Pathway for the use of PCSK9 Inhibitors

Hypercholesterolaemia and mixed lipidaemia are conditions with high concentrations of cholesterol and/or triglycerides in the blood.

In primary non-familial hypercholesterolaemia, a number of genes interact with dietary and other factors such as alcohol intake and lack of exercise to cause high cholesterol levels. Primary non-familial hypercholesterolaemia affects an estimated 1.5 million people in England.

Primary heterozygous-familial hypercholesterolaemia is an inherited condition caused by a faulty gene and affects more than 100,000 people in England. People with this condition have raised cholesterol levels from birth.

Patients with hypercholesterolaemia have an increased risk of cardiovascular disease (CVD) due to accelerated atherosclerosis eventually leading to angina, heart attacks and strokes. CVD is a common cause of death in England, accounting for approximately 150,000 deaths in 2012.

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

Proprotein convertase subtilisin/kexin 9 (PCSK9) inactivates the receptors on the liver cell surface that transport low density cholesterol (LDL) into the liver for metabolism. PCSK9 inhibitors are monoclonal antibodies that inactivate PCSK9 in the liver. This inhibition of PCSK9 leads to more receptors available to capture LDL for metabolism and removal from the blood.

Indications for PCSK9 Inhibitors

- Primary hypercholesterolaemia (heterozygous-familial and non-familial), mixed lipidaemias
  - PCSK9 Inhibitors are indicated
    - in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or
    - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
  - Homogenous familial hypercholesterolaemia

Dosage of PCSK9 Inhibitors

Alirocumab (Praluent®, Sanofi) - 75 mg or 150 mg every 2 weeks.
Evolocumab (Repatha®, Amgen) - 140mg every 2 weeks.

Refer all patients who fulfil the below criteria to the specialist lipid clinic at York or Scarborough hospital for evaluation and initiation of PCSK9 inhibitors.
Eligible patients

Table 1: Low-density lipoprotein cholesterol concentration above which evolocumab or alirocumab is recommended in all dyslipidaemias except homozygous familial hypercholesterolemia.

<table>
<thead>
<tr>
<th>Without CVD</th>
<th>With CVD</th>
<th>High risk of CVD¹</th>
<th>Very high risk of CVD²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary non-familial hypercholesterolaemia or mixed dyslipidaemia</td>
<td>Not recommended at any LDL-C concentration</td>
<td>Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre</td>
<td>Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre</td>
</tr>
<tr>
<td>Primary heterozygous-familial hypercholesterolaemia</td>
<td>Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre</td>
<td>Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre</td>
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¹ High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease.
² Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

NHS England has commissioned evolocumab for homozygous familial hypercholesterolaemia for patients aged 12 years or over from 20th September 2016.

- The dosage is 420 mg every 2 weeks (following an initial titration of 420mg monthly over 12 weeks).
- Low-density lipoprotein concentrations are persistently above the thresholds specified in Table 2 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance.
- Treatment must be stopped if there is less than a 30% drop in LDL-C concentration after 12 weeks of treatment.

The following centres will be commissioned to prescribe evolocumab according to the criteria listed above:

- Central Manchester University Hospitals NHS Foundation Trust
- Queen Elizabeth Hospital Birmingham
- Royal Brompton and Harefield NHS Foundation Trust
- Imperial College NHS Trust
- University Hospitals Bristol NHS Foundation Trust
Table 2: Low-density lipoprotein cholesterol concentration above which evolocumab is recommended in homozygous familial hypercholesterolemia.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>High risk of CVD&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Primary homozygous familial hypercholesterolaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre</td>
<td></td>
<td>Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre</td>
</tr>
</tbody>
</table>

<sup>1</sup> High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease.

<sup>2</sup> Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

**Abbreviations:** CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

**Statin intolerance**

Intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. Inform the patient that any statin at any dose reduces cardiovascular disease risk.

If a patient reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group.

It’s recommended to try at least 3 different statins including rosuvastatin.

**Use of this online tool is recommended to evaluate the possibility of statin intolerance.**
http://tools.acc.org/StatinIntolerance/#!/content/evaluate/calculator/

There is no evidence that fibrates reduce cardiovascular risk so they are not included in the pathway. They remain an option in familial hypercholesterolaemia.
The local CCG guidance on statin use is available on the following link:
http://www.yorkandscarboroughformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=2&SubSectionRef=02.12&SubSectionID=E100#83.

NICE CG181–Cardiovascular disease: risk assessment and reduction including lipid modification is available on the following link:

Seek specialist advice about options for treating people at high risk of cardiovascular disease such as those with chronic kidney disease, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with cardiovascular disease, who are intolerant to 3 different statins.

References
2. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. NICE technology appraisal guidance [TA393]Published date: 22 June 2016
3. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. NICE technology appraisal guidance [TA394] Published date: 22 June 2016
Appendix 1 - Local lipid lowering pathway

- Primary Hypercholesterolaemia (heterozygous-familial and non-familial), mixed dyslipidaemia

**Heterozygous familial hypercholesterolaemia**

**Mixed Hyperlipidaemia**

**Other dyslipidaemia with CVD risk**

Lifestyle changes +/- atorvastatin
- Use local CCG/ local authority guidance on services available to support patients.
- NICE CG 181 – cardiovascular disease : risk assessment and reduction including lipid modification (see link in reference list)

**LDL/non-HDL targets not achieved after optimisation***

**Intolerant of 3 statins (including rosuvastatin) +/- ezetimibe**

CVD

No

- **Heterozygous Familial hypercholesterolaemia**
  - LDL >5.0mmol/L

Yes

- **Heterozygous Familial hypercholesterolaemia**
  - LDL>3.5mmol/L

- **Very High risk of CVD**

- **High risk of CVD**
  - LDL>4.0

**PCSK9 inhibitors**
- Alirocumab or Evolocumab

• **Targets aimed for reduction using statins and/or ezetimibe.**
  - 40% reduction in non HDL cholesterol in mixed hyperlipidemia and non familial hypercholesterolemia.
  - 50% reduction in LDL cholesterol in heterozygous familial hypercholesterolemia.
Check list prior to initiation of PCSK9 Inhibitors:
1. Establish current lipid lowering therapy if any.
2. Check baseline liver function, renal function, lipid profile, creatinine kinase, thyroid function, coagulation screen.
3. Assess patient suitability for self-administration. Establish treatment targets for LDL-Cholesterol to judge value of persisting with treatment after 12 months.
4. Data entry on local PCSK9I database.

Cautions:
1. Age ≤ 18 yrs.
2. Caution in CKD Stage 4 and 5.
3. Patients with severe hepatic impairment (Child Pugh C), cirrhosis- Bilirubin >34 umol/L, Albumin < 35 g/L, INR ≥ 1.7, documentation of ascites/encephalopathy.
4. Allergy or hypersensitivity to any excipients/ active substance.
5. Pregnant and Lactating women.
6. Avoid PCSK9 Inhibitors in patients with history of Hepatitis C viral infection.
7. Avoid evolocumab in patients with latex allergy.

Initiation of PCSK9 Inhibitors:
1. Check allergy history.
2. Patient education, self-administration, storage, travels etc.
3. Explain adverse reactions – injection site reactions- erythema, swelling, redness, itching, pain; upper respiratory tract signs and symptoms, pruritus, urticarial, hypersensitivity reactions, hypersensitivity vasculitis, eczema.
4. Encourage patient to report any new/unusual symptoms- provide contact details.
5. Provide starter kit, get consent and enrol to patient support programme.
6. Biochemistry request cards for follow up liver function, renal function, lipid profile, and creatinine kinase – for 12 week check.
7. Prescribe 2 months’ supply.
8. Drug interactions- unknown, but no CYP 450 interactions anticipated as biological product- but warn patients on warfarin to check INR pre and post.

Follow up plans:
1. Check liver function, renal function, lipid profile, Creatinine kinase- 12 weeks post initiation.
2. Arrange further prescriptions through pharmacy.
3. Check injection technique and side effect profile.
4. Establish if treatment targets achieved for LDL-Cholesterol.
5. Arrange further prescriptions through manufacturers.
6. Follow up with lipid clinic after 3 months and 1 year after initiation of treatment.
7. Increase the dose of Alirocumab to 150 mg s/c fortnightly if 30% reduction in LDL is not achieved in 12 weeks.
8. If LDL reduction target is not achieved or patient develops adverse effects discontinue and switch to the product from different manufacturer i.e alirocumab to evolocumab and viceversa.