Identification of a lipid abnormality in the context of global cardiovascular risk assessment

Hypercholesterolaemia, mixed dyslipidaemia and certain hypertriglyceridaemias, along with diabetes, arterial hypertension and smoking, are major risk factors for atherosclerosis involved in the occurrence of cardiovascular diseases (ischaemic heart disease, ischaemic strokes, peripheral arterial disease, etc.), the second leading cause of death in France. These risk factors are often associated in particular with abdominal obesity and behavioural factors such as sedentary lifestyle, unbalanced diet, alcohol or stress.

It is recommended that a lipid profile be performed in the context of global cardiovascular risk (CVR) assessment.

Cardiovascular risk assessment

It is recommended that cardiovascular risk be assessed as primary prevention using the SCORE (Systematic Coronary Risk Estimation) tool, except for patients with diabetes, chronic kidney failure, severe hypertension (BP ≥ 180/110 mmHg) or familial hypercholesterolaemia (see memo sheet “Cardiovascular risk assessment”).

In case of documented cardiovascular disease, in secondary prevention, cardiovascular risk is immediately considered very high.

Identification of a lipid abnormality

A lipid profile is recommended:

- in the context of a global CVR assessment in men over 40 years of age and women aged 50 years or older or menopausal. After 80 years of age, the performance of a lipid assessment is not justified;
- during a prescription of an oestrogen-progesterone hormonal contraceptive (pill, patch, ring). Fasting blood sugar should be used.

Regardless of age, some elements lead to a global CVR assessment, including a lipid profile (see memo sheet “Main dyslipidaemias: management strategies”).

Methods for performing a lipid profile

A lipid profile includes total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL-C) and low-density lipoproteins (LDL-C) concentrations calculated as part of the CVR assessment and the characterisation of the dyslipidaemia.

The blood sample must be collected after 12 hours of fasting [LDL-C calculated by the Friedewald equation if TG ≤ 3.4 g/L (3.9 mmol/L), or assayed if TG > 3.4 g/L].

If the profile is normal, repeating a lipid profile more than once every 5 years is not justified in the absence of a cardiovascular event or weight gain, changes in lifestyle or initiation of treatment likely to alter the lipid assessment or risk factors.
Management of hypercholesterolaemia

In addition to the hypercholesterolaemia, other CVR factors must be addressed: smoking, arterial hypertension, diabetes, obesity, etc.

In subjects with an LDL-C $\geq 1.9$ g/L (4.9 mmol/L), testing for heterozygous familial hypercholesterolaemia is recommended (see paragraph Heterozygous familial hypercholesterolaemia).

Objectives and therapeutic strategies

For the sake of clarity, the therapeutic objectives have values equivalent to the therapeutic intervention thresholds. The objective is to obtain and maintain an LDL-C concentration below the therapeutic intervention threshold.

The therapeutic strategy varies according to cardiovascular risk and LDL-C concentration.

In first line, lifestyle changes are recommended when LDL-C is above the target value, only when the risk is low or moderate, associated with lipid-lowering drug when the risk is high or very high (see memo sheet “Lifestyle changes in the management of cardiovascular risk”).

In second line, if the target value is not reached after 3 months of a first-line intervention properly followed by the patient, a lipid-lowering drug will be introduced or intensified, depending on the risk level (see paragraph Monitoring the management of hypercholesterolaemia).

Statins are the first-line of drug therapy for isolated hypercholesterolaemia, where justified; the recommended statins (best cost-effectiveness) are simvastatin and atorvastatin. Another statin may be used in case of intolerance.

The choice of dose of simvastatin or atorvastatin is made considering the patient’s initial LDL-C level, the initial cardiovascular risk level and the target value.

If the target value is not reached, it is recommended that the therapeutic regimen be intensified (increase to maximum tolerated dose, replacement with a more powerful statin).

If the target value is not reached with the maximum tolerated dose of statin, a combination of a statin and ezetimibe is recommended, or lastly in combination with cholestyramine.

In case of intolerance to statins, it is recommended that ezetimibe or cholestyramine be used.

Because elderly subjects often have comorbidities and impaired metabolic capacities, it is recommended that lipid-lowering drug be started at a low dose and that the dosage then be carefully adjusted to achieve target LDL-C concentrations identical to those of the young subjects.

<table>
<thead>
<tr>
<th>Level of cardiovascular risk</th>
<th>Target LDL-C</th>
<th>First-line intervention</th>
<th>Second-line intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low SCORE &lt; 1%</td>
<td>&lt; 1.9 g/L (4.9 mmol/L)</td>
<td>Lifestyle change</td>
<td>Lifestyle change + lipid-lowering drug</td>
</tr>
<tr>
<td>Moderate 1% ≤ SCORE &lt; 5%</td>
<td>&lt; 1.3 g/L (3.4 mmol/L)</td>
<td>Lifestyle change</td>
<td>Lifestyle change + lipid-lowering drug</td>
</tr>
<tr>
<td>Type 1 or 2 diabetes &lt; age 40 with no CVR factor or target organ disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High 5% ≤ SCORE &lt; 10 %</td>
<td>&lt; 1.0 g/L (2.6 mmol/L)</td>
<td>Lifestyle change</td>
<td>Lifestyle change + Intensification of lipid-lowering drug</td>
</tr>
<tr>
<td>Type 1 or 2 diabetes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; age 40 with at least one CVR factor or target organ disease; ≥ age 40 with no CVR factor or target organ disease</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patient with moderate chronic kidney failure</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BP ≥ 180/110 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high SCORE ≥ 10%</td>
<td>&lt; 0.70 g/L (1.8 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 or 2 diabetes ≥ age 40 with at least one CVR factor or target organ disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient with severe chronic kidney failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented cardiovascular disease (secondary prevention)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* See paragraph Monitoring the management of hypercholesterolaemia.
Choice of statin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>5 10 20 40 80</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>5 10 20 40 80</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
</tbody>
</table>

- Low intensity (percentage of reduction of LDL-C: 20-29%)
- Moderate intensity (percentage of reduction of LDL-C: 30-39%)
- High intensity (percentage of reduction of LDL-C: > 40%)
- Off-label/not recommended

✓: the most efficient statins.

Atorvastatin and rosuvastatin do not have validated indication (MA) in secondary prevention.

Monitoring the management of hypercholesterolaemia

It is recommended that a therapeutic education approach be implemented to improve compliance with lifestyle changes and to encourage patient adherence to the drug therapy.

Effectiveness of the monitoring

After starting management, a lipid assessment is recommended within 12 to 24 weeks for low and moderate CVR levels, and 8 to 12 weeks for high and very high CVR levels. Following this, a lipid assessment is recommended 8 to 12 weeks after each adjustment of the treatment, until the target values are reached.

As soon as the target cholesterol level is reached, an annual consultation is recommended with an assessment to discuss treatment adherence, lifestyle changes and CVR factors.

In subjects with insufficient therapeutic response, it is recommended that adherence be reinforced:

- to lifestyle changes, regardless of CVR;
- to the lipid-lowering drug, if it was initiated.

Intensification of the lipid-lowering drug is foreseeable in case of insufficient therapeutic response despite well-followed management (lifestyle changes and lipid-lowering drug).

Hepatic monitoring (ALT)

- Before treatment.
- 8 weeks after the start of drug treatment or after any dosage increase.
- Then every year if ALT < 3 × N (normal).
- If ALT ≥ 3 × N: stop the statin or reduce the dosage, check the liver enzymes again after 4 to 6 weeks and carefully reintroduce the treatment once ALT has returned to a normal value.

Muscle monitoring

- There is no need to measure creatine kinase (CK) in patients treated with a lipid-lowering drug prior to initiation of the treatment, except in the following risk situations: pre-existing muscle pain, moderate to severe kidney failure, hypothyroidism, personal or family history of genetic muscle disease, alcohol abuse, age over 70 years, especially since there are other muscular risk factors.
- If the initial CK level is > 5 × N, it is recommended not to start the drug treatment and to check the muscle enzyme levels.

The consumption of grapefruit or its juice is discouraged with treatment with simvastatin.

- If adverse effects occur with a statin, the possible alternatives should be discussed with the patient: stop the statin and reintroduce it to the resolution of the symptoms to verify that these are related to the statin;
- reduce the dose or replace with another statin of the same intensity;
- in the absence of improved tolerance, prescribe a statin of lower intensity.

It is recommended to seek a specialised advice on treatment options of a patient at high cardiovascular risk intolerant to statins.
**Treatment of mixed dyslipidaemia and isolated hypertriglyceridaemia**

Lifestyle changes are recommended as first line. The triglyceride (TG) concentration considered normal is TG < 1.5 g/L.

<table>
<thead>
<tr>
<th>Moderate hypertriglyceridaemia: 2 g/L (2.3 mmol/L) ≤ TG &lt; 5 g/L (5.6 mmol/L)</th>
<th>Severe hypertriglyceridaemia: TG ≥ 5 g/L (5.6 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>non-HDL-C</strong> or <strong>LDL-C</strong> at target</td>
<td>Prescription of fibrate</td>
</tr>
<tr>
<td>Prescription of statin</td>
<td>If 2 ≤ TG &lt; 5 g/L</td>
</tr>
<tr>
<td>If <strong>non-HDL-C</strong> or <strong>LDL-C</strong> target not achieved</td>
<td>And <strong>non-HDL-C</strong> or <strong>LDL-C</strong> at target</td>
</tr>
<tr>
<td>With normal HDL-C and low to moderate CVR: continue the statin</td>
<td>Combination with ezetimibe</td>
</tr>
<tr>
<td>With high to very high CVR: prescription of fibrate</td>
<td>Combination with a statin</td>
</tr>
<tr>
<td><strong>Non-HDL-C cholesterol</strong> = (TC – HDL-C), with target: non-HDL-C &lt; 1.3 g/L in patients with high CV risk; non-HDL-C &lt; 1.0 g/L in patients with very high CV risk.</td>
<td></td>
</tr>
</tbody>
</table>

Fibrates are contraindicated for doses ≥ 40 mg of rosuvastatin. Moreover, gemfibrozil is contraindicated in combination with simvastatin, and not recommended with other statins.

Fibrates are contraindicated in patients with chronic renal failure.

**Management of heterozygous familial hypercholesterolaemia**

The diagnosis is suggested in case of:
- high LDL-C concentration [1.9 g/L (4.9 mmol/L) to 4.0 g/L (10.3 mmol/L)];
- parents with familial hypercholesterolaemia;
- extravascular cholesterol deposits (especially tendon xanthomas);
- early personal or family strokes.

The diagnosis may be suspected when LDL-C is 1.9 g/L (4.9 mmol/L) in adults and 1.6 g/L (4.1 mmol/L) in children.

It is recommended that the diagnosis be confirmed by a score established according to the clinical and laboratory criteria of the Dutch Lipid Clinic Network or, if possible, by genetic testing.

Cascade screening (testing for the disease in a patient’s family members) for familial hypercholesterolaemia is recommended in first-degree relatives of patients with diagnosed familial hypercholesterolaemia.

The therapeutic objectives in patients aged 20 years and younger are: LDL-C < 1.3 g/L (3.4 mmol/L).

After 20 years of age, the therapeutic objectives in patients with high or very high CVR or as secondary prevention are the same as those for isolated hypercholesterolaemia.

The treatment is the same as that for isolated hypercholesterolaemia. In case of treatment resistance, it is recommended to seek a specialised advice.