

Monitoring of Lipids, Enzymes, and Creatine Kinase in Patients on Lipid-Lowering Drug Therapy

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Abstract A number of plasma lipid parameters have been used to estimate cardiovascular risk and to be targets for treatment to reduce risk. Most risk algorithms are based on total cholesterol (T-C) or low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and most intervention trials have targeted the LDL-C levels. Emerging measures, which in some cases may be better for risk calculation and as alternative treatment targets, are apolipoprotein B and non-HDL-C. Other lipid measures that may contribute in risk analysis are triglycerides (TG), lipoprotein(a), and lipoprotein-associated phospholipase A₂. The primary treatment target in cardiovascular prevention is LDL-C, and potential alternative targets are apoB and non-HDL-C. In selected individuals at high cardiovascular (CV) risk, TG should be targeted, but HDL-C, Lp(a), and ratios such as LDL-C/HDL-C or apoB/apoAI are not recommended as treatment targets. Lipids should be monitored during titration to targets. Thereafter, lipids should be checked at least once a year or more frequently to improve treatment adherence if indicated. Monitoring of muscle and liver enzymes should be done before the start of treatment. In stable conditions during treatment, the focus should be on clinical symptoms that may alert muscle or liver complications. Routine measurement of CK or ALT is not necessary during treatment with statins.

Keywords Dyslipidemia · Cardiovascular prevention · Statin · Lipoprotein · Myalgia · Treatment · Lipids · Enzymes · Creatine kinase · Lipid-lowering drug therapy

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Introduction

An overwhelming number of studies in the past decades have established dyslipidemia as the major risk factor for the development of atherosclerotic cardiovascular disease. Recent reductions in plasma cholesterol levels have contributed to a dramatic decrease in the incidence of premature coronary heart disease in the western world [1, 2]. However, atherosclerotic cardiovascular disease remains the main killer in the western world and its impact is increasing worldwide.

Although lifestyle factors, primarily dietary habits, are the fundamental targets for lipid lowering, the development of pharmacological interventions—in particular, statins—has been a major contributor to reduction of disease. Statins are now used by millions of people worldwide and their dramatic effect on cardiovascular disease has been shown in a large number of trials and also in meta-analyses. Based on results from cohort studies the total CV risk can be estimated with risk estimation tools that have been developed for that purpose. Armed with increased knowledge of lipid and lipoprotein metabolism and of the role of lipoproteins in the development of atherosclerosis, it is important to determine which lipid measurements are the most informative in risk estimation and which lipid measures are the best to target for therapy. An active discussion on these subjects has taken place in recent years. Furthermore, recent guidelines suggest more intense lipid lowering in selected patients [3, 4]. However, intense lipid lowering increases the risk of side effects from pharmacological treatment and the question on how to monitor safety during treatment has become more important.

In this review, the advantages and disadvantages of the different lipid measures and lipid targets are discussed in relation to the current literature. Safety monitoring is also discussed and updated with regard to recent studies.

Which Lipid Parameters Should Be Used to Estimate Cardiovascular Risk?

A first step in cardiovascular prevention is to estimate the risk for cardiovascular disease (CVD) in the individual. Performing a risk analysis is important from several aspects. First, the intervention can be targeted to subjects with high risk. The absolute reduction of CV events is higher in the high risk patients. Consequently, the cost per prevented event is lower in subjects with high risk. Risk analysis is also an important tool for the design of prevention. Which factors should be treated? Furthermore, the level of target to reach can be adapted to the risk level. Risk analysis will also educate the patient to improve the adherence to treatment. Some patients have an underlying condition associated with high risk, and in these cases no further risk analysis has to be done. This is the case in patients with established CVD, diabetes, chronic kidney disease (CKD), or markedly elevated single risk factor, such as familial hypercholesterolemia. A number of plasma lipid parameters have been used to estimate cardiovascular risk and to be targets for treatment to reduce risk. Most risk algorithms, such as SCORE, Framingham score and Reynolds Risk score, are based on total cholesterol (T-C), or low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and most intervention trials have targeted the LDL-C levels. However, a disadvantage of LDL-C is that it does not include the triglyceride-rich atherogenic particles intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL) [5]. These are better described using non-HDL-C (calculated as T-C minus HDL-C) or apolipoprotein B (apoB; the protein component of atherogenic lipoproteins). Because there is only one apoB molecule per lipoprotein particle, apoB concentration is a measure of particle number. Non-HDL-C and apoB have therefore been suggested as alternative or even preferred lipid variables for risk estimation [6, 7].

The use of non-HDL-C and apoB may be especially advantageous in patients with combined hyperlipidemia, such as in the metabolic syndrome or type 2 diabetes. Furthermore, LDL-C cannot be calculated with the Friedewald formula [3•] in hypertriglyceridemia (TG >400 mg/dl or >4.5 mmol/L). A number of studies indicate that apoB is a better predictor than cholesterol measures of cardiovascular risk [6, 7], most recently in a meta-analysis of 233,455 subjects and 22,950 events [8]. However, several analyses do not support the conclusion that apoB adds to the information given by the lipid markers including non-HDL-C [9, 10•, 11]. Some studies support non-HDL-C and apoB as better risk indicators in obesity or diabetes [12, 13], but 1 study on obesity reports that apolipoproteins do not contribute to risk prediction [11]. The choice between assessments of cholesterol and apolipoproteins for risk analysis seems to be more dependent on practical considerations, such as cost,

availability and tradition, than on major differences in risk estimation [9].

Low HDL-C and elevated triglycerides (TG) are both independent risk factors for cardiovascular disease. HDL-C is included in several of the risk algorithms and should always be analyzed to evaluate cardiovascular risk [3•, 4]. Although not so strong when corrected for other risk factors, TG also contributes to risk assessment [14]. Furthermore low HDL-C and high TG are ingredients of the dyslipidemia often associated with the metabolic syndrome and type 2 diabetes. HDL-C and TG therefore may indicate the cause of the dyslipidemia and also guide the selection of therapy. Patients with very high TG (>10 mmol/L or >900 mg/dL) should immediately start therapy because of the risk of pancreatitis [15].

The different ratios (apoB/apoAI, T-C/HDL-C, non-HDL-C/HDL-C) give similar information as their components, but may be practical for screening. However, focusing on ratios may hide essential diagnostic information.

New lipid markers for risk estimation have recently emerged, but most of the new variables (such as lipoprotein subclasses and particle size) have yet to prove that they contribute to the total risk estimation above that provided by conventional lipid analyses [16]. In a meta-analysis of 165,544 subjects and 15,126 events, only 2 markers significantly improved the prediction of future cardiovascular events: lipoprotein(a) (Lp(a)) and lipoprotein-associated phospholipase A2 (LpPLA₂) [10••]. This is supported by a recent population study from Copenhagen, which suggests that extreme Lp(a) levels substantially improves CVD prediction [17]. Lp(a) has been discussed as a risk factor for decades, and recent data from genetic analyses have shown that Lp(a) most probably has an etiologic role in atherosclerosis [18, 19]. Lp(a) levels are highly genetically determined and may add information on risk especially in subjects with a family history of cardiovascular disease. Lp-PLA₂ also seems to have an etiological role and its potential as a therapeutic target is now being studied in clinical trials [20, 21].

Which Lipid Parameters Should be Targeted by Treatment to Reduce Cardiovascular Risk?

The primary reason to monitor lipids during lipid-lowering treatment should be to evaluate if treatment targets have been reached. Guidelines for target levels of plasma lipids are based on results from randomized controlled trials and from meta-analyses. The absolute target levels still are under debate, but most guidelines have similar approaches in identifying and defining targets [4, 22–26] and most identify LDL-C levels as the primary target for treatment. In European guidelines [3•, 4],

the target of LDL-C is adapted to total CV risk level (Table 1) with a lower level for subjects with very high cardiovascular risk (Table 2). The lower targets suggested in recent guidelines are based on studies comparing different treatment regimens and on meta-analyses of a large number of statin trials [27•, 28]. Although these studies give good support for the low LDL-C targets, the “lower the better” approach is still under debate [29, 30]. ApoB and non-HDL-C have not been studied as primary targets in randomized studies, but post-hoc analyses suggest that both may be used [31–33] and these analyses form the basis for target levels in guidelines (Table 2).

The concept that more may be achieved with more intense treatment is supported by observations on residual risk during statin treatment. In 1 recent analysis of the JUPITER trial on treatment levels of LDL-C, non-HDL-C, and apoB were found to identify residual risk [34]. Similar observations are reported from the Treating to New Targets (TNT) study [32] and in a recent meta-analysis [33] on association of LDL-C, non-HDL-C and apoB levels with cardiovascular events among patients treated with statins.

Should HDL-C be a target for treatment and monitored during therapy? Recent guidelines do not suggest HDL-C as a treatment target, despite its importance as a marker for future cardiovascular disease [3•, 4]. However, based on epidemiological data, optimal HDL levels are suggested to be >1.0 mmol/L (>40 mg/dL) for men and >1.2 mmol/L (>45 mg/dL) for women. The potent HDL-elevating drugs cholesteryl ester transfer protein (CETP) inhibitors have not been found to reduce cardiovascular disease; the first CETP inhibitor tested actually showed increased mortality in the treated group, probably due to off-target effects [35], and a study with another CETP inhibitor was prematurely terminated due to lack of effect [36]. Furthermore, genetic studies using mendelian randomization do not support HDL as a direct causative agent for disease [37].

The data supporting TG as a target for drug treatment are less robust than for LDL-C. The optimal TG level is suggested to be below 1.7 mmol/L (150 mg/dL), primarily based on epidemiological data [22]. European guidelines suggest that the use of drugs should only be considered if TG is over

2.3 mmol/L (200 mg/dL) and cannot be lowered by life-style changes, and if the subject is at high risk of cardiovascular disease [22].

Levels of Lp(a) above 30 mg/dL are associated with increased risk of cardiovascular disease, but there is no evidence at present to show that intervention against high Lp(a) reduces cardiovascular risk. Thus, no target level for treatment has been recommended [18, 19].

Selection of Drugs

Five main groups of pharmacological agents are, at present, available for the treatment of hyperlipidemia.

Statins

Statins (HMG-CoA-reductase inhibitors: simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, and pitavastatin) cause a reduction in intracellular cholesterol levels, leading to increased LDL receptor expression on hepatocyte membranes with a subsequent reduction in the circulating levels of apoB-containing lipoproteins (LDL, IDL, VLDL). A large body of evidence shows that statins are effective in the reduction of LDL-C and cardiovascular events [27•, 28], and statins are the first-line treatment for individuals with high levels of LDL-C or combined hyperlipidemia both in primary and secondary prevention. Depending on dose and potency of the statin (rosuvastatin, atorvastatin and pitavastatin being the most potent), a reduction of LDL-C of up to 55 % may be achieved [38]. In patients with moderately elevated TG, statins may reduce TG by about 15 %–20 %. A moderate increase in HDL-C (5 %–10 %) is also achieved.

Ezetimibe

Ezetimibe inhibits intestinal and biliary cholesterol absorption, probably via interaction with Niemann-Pick C1-like protein 1 (NPC1L1) [39]. It reduces absorption of dietary

Table 1 Global risk stratification according to the European guidelines on cardiovascular disease prevention in clinical practice (2012)

Risk level	SCORE (10-year risk of fatal CVD,%) or risk conditions
Low	<1 %
Moderate	≥1 % to <5 %
High	≥5 % to <10 %, or markedly elevated single risk factor (eg, familial dyslipidemia or severe hypertension), or type 1 or 2 diabetes without CV risk factors or target organ damage, or moderate CKD (GFR 30–59 mL/min/1.73 m ²).
Very high	≥10 %, or documented CVD, or type 1 or 2 diabetes with 1 or more CV risk factors and/or organ damage, or severe CKD(GFR <30 mL/min/1.73 m ²)

(Modified from [4]).

Table 2 Treatment targets for LDL-C, non-HDL-C, and apoB at different levels of cardiovascular risk

Risk level	Treatment targets		
	LDL-C	Non-HDL-C	ApoB
Moderate	<3.0 mmol/L (<115 mg/dL)	<3.8 mmol/L (<145 mg/dL)	
High	<2.5 mmol/L (<100 mg/dL)	<3.3 mmol/L (<130 mg/dL)	<100 mg/dL
Very high	<1.8 mmol/L (<70 mg/dL)	<2.6 mmol/L (<100 mg/dL)	<80 mg/dL
	Desirable level of TG <1.7 mmol/L (<150 mg/dL).		
	Desirable level of HDL-C >1.0 mmol/L (>40 mg/dL) for men, >1.2 mmol/L (>45 mg/dL) for women.		

Modified from [61].

and biliary cholesterol as it blocks the enterohepatic circulation, and reduced cholesterol transport to the liver induces increased LDL receptor expression on hepatocytes. Ezetimibe induces a reduction of LDL-C of approximately 15 %–20 %. It is primarily used in combination with a statin with a 22 %–26 % reduction of LDL-C beyond that obtained by statin alone [40, 41]. Effects on cardiovascular end-points in randomized trials are still lacking, but 1 study, IMPROVE-IT, will report in 2013 [42].

Bile Acid Sequestrants

Bile acid sequestrants (cholestyramine, colestipol, and colesevelam) remove bile acids from the enterohepatic circulation. Because bile acids are synthesized from cholesterol, LDL receptor expression is increased in the bile-depleted liver resulting in reduced LDL-C levels. An 18 %–25 % reduction in LDL-C has been observed with bile acid sequestrants, and they are primarily used to reduce LDL-C in patients intolerant to statins or in combination, where targets are not reached with statin alone. Bile acid sequestrants have been shown to reduce cardiovascular morbidity [43].

Niacin

Niacin (also known as vitamin B3 or nicotinic acid) has a broad effect on modulating lipoprotein levels (at a dosage of 2 g/day): it increases HDL-C by 15 %–35 % and reduces TG by 20 %–40 % and LDL-C by 15 %–18 %. The effect on LDL-C and TG is primarily mediated by retention of VLDL by the liver. Niacin is used in patients with hypertriglyceridemia or combined hyperlipidemia often in combination with a statin. In clinical trials, niacin has been shown to reduce cardiovascular morbidity but not mortality [44]. Niacin is the most potent drug to increase HDL-C and at present the only drug that reduces Lp(a). The clinical significance of this, however, has not been shown. The recent failure of the AIM-HIGH [45] and the HPS-2 THRIVE [46](THRIVE home Page: www.thrivestudy.org) studies

makes the future of niacin in cardiovascular prevention doubtful .

Fibrates

Fibrates (fenofibrate, gemfibrozil, clofibrate, ciprofibrate, and bezafibrate) cause a reduction in the levels of TG-rich particles, both in the fasting and in the postprandial state, due to their agonist effect on peroxisome proliferator-activated receptor (PPAR) α . Fibrates also result in a modest increase of HDL-C. They are primarily used in individuals with hypertriglyceridemia or in high-risk patients with mixed hyperlipidemia [44]. In clinical trials fibrates have shown a reduction in the rate of non fatal myocardial infarction, however, often only in post-hoc analyses [47].

Combination Therapy

In many cases targets are not reached with the highest dose of 1 drug, or the dose has to be kept low due to side effects. In these cases combination therapy should be considered. However, the number of clinical trials showing clinical benefit from combination therapy is limited. In patients with hypercholesterolemia statin can be combined with a bile acid sequestrant or a cholesterol absorption inhibitor. In the SHARP trial the combination of simvastatin and ezetimibe was shown to reduce CVD in patients with CKD [48]. The combination of fibrate and statin has been shown to improve reduction in both LDL-C and TG. The results from clinical trials have not shown a reduction in CV. However, in post hoc analyses from studies patients with high TG and low HDL seem to benefit from the combination of fenofibrate and a statin. Therefore the combination may be considered in certain patients at high risk [5]. In combination therapy drug interactions have to be considered. This especially refers to the interaction between statins and fibrates, since both drugs are associated with increased risk of myopathy (see below). Furthermore the combination of niacin/laropiprant and statin is associated with increased frequency of myopathy as shown in HPS2-THRIVE [46].

How Should Lipids Be Monitored?

Before initiation of therapy, lipids should be measured at least twice and the lipid levels evaluated as a part of global risk estimation, preferentially using 1 of the available risk calculators such as SCORE [4]. Dyslipidemia should be diagnosed with complete lipid status including (at least) T-C, LDL-C, TG, and HDL-C (similar information may be obtained by non-HDL-C, apoB, and apoAI). Possible underlying metabolic disturbances and other diseases should be excluded by measuring (at least) glucose, alanine, and aspartate transaminases (ALT and AST), creatinine and thyroid-stimulating hormone.

Lipids should be checked 6–8 weeks after initiation of therapy and also after any change to drug therapy, such as dose change, change of compound, or starting combination therapy. The effect of statins is seen already after 4 weeks but other drugs may take longer. A longer time-frame is required to see the effect of lifestyle changes such as diet, weight reduction, and increased physical activity. Patients who have reached therapeutic goals and are in a stable condition often only need to be checked once a year. However, more frequent controls should be considered to improve adherence to lifestyle changes and to pharmacological treatment. The importance of regular lipid monitoring has been reported in several studies [49].

The lipid parameters that are analyzed in the regular checks should be determined by the original dyslipidemia. As a minimum, T-C should be measured, but better management and probably better patient compliance are achieved if a full lipid profile (including LDL-C, HDL-C, and TG) is obtained. ApoB and non-HDL-C are alternative measures that may be used, especially in patients with hypertriglyceridemia. Non-HDL-C is a good marker for TG and TG-rich remnant particles [5, 9]. The experience with apoB is, however, still limited in routine clinical settings.

A disadvantage of measuring a single plasma lipid at 1 occasion is that there is considerable intra-individual variation, estimated at about 7 % for cholesterol and 28 % for triglycerides [50]. This variation results from analytical error, individual variation due to other factors and seasonal variation, with highest levels during the summer and lowest during the winter [51]. These intra-individual variations should be taken into account, and small changes should be checked before therapy is changed.

Safety Monitoring

Statins

Statins are considered to be relatively safe drugs. The most important side effects, which should be monitored, are muscle

or liver related. Side effects are dose dependent and influenced by other conditions such as: age, female gender, small body size, alcohol abuse, presence of multisystemic diseases, reduced kidney or liver function, and interaction with other drugs.

Monitoring of Muscle-Related Side Effects

Muscle symptoms are the most common and serious side effects of statins [52, 53•], leading to poor compliance or statin intolerance. It is essential during follow up that both the patient and the physician are aware of the possible association between muscle symptoms and statins, since the symptoms often are vague and difficult to interpret. As long as levels of the circulating muscle enzyme creatine kinase (CK) remain normal, statin therapy may continue if the symptoms are acceptable to the patient (Table 3).

Myalgia may be defined as the presence of muscle pain or tenderness without elevation of CK. The frequency of myalgia varies from 1.5 %–5 % in randomized studies [54, 55] to 5 %–10 % in observational studies [56, 57]. The symptoms are most often located to bigger proximal muscle groups, but can also have other locations [53•]. They often appear within a couple of months of starting therapy or after dose adjustment. The cause of the symptoms is unclear [53•, 58].

Severe myopathy (rhabdomyolysis) is characterized by severe muscular pain, with an elevation of the muscle enzymes to more than 10 times the upper limit of normal. In addition, the patient may develop myoglobinuria and, eventually, renal insufficiency. The incidence of rhabdomyolysis has been estimated to be 1–3 cases per 100,000 patient years [54]. Death occurring after rhabdomyolysis has been estimated to occur in 0.15 per million treated patients [59].

The monitoring of possible muscular side effects should be especially directed towards the risk groups. Myalgia is more common in physically active subjects. Myopathy is more common in patients with previously high CK, women, the elderly, and patients with reduced renal or liver function. The genetic background is also involved in the development of muscular symptoms since family history is a risk factor. Indeed, genetic variations in transport proteins and cytochrome P450 (CYP) enzymes have been identified as risk factors for myopathy [53•, 58].

The most common cause of severe myopathy is probably interactions with other drugs. Many drugs are dependent on CYP3A4 for their catabolism, and these may thus interact with the CYP3A4-dependent statins simvastatin, lovastatin, and atorvastatin. Pravastatin, rosuvastatin, and fluvastatin are catabolized through other enzymes (CYP2C9). Statins combined with gemfibrozil are associated with increased risk of rhabdomyolysis while this risk is much smaller when statins are combined with fenofibrate or niacin. Examples of drugs that potentially interact with statins are given in Table 4.

Table 3 Safety monitoring during treatment with lipid lowering drugs

 Monitoring liver enzyme (ALT) during treatment with statins.

- Before treatment.
- During treatment routine check is not necessary.
- Stop treatment if signs/symptoms of liver disease occur and measure liver function.

Monitoring of muscle enzyme (CK) during treatment with statins.

- Before treatment
- If baseline CK is $>5 \times \text{ULN}$, do not start therapy, recheck.
- Routine monitoring is not necessary.
- Measure CK if patient develops myalgia.

What if CK becomes elevated during treatment?

- If CK $>5 \times \text{ULN}$
 - Stop treatment, check renal function and monitor CK every 2 wk.
 - Consider CK elevation for other reasons, such as muscle exertion.
 - Consider secondary causes of CK elevation if CK remains elevated
 - If CK $<5 \times \text{ULN}$
 - If no muscle symptoms, continue therapy. Alert patient to report symptoms. Consider check of CK.
 - If symptoms, monitor symptoms and CK regularly.
-

ALT alanine aminotransferase,
CK creatinine kinase, ULN upper
limit of normal

Modified from [3•].

The risk for myopathy increases with dose [60]. There is no conclusive evidence that risk for myopathy varies between the statins when used at regular doses, with the exception of cerivastatin. However, the US Food and Drug Administration (FDA) recently concluded that high-dose simvastatin (80 mg/d) is associated with higher risk and should not be used; the interaction between lower doses of simvastatin and other drugs was also emphasized [61].

In addition to actively asking for symptoms, CK elevation is the most important tool to detect severe myopathy. CK should be checked before initiation of therapy; if elevated, it should be checked again and, if still elevated, the use of statins should be reconsidered. CK elevations are often seen spontaneously and can be caused by several factors such as high physical activity. Therefore, CK elevation without symptoms has a very poor specificity, and a routine check of CK is not recommended. According to current guidelines, CK should be checked if muscle symptoms appear. If CK is less than 5 times the upper limit of normal, continue statins and monitor CK. If CK is over 5 times the upper limit, stop

treatment, check renal function, and monitor CK every 2-weeks (Table 3). It is also important to consider other reasons for the CK elevation [3•, 4].

Monitoring of Liver Enzymes

Treatment with statins tends to increase hepatic transaminases. This effect is dose-dependent and meta-analyses of randomized placebo controlled trials demonstrate that low to moderate doses of statins are not associated with clinically significant elevations in transaminases ($>3 \times \text{ULN}$) [62, 63]. Maximal doses of all statins are associated with a modest but significant elevation of transaminase levels [63, 64]. Until recently, guidelines have recommended that liver enzymes should be monitored before statin treatment and regularly during treatment [3•]. In 2006, the National Lipid Association Statin Safety Task Force published an assessment of statin safety as well as conclusions and recommendations [65, 66]. The task force found that significant liver disease caused by statin treatment was extremely uncommon, and elevations of liver enzymes will often resolve with continued therapy. Based on this information FDA in 2012 changed the recommendation regarding control of liver enzymes during statin therapy. The new recommendation says that hepatic function test should be performed before starting therapy and as clinically indicated thereafter, not as a routine monitoring (FDA Drug Safety Communication (February 28, 2012) [67]. Special attention should be directed towards clinical symptoms in patients with increased risk for statin related side effects.

The presence of non alcoholic fatty liver disease should not be a contraindication to statin therapy [68–70]. Moderately elevated liver enzymes do not seem to be associated

Table 4 Drugs that potentially interact with statins leading to increased risk of myopathy and rhabdomyolysis

Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Cyclosporine
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil

Modified from [61].

with increased risk of hepatotoxicity. There are even studies suggesting that statins may improve the liver disease [71–74].

Monitoring of Diabetes

Many patients with diabetes are treated with lipid-lowering drugs. Recent meta-analyses have shown an increased risk of developing diabetes during statin treatment [75, 76]. The risk is higher with high-dose statins [77, 78], in older patients and in groups with known risk factors for diabetes. Statin therapy was associated with a 9 % increased risk for incident diabetes. Treatment of 255 patients with statins for 4 years resulted in 1 extra case of diabetes [75]. The clinician should consider screening for diabetes in patients with risk factors for developing diabetes [67, 79, 80].

Fibrates

Fibrates are in general well tolerated. Myopathy is reported at a similar or even somewhat higher frequency compared with statins [81]. Elevations of liver enzymes are also observed. Consequently muscular symptoms and CK should be monitored according to the same recommendations as for statins (Table 3). Regular control of ALT is still recommended during fibrate treatment. Fibrates are also reported to raise creatinine, but it is not clear whether this reflects change in kidney function. Monitoring of creatinine is recommended yearly for patients with risk factors such as type 2 diabetes or already elevated creatinine levels [3, 81]. Fibrates may also increase homocysteine levels; this has not been shown to be of clinical relevance, and monitoring of homocysteine is not recommended.

Niacin

Elevated liver enzymes are also reported with niacin and should be monitored as suggested for fibrates. Niacin may increase blood glucose, which should be monitored in patients with diabetes or at risk of developing diabetes [44, 82, 83]. In combination with statin, niacin is associated with increased risk of myopathy [46], and CK should be monitored if muscle symptoms appear.

Ezetimibe and Bile Acid Sequestrants

Because the main site of action of these compounds is in the intestine, they do not require any specific monitoring in addition to their effects on plasma lipid levels [39, 84–86].

Safety Monitoring in the Elderly

The use of lipid-lowering drugs in the elderly is still a controversial issue but available data suggest that hyperlipidemia should be treated according to the general guidelines at least up to the age of 70. In a meta-analysis by the Cholesterol Treatment Trialists' (CTT) collaboration, the reduction in cardiovascular end points was significant up to age 75 years and also older, although only a few people were included [28]. There are also data supporting statin treatment in secondary prevention for patients above 80 years [87•].

The risk of side effects increases with age because of organ dysfunction (liver and kidney) and polypharmacy with the resulting increase in the potential for drug interactions [67, 88]. Many drugs commonly used in the elderly interact through the CYP3A system, which should be considered. The doses should be adjusted and potential side effects monitored more vigorously. High age is a risk factor for severe myopathy, and clinicians should actively ask about muscular symptoms; when positive, CK should be checked. In the elderly, even minor muscle symptoms may seriously affect the quality of life. Increased ALT is a common side effect but this has not been found to be more common among the elderly.

A few case reports on cognitive disturbances in the elderly have been published [89]. At present, these reports are considered to be of minor significance and, according to the FDA, should not support any changes in the use of statins among the elderly [67].

Conclusions

Based on available risk algorithms and intervention trials, TC and LDL-C should be the first variables used to assess cardiovascular risk. Other risk factors include HDL-C (an important independent risk factor for cardiovascular disease), TG (an indicator of the metabolic status), and non-HDL-C and apoB (which should especially be considered in patients with hypertriglyceridemia or mixed hyperlipidemia). Other main risk factors (diabetes mellitus, smoking, hypertension etc.) should also be considered to give an overall cardiovascular risk assessment. New markers such as Lp(a) and Lp-PLA₂ are emerging as cardiovascular risk factors, but future studies are required to understand how to use these in clinical practice.

The primary treatment target in cardiovascular prevention is LDL-C and potential alternative targets are apoB and non-HDL-C. In selected high-risk individuals, TG should be targeted with drug treatment, but HDL-C, Lp(a), and ratios such as LDL-C/HDL-C or apoB/apoAI are not recommended as treatment targets. Lipids should be monitored during

titration to targets and, thereafter, at least once a year or more frequently to improve treatment adherence if indicated.

Monitoring of muscle and liver enzymes should be done before the start of treatment. In stable conditions during treatment, the focus should be on clinical symptoms that may alert muscle or liver complications. Routine measurement of CK or ALT is not necessary during treatment with statins.

Compliance with Ethics Guidelines

Conflict of Interest Olov Wiklund has been a consultant for Sanofi-Aventis; and has received honoraria from AstraZeneca, Pfizer, Sanofi-Aventis, and Merck. Carlo Pirazzi declares that he has no conflict of interest. Stefano Romeo declares that he has no conflict of interest.

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

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- Of outstanding importance

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