A clinical approach to dyslipidaemia

Lipids are vital to life, but are important contributors to pathology.

DIRK J BLOM, *MB ChB, FCP (SA), MMed, PhD*
Lipidology Division of Internal Medicine, Groote Schuur Hospital and University of Cape Town

Dirk Blom is a graduate of the University of Cape Town. He specialised in internal medicine at Groote Schuur Hospital and subsequently joined the Lipid Clinic. His special interests are in mixed hyperlipidaemia, diabetes and lipodystrophy.

Life as we currently know it could not exist without lipids. For example, the much-maligned cholesterol molecule plays critical roles in membrane organisation, signal transduction, bile acid and steroid hormone synthesis – and these are just a few of its many roles. The critical importance of cholesterol is underscored by the large number of genes that regulate its metabolism and the devastating clinical consequences of the (luckily) very rare disorders in which 'abnormal' sterol molecules accumulate or cholesterol synthesis is disrupted. Yet excessive circulating cholesterol is an important contributor to atherosclerosis, which is the leading cause of death in the developed world and rapidly increasing in the developing world.

Lipids are not soluble in water. Cholesterol and triglycerides, which are the clinically relevant lipids considered in this article, are not found dissolved in plasma, but are transported in lipoproteins (see the article on lipoprotein metabolism for more details). When we talk to patients about 'good' or 'bad' cholesterol the cholesterol molecule itself is always the same. The amount of cholesterol carried in different lipoprotein classes, with differing atherogenic potential, is what matters.

Two patients with identical lipid profiles may be treated very differently once their medical history and other cardiovascular risk factors have been reviewed.

Disorders of lipoprotein metabolism alter the concentration or composition of lipoproteins. This is what we call dyslipidaemia. Dyslipidaemia is common in clinical practice. In many patients the discovery will be incidental as a result of routine screening or insurance examinations. In others the presence of other cardiovascular risk factors such as hypertension, smoking, diabetes or a positive family history prompts lipid testing. Clinically overt atherosclerotic cardiovascular disease is an absolute indication for lipid testing. Once the results of the lipogram are available the doctor's real work starts. The result must be interpreted in the clinical context of the specific patient and a course of action decided upon. Two patients with identical lipid profiles may be treated very differently once their medical history and other cardiovascular risk factors have been reviewed.

Decisions regarding lipid-lowering therapy should be considered carefully. Therapy will be lifelong for almost all patients, with significant financial implications. Although most lipid-lowering drugs have a highly favourable side-effect profile, the risk of side-effects is not zero. On the other hand, not prescribing lipid-lowering therapy when it is needed may have catastrophic clinical consequences such as acute pancreatitis or myocardial infarction (MI). Failure to recognise the genetic nature of a dyslipidaemia is a missed opportunity for family screening. The time spent gathering all the information necessary to make a reasoned decision and then explaining the therapeutic strategy to the patient is a worthwhile investment.

Atherosclerosis and acute pancreatitis are the two major complications of dyslipidaemia. Atherosclerosis generally develops over several years, while acute pancreatitis secondary to severe hypertriglyceridaemia may set in suddenly and is associated with high short-term morbidity and mortality. Severe hypertriglyceridaemia must therefore be regarded as a medical emergency and evaluation and treatment must proceed rapidly.

When evaluating patients with dyslipidaemia it is best to stick to the time-honoured clinical path of information gathering (history, examination and investigations) followed by synthesis and analysis of the information (diagnosis). Once all the information has been gathered and processed a management strategy and goals (management) can be formulated.

Triglycerides can fluctuate markedly between the fasted and fed states, while the total cholesterol is not much affected.

History

When taking the history it is useful to pay special attention to the following points.

Lipogram results

- Did the patient fast adequately before blood was taken? Triglycerides can fluctuate markedly between the fasted and fed states, while the total cholesterol is not much affected. If LDL cholesterol (LDLC) is calculated using the Friedewald equation rather than directly measured (LDLC methods differ between laboratories) a fasting specimen is essential.
- Is the patient taking any lipid-lowering medication or were lipid-lowering medications perhaps recently discontinued? LDL has a long half-life (approximately 3 days) and it is best to wait about 4 weeks following any intervention to allow steady-state conditions to return.
- If the lipogram reflects the effects of treatment, is it at all possible to trace an untreated result?

Always specifically ask about smoking, as most patients will not tell you themselves!

- Is the patient taking any medications that may contribute to dyslipidaemia or are there any other medical disorders that may contribute to dyslipidaemia? (See the article on secondary dyslipidaemia for more details.)
- Was there a recent severe physiological stressor such as a myocardial infarction (MI), major surgery or other significant illness? Lipid levels may then be falsely low as part of the acute phase response.

Family history

- As cardiovascular disease is the commonest cause of death worldwide nearly all patients will have a family member with 'heart disease'. This should not be accepted unquestioningly as a positive family history, but further details must be obtained.
- Severe monogenic dyslipidaemia is particularly common in South Africa as there are several founder populations for familial hypercholesterolaemia (FH). The worldwide prevalence of FH is about 1:500 but may approach 1:70 in founder populations. The populations at risk in South Africa are Afrikaners, Lithuanian Jews and Indians with Guajarati ancestry. Drawing a family tree with as much information as possible (3 - 4 generations, known hypercholesterolaemia, cardiovascular disease, age and cause of death) is very helpful in detecting the autosomal dominant pattern of FH. Cardiovascular disease is conventionally (and somewhat arbitrarily) considered premature in men under the age of 50 years and in women younger than 55 years.
- Type 2 diabetes has a very strong heritable component and a positive family history signals greatly increased risk.

Additional risk factors

- Diabetes and hypertension are well-known cardiovascular risk factors.
- Always specifically ask about smoking, as most patients will not tell you themselves! Try to quantify (pack years) how much the patient has smoked and explore their willingness to quit. Newer research shows a dose-response curve for smoking and MI. Total smoking cessation should always be the goal, but a significant reduction is likely to be beneficial as well.
- Psychosocial stress was a significant risk factor for MI in the Interheart study,[1] but is difficult to measure objectively in routine clinical practice.
- Living under conditions of social deprivation is an independent cardiovascular risk factor in Britain and a risk algorithm that takes this into account, using the residential postcode, has been developed. No similar data are available for South Africa.[2]

Diet and exercise

- Taking a brief dietary history is often worth the time and effort. Many patients claim to be following a 'low-cholesterol diet', but have not actually grasped the important concepts (see the article on diet in this issue).
- There is large variation between individuals in their lipid responses to dietary modification, but knowing how 'bad' the baseline is does allow one to judge the potential for improvement.
- Low consumption of fruit and vegetables is an independent risk factor for MI.[1]
- Almost all patients will benefit from seeing a dietician.
- Exercise has important cardiovascular (and other) benefits. Giving the patient an exercise prescription emphasises the value of exercise.

Complications of dyslipidaemia

- Patients with clinically obvious ischaemic heart disease, peripheral vascular disease or cerebrovascular disease have declared themselves to be at high risk and bypass any further risk assessment.[3]
- A history of severe unexplained abdominal pain with nausea and vomiting in a hypertriglyceridaemic patient may suggest previous pancreatitis.

Examination

Examination of the dyslipidaemic patient is directed at screening for physical signs of dyslipidaemia, complications of dyslipidaemia and possible secondary causes of hyperlipidaemia.

The physical signs of dyslipidaemia are easy to find. All that is required is inspection (and palpation in some cases) of skin, tendons, fundi and plasma (or serum) if available. The article on physical signs in dyslipidaemia provides more details, but the most important physical signs are tendon xanthomata (usually felt as nodules or thickening of the Achilles tendons) and skin xanthomata (excluding xanthelasma which are not very helpful). Tendon xanthomata are diagnostic of FH in the vast majority of cases, while cutaneous xanthomata generally indicate hypertriglyceridaemia or extreme hypercholesterolaemia.

Measure and document height and weight, but also waist circumference. Abdominal obesity is the central feature of the metabolic syndrome. Acanthosis nigricans and excess skin tags are often seen in insulin-resistant patients.

Laboratory investigations

The fasting lipogram is central to the investigation of dyslipidaemia. Total cholesterol (TC), triglycerides (TG) and HDLC are measured while LDLC may be calculated or measured. If the TG exceeds 4.5 mmol/l LDLC cannot be calculated. The formula to calculate LDLC is LDLC = TC - HDLC - (TG/2.2).

All lipoproteins contain cholesterol and triglycerides, but in varying proportions. If the TG is very high then TC also rises as triglyceride-rich lipoproteins are not cholesterol-free. In fact, the commonest cause of severe hypercholesterolaemia (TC >15 mmol/l) in clinical practice is extreme hypertriglyceridaemia. The high cholesterol often inappropriately becomes the focus of attention. Marked elevations of LDLC as seen in homozygous FH are not usually associated with increased TG as LDL contains very little triglyceride.

The following tests are also indicated in most patients, especially if drug treatment is to be started.

- **Urine dipstick** to screen for renal disease. Nephrotic syndrome may cause severe hypercholesterolaemia.
- Renal function is assessed by **creatinine** measurement and most laboratories will automatically calculate the estimated glomerular filtration rate (GFR). Renal disease is an important cardiovascular risk factor and the dosage of many drugs, including fibrates, needs to be adjusted in renal failure.

The commonest cause of severe hypercholesterolaemia (TC >15 mmol/l) in clinical practice is extreme hypertriglyceridaemia.

- Thyroid disease is easy to miss clinically and is a relatively common cause of secondary hyperlipidaemia. **Thyroid-stimulating hormone (TSH)** testing is an effective screen for primary hypothyroidism.
- Fasting **glucose** is an essential component of cardiovascular risk assessment.
- Baseline **liver function tests** are helpful in excluding cholestasis as a secondary cause of hyperlipidaemia. Non-alcoholic fatty liver disease (NAFLD) is also common in dyslipidaemia, especially if there is an element of hypertriglyceridaemia. Should there be concern about elevated liver function tests once the patient is on lipid-lowering treatment it is very handy to have an untreated baseline to compare with.
- Measuring **creatine kinase (CK)** at baseline creates a useful reference point. Patients with persistently elevated CK at baseline should be evaluated for underlying causes of myopathy before statin treatment is contemplated.

For more information on other tests see the article on the rational use of laboratory investigations in dyslipidaemia.

Diagnosis

The next step is to formulate a diagnosis. The diagnosis may be a fairly simple phenotypic description of the lipoprotein abnormalities or may be taken to a molecular level with the identification of a mutation in a specific gene. The level to which the diagnostic evaluation can be taken is dependent on the information the patient is able to supply, the clinical findings, laboratory facilities, clinical expertise and finally the enthusiasm of the doctor in pursuing a molecular diagnosis.

The lipoprotein phenotype should always be described more accurately than just saying 'high cholesterol'. Most patients will fall into one of the broad categories described below.

- Predominant **LDLC hypercholesterolaemia**. In these patients high levels of LDLC are the primary abnormality. The problem may be mild, moderate, severe or extremely severe. TG may be elevated moderately but generally does not exceed 2.5 - 3.5 mmol/l.
- **Predominant hypertriglyceridaemia.** TG elevation is the major problem here and the TG>TC. The underlying problem is usually excess VLDL or chylomicrons.
- **Mixed hyperlipidaemia**. In mixed hyperlipidaemia both TG and TC are elevated. The most important category is that of severe mixed hyperlipidaemia (TG>2.5 mmol/l and TC>7.5 mmol/l).
- **Hypo- or hyperalphalipoproteinaemia.** These patients have abnormally low or high levels of HDL. Hypoalphalipoproteinaemia and hypertriglyceridaemia are often found together.
- The **atherogenic lipid phenotype** is often seen in patients with the metabolic syndrome or diabetes. There is moderate hypertriglyceridaemia, low HDLC and LDLC concentrations are in the usual range or only modestly raised. These abnormalities in combination are highly atherogenic, hence the name.

The above phenotypes may be secondary to other disorders or be primary abnormalities (see the article on secondary dyslipidaemia for details). Primary hyperlipidaemia may be the result of multiple genetic (polygenic) and environmental influences or may be due to a single gene mutation. In most patients with mild to moderate hyperlipidaemia no single gene defect can be identified. Monogenic disorders usually cause severe dyslipidaemia. The following section briefly introduces a selection of clinically important monogenic lipid disorders and their usual phenotypes.

Monogenic hyperlipidaemia

- Predominant **LDLC hypercholesterolaemia**. Patients with LDLC hypercholesterolaemia (LDLC usually >5.0 mmol/l), tendon xanthomata and an autosomal dominant pattern of inheritance (except for autosomal recessive hypercholesterolaemia (ARH)) have FH. So far four genes have been identified that cause this phenotype. At a clinical level it is not possible to tell what the causative gene is. The genes are the LDL-receptor (by far the commonest cause worldwide), apoB, PCSK9 and ARH. A homozygous phenotype with extremely high LDLC (usually >15 mmol/l) and very premature heart disease exists. The homozygous phenotype has been described with LDL-receptor mutations and is the only phenotype with ARH, which is a recessive condition.
- **Predominant hypertriglyceridaemia**. This is a secondary problem in the vast majority of patients (diabetes, alcohol, drugs), but if found in infants or children consider lipoprotein lipase or apoCII deficiency. Both are recessive conditions and the parents mostly have unremarkable lipids.
- **Mixed hyperlipidaemia**. This may be the result of mutations in apoE. The disorder is called dysbetalipoproteinaemia and is usually recessive.

Management

Lipid management is risk management. All decisions are based on assessment of the absolute risk of a complication of dyslipidaemia occurring. Lipid values are just one factor in the risk equation. The patient needs treatment, not the laboratory abnormality.

Pancreatitis risk

Triglycerides of >10 - 15 mmol/l may trigger acute pancreatitis, which can be fatal. The onset of acute pancreatitis is unpredictable; it may occur shortly after the onset of hypertriglyceridaemia or may not occur at all. The TG level at which pancreatitis develops is also highly variable. TG levels may vary markedly with food intake and a patient with a fasting TG of 15 mmol/l measured on a weekday may easily reach a postprandial TG of 30 mmol/l or more following a fat- and alcohol-rich weekend braai. Severe hypertriglyceridaemia must therefore always be taken seriously and handled as a medical emergency. The principles of management are:

- Institution of a very low triglyceride diet (<20 - 25 g/day of triglyceride). Initially one may prescribe an extremely low fat diet (≈ 8 g/day of triglyceride). This is colloquially known as the 'rescue diet' and helps to lower the triglycerides rapidly, but is not sustainable in the long term (Table I).
- Correction of precipitating factors such as uncontrolled diabetes, alcohol abuse or medications.
- Fibrate drugs (bezafibrate, fenofibrate, gemfibrozil).
- Ideally all patients with severe hypertriglyceridaemia should be seen by a doctor experienced in lipid management. This will usually be a lipid specialist, endocrinologist or physician.

Atherosclerosis risk

Cardiovascular risk is a composite of multiple individual risk factors. In some patients dyslipidaemia may play a relatively minor role, while in other patients, such as those with FH, it may be the primary driving force. There is excellent evidence from many trials that lipid-lowering treatment with statins can reduce cardiovascular risk in most situations, even if the dyslipidaemia does not seem 'severe'. The higher the absolute risk, the bigger the benefit. In other words, as absolute risk increases the number of patients that need to be treated to prevent one cardiovascular event (e.g. MI) decreases.

Table I. 'Rescue diet' for severe hypertriglyceridaemia with information on triglyceride content – daily menu

Breakfast (1.7 - 1.9 g)

125 ml orange juice (0.3)

1 banana (0.4)

3/4 cup rice crispies (0.0)

250 ml skim milk (0.5)

1 slice white (wheat) bread (0.5 (0.7))

15 ml honey (0.0)

Lunch (1.6 - 2.4 g)

2 medium potatoes (2 slices bread) (0.2 (1.0))

Salad (lettuce, cucumber, tomato) (0.5)

60 g fat-free cottage cheese (0.9)

Supper (2.4 - 3.6 g)

375 ml white rice (pasta) (0.6 (1.6))

125 ml tomato/onion mix (0.4)

Vegetables (carrot, broccoli) (0.4)

125 ml lentils (0.4)

Fruit (3 slices pineapple) (0.6)

Snacks (1.3 g)

Apple, morning (0.6)

Pear, afternoon (0.7)

Other supplements

Non-diabetics	*Diabetics*
Beverages	
Carbonated drinks including colas	Sugar-free cold drinks
Lucozade	Low-calorie: Lecol, Oros
Fruit juice including orange, apricot, apple, grape	
Sweets	
Boiled sweets	Artificially sweetened
Jelly babies, wine gums, marshmallows	
Peppermints, vitamin C sweets	
Spreads	
Sugar syrup, honey, molasses	'Diabetic' jams
Jam, marmalade	
Desserts	
Jelly, canned fruit, custard made with skim milk (0.4 g fat/250 ml)	Artificially sweetened jelly Low-calorie canned fruit
Meringues without cream	
Dried fruit	

Comments

Fats are often poorly declared on food labels, and recipes may variably include fats and are best not trusted. Medium-chain triglycerides, though not necessarily destined to chylomicrons, could still undergo chain elongation and enter chylomicrons and thus aggravate hypertriglyceridaemia. Intravenous lipid supplementation (Intralipid, Lipovenous) is contraindicated.

Number needed to treat links lipid management to economics. This is an unavoidable fact of life. Risk thresholds at which lipid-lowering therapy is started and treatment targets are at least partially determined by affordability issues. Not all patients can access optimal treatment, but they will still gain some benefit from less intensive lipid lowering. The treatment guidelines presented in the following section are those adopted by the South African Heart Association and the Lipid and Atherosclerosis Society of South Africa.[3] The South African guidelines are based on those of the European Society of Cardiology.

Lipid management is risk management.

All patients should be advised on lifestyle modification. This includes dietary modification (see article), smoking cessation and increased physical activity. Lifestyle modification must be promoted actively and enthusiastically. Not modifying the lifestyle cannot be fully compensated for by intensified pharmaceutical therapy. Hypertension and diabetes should be treated according to relevant guidelines and aspirin should be prescribed when indicated (details not reviewed in this article).

Risk assessment

Patients with clinically overt atherosclerosis in any arterial territory are at high risk of further cardiovascular events. The same applies to patients with type 2 diabetes or type 1 diabetics who have microalbuminuria.[3] Risk assessment is not needed and lipid-lowering therapy is required even if the lipids are not elevated. Severe monogenic hyperlipidaemia is also associated with very high cardiovascular risk that is severely underestimated by conventional risk calculation algorithms. In South Africa the latter is relevant, as FH is highly prevalent and many patients are denied lipid-lowering therapy by medical funders after inappropriate risk assessment. All patients with FH will require lipid-lowering therapy; the question is just at what age should treatment start? Adults definitely need treatment and some children should also be treated. Consultation with a lipid specialist may be helpful.

In patients who are not obviously at very high risk the next step is risk assessment using an algorithm. These algorithms mostly predict the 10-year risk of coronary heart disease. See Table II for the algorithm currently recommended for South Africa. The algorithm is based on American data (Framingham), as there are not sufficient local data to construct a South African algorithm. Risk assessment algorithms can be criticised on many levels (lack of local data, 10-year v. lifetime risk, exclusion of family history, continuous variables considered categorically, etc.), but they are currently the best and most accessible tool we have to estimate risk and make treatment decisions.

Table II. Framingham Risk Chart*

Men

Age	**Points**
20 - 34	-9
35 - 39	-4
40 - 44	0
45 - 49	3
50 - 54	6
55 - 59	8
60 - 64	10
65 - 69	11
70 - 74	12
75 - 79	13

	Age				
Total cholesterol	**20 - 39**	**40 - 49**	**50 - 59**	**60 - 69**	**70 - 79**
<4	0	0	0	0	0
4.1 - 5	4	3	2	1	0
5.1 - 6.2	7	5	3	1	0
6.21 - 7.2	9	6	4	2	1
≥7.2	11	8	5	3	1
Non-smoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mmol/l)	**Points**
≥1.6	-1
1.30 - 1.59	0
1.00 - 1.29	1
<1	2

Systolic BP (mmHg)	**If untreated**	**If treated**
<120	0	0
120 - 129	0	1
130 - 139	1	2
140 - 149	1	2
≥160	2	3

Points total	**10-year risk %**
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

Table II. Continued

Women

Age	**Points**
20 - 34	-7
35 - 39	-3
40 - 44	0
45 - 49	3
50 - 54	6
55 - 59	8
60 - 64	10
65 - 69	12
70 - 74	14
75-79	16

	Age				
Total cholesterol	**20 - 39**	**40 - 49**	**50 - 59**	**60 - 69**	**70 - 79**
<4	0	0	0	0	0
4.1 - 5	4	3	2	1	1
5.1 - 6.2	8	6	4	2	1
6.21 - 7.2	11	8	5	3	2
≥7.2	13	10	7	4	2
Non-smoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mmol/l)	**Points**
≥1.6	-1
1.30 - 1.59	0
1.00 - 1.29	1
<1	2

Systolic BP (mmHg)	**If untreated**	**If treated**
<120	0	0
120 - 129	1	3
130 - 139	2	4
140 - 149	3	5
≥160	4	6

Points total	**10-year risk %**
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

* These charts calculate the risk of major coronary events in adults without diabetes. They do not consider family history of cardiovascular disease or the metabolic syndrome. The charts should not be used in patients whose TC is >7.5 mmol/l as risk will be underestimated.

Risk assessment needs to be combined with clinical judgement, but most medical funders make no allowance for this. The guidelines recommend treatment if the 10-year risk is more than 20%.

Subclinical atherosclerosis can be detected by imaging techniques such as electron beam CT or carotid artery intima media thickness measurement. This may be helpful when risk is indeterminate or where there is concern that risk may be underestimated by algorithms (see the article on atherosclerosis imaging for more details).

Lipid-modifying therapy

HMG CoA reductase inhibitors or statins are the drugs of choice for patients with hypercholesterolaemia. They are safe and effective and well tolerated by the majority of patients. Combinations of lipid-lowering drugs will be necessary in some patients. The usual reasons are either severe hyperlipidaemia or statin intolerance. Some common combinations are a statin + fibrate for severe mixed hyperlipidaemia or statin + ezetimibe (or cholestyramine) for severe LDLC hypercholesterolaemia. The article on lipid-modifying drugs provides more information in this regard. Combination therapy is associated with increased risk of side-effects and specialist consultation is advisable before commencing treatment.

LDLC targets

Multiple studies have shown that 'lower is better' for LDLC.[4] Unfortunately 'high-dose' statin therapy is also more expensive than 'conventional-dose' therapy and the incremental cost of an additional life year gained is high.[5] The currently recommended target in South Africa is an LDLC of 2.5 mmol/l or less. The American National Cholesterol Education Programme has suggested a target of 1.8 mmol/l for very high-risk patients (diabetics with cardiovascular disease (CVD), persistent smokers with CVD, poorly controlled hypertension with CVD, recent MI, CVD and multiple metabolic syndrome factors).[6] Achieving a LDLC of 1.8 mmol/l may be difficult. Currently available lipid-lowering medication may not be powerful enough in some patients, others may not tolerate high doses of statins and many patients simply cannot access the treatment.

The LDLC targets achievable in practice will at least in part reflect societal ability and willingness to pay for lipid-lowering therapy. Within these constraints the aim still is to achieve the lowest LDLC possible for that particular patient. CVD risk reduction comes as a 'package deal' and lifestyle modifications and control of other risk factors remain critical. It is easy to lose focus and become too 'cholesterol-centric' and ignore the fact that although statins are highly effective agents in atherosclerosis they do not 'cure' the disease and only provide partial risk reduction.

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In a nutshell

- Dyslipidaemia (↑LDLC, ↓HDLC) is a major risk factor for atherosclerosis.
- Severe hypertriglyceridaemia (TG> 10 - 15 mmol/l) can cause acute pancreatitis.
- The assessment of dyslipidaemic patients should focus on the exclusion of secondary disorders, global evaluation of cardiovascular risk, lifestyle evaluation and identification of monogenic lipid disorders.
- Familial hypercholesterolaemia (FH) is common in South Africa.
- FH is identified by family history and the finding of tendon xanthomata.
- Risk calculation is inaccurate for patients with FH.
- Treatment decisions are based on assessment of absolute risk.
- Patients with overt cardiovascular disease, FH, type 2 diabetes or type 1 diabetes with microalbuminuria must be treated with lipid-lowering medication.
- In asymptomatic patients a 10-year risk of coronary heart disease >20% requires treatment.
- Lifestyle interventions are very effective and cheap and should be recommended to all patients.