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Practical recommendations for the management of hyperlipidemia

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Abstract

Hyperlipidemia is a risk factor for atherosclerosis. Raised low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) levels are severe risk factors for atherosclerosis. The role of high-density lipoprotein cholesterol (HDL-C) is controversial.

Total cholesterol, LDL-C, HDL-C, triglycerides and lipoprotein(a) levels should be determined in a fasting state.

The basis of treating hyperlipidemia remains diet, physical exercise and weight reduction. Olive oil and nuts have been shown to be beneficial. Statins remain first line drug treatment. Further treatment options are ezetimibe, bile acid sequestrants, fibrates and fish oil. Side effects of statins include myopathies and, as shown during the last years, also an increased risk of diabetes mellitus. In patients with statin-related myopathies first results of a gene analysis have been published showing a means of predicting which statin can be administered at which dose for the individual patient with least risk of side effects. Most convincing data have been shown for simvastatin.

Patients with renal insufficiency have been shown to have a raised cardiovascular risk. In the SHARP Study the combination of simvastatin plus ezetimibe was effective in reducing cardiovascular events in patients with severe renal insufficiency (especially before dialysis but also in dialysis dependent patients).

Important aspects of treating patients with chylomicronemia syndrome are illustrated.

Treating young patients with hyperlipidemia as primary prevention remains problematic.

Keywords: Raised LDL-C values; Raised lipoprotein(a) levels; Side effect of statins; Diagnostics of myopathies; Cardiovascular risk in patients with renal insufficiency; Lipid-lowering therapy in special situations; Chylomicronemia syndrome

Lipid disorders are a severe risk factor for coronary heart disease and extra-coronary atherosclerosis.

The severity of an increase of low-density lipoprotein cholesterol (LDL-C) levels is underlined by the fact that lowering the latter by 1 mmol/l (39.5 mg/dL) reduces the rate of coronary events by 20% and total mortality by 12%, irrespective of baseline risk [1]. The all-cause mortality is also reduced by lowering LDL-C. Therapy goals are illustrated in the European guidelines from 2011 [2]. In high risk patients you should aim for a LDL-C of <2.6 mmol/l (100 mg/dL) or better of <1.8 mmol/l (70 mg/dL). Patients with a lifelong low cholesterol level have a clear advantage [3].

A raised lipoprotein(a) (Lp(a)) level is a severe independent cardiovascular risk factor, as could be shown during the last years [4]. It should be measured in patients with premature cardiovascular events/atherosclerosis or progressive cardiovascular disease as well as in patients with an unfavorable family history.

However, to date, the correlation of low high-density lipoprotein cholesterol (HDL-C) and atherosclerosis is controversial. Patients with high levels of HDL-C appear to be at low risk for atherosclerosis [5], however studies which aimed to show a cardioprotective effect of raising HDL-C failed. Using medications to raise HDL-C did not result in a significant reduction of cardiovascular events.

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High levels of triglycerides (TG) lead to an increased risk of cardiovascular complications in diabetic patients. Very high levels of TG >10 mmol/l (>875 mg/dL) may result in acute pancreatitis [5].

1. Laboratory diagnostics

In primary diagnostics and in follow-up consultations the following laboratory parameters should be assessed: total cholesterol (TC), TG, HDL-C and LDL-C.

In patients with TG levels exceeding 2.3 mmol/l (>200 mg/dL) we recommend to calculate non-HDL-cholesterol (Non-HDL-C) [5]:

$$\text{Non-HDL-C} = \text{TC} - \text{HDL-C}\ (\text{in mmol/L or mg/dL})$$

Blood should be drawn in a fasting state since there are no reference values for postprandial TG.

Lp(a) levels should only be measured once in high risk patients, as this value is genetically determined in 70–80%. Lp(a) levels should not be measured during states of infection.

Before initiating drug therapy liver function tests, kidney values and creatine kinase should be assessed. In order to rule out diabetes or to evaluate diabetic therapy, fasting plasma glucose and HbA1C should be measured. TSH should also be determined in every patient with hyperlipidemia in order to rule out hypothyroidism or hyperthyroidism.

2. Therapy

2.1. Principles of drug therapy

Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimized if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidemia should be treated.

The basis remains dietary advice, cessation of smoking, weight reduction and, after ruling out contraindications, taking up physical exercise. The PREDIMED-study showed positive effects of olive oil [6]; nuts have also been shown to be beneficial. Trans-fatty acids, however, are unfavorable.

Due to excellent data statins are the first line therapy in patients with hypercholesterolemia, mixed hyperlipidemia and a history of cardiovascular disease (Table 1). In patients with intolerance to a statin, we recommend trying another statin, since metabolic pathways of statins differ. Atorvastatin, simvastatin and lovastatin are metabolized via cytochrome P450, 3 A4, Fluvastatin via cytochrome P450, 2C9, Pravastatin via sulfation (7) and rosuvastatin via different enzymes (Cytochrome P450, 3A4, 2C9, 2C19, 2D6). The most potent statins are rosuvastatin, atorvastatin and simvastatin. Pravastatin and fluvastatin are weaker but clinical experience shows that the latter are often better tolerated in patients with intolerance to other statins [7]. Following data of the SEARCH-study simvastatin should not be titrated up to 80 mg, as it is associated with an increased risk of myopathy (FDA warning 06/2011) [8]. In patients who do not reach their target values under 40 mg simvastatin, a more potent statin such as atorvastatin or rosuvastatin should be considered [7].

Table 1
Drug therapy in accordance to phenotype of prevalent hyperlipidemia.

Hypercholesterolemia and/or history of cardiovascular events	Statins Ezetimibe Bile acid sequestrants (may lead to slight elevation of TG) Statin plus Ezetimibe Statin plus bile acid sequestrant
Hypertriglyceridemia	Fibrates Fish oil
Mixed hyperlipidemia	Statins (when hypercholesterolemia is dominant or in patients with a history of cardiovascular events) Ezetimibe Fibrates (when hypertriglyceridemia is dominant or in patients with a history of acute pancreatitis due to hypertriglyceridemia) Fish oil Statins plus Ezetimibe Statins plus Fish oil

In case of intolerability of all statins, the following lipid-lowering medications are available:

- Ezetimibe
- bile acid sequestrants

The clinical end-point study (IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) compared the efficacy of simvastatin 40–80 mg versus simvastatin 40–80 mg plus ezetimibe 10 mg in reducing cardiovascular outcomes (in 18,144 patients with a LDL-C: untreated <3.2 mmol/l (124 mg/dL) and in patients under statin therapy <2.6 mmol/L (100 mg/dL)).

Results have been demonstrated at the American Heart Association Meeting in 2014. The additional application of ezetimibe induced a further reduction of the primary end-point (cardiovascular death, myocardial infarction, hospitalisation due to angina, revascularisation, stroke) by 6.4%.

In patients with hypertriglyceridemia and without a history of cardiovascular disease, fibrates are indicated (but only in patients with normal renal function, GFR > 60 ml/min/1,73). Alternatively, fish oils may be used (Table 1).

Since a lot of patients are on a polypharmacy regimen, interactions should be tested before starting a lipid-lowering medication. There is a substantial risk in combining statins with immunosuppressants.

In patients where therapeutic goals cannot be reached due to either intolerability of higher statin doses or severity of the disease, a lipid-lowering combination therapy should be considered (Table 1). Gudzune KA et al. summarized