March 2017

PCSK9 inhibitors in the treatment of hypercholesterolaemia

Recommendation:

Alirocumab▼ and evolocumab▼ in the treatment of non-familial hypercholesterolaemia, mixed dyslipidaemia and heterozygous-familial hypercholesterolaemia (HeFH).

1. This recommendation provides clarification of NICE TAs 393[1], and 394[2].
2. PCSK9 inhibitors should be initiated only by lipid specialists. CHD patients being considered for use should be referred to a lipidologist.
3. This recommendation does not apply to the treatment of Homozygous familial hypercholesterolaemia (HoFH) which is commissioned by NHS England.
4. Consider use when:
   Low-density lipoprotein concentrations are **persistently** above the thresholds specified in table 1 despite **maximal tolerated lipid-lowering therapy (statins plus ezetimibe)**. That is, either the maximum dose has been reached, or further titration is limited by intolerance (as defined in NICE guideline on familial hypercholesterolaemia: identification and management).
5. The product with the lowest acquisition cost should be selected (taking account of the discounts agreed in the patient access schemes from manufacturers)
6. Consider stopping if at least a 30% reduction in LDL-C has not been achieved after 3 months of adherent treatment.

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▼ Newly marketed drugs and vaccines are intensively monitored for a minimum of two years, in order to confirm the risk / benefit profile of the product. Healthcare professionals are encouraged to report all suspected adverse drug reactions regardless of the severity of the reaction.

Agreed Greater Manchester approach:

Low-density lipoprotein:

May be calculated on either a fasting sample or a non-fasting sample but use of a fasting sample is recommended if levels are near cut-off levels for treatment.

Persistent:

At least 2 samples a minimum of 3 months apart

Maximal tolerated lipid-lowering therapy

NICE definition (from CG71 familial hypercholesterolaemia, paragraph 1.3.1.11)

…the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.

Biochemistry

CK>5x ULN or ALT>3x ULN suggest significant pathology and a need to review statin treatment (hypothyroidism and macro-CK are alternative causes of a high CK), but the overwhelming proportion of patients who describe myopathic pain have normal CK levels.

Myopathy

Usually appears within 4-6 weeks of commencing statin therapy. About 10% of patients describe some degree of myopathy, and the true increase of statin-related myopathy over placebo is around 5%. The risk of intolerance is higher in the elderly and in East Asians. For many patients, emergent myopathy is likely to represent pre-existing osteological or neurological complaints and is not related to statin treatment.

Statin use

Atorvastatin or rosuvastatin should be tried initially and titrated up to maximum dose tolerated (in terms of adverse effects of new or worsening myopathy, GI disturbance or abnormal LFTs).

Confirmation of the causal effect of statins should include cessation of symptoms on stopping statin, and recurrence on reintroduction.

For suspected intolerance, swap to the other; no need to use simvastatin as both simvastatin and atorvastatin are lipophilic and metabolised by the same pathway. If standard doses are not tolerated, consider low-dose rosuvastatin (5mg 2-3 times/week).

Check adherence to therapy.

Additional lipid lowering therapies

1 If target LDL-C level is not attained on statins alone, **add ezetimibe** and trial for at least 3 months.

2 If target LDL-C level is still not attained, consider PCSK9 inhibitor, subject to NICE criteria in table 1, **in addition** to existing lipid lowering therapy.

Table 1. LDL-C concentrations above which PCSK9s are recommended by NICE[1,2]

	Without CVD	With CVD	
		High risk of CVD[a]	**Very high risk of CVD[b]**
Non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

[a]High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, peripheral arterial disease.

[b]Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations

ALT	Alanine transaminase
CK	Creatine kinase
CVD	Cardiovascular disease;
LDL-C	Low-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin / kexin type 9 inhibitors: alirocumab▼, evolocumab▼ and any further drugs within this class
ULN	Upper limit of normal

References

1 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia NICE TA 393 https://www.nice.org.uk/guidance/ta393

2 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. NICE TA 394 https://www.nice.org.uk/guidance/ta394

3 Familial hypercholesterolaemia: identification and management. NICE CG 71 https://www.nice.org.uk/guidance/cg71/