Problem patients in primary care
Patient 4: Peripheral artery disease

Dr Terry McCormack
Hambleton Richmond Whitby Clinical Commissioning Group Research Lead
Declaration Of Interests

- Research Grants – Amgen, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, NIHR, Servier
- Advisory Boards and Speaker Fees – Alere, Astellas, AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Lundbeck, MSD, Roche, Sunovian
A Case History – MW – now 55

• Intermittent Claudication aged 39
  – Stops smoking
  – Total cholesterol 11.4 mmol/l = mixed hyperlipidaemia
  – Left and right saphenous-femoral angioplasty

• Family History
  – Father suffered MI age 49, died aged 58 MI
  – Aunt died age 47 MI
  – Grandfather died age 47
  – Brother lost leg to peripheral arterial disease

• TIA age 44

• ACS and coronary artery stent age 48

• Long term depression
A Case History – MW – now 55

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La Place II – FH patients - Evolocumab

**Autoinjector/Pen**
140 mg (1 injections of 1 mL @ 140 mg/mL) Q2W

**Autoinjector/Pen**
420 mg (3 injections of 1 mL @ 140 mg/mL) QM

**OR:**
3.5 mL **Personal Injector** + CZ Cartridge
420 mg (3.5 mL @ 120 mg/mL) QM
## A Case History – MW – now 55

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History

• Nikolai N. Anichkov (1885–1964) links cholesterol and atherosclerosis in 1913

• Scandinavian Simvastatin Survival Study 1993

• Nature Genetics 34, 154 - 156 (2003) ... Marianne Abifadel et al discovers role of PCSK9
Hepatic LDLR Plays a Central Role in Cholesterol Homeostasis

Recycling of LDLR Enables Efficient Clearance of LDL Particles

**PCSK9 Regulates the Recycling of LDLR by Targeting the LDLR for Degradation**

**PCSK9 is a Novel Regulator of Hepatic LDL Receptor Expression**

### Absence of PCSK9

- More LDL-R
- Lower plasma LDL-C

### Presence of PCSK9

- Less LDL-R
- Higher plasma LDL-C

Inhibition of PCSK9 is a compelling new hypercholesterolemia target

- Rashid S et al. PNAS 2005;102:5374-5379
AMG 145 is a **Fully Human** Monoclonal Antibody Against PCSK9 and Blocks PCSK9/LDL-R Interaction

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**Increased LDL-Rs and Lower LDL-C**

**Increased LDL-R Recycling**

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- LDL/HMG CoA
- HDL/CETP
- Triglycerides/tredaptive
- Ezetimibe
- PCSK9
Four PCSK9 Inhibitor Compounds

- AMGEN – Evolocumab 7820
- Pfizer – Bococizumab 3439
- Sanofi/Regeneron - Alirocumab 4892
- Lilly ?
Welcome to this Online FOURIER meeting Dec 12\textsuperscript{th} 2013 2.30-3.00pm

1. If you can see this slide and you are logged in correctly. The meeting will start shortly.
2. If you are unable to hear the presentation, please check that you have \textbf{enabled audio on Lync} and that you have \textbf{turned up the volume in your computer’s settings} both for the computer’s own speaker and specifically for the Lync programme. If still can’t hear via your computer, you can join by phone on 0207 594 1111 conference ID: 674561
FOURIER

• **Further Cardiovascular Outcomes Research** With PCSK9 Inhibition in Subjects With Elevated Risk

• A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When AMG 145 is Used in Combination with Statin Therapy in Patients with Clinically Evident Cardiovascular Disease
Study Design and Treatment Schema

- **Lipid Therapy Titration**: (Titration visits approximately Q2W as needed to optimise lipid-lowering therapy)

  - **Placebo Injection**
  - **Final Screening**
  - **LDL-C ≥ 1.8 mmol/l or Non-HDL-C ≥ 2.6 mmol/l**

- **Randomisation 1:1**

- **AMG 145 SC 140 mg Q2W or 420 mg Q4W (per subject preference)**

  - **Optimal lipid lowering therapy, including an effective dose of atorvastatin, rosuvastatin or simvastatin**
  - ~11,250 Subjects

- **Placebo Q2W or Q4W (per subject preference)**

  - **Optimal lipid lowering therapy, including an effective dose of atorvastatin, rosuvastatin or simvastatin**
  - ~11,250 Subjects

- **Maximum approximately 15 weeks**

- **IP administered Q2W or Q4W**

- **Atorvastatin dispensed: Q12W**

- **Laboratory assessment:**
  - Day 1
  - Week 4
  - Week 12
  - Week 24
  - Q2W

- **Number of key 2^0 EPs achieved**

- **Study will end when 1630 subjects have experienced a key secondary endpoint of cardiovascular death, myocardial infarction or stroke. (3550 primary endpoints expected). End of study estimated to be 40 months after last patient is enrolled.**

HDL-C = high-density lipoprotein-cholesterol; ; QD = once daily; Q2W = every 2 weeks; Q4W = once 4 weeks; Q24W = once every 24 weeks; EP = endpoints; 2^0 = secondary. Data on file, Amgen; [AMG 145 Protocol 20110118 Amendment 4; July 16, 2013].
Identifying Eligible Patients I

Adult aged 40-85

Post-MI §

Post-stroke § (non-haemorrhagic)

Symptomatic PAD
- intermittent claudication (ABI < 0.85)
- peripheral revascularisation,
- or amputation due to atherosclerosis

with one or more of the following major risk factors

Diabetes (type I or II)
Age ≥ 65 (and ≤85)
Daily smoker

- Index episode within 6 mts
- Previous MI or stroke before index episode

Symptomatic PAD (MI/stroke patients)

Lipid stabilisation period

PAD: Peripheral Arterial Disease
§ Limit to proportion of patients with index event > 5 years ago
Identifying Eligible Patients II

Adult aged 40-85

Post-MI §

Post-stroke §
(non-haemorrhagic)

Symptomatic PAD
• intermittent claudication (ABI < 0.85)
• peripheral revascularisation,
• or amputation due to atherosclerosis

with ≥2 of the following minor risk factors:

Metabolic factors
• LDL-C > 3.4 mmol/L or non-HDL-C ≥ 4.1 mmol/L
• HDL-C < 1.0 mmol/L in ♂
  or < 1.3 mmol/L in ♀
• hsCRP > 2.0 mg/dL
• Metabolic syndrome

Coronary factors
• Non-MI related coronary revascularisation
• Residual CAD (≥40% stenosis in 2 or more large vessels)

Lipid stabilisation period

PAD: Peripheral Arterial Disease
§ Limit to proportion of patients with index event > 5 years ago
Evaluating lipid levels: Inclusion Criteria

At Screening:
- Fasting triglycerides ≤ 4.5 mmol/L (400 mg/dL)

After 2 weeks of stable lipid-lowering therapy, subject eligible for inclusion if:
- Fasting LDL-C ≥ 1.8 mmol/L (≥ 70 mg/dL)
  OR
- non-HDL-C ≥ 2.6 mmol/L (≥100 mg/dL)

*per local regulatory approval
• **Atorvastatin, simvastatin** or **rosvastatin** all eligible as background statin therapy.

• Only atorvastatin (20 mg, 40 mg and 80 mg) is provided by Amgen

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<thead>
<tr>
<th>Background Statin</th>
<th>Atorvastatin</th>
<th>Simvastatin</th>
<th>Rosuvastatin</th>
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<tbody>
<tr>
<td><strong>Acceptable Doses</strong></td>
<td>20 mg</td>
<td>40 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>80 mg</td>
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Where locally approved, **highly effective statin therapy** (at least atorvastatin 40mg/day or equivalent) is recommended. As a minimum, all subjects must receive at least an **effective statin dose** (at least atorvastatin 20mg/day or equivalent).

For subjects with LDL-C >2.6 mmol/l not receiving highly effective statin therapy, investigator must attest that higher dose statin therapy is not appropriate for this subject (e.g. subject refused, dose not tolerated, other significant concern)
Any Questions?

The best thing you can do is give up smoking, drinking and fried food.

What's the second best?