Managing elevated lipids in primary care

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Abstract

Cardiovascular disease (CVD) is the most important preventable disorder, which represents a high burden to affected individuals and societies. Elevated lipid profile is a major CVD risk factor, specifically high low-density lipoprotein cholesterol (LDL-c) levels. A number of lipid-lowering therapies have been demonstrated to lower CV risk. Still, many people remain at high risk of CV events, due to poor treatment adherence, perceived side effects of treatment, inadequate use of existing therapies and/or inter-individual response to treatment.

This EPCCS Practical Guidance Document provides a brief scientific background on the need for lipid lowering in individuals at high CV risk, and practical guidance on management of persons with dyslipidaemia in primary care, with a focus on challenges faced in clinical reality. The document considers how to deal with (perceived) statin intolerance, and with the effect of negative news stories on lipid-lowering treatment. Finally, advances in personalised medicine are discussed, and how this will affect treatment decisions and risk communication with patients.

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Introduction

Cardiovascular disease (CVD) is the most important preventable disorder that challenges most societies around the world (1); both in terms of the hardships faced by the affected individuals, and their premature mortality, and of the burden to healthcare systems due to the large numbers of patients and associated costs, especially hospitalisation and social care costs.

There is a huge evidence base to guide management strategies aimed at reducing the classical CV risk factors

and modifying prognosis after events. One of the most important CVD risk factors is elevated lipid profiles, specifically low-density lipoprotein cholesterol (LDL-c) and its impact on total cholesterol levels. This is the focus of this document.

Multiple CVD risk and risk assessment

Though this guideline focuses upon lipid modification, it is important to stress that for most patients a comprehensive risk factor management approach, or modifying all elevated risk factors simultaneously, is needed to help lower risk of a CVD event. Dyslipidaemia, high blood pressure and hyperglycaemia all contribute to CV risk, and national and international (2) guidelines consider the management options for all of these domains at once. Furthermore, the decision of which patients have sufficient CVD risk to warrant treatment is based upon formal risk assessment, calculated using all the main risk factors in a validated clinical score (such as SCORE, Framingham, or QRisk). The reason for this is that many patients with modest levels of multiple risk factors may have very elevated overall CVD risk. Guidance on management of single risk factors remains relevant, however, as many patients in primary care (PC) have isolated risk factors. Further, once a decision is taken to offer lipid modification as part of an overall CVD risk reduction strategy, the treatment options need to be clear.

This document covers overall CV risk assessment strategies, to determine which patients warrant lipid modification, but for therapeutic strategies beyond lipid lowering, we refer to the ESC Guidelines on CVD prevention (2), and other ESC Guidelines on management of individual risk factors. Moreover, other EPCCS Guidance Documents are available that focus specifically on PC, and cover stroke prevention in atrial fibrillation, management of heart failure patients, and how to stimulate behaviour change to lower CV risk (see ipccs.org). Diabetes and hypertension guidelines are also under development.

Lipid management

A number of lipid-lowering therapies that have been shown to lower CV risk are available, but many people remain at high risk of CV events. Various factors contribute to this, including poor treatment adherence, sometimes due to perceived side effects of treatment, and inadequate use of existing therapies. Moreover, a large variability exists in patients' responses to treatment.

Scientific efforts are advancing towards more individualised medicine; big data help to gain better insight into how to deliver the right treatment to the right person at the right time. Among the greatest challenges for a clinician is the need to translate the results of randomised clinical trials (RCTs), to treatment of the individual patient.

All of these aspects will be discussed in this document that aims to guide general practitioners (GPs) and other primary care physicians on how to manage elevated lipids in PC. This document is based on the summary evidence for lipids and their modification presented during the 2018 European Primary Care Cardiovascular Society (EPCCS) Annual CV Summit, and the discussion thereafter among PC physicians from all across Europe. It provides a brief scientific background and practical guidance, focussing on challenges faced in clinical reality.

Evidence for lipid-lowering therapy to lower CV risk

LDL-c is an important risk factor

Cholesterol and triglycerides circulate in blood plasma as lipoproteins, bound to proteins. Elevated lipids are among the most important CV risk factors, with most attention going to LDL-c, the main carrier of cholesterol in plasma. Across a wide range of plasma cholesterol concentrations, strong and graded positive associations exist between both total cholesterol and LDL-c, and risk of CVD (3). The evidence base demonstrating that LDL-c is an atherogenic particle associated with CVD is overwhelming (3).

For instance, the INTERHEART (4) study examined risk factors associated with acute myocardial infarction (MI). INTERHEART is one of the largest studies in CV medicine, involving over 30,000 patients with MI, in 52 countries. Risk estimates were adjusted for age, gender and geographic region. The data revealed that smoking, diabetes, hypertension and abdominal obesity are important risk factors, with odds ratios (ORs) in the range of 2 to 4. The LDL-c/HDL-c (high-density lipoprotein cholesterol) ratio showed the highest OR, making it the most important risk factor for development of acute MI in INTERHEART. On the other side of the spectrum, the study revealed cardioprotective effects of eating fruit and vegetables, physical activity, and a moderate intake of alcohol, the latter two more so in females than in males (4).

A very large number of intervention trials, with most data for statin therapy, have shown that lowering LDL-c reduces CVD events substantially and consistently (23% risk reduction of CV events, 21% for CV plus stroke, for every 1 mmol reduction of LDL-c) (5), and proportionately regardless of baseline LDL. Although virtually all people will derive a similar relative risk reduction with statin treatment at any baseline LDL level, the absolute derived risk reduction will naturally benefit those at higher risk. Therefore, on cost effectiveness grounds, and to avoid medicating the majority of the adult population, most countries define a threshold of LDL that 'warrants' treatment. In most European countries, an LDL-c level of 2.6 mmol/L (100 mg/dL) is the main treatment threshold for patients with an increased risk for CV events, but this drops in patients at very high risk (such as after CV events) to as low as 1.8 mmol/L (70 mg/dL). Therefore, recommendations on treatment goals are refined based on different risk levels, as will be discussed below.

In addition to stressing the importance of reducing elevated LDL-c levels to lower CV risk, it is also important to realise that elevated LDL-c is a risk factor, not a diagnosis. Thus, it is worthwhile to search for underlying disease, for instance a genetic cause of hypercholesterolemia, or hypothyroidism. Patients with a genetic dyslipidaemia should be referred to specialist care. In the case of hypothyroidism, treatment of underlying disease may improve hyperlipidaemia without the need for lipid-lowering therapy.

Other lipids and lipoproteins as risk markers

In addition to LDL-c, Mendelian randomisation studies have suggested a causal role for remnant cholesterol [=total cholesterol – (LDL-c + HDL-c)] in atherogenesis. High levels of triglycerides are also an independent risk factor, but the association of hyper-triglyceridaemia with CVD is weaker than that of hypercholesterolaemia (6). Due to limited RCT evidence, no treatment targets have been defined for triglycerides. Fasting triglycerides >1.7 mmol/L (>150 mg/dL) are, however, currently considered a marker of increased risk. Levels below this threshold are not evidence-based targets for therapy.

Low HDL-c levels are another independent and important risk marker for CVD (7). In trials evaluating pharmacological means to increase HDL-c levels, this increase could not be linked to meaningful clinical benefit. HDL-c level should therefore be considered a risk marker rather than risk factor. A Mendelian randomisation study recently also suggested that HDL-c is no causal factor in CVD (8). Thus, low HDL-c is a risk marker, but not a therapeutic target, although physical activity and other healthy lifestyle habits remain important for increasing HDL-c levels (2).

Lipid and lipoprotein measurements other than LDL-c are sometimes used to refine risk evaluation (2). Lipoprotein(a) [Lp(a)] is another strong independent CVD risk factor. Its levels are largely genetically determined and at present, therapeutic targeting of Lp(a) is not recommended (2, 9).

ApoB levels appear to have similar CVD predictive value to LDL-c (10). Especially in individuals with hyper-triglyceridaemia (>3.4 mmol/L or >300 mg/dL), measurement of apoB is more accurate than that of LDL-c (11). ApoB levels have not been incorporated in currently recommended risk calculators to date. Hence, LDL-c remains the most important treatment target to lower CVD risk.

LDL-c as a therapeutic target

Ample evidence exists that shows that lipid-lowering therapy is effective to lower CVD risk. A large number of studies have shown that the lower the LDL-c level, the lower the CV risk (12). More precisely, a meta-analysis of over 174,000 participants in 27 statin trials revealed a dose-dependent relative reduction of CVD with LDL-c lowering, such that every 1.0 mmol/L reduction in LDL-c is associated with about 20-25% relative reduction in CVD mortality and non-fatal MI (5, 13). This effect of LDL-c lowering was very consistent across trials, both for patients with a history of vascular disease and those with no known history of vascular disease, and it is similar for men and women (13). Moreover, a higher dose of a statin was more effective at lowering CV events in patients with stable coronary disease, than a low dose (atorvastatin 80 mg vs 10 mg) (14). Similarly, the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial showed higher efficacy of high-intensity statin as compared with lower intensity statin treatment for secondary prevention in patients after an MI (15).

Take home messages

Overwhelming evidence has demonstrated that LDL-c is an atherogenic particle and major risk factor for CVD.

Lowering LDL-c reduces CVD events substantially and consistently.

Levels of lipids and lipoproteins other than LDL-c can serve as risk markers, but LDL-c is currently the only lipid risk factor (lowering the risk marker modifies disease) and an important treatment target to lower CVD risk.

CV risk assessment

Most LDL-c-lowering RCTs have compared different treatment regimens and intensities, rather than the clinical effect of specific treatment goals. Most guidelines do, however, recommend starting treatment above specific threshold LDL-c levels in patients with an elevated risk of CV events. By lack of RCT-evidence on the benefit of these treatment targets, they are, consequently, mostly consensus-based. Different treatment goals have been defined for different risk levels; a distinction is made between low or moderate (LDL-c <3.0 mmol/L or <115 mg/dL), high (LDL-c <2.6 mmol/L or <100 mg/dL) and very high risk (LDL-c <1.8 mmol/L or <70 mg/dL).
Multiple CV risk assessment tools are available to help determine which patients without established CVD should be offered treatment. Certain patients with specific diseases such as renal failure or diabetes mellitus can be classified directly in the category of high risk, without the need for CV risk assessment. For others, the ESC guidelines recommend using SCORE, to assess the 10-year risk of a first fatal atherosclerotic event, based on total/HDL cholesterol ratio, age, sex, smoking status and systolic blood pressure (2, 16). Other validated CV risk tools include the Framingham risk score model for 10-year CVD incidence or death (17) and the British QRISK2 score model for 10-year CVD incidence and death (18). The SMART (Second Manifestations of Arterial Disease) score has been validated for use in patients with vascular disease (19). Calculating CV risk can guide management decisions and prevent both under- and overtreatment. It should be noted that the risk of non-fatal events is higher than the risk of fatal events as estimated with SCORE. A study based on data in The Netherlands, suggests that the total CV event risk is about four times higher than the risk of fatal CVD for men, and for women, a multiplier of the SCORE risk of about 4 can be used. For older persons, the multiplier is lower than three; as for them a first event is more likely to be fatal (20).

Special patient groups
When applying the SCORE risk tables, both younger and older individuals require specific attention. Younger persons may have a low absolute risk according to the SCORE chart, but their relative risk may be high, as a consequence of high levels of risk factors requiring lifestyle modification. In risk conversations, it may be illustrative to speak about their risk relative to others of their age or calculating their risk age or lifetime risk or lifetime benefit expressed as disease-free life years gained. Lifestyle changes can importantly lower the relative risk, and reduce the increase in risk that occurs with ageing.

According to the SCORE risk table, everybody aged 65 years and older is at high or very high risk. That would imply that most elderly are eligible for lipid-lowering treatment. It is debatable whether that is a very good strategy, because the SCORE risk chart does not take into account competing risks. In fact, the risk distribution in elderly (≥70 years old) is very wide, according to a study that analysed data of the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm) trials (21). This study showed that about 25% of elderly without vascular disease have a 10-year risk <20% of MACE (MI, stroke and vascular death). In those without vascular disease, the median risk was 26.4%. In elderly with vascular disease, only 1.4% of patients, have a 10-year risk of <10%, and the median risk of MACE is 46.9%. Thus, because of the high risk of a recurrent CV event, for secondary prevention of MACE, treating all elderly patients with pharmacotherapy is more beneficial than prediction-based treatment. In fact, the same study showed a median 10-year absolute risk reduction (ARR) in MACE of 7.8% (interquartile range, IQR: 6.8-8.6). In elderly without vascular disease, the median 10-year ARR was 2.9% (IQR: 2.3-3.6%)(21). It has been described that lipid-lowering reduces CV risk by on average 20% (22), and this effect is mostly driven by those with a history of vascular disease. Thus, in elderly without a history of CV events, it is less clear whether they will benefit from primary prevention with statin therapy. Especially in the frail and/or elderly patients, polypharmacy (≥5 substances) complicates CV risk management. Since lipid-lowering therapy is mainly targeting a calculated 10-year risk, the life expectancy of the individual patient should be

taken into account and weighed against side effects of an intensive lipid-lowering therapy.

In summary, CV risk is often overestimated in the elderly. CV risk management in elderly benefits from a risk calculator specifically developed for this patient subgroup (23), especially one that takes competing risks into account (21).

Take home messages

Different treatment goals have been defined for different risk levels; the higher the risk, the lower the goal.

CV risk assessment tools can guide management decisions and prevent under- and overtreatment.

SCORE risk tables may underestimate risk in young persons, and overestimate risk in elderly persons. In young individuals, it is more illustrative to speak of risk relative to others of the same age, or of risk age or lifetime risk. A risk calculator specifically developed for elderly patients should be used.

Management options for hypercholesterolaemia

Non-pharmacological control of plasma cholesterol

In individuals at low and moderate risk, the goal of <3.0 mmol/L should be targeted without medical treatment. Lifestyle modifications are effective not only on the human lipid structure, but are also considered effective in a general CV risk reduction, albeit to a modest extent (2, 24). The modest effect is a consequence of the lower risk associated with dietary and lifestyle interventions. Moreover, additional favourable effects contribute to lowering CV risk, e.g. weight management, systemic inflammation and insulin sensitivity. General lifestyle changes can reduce LDL-c by 6-10%.

Dietary fatty acids and cholesterolaemia

Overall, available data suggest that, the consumption of saturated and trans fatty acids tend to increase total cholesterol and LDL-c levels. Conversely, polyunsaturated, cis-fatty acids (namely those of the n-6 series such as linoleic acid) induce opposite effects. Mono-unsaturated fatty acids such as oleic acid also reduce total cholesterol and LDL-c levels, although to a lesser extent than n-6 polyunsaturates (25).

A lipid intake of 30-35% of total calories is probably adequate to control total and LDL-cholesterolaemia in Western countries. Saturates intake should be limited to <10%, while intake of trans fatty acids should be narrowed to those from dairy products and limited to <1% of total energy intake.

Dietary cholesterol and cholesterolaemia

The exact role and contribution of dietary cholesterol (cholesterol is only present in animal-derived food items) to cholesterolaemia and atherogenesis are still debated, although it has been proven that dietary cholesterol increases LDL-c levels. However, the effect of dietary cholesterol on LDL-c levels is much less prominent than that of saturated or trans fatty acids.

The most recent evidence puts the role of dietary cholesterol in cholesterolaemia management in a new perspective. Still, it seems advisable not to exceed a daily cholesterol intake of 300 mg.

Dietary fibre and cholesterolaemia

Dietary fibre induces notable effects on plasma lipids and lipoproteins. This effect is more pronounced for soluble or gel-forming fibres, i.e. pectines, gum, beta-glycans, mucilages and hemicellulose, which are found in cereals such as barley and oat, and legumes. Consumption of 5-10 gr/day of soluble fibre such as beta-glycans, glycomannan, guar and psyllium reduces LDL cholesterolaemia by ~5% (26). A meta-analysis (27) concluded that each gram of soluble fibre reduces total cholesterolaemia by ~2 mg/dl and LDL cholesterolaemia by ~2.5 mg/dl, with small variations due to the studied study groups and doses. Fibre reduces cholesterol absorption by the ileum and increases faecal excretion. By contrast, soluble fibre does not impact significantly on plasma concentrations of triacylglycerols and HDL-c.

A daily fibre intake of 25-30 g may play a significant cholesterol-lowering role; soluble and gelifying fibre is more effective than non-soluble fibre, and increasing its intake by 5 gr/day can reduce total and LDL cholesterolaemia.

Body weight changes and cholesterolaemia

Alterations in plasma lipid profile occur in overweight or obese patients. Weight loss is, however, associated with a modest, yet statistically significant, decrease in plasma total cholesterol and LDL-c levels. The effects on triglycerides are usually more pronounced. Changes in HDL-c vary (6).

Physical activity and cholesterolaemia control
Regular physical activity is beneficial for many risk factors through improving the plasma lipid profile, and it can aid in, for instance, weight and hypertension control (28). Observational studies indicate that the impact of physical activity on lipid fractions is greatest for HDL-c, which tends to increase, and for triglycerides, which tend to fall in active individuals as compared with inactive controls. By contrast, changes in plasma total cholesterol and LDL-c values are less consistent.

Lifestyle modification, including healthy diet, exercise, quitting smoking, should be discussed and encouraged, keeping the insights described above in mind. PC professionals are in a good position to observe which lifestyle interventions might benefit an individual, but they may not always know how they can stimulate health behaviour change in their patients. Another EPCCS Guidance Document for Primary Care summarised evidence on ingredients of successful behaviour change strategies and motivational interviewing, as well as which CV risk behaviours and clinical outcomes may be improved with various types of strategies (See: ipccs.org).

Guideline-recommended pharmacological therapeutic options
Very briefly, for the higher risk categories, when pharmacotherapy is needed to attain the recommended targets, the ESC Guidelines on CVD prevention (2) consider statins the first-line treatment. Statins should be prescribed at the highest recommended or tolerable dose to reach the goal. If the goal is not met, statin treatment can be combined with ezetimibe and/or bile acid sequestrants. These types of agents can also be considered in individuals with statin intolerance (discussed in more detail later). In patients at very high risk, persistently elevated LDL-c despite maximally tolerated statin treatment in combination with ezetimibe, additional treatment with a PCSK9 inhibitor may be considered (2).

Take home messages

Lifestyle modification can lower LDL-c and is considered effective for general CV risk reduction, albeit to a modest extent.

- Dietary fatty acid intake should be limited to 30-35% of total calorie intake, and saturated and trans fatty acids should be lower than 10% and 1% of intake, respectively.
- The effect of dietary cholesterol is less clear, but less prominent than that of saturated and trans fatty acids.
- Dietary fibre (25-30 g/day, mostly soluble) can lower total cholesterol and LDL-c levels.
- Body weight control can reduced plasma total cholesterol and LDL-c and triglyceride levels, especially in obese subjects.
- Regular physical activity mostly increases plasma HDL-c and lowers triglycerides.

After lifestyle modification, statins at the highest tolerable dose are first line treatment to lower LDL-c in high-risk patients with LDL-c >3.0 mmol/L. If treatment targets are not met, other lipid-lowering agents can be added.

Currently available lipid-lowering therapies

Statins
Statins are the first choice of treatment to lower elevated LDL-c levels. Statins block the pathway that synthesises cholesterol in the liver. Cholesterol synthesis occurs mostly at night, thus statins with a short half-life should be taken in the evening. Different potencies exist, with rosuvastatin and atorvastatin having the highest potency (and are long acting), and simvastatin, lovastatin, pravastatin and fluvastatin having lower potency.

Red yeast rice is known to naturally contain statin and supplements are available for sale. However, using these is not recommended, as the exact concentration in these supplements is not subject to quality control and therefore unknown and/or variable.

Fibrates and bile acid sequestrants
Fibrates lower triglycerides, and to a lesser extent also LDL-c. Fibrates activate peroxisome proliferator-activated receptors (PPARs), a class of nuclear receptors that alters transcription of genes involved in carbohydrate and lipid metabolism. Fibrates can be used alone or in combination

with statins, although warnings about the safety and efficacy of the combinations apply to most statins. Although fibrates generally increase HDL-c levels, in some patients using fenofibrate they show a reduction of HDL-c. Thus, it is recommended that HDL-c levels are monitored after initiation of fibrate therapy and to discontinue treatment in case of severely depressed HDL-c levels.
Bile acid sequestrants also lower LDL-c. Since they are poorly tolerated and may increase triglyceride levels, their use is not recommended for routine lipid lowering.

Additional lipid-lowering therapy: ezetimibe and PCSK9 inhibitors

Before deciding to add other non-statin agents to current statin treatment, it is critical to ensure that the dose of the statin is titrated to the highest tolerable dose and that patients are adhering to the prescribed dosing regimen. To attain recommended treatment goals other therapies might need to be added. Further LDL-c lowering can be achieved in CV patients with the cholesterol absorption inhibitor ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, on top of statin therapy (29, 30). In patients without any known CV disease, the use of PCSK9 inhibitors is not recommended for risk-adjusted therapy, since PCSK9 inhibiting therapy has not been evaluated in this patient group in any trial.

It is important to note that the clinical benefit of combination therapy has only been demonstrated for treatment with ezetimibe and statins (29) and for PCSK9 inhibitors on top of statins with or without ezetimibe (30, 31). IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) showed that addition of ezetimibe to statin therapy in patients with an acute coronary syndrome (ACS) in the ten days preceding enrolment lowered the median time-weighted average LDL-c level at 1 year to 53.2 mg/dL (1.4 mmol/L) in the simvastatin-ezetimibe group, as compared with to 69.9 mg/dL (1.8 mmol/L) in the simvastatin monotherapy group, representing a further 24% LDL-c lowering (difference of 16.7 mg/dL [0.43 mmol/L]) with addition of ezetimibe (P<0.001). At 7 years, the Kaplan-Meier event rate for the primary endpoint of CV death, nonfatal MI, unstable angina requiring rehospitalisation, coronary revascularisation (≥30 days after randomisation) and nonfatal stroke was 32.7% in the combination therapy group, as compared with 34.7% in the monotherapy group (HR: 0.936, 95%CI: 0.89-0.99, P=0.016) (29).

Evolocumab, a monoclonal antibody directed at PCSK9 and administered as a subcutaneous injection every 2 weeks, was evaluated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial. Evolocumab yielded 59% additional LDL-c reduction on top of statins, as compared with placebo, in patients with atherosclerotic CVD (from a median baseline value of 92 mg/dL [2.4 mmol/L] to 30 mg/dL [0.78 mmol/L] (P<0.001)). Evolocumab treatment also reduced the risk of the primary composite end point of CV death, MI, stroke, hospitalisation for unstable angina and coronary revascularisation, by 15% relative to placebo (9.8% vs. 11.3%) over a median duration of 2.2 years (15). A secondary ad hoc analysis of the FOURIER trial compared randomised treatment in two groups of patients classified by a baseline LDL-c of less than 70 or at least 70 mg/dL and by statin intensity. Evolocumab reduced the risk of the primary endpoint to a similar degree in both groups based on baseline LDL-c level. No statistically significant interaction was seen between effect of treatment and whether patients received a maximal-potency statin at baseline. No major safety concerns were noted in either group (32).

Results of another monoclonal anti-PCSK9 antibody, alirocumab, evaluated in the ODYSSEY Outcomes trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) were presented at the American College of Cardiology's 67th Annual Scientific Session (31), but have not been published yet. Treatment with alirocumab was evaluated in patients who had suffered a recent ACS. The risk of major adverse CV events (MACE: MI, ischemic stroke, death from coronary heart disease (CHD) or unstable angina requiring hospitalisation) was reduced by 15% upon treatment with alirocumab, as compared with placebo, in addition to maximally-tolerated statins. A nominal significant reduction in all-cause death of 15% was also observed with alirocumab treatment (note that this was not a primary outcome)(31).

Benefit of lipid-lowering therapy across the spectrum of LDL-c levels

When all data of LDL-c lowering trials are combined, a straight relationship is seen between the reduction in LDL-c and the proportional reduction in major vascular events, irrespective of the chosen strategy for lipid-lowering (33). A large meta-regression analysis evaluated the associations between lowering LDL-c and relative CV risk

reduction across different statin and non-statin therapies. Therapies that act via upregulation of LDL-receptor expression to reduce LDL-c, both statins or non-statins, were associated with similar relative risk reduction of major vascular events per change in LDL-c, namely 23% event reduction per 1 mmol/L LDL-c lowering. Fibrate therapy showed a larger risk reduction than expected based on the degree of LDL-c reduction in the trials, but they are not recommended in any guideline. Cholesteryl ester transfer protein inhibitors (CETP) inhibiting therapy showed a lower than expected risk reduction. To date, only anacetrapib therapy has been shown to result in a modest reduction of CV events, and other CETP inhibitors have been associated with safety issues (34). The observed relative risks of niacin therapy (removed from guideline recommendations for safety reasons) and PCSK9 inhibition did not significantly differ from the expected relative risk (35).

Importantly much lower LDL-c levels can now be achieved with PCSK9 inhibitors, than were previously commonly attained with conventional lipid-lowering therapy. A study evaluating alirocumab treatment (median drug exposure: 1.5 years) in over 5,000 patients, observed that LDL-c as low as <25 mg/dL (<0.65 mmol/L) were well tolerated; no meaningful imbalances in neurocognitive, neurological, musculoskeletal, ophthalmological and hepatic events were observed between those with LDL-c <25 or even <15 mg/dL (<0.39 mmol/L) and those with higher LDL-c levels. The incidence of cataract may be higher in the group achieving LDL-c <25 mg/dL (2.6% vs. 0.8%) (36).
The very low LDL-c levels seen in the evolocumab studies were well tolerated and patients with very low LDL-c levels showed no cognitive impairment in the EBBINGHAUS study (37), despite careful assessment of cognitive change using the sensitive Cambridge Neuropsychological Test Automated Battery. These tests have been found to be sensitive to effects, both positive and negative, of drugs on cognition (38, 39).
Long-term safety of very low LDL-c levels remains to be established. Taken together, the evidence points at a benefit of LDL-c lowering, also beyond LDL-c targets currently suggested by guidelines.

Take home messages

Statins are the first choice of treatment to lower elevated LDL-c levels to reduce CV risk and should be titrated to the highest tolerated dose before adding a non-statin.

Further LDL-c reduction can be achieved by adding other lipid-lowering therapies, but the clinical benefit of combination therapy has only been demonstrated of treatment with ezetimibe and statins, and of PCSK9 inhibitors on top of statins with or without ezetimibe.

The impact of LDL-c lowering on reduction of major vascular events is similar across the spectrum of LDL-c levels.

Very low LDL-c levels (<25 mg/dL), as achieved with PCSK9 inhibitors, have been found to be safe, although long-term (many years) safety of very low LDL-c levels remains to be established.

Challenges faced in clinical reality

Although the physician's toolbox nowadays contains several effective lipid-lowering therapies, many patients at high CV risk fail to achieve LDL-c goals. In this next section, we discuss several factors that contribute to suboptimal CV risk management.

Following the guidelines
In daily practice, a variety of factors contribute to patients not adhering to optimal treatment, and not reaching treatment goals. The pan-European EUROASPIRE IV study (40) reported on adherence to lipid-lowering therapy in patients with CHD. 79 Centres in 24 European countries participated, from May 2012 to April 2013. Included patients had coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), acute MI or acute myocardial ischemia in the 6-36 months preceding a standardised interview. One analysis of EUROASPIRE focussed on statin therapy (and intensity thereof) at hospital discharge and at the time of the interview. On average, 52.7% of patients were on low or moderate-intensity statins at discharge, 37.6% were prescribed high-intensity statins, and 9.6% of patients did not go home with a statin prescription. At the time of the interview, on average 53.2% were on low or moderate-intensity statins, 32.7% on high-intensity statins, and 14.0% did not take statins

at all. The shift towards less prescription of statin therapy was statistically significant between hospital discharge and the interview, at least 6 months later. When statin treatment was decreased, this was both due to people discontinuing their treatment, and physicians lowering the dose. Differences between individual countries were observed. The patterns could not be explained by income differences, socioeconomic situations and differences in reimbursement policies (40).

In this EUROASPIRE analysis, 10% of men and 6% of women not on any statins had fasting LDL-c <1.8 mmol/L at the time of the interview, the European recommended goal for these patients. 18% of men and 16% of women on low or moderate-intensity statins and 29% and 20% of men and women, respectively, at high-intensity statin therapy reached that goal (40).

These treatment patterns were seen despite both European and national guideline recommendations on the benefit of statin therapy. It is worrying that the majority of CHD patients are not treated with adequate statin therapy. The PC physician can play an important role in ensuring a patient gets and maintains sufficient lipid-lowering therapy: not only to encourage a patient to keep taking the prescribed medication, but also to initiate or increase high-intensity statins when none at all, or too low intensity statins were prescribed at discharge (40).

Statin intolerance – facts and solutions

A common reason for patients to discontinue statins, is that they experience muscle symptoms. A European Atherosclerosis Society (EAS) Consensus Panel has published a useful document about statin-associated muscle symptoms (SAMS), which gives advice on how to deal with patients who experience SAMS (41). The document includes a flow chart with steps to take if a patient comes in with a potential statin problem: the recommendation is to rechallenge. The current statin should be stopped for two weeks, after which the patient can be rechallenged with either a lower dose of the same statin, or with another statin. If unsuccessful, the same step can be repeated with yet another statin or dose, with or without ezetimibe (41).

This recommendation is backed up by solid evidence obtained in a retrospective study involving over 100,000 U.S. adults who were prescribed statin therapy between 1 January 2000 and 31 December 2008 (42). 57,292 out of 107,835 (53%) patients discontinued statins at least temporarily. Information on reasons for statin discontinuation was obtained from a combination of structured electronic medical record entries and analysis of electronic provider notes by validated software. Statin-related events were reported for 18,788 (17.4%) patients. 11,124 had statins discontinued at least temporarily, and 6,579 (59.1%) patients were rechallenged with a statin during the next year. The vast majority of patients who were rechallenged, namely 92.2% were still taking a statin 12 months after the statin-related event. Interestingly, among 2,721 patients who were rechallenged with the same statin on which the statin-related event occurred, 1,295 were receiving the same statin a year later, and 996 of them received the same or even a higher dose (41).

Thus, although statin-related events are common and often a reason for statin discontinuation, rechallenging with another dose or another statin is a successful strategy. True statin intolerance is rare and probably relates to genetic variation to statin metabolism in muscles. For the majority of patients, whether muscle effects are psychological or not is immaterial since physicians need to deal with patients not taking their medication, explaining that statins are effective and safe drugs to lower their CV risk. However, any treatment decision should be based on shared-decision making between the patient and his GP.

The EAS Consensus Panel recently published another useful report, which summarises and critically reviews the available evidence on adverse effects attributed to statins (43). It considers effects on glucose homeostasis, effects on cognitive, renal and hepatic function, haemorrhagic stroke, and cataract. Based on objective appraisal of the available literature, the Consensus Panel concluded that statin treatment is remarkably safe. Statin treatment does confer a modest risk of new onset diabetes, but per case of diabetes, five CV events are avoided. Thus, the Consensus Panel write that clinicians should be reassured by the long-term safety of statin therapy, and the low risk of clinically relevant adverse effects. They conclude that the benefits of statin therapy far outweigh the risk of any adverse effect (43).

Statin-related media coverage affects adherence

Another barrier to treatment adherence is negative media attention about supposed risks of the treatment. Some studies have looked into the effects of statin-related news in the media (44, 45). For instance, Nielsen and Nordestgaard reported that after negative news stories

on statins appeared in the Danish media, more people in the Danish population discontinued their statin therapy. The authors even observed a higher risk of MI and death from CVD associated with statin discontinuation. Alternatively, also positive stories on statins were published, which was associated with more patients starting therapy (44). A recent study assessed the number of websites discussing side effects of statins in the native language of 13 countries, normalised to the overall number of websites in that country in relation to the prevalence of statin-intolerance. The authors describe a strong positive correlation (Pearson's r=0.868) between the two variables. English-speaking countries showed the highest rate of websites discussing side effects, thus inhabitants of these countries were more likely to encounter this type of information. These countries also had higher prevalences of statin intolerance (46).

Negative news stories on statins have also been described to affect people taking their blood pressure medication. Thus, negative media coverage has effects beyond cholesterol management; it impacts on CV risk prevention in a broader sense. Indeed, about 26% higher risk of CV events has been described after negative media coverage on statins (44). In a letter to European Heart Journal (47), Nordestgaard advocates that clinicians use the media to report positively on statins and cholesterol lowering. Considering the large numbers of people taking statins, we should accept that media will keep reporting on them. Rather than getting too frustrated about negative stories, physicians could use the media to their and their patients' advantage, by telling positive stories (47).

Individual variability in treatment response

Patients may ask how much intensification of lipid-lowering therapy will lower their risk of a recurrent event after having had an ACS. Most available trial evidence reflects average treatment effects. In fact, in RCT results, data with large inter-individual variability in patient characteristics and treatment outcomes, are squeezed into few summary statistics. Consequently, these summarising study outcomes are applied to a broad range of different patients in clinical practice. Hence, a lot of information is lost in current practice. It would be valuable if the data on individual variation within a study would be benefitted from in the consultation room.

Indeed, an analysis of data of the Treating to New Targets trial (TNT; n=10,001) and the IDEAL trial (n=8,888) showed a wide range of baseline risk in coronary artery disease (CAD) patients, based on 13 easy-to-determine clinical predictors, as well as a broad distribution of treatment effect of high- vs. usual-dose statins (48). The model that was developed in this study, allows identification of high-risk patients who benefit more from intensified lipid-lowering therapy. Other patients will not have much additional benefit from additional or higher intensity treatment (48). Another study estimated the individual benefit of PCSK9-inhibiting treatment with evolocumab in patients with stable CAD, who were on high-dose statin therapy, based on the individual risk reduction (LDL-c lowering) and individual CVD prognosis. The potential incremental benefit of PCSK9 inhibition showed large variability across patients, ranging from a few months to over a year gain in life expectancy free of recurrent stroke or MI. Younger patients (40-60 years old) with a high risk factor burden and high LDL-c levels are expected to benefit most from this treatment (49). Such assessments can also help choosing which patients will likely benefit from relatively expensive treatment.

Using big data methods, efforts are now being made to categorise patients more precisely, to tailor therapies to their individual characteristics and risks. Moreover, some of these methods (for instance U-Prevent, unpublished data, launch of U-prevent.com mid-August 2018) aim to predict the benefit that can be achieved with initiation or intensifying therapy in an individual, rather than to only focus on risk categories. This can facilitate better communication between physicians and patients, and allow shared decision-making based on anticipated disease-free life-years gained and associated risks. Examples of useful European websites for risk assessment and risk communication are listed in table 1.

Table 1 | Useful websites for risk assessment and risk communication

Europe	HeartScore	http://www.heartscore.org
United Kingdom	QRISK	https://www.qrisk.org/three/
	JBS3	http://www.jbs3risk.com/pages/risk_calculator.htm
	NHS Heart Age	www.nhs.uk/tools/pages/heartage.aspx
Germany	ARRIBA	https://www.arriba-hausarzt.de
	PROCAM	http://www.drkewitz.de/Praxis/diabetes-und-co/interaktive-tests/pro-cam-risiko-rechner/
The Netherlands	U-Prevent	www.U-prevent.com
Spain	ReGiCor	https://www.imim.cat/ofertadeserveis/software-public/regicor/?1
Italy	Cuore.exe	http://www.cuore.iss.it/sopra/calc-rischio.asp

Hence, these novel methods may represent a big step towards personalising medicine and CV prevention. Rather than estimating 10-year risk, it would be more informative to estimate lifetime risk, as the aim of treatment is not limited to the next decade. Moreover, it may be more intuitive to patients to talk about lifetime benefit, in terms of disease-free lifetime years gained. Ideally, models will become available for specific patient groups, including those with diabetes mellitus or vascular disease and the elderly, benefitting from the available individual trial data that are hiding behind the summary outcomes. Hopefully, applying these new communication tools will improve treatment adherence.

Take home messages

The majority of patients eligible for lipid-lowering therapy are not treated with adequate statin therapy.

Statin therapy is remarkably safe. In case of (perceived) statin intolerance, rechallenging with another statin or a lower dose, is a successful strategy.

Negative media attention on statins can affect therapy adherence, but so can positive stories. Physicians are encouraged to use the media to their and their patients' advantage, by spreading positive news stories.

Big data methods increasingly allow to categorise patients more precisely and to tailor therapy to an individual's need and risk. Some methods allow predicting the anticipated benefit of initiating or intensifying therapy.

Take home messages

This EPCCS document aims to guide GPs on how to manage elevated lipid in PC, based on the summary evidence on the impact of lipid modification and by taking into account the challenges faced in daily clinical practice. All take home messages are combined in box 1. Gaps in the evidence related to what was discussed are listed in table 2.

BOX 1 | Take home messages

LIPID-LOWERING THERAPY TO LOWER CV RISK

- Overwhelming evidence has demonstrated that LDL-c is an atherogenic particle and major risk factor for CVD.
- Lowering LDL-c reduces CVD events substantially and consistently.
- Levels of lipids and lipoproteins other than LDL-c can serve as risk markers, but LDL-c is currently the only lipid risk factor (lowering the risk marker modifies disease) and an important treatment target to lower CVD risk.

CV RISK ASSESSMENT

- Different treatment goals have been defined for different risk levels; the higher the risk, the lower the goal.
- CV risk assessment tools can guide management decisions and prevent under- and overtreatment.
- SCORE risk tables may underestimate risk in young persons, and overestimate risk in elderly persons. In young individuals, it is more illustrative to speak of risk relative to others of the same age, or of risk age or lifetime risk. A risk calculator specifically developed for elderly patients should be used.

GUIDELINE-RECOMMENDED MANAGEMENT OPTIONS FOR HYPERCHOLESTEROLAEMIA

- Lifestyle modification can lower LDL-c and is considered effective for general CV risk reduction, albeit to a modest extent:
  - Dietary fatty acid intake should be limited to 30-35% of total calorie intake, and saturated and trans fatty acids should be lower than 10% and 1% of intake, respectively.
  - The effect of dietary cholesterol is less clear, but less prominent than that of saturated and trans fatty acids.
  - Dietary fibre (25-30 g/day, mostly soluble) can lower total cholesterol and LDL-c levels.
  - Body weight control can reduced plasma total cholesterol and LDL-c and triglyceride levels, especially in obese subjects.
  - Regular physical activity mostly increases plasma HDL-c and lowers triglycerides.
- After lifestyle modification, statins at the highest tolerable dose are first line treatment to lower LDL-c in high-risk patients with LDL-c >3.0 mmol/L. If treatment targets are not met, other lipid-lowering agents can be added.

CURRENTLY AVAILABLE LIPID-LOWERING THERAPIES

- Statins are the first choice of treatment to lower elevated LDL-c levels to reduce CV risk and should be titrated to the highest tolerated dose before adding a non-statin.
- Further LDL-c reduction can be achieved by adding other lipid-lowering therapies, but the clinical benefit of combination therapy has only been demonstrated of treatment with ezetimibe and statins, and of PCSK9 inhibitors on top of statins with or without ezetimibe.
- The impact of LDL-c lowering on reduction of major vascular events is similar across the spectrum of LDL-c levels.
- Very low LDL-c levels (<25 mg/dL), as achieved with PCSK9 inhibitors, have been found to be safe, although long-term (many years) safety of very low LDL-c levels remains to be established.

CHALLENGES FACED IN CLINICAL REALITY

- The majority of patients eligible for lipid-lowering therapy are not treated with adequate statin therapy.
- Statin therapy is remarkably safe. In case of (perceived) statin intolerance, rechallenging with another statin or a lower dose, is a successful strategy.
- Negative media attention on statins can affect therapy adherence, but so can positive stories. Physicians are encouraged to use the media to their and their patients' advantage, by spreading positive news stories.
- Big data methods increasingly allow to categorise patients more precisely and to tailor therapy to an individual's need and risk. Some methods allow predicting the anticipated benefit of initiating or intensifying therapy.

Table 2 | Gaps in the evidence

How effective is the use of risk tools, in terms of treatment adherence and outcomes?
What is most effective in terms of clinical outcomes: targeting specific LDL-goals or a fire-and-forget strategy aiming for ever lower LDL levels with fixed dose statins?
What is a clinically relevant threshold to consider a patient to be at high lifetime risk?
What is the mechanism behind HDL being a risk marker in primary prevention, and is it useful as a treatment target (in some situations)?
When and how may lipid-lowering therapy be considered in the very elderly?

References

1. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.
2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81.
3. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med. 1992;152(7):1490-500.
4. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
5. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.
6. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450-8.
7. Chapman MJ, Ginsberg HN, Amarenco P, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32(11):1345-61.
8. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012;380(9841):572-80.
9. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844-53.
10. McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet. 2008;372(9634):224-33.
11. Emerging Risk Factors C, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993-2000.
12. European Association for Cardiovascular P, Rehabilitation, Reiner Z, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769-818.
13. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397-405.
14. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425-35.
15. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294(19):2437-45.
16. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.
17. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. Am Heart J. 1991;121(1 Pt 2):293-8.
18. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336(7659):1475-82.
19. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016;134(19):1419-29.
20. van Dis I, Geleijnse JM, Boer JM, et al. Effect of including nonfatal events in cardiovascular risk estimation, illustrated with data from The Netherlands. Eur J Prev Cardiol. 2014;21(3):377-83.
21. Stam-Slob MC, Visseren FL, Wouter Jukema J, et al. Personalized absolute benefit of statin treatment for primary or secondary prevention of vascular disease in individual elderly patients. Clin Res Cardiol. 2017;106(1):58-68.
22. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360(9346):1623-30.
23. Cooney MT, Selmer R, Lindman A, et al. Cardiovascular risk estimation in older persons: SCORE O.P. Eur J Prev Cardiol. 2016;23(10):1093-103.
24. Poli A, Marangoni F, Paoletti R, et al. Non-pharmacological control of plasma cholesterol levels. Nutr Metab Cardiovasc Dis. 2008;18(2):S1-16.
25. Clarke R, Frost C, Collins R, et al. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. BMJ. 1997;314(7074):112-7.
26. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
27. Brown L, Rosner B, Willett WW, et al. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr. 1999;69(1):30-42.
28. Miller WM, Nori-Janosz KE, Lillystone M, et al. Obesity and lipids. Curr Cardiol Rep. 2005;7(6):465-70.
29. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387-97.
30. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-22.
31. Praluent® (alirocumab) significantly reduced risk of cardiovascular events in high-risk patients, and was associated with lower death rate [press release]. Paris and Tarrytown, N.Y.: Sanofi and Regeneron Pharmaceuticals, Inc., March 10, 2018.

32. Giugliano RP, Keech A, Murphy SA, et al. Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin: Secondary Analysis of Patients With Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial. JAMA Cardiol. 2017;2(12):1385-91.
33. Ference BA, Cannon CP, Landmesser U, et al. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. Eur Heart J. 2017.
34. Group HTRC, Bowman L, Hopewell JC, et al. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. N Engl J Med. 2017;377(13):1217-27.
35. Silverman MG, Ference BA, Im K, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA. 2016;316(12):1289-97.
36. Robinson JG, Rosenson RS, Farnier M, et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab: Pooled Data From Randomized Trials. J Am Coll Cardiol. 2017;69(5):471-82.
37. Giugliano RP, Mach F, Zavitz K, et al. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med. 2017;377(7):633-43.
38. Barnett JH, Blackwell AD, Sahakian BJ, et al. The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research. Curr Top Behav Neurosci. 2016;28:449-74.
39. Muller U, Rowe JB, Rittman T, et al. Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. Neuropharmacology. 2013;64:490-5.
40. Reiner Z, De Backer G, Fras Z, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. Atherosclerosis. 2016;246:243-50.
41. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36(17):1012-22.
42. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158(7):526-34.
43. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018.
44. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J. 2016;37(11):908-16.
45. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ. 2016;353:i3283.
46. Khan S, Holbrook A, Shah BR. Does Googling lead to statin intolerance? Int J Cardiol. 2018;262:25-7.
47. Nordestgaard BG. Why do the Media report negative news about statins? Eur Heart J. 2018;39(5):337-8.
48. Dorresteijn JA, Boekholdt SM, van der Graaf Y, et al. High-dose statin therapy in patients with stable coronary artery disease: treating the right patients based on individualized prediction of treatment effect. Circulation. 2013;127(25):2485-93.
49. Kaasenbrood L, Ray KK, Boekholdt SM, et al. Estimated individual lifetime benefit from PCSK9 inhibition in statin-treated patients with coronary artery disease. Heart. 2018.

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In this series of practical guidance for primary care physicians, we have previously published the following documents:

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