subsequent risk reduction ("the lower the better"). Because of the documented benefit, all patients with diabetes mellitus should receive a statin.[2]

Statin therapy is associated with a modest increase in the risk of new-onset diabetes mellitus (about one per thousand patient-years, defined by laboratory findings of glycated hemoglobin [HbA_{1C}] ≥6.5). This risk is significantly higher with the metabolic syndrome or prediabetes.[13] Statin treatment does not adversely affect cognitive function, renal function, or development of cataracts. Clinically apparent liver injury associated with statin therapy is a very rare class effect of statins. The evidence base does not support an increased risk of hemorrhagic stroke.

Statins very rarely cause serious muscle damage (eg, myopathy, or rhabdomyolysis). However, the prevalence of statin-associated muscle symptoms (SAMS) is probably 5% of the people who receive statins[14] The etiology of SAMS is heterogeneous. SAMS may result in significant limitations in the quality of life and often lead to reduction in the statin dose, eg, they may affect the adherence to statins.

Many large randomized trials have shown that true statin intolerance is rare and that it is generally possible to institute some form of statin therapy (eg, by changing the statin, or reducing the dose) in the overwhelming majority of patients at risk of ASCVD. After optimization of the treatment (change of statin dosage or frequency of administration), more than 90% of patients can be treated with statins long term. This is important, as the potential efficacy of statins may otherwise not be achieved, especially in high-risk patients. If LDL-C reduction is insufficient on treatment with the maximally tolerated statin dosage, combination therapy is indicated.

In summary, long-term statin treatment is remarkably safe with a low risk of clinically relevant adverse effects. Importantly, the established CV benefits of statin therapy far outweigh the risk of adverse effects.[13]

◆ *Ezetimibe*

Ezetimibe inhibits intestinal uptake of cholesterol by interaction with the Niemann-Pick C1-like protein 1 which reduces the amount of cholesterol delivered to the liver, leading to upregulation of LDLR and subsequent increase of the removal of LDL-C from the plasma. Ezetimibe in monotherapy reduces LDL-C by about 15% to 20% and in addition to statin treatment by about 20% to 27%. The combination of ezetimibe with statin provides greater reductions in LDL-C than doubling of the respective statin dose (13%-20%). Ezetimibe is well tolerated and safe. If a patient does not respond to a statin-ezetimibe combination, the most likely cause is lack of intake/nonadherence. Based on the reduction in ASCVD demonstrated in trials such as IMPROVE-IT, current guidelines recommend ezetimibe as second-line therapy added to statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in case a statin cannot be prescribed.[1,2]

◆ *PCSK9-Inhibitors*

PCSK9 is a regulator of the LDLR. Reduction in or inhibition of PCSK9 reduces the lysosomal catabolism of the LDLR, increasing their expression at the surface of hepatocytes.[15] Lower levels or function of PCSK9 thereby results in lower plasma LDL-C levels. Currently approved and available are the two fully human monoclonal antibodies alirocumab and evolocumab. Either alone or in combination with statins and/or other lipid-lowering therapies, these agents lower LDL-C by an additional 50% to 60%. In contrast to statins, they also reduce Lp(a) plasma levels by about 30%, although the clinical significance of this effect is unknown.[16] Large trials (FOURIER, ODYSSEY Outcomes) have shown that PCSK9 inhibitors further reduce ASCVD risk and mortality when given on top of statin-based therapy. The effect corresponds to LDL-C reduction. There is no lower limit or "J-curve" of the relationship of achieved LDL-C and relative CV risk. They are very well tolerated, even by individuals who cannot tolerate statins. No relevant adverse effects have been reported to date, even at very low LDL-C concentrations (eg, below 1 mmol/L).

At present, anti-PCSK9 antibodies are costly, although prices are decreasing worldwide. For economic reasons, their use has to be restricted by the different health care systems, and patient selection is important.[17] As with any LDL-C–lowering therapy, the absolute risk reduction corresponds to the baseline vascular risk and the baseline LDL-C *(Table II, page 122)*.[5] Therefore, the highest absolute benefit (ie, the lowest number needed to treat) of PCSK9 inhibition relates to patients with very high ASCVD risk and high LDL-C despite optimal oral lipid-lowering therapy. The current AHA/ACC guidelines recommend to consider addition of nonstatins to statin therapy in very-high–risk ASCVD with a LDL-C threshold of 70 mg/dL (1.8 mmol/L).[2]

◆ *Medication adherence*

Despite the availability of high-potency statins at minimal costs and despite the overwhelming evidence and clear guideline recommendations, goal attainment for lipid-lowering therapies is very low. Indeed, less than 20% of high-risk patients

10-year absolute risk of CVD (%)	Baseline LDL-C mmol/L (mg/dL)	LDL-C after 50% reduction mmol/L (mg/dL)	Proportional risk reduction (%)	10-year absolute risk after 50% LDL-C reduction	ARR	NNT
20	5 (200)	2.5 (100)	42.8	11.4	8.6	11.7
20	4 (160)	2.0 (80)	36	12.8	7.2	13.9
20	3 (120)	1.5 (60)	28.4	14.3	5.7	17.6
20	2 (80)	1.0 (40)	20	16	4	25
15	5 (200)	2.5 (100)	42.8	8.6	6.4	15.6
15	4 (160)	2.0 (80)	36	9.6	5.4	18.5
15	3 (120)	1.5 (60)	28.4	10.7	4.3	23.4
15	2 (80)	1.0 (40)	20	12	3	33.3
10	5 (200)	2.5 (100)	42.8	5.7	4.3	23.4
10	4 (160)	2.0 (80)	36	6.4	3.6	27.8
10	3 (120)	1.5 (60)	28.4	7.2	2.8	35.2
10	2 (80)	1.0 (40)	20	8	2	50
5	5 (200)	2.5 (100)	42.8	2.9	2.1	46.8
5	4 (160)	2.0 (80)	36	3.2	1.8	55.6
5	3 (120)	1.5 (60)	28.4	3.6	1.4	70.3
5	2 (80)	1.0 (40)	20	4	1	100

Table II. *Short-term absolute risk reduction and number needed to treat.*
Abbreviations: *ARR, absolute risk reduction; CVD, cardiovascular disease; LDL-C, low-density-lipoprotein cholesterol; NNT, number needed to treat.*
After reference 5: *Ference et al.* Eur Heart J. *2017;38(32):2459-2472. © 2017, The Author. Published on behalf of the European Society of Cardiology.*

achieve a goal of <1.8 mmol/L (70 mg/dL).[18,19] Several factors contribute to this observation; among those, physician's inertia plays an important role. The single most important lifestyle-related factor for the effect of lipid-lowering therapy is medication adherence.[20] Up to one-third of lipid (and BP)-lowering tablets are not taken as intended by the prescribing physician. The importance of this problem is underscored by the observations that adherence to statin therapy is directly correlated with survival both in primary and secondary prevention.[21] A recent cross-sectional study in Germany on ambulatory patients with hypercholesterolemia revealed that high or moderate adherence to lipid-lowering medication compared with low adherence was associated with lower LDL-C levels, lower BP, and with a higher proportion of patients achieving the guideline-recommended LDL-C and BP targets.[22] Adherence and risk factor control was worse in patients with depression. A low adherence and the diagnosis of depression identify patients at risk for uncontrolled LDL-C and BP who would probably benefit from intensified care.

Medication adherence negatively correlates with the number of pills prescribed per day.[20] Several studies have demonstrated that fixed-dose combinations reduce BP to a greater extent than the components given separately.[20,23] The observed correlation of the medication adherence for lipid- and BP-lowering medication implies that the data on the potential benefit of fixed-dose combinations may be extrapolated from BP lowering to lipid lowering.[22]

Therefore, strategies shown to increase adherence, such as combination therapy to reduce the number of daily tablets, provide an important opportunity for use in lipid-lowering therapy. ■

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