HoFH and HeFH
The Role of Lipoprotein Apheresis

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Declaration

• Received research grants from Synageva, Pfizer, Amgen, MSD

• Received personal fee from Aegerion, Amgen, Johnson & Johnson, Lilly, MSD, Pfizer, Sanofi, Synageva.
1. Introduction

2. Current medical therapy

3. Lipoprotein apheresis
   1. HoFH
   2. HeFH
   3. Guidelines and targets
   4. Challenges

4. New Therapies

5. Conclusion
HoFH

• Rare...

• Mutations effect
  – LDL receptor
  – apolipoprotein B
  – Proprotein convertase subtilisin/kexin type 9 (PCSK9) protein
  – LDL adaptor protein (LDLRAP1) (ARH)

• CHD before age of 20 years and often in childhood
Some now survive longer
- with potent statins
- other lipid modifying agents
- extracorporeal removal of LDL and
- heart surgery/intervention

The current standard treatment for adults and children is lipoprotein apheresis combined with maximum doses of rosuvastatin or atorvastatin, ezetimibe and bile acid sequestrants (BAS)
HoFH just double trouble?

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased clearance of LDL-C</td>
<td>but 90% have 2-25% residual receptor function</td>
</tr>
<tr>
<td>Two- to three-fold increase in apoB–LP turnover with increase in apoB–LP assembly and secretion</td>
<td></td>
</tr>
<tr>
<td>increased SRB1-mediated bulk flow of cholesterol</td>
<td></td>
</tr>
<tr>
<td>Increase in cholesteryl ester production</td>
<td></td>
</tr>
<tr>
<td>High LP(a)</td>
<td></td>
</tr>
<tr>
<td>Delayed clearance of apoB 48 containing particles</td>
<td></td>
</tr>
</tbody>
</table>

# HoFH

## just double trouble?

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDL Cholesterol</td>
<td>LXR underactivation which affect production of pre-beta HDL. Reduced ABCA1 and ABCG1 cholesterol egress</td>
</tr>
<tr>
<td>Increased PCSK9 and E3-ubiquitin ligase inducible degrader of the LDL receptor (IDOL)</td>
<td>IDOL acts post-translationally to reduce LDLR recycling</td>
</tr>
<tr>
<td>Biliary free cholesterol is increased</td>
<td>probably via SRBI</td>
</tr>
<tr>
<td>Possible decreased trans-intestinal cholesterol transport</td>
<td></td>
</tr>
</tbody>
</table>

PCSK9 in HoFH and HeFH

PCSK9 levels are elevated in untreated FH patients, particularly in those with HoFH. High-dose statin therapy further increases PCSK9 levels. PCSK9 inhibitors might be a beneficial therapy for FH patients, even in those with HoFH. 

Raal et al. JAHA 2011
LDL receptor activity and prognosis

LDL receptor activity

Goldstein et al 1993

Kalonsky et al. Am J Cardiology 2008

### LDLR Negative (n = 18) vs. LDLR Defective (n = 16)

<table>
<thead>
<tr>
<th></th>
<th>LDLR Negative</th>
<th>LDLR Defective</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at visit 1 (yrs)</td>
<td>11.5 (3.3–29)</td>
<td>28.1 (3.3–44.6)</td>
<td>0.0083</td>
</tr>
<tr>
<td>Age at first xanthomas (yrs)</td>
<td>2.0 (0.25–4)</td>
<td>7.0 (1–15)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age at FH diagnosis (yrs)</td>
<td>3.0 (0.5–7)</td>
<td>8.0 (2–17)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total cholesterol at diagnosis (mg/dl)</td>
<td>903 ± 187</td>
<td>715 ± 124</td>
<td>0.0019</td>
</tr>
<tr>
<td>Age at start of treatment (yrs)</td>
<td>5.0 (1.2–10)</td>
<td>16.0 (2–31)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Age at CAD (yrs)</td>
<td>12.5 (6–16)</td>
<td>22.0 (16–37)</td>
<td>0.0039</td>
</tr>
</tbody>
</table>
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5. Conclusion
Mean (SD) percentage change in low-density lipoprotein (LDL) cholesterol by week and dose of rosvastatin (RSV). Observed data for all patients in the intention-to-treat population are shown in the solid line for weeks 6 ($n = 40$), 12 ($n = 36$), and 18 ($n = 35$), and week 18 last observation carried forward (LOCF) ($n = 40$). Mean (SD) baseline LDL cholesterol was 13.3 (3.0) mmol/L. The data for patients who neither had portacaval shunts nor were receiving plasmapheresis are shown in the dashed line for week 6 ($n = 28$), week 12 ($n = 27$), week 18 ($n = 26$), and week 18 LOCF ($n = 28$). Mean (SD) baseline LDL cholesterol for this group of patients was 14.0 (2.9) mmol/L.

David Marais et al Atherosclerosis 2008
Statin Therapy in HoFH

- 149 patients (81 females, 68 males)
- Lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in patients with homozygous familial hypercholesterolemia.

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Untreated</th>
<th>Taking Lipid-Lowering Therapy</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>17.3±3.8</td>
<td>13.1±3.3*</td>
<td>−24.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28±0.81</td>
<td>1.18±0.63</td>
<td>−7.8</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.89±0.33</td>
<td>0.91±0.25</td>
<td>2.2</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>15.9±3.9</td>
<td>11.7±3.4*</td>
<td>−26.4</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>21.4±10.9</td>
<td>13.5±5.9*</td>
<td>−36.9</td>
</tr>
</tbody>
</table>

• HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Results are expressed as mean±SD. ↩️* P<0.0001.

Cox proportional hazards model with time-varying benefit from statin therapy comparing treated and untreated in patients with homozygous familial hypercholesterolemia, with year of birth fixed as mean year of birth

A) survival

B) first major adverse cardiovascular event (MACE)
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ἀφαίρεσις = to take away

ApoB containing particles
Lipoprotein (a)
Historical development of LDL apheresis

Manual plasmapheresis
• 1964 Myant & Lewis
• 1967 De Gennes et al

Continuous flow plasma exchange
• 1972 Turnberg et al
• 1975 Thompson et al

Selective LDL removal
• 1976 Lupien et al
• 1980 Agishi et al
• 1981 Stoffel et al
Fluctuation of LDL-C levels following a single apheresis procedure.


Remains >4mmol/L even with weekly apheresis.
Treatment of homozygous FH (initial cholesterol 18-20mmol/l)

Patient received plasmapheresis every 2 weeks. At A she commenced atorvastatin 80mg daily and at A+E ezetimibe 10mg daily was added.
Lipoprotein Apheresis – HoFH
Case presentations

Patient 1
- HoFH c.2054C>T mutation
- Diagnosed age 4yrs
  - On treatment age 9 years
- On lipoprotein apheresis since age of 13
- Very compliant with apheresis

- Two successful pregnancies
  - Apheresis increased to weekly
  - C-section
    - Failure to progress
    - Placenta privia
- Age 39 in a good health
- Most recent echo AS
- Coronary angiogram
  - No obstructive lesions

Patient 2
- HoFH c.2054C>T mutation
- Diagnosed age 5yrs
  - On treatment age 10 years
- On lipoprotein apheresis since age of 13
- Poor compliance with apheresis
  - CHD age 17...apheresis
  - CABG age 23

- Two successful pregnancies
  - Apheresis increased to weekly

- Stopped lipoprotein apheresis

- Died age 27, was 4 months pregnant

Unpublished data
In a longer and larger observational study of German patients, followed up for 1–31 years, mortality was 43% among the seven untreated homozygotes compared with 21% in the 14 who were treated with lipoprotein apheresis for ≥1 year.

All of the untreated siblings had died (mean age of death 17.7 years), whereas four of the five siblings treated for 8.4 years with plasma exchange survived, with a mean age of 23.2 years at the time of the report (p = 0.03).

Lipoprotein Apheresis
HoFH

Comparison of pre- and on-treatment serum total cholesterol (TC) in dead and alive HoFH.

What about HeFH?

Thompson GR et al 2015
Reaching LDL-C target in patients with high baseline LDL-C concentrations

Average LDL-C decrease needed depending on baseline levels

<table>
<thead>
<tr>
<th>Baseline LDL-C concentrations</th>
<th>4.9 mmo/l 190 mg/dl</th>
<th>5.7 mmo/l 220 mg/dl</th>
<th>6.5 mmo/l 250 mg/dl</th>
<th>7.2 mmo/l 280 mg/dl</th>
<th>8 mmo/l 310 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>To reach LDL-C &lt; 4.1 mmo/l (&lt;160 mg/dl)</td>
<td>-16%</td>
<td>-27%</td>
<td>-36%</td>
<td>-43%</td>
<td>-48%</td>
</tr>
<tr>
<td>To reach LDL-C &lt; 2.6 mmo/l (&lt;100 mg/dl)</td>
<td>-47%</td>
<td>-55%</td>
<td>-60%</td>
<td>-64%</td>
<td>-68%</td>
</tr>
<tr>
<td>To reach LDL-C &lt; 1.8 mmo/l (&lt;70 mg/dl)*</td>
<td>-63%</td>
<td>-69%</td>
<td>-72%</td>
<td>-75%</td>
<td>-78%</td>
</tr>
</tbody>
</table>

Patients with high LDL-C concentrations at baseline may be categorized as having “severe FH”, regardless of the diagnosis based on DNA analysis (i.e. HoFH or HeFH)

*CPercentage calculated

Lipoprotein Apheresis - HeFH
Frequency of coronary angiographic change (weighted means) in HoFH trials of 2 years duration

Kaplan-Meier curves of coronary events in HeFH

Mabuchi H et al Am J Cardiol 1998
Mean changes in lipid and lipoprotein levels over the 18-month study period, according to treatment group. The p values are given for the comparison between the two treatment groups at 18 months. The vertical bars indicate the standard deviation. HDL-C...
HEART UK indications for LDL apheresis

*(Atherosclerosis 2008;198:247-55)*

• **Homozygous FH** aged > 7 years if TC remains > 9 mmol/l or decreases < 50% on maximal drug therapy

• **Heterozygous FH** with progressive CAD if LDL-C remains > 5 mmol/l or decreases < 40% on maximal drug therapy

• **Patients with Lp(a) > 60 mg/dl with progressive CAD** (if LDL-C is > 3.2 mmol/l) *despite maximal drug therapy*
Target levels (percentage decreases) of total cholesterol (TC), LDL cholesterol (LDL-C) and lipoprotein (a) [Lp(a)] for lipoprotein apheresis

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Lipid Profile</th>
<th>Baseline mmol/L (% decrease)*</th>
<th>Interval mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH</td>
<td>TC</td>
<td>&lt;9 (&gt;50%)</td>
<td>&lt;7 (%60)</td>
</tr>
<tr>
<td></td>
<td>LDL-C</td>
<td>&lt;8.5 (&gt;55%)</td>
<td>&lt;6.5 (%65)</td>
</tr>
<tr>
<td>HeFH</td>
<td>LDL-C</td>
<td></td>
<td>&lt;2.6 (&gt;60)</td>
</tr>
<tr>
<td>High Lp(a)</td>
<td>Lp(a)</td>
<td></td>
<td>&lt;500g/L (50mg/dl)</td>
</tr>
</tbody>
</table>

*Compared with baseline value of all lipid-lowering treatment

Thompson GR, Atherosclerosis 2013.
The Food and Drug Administration (FDA) has approved the use of DSA and HELP apheresis in three categories of patient in the USA:

- **HoFH**, with LDL-C > 13 mmol/l
- **HeFH**, with LDL-C > 7.8 mmol/l
- **HeFH**, with documented CHD and LDL-C > 5.2 mmol/l
Germany

German Federal Committee of Physicians and Health Insurance Funds

The Federal Committee of Physicians and Health Insurance Funds has authorised the use of LDL apheresis in the following categories of patient:

- FH + LDL-C ≥ 4.2 mmol/L (160 mg/dL) + family history
- Secondary prevention: progressive CVD events + LDL-C 3.1 - 3.4 mmol/L (120 - 130 mg/dL)
- Progressive CVD assessed by imaging and Lp(a) > 60 mg/dL

Other indication?
Hypertriglyceridaemic acute pancreatitis?

If serum triglycerides > 10 mmol/l

AND

clinical evidence of acute pancreatitis
Challenges

Availability

A. Knowledge of apheresis in lipid clinics
   i. Access to treatment in UK & geographical variation
   ii. Germany 2 per 100 000
   iii. North America 0.13 per 100 000
   iv. UK 0.06 per 100 000

B. Establishing new patients on treatment

C. Justifying ongoing funding

Walji et al Clin Lip 2013
Challenges

Patients...

Vascular access

1. Native vein
2. AV fistula and shunt
3. Central line

Complications

Progress of atherosclerosis despite lipoprotein apheresis

MORE THERAPEUTIC OPTIONS NEEDED
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Mipomersen crosses the hepatocyte and nuclear membrane to target the mRNA for apoB

Adapted from Figure 1.10 in Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies and Applications*. 2nd edn. 2008:601
Mipomersen: a second-generation ASO that targets apoB-100

• Apo B-100 is a key structural and functional component of all atherogenic lipoproteins produced by the liver
• Blocking Apo B-100 synthesis blocks production of VLDL and LDL
• Mipomersen is a 2nd generation antisense oligonucleotide (ASO) designed to inhibit Apo B protein synthesis

Davis RA. Biochim Biophys Acta 1999;1440:1
### Phase III: efficacy on top of maximally-tolerated lipid-lowering therapies

#### Percentage change from baseline in LDL-C, apoB, Lp(a), TG and HDL-C in patients treated with mipomersen

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Baseline LDL-C (mg/dl)</th>
<th>LDL-C Mean</th>
<th>ApoB Mean</th>
<th>Lp(a) Median</th>
<th>TG Median</th>
<th>HDL-C Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH</td>
<td>439</td>
<td>-25%</td>
<td>-27%</td>
<td>-32%</td>
<td>-18%</td>
<td>19%</td>
</tr>
<tr>
<td>Severe HC</td>
<td>276</td>
<td>-36%</td>
<td>-36%</td>
<td>-39%</td>
<td>-15%</td>
<td>6%</td>
</tr>
<tr>
<td>HeFH with CAD</td>
<td>153</td>
<td>-28%</td>
<td>-26%</td>
<td>-21%</td>
<td>-14%</td>
<td>3%</td>
</tr>
<tr>
<td>HC at high risk for CAD</td>
<td>123</td>
<td>-37%</td>
<td>-38%</td>
<td>-26%</td>
<td>-26%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Raal FJ *et al.* *Lancet* 2010;375:998  
Tardif JC *et al.* *J Am Coll Cardiol* 2011;57:Oral 920-3  
Stein EA *et al.* *Circulation* 2012;126:2283  
Cromwell W *et al.* *J Am Coll Cardiol* 2011;57:Poster 1011-304
TG results in ↑ hepatic fat

↑TG contributes to GI tolerability issues

Liver Cell

Intestinal Epithelial Cell

Apo B100 Degraded

Apo B48 Degraded

Lomitapide Assembly and Release of Apo B Containing Lipoproteins and MTP (microsomal triglyceride transfer protein)

Phase 3 Study Design:
78 week study with 3 time periods: Safety Phase

Patients must have been diagnosed as having functional HoFH defined by at least one of the following criteria:

- Documented functional mutation(s) in both LDL receptor alleles or alleles of other genes known to affect LDL receptor functionality
- Skin fibroblast LDL receptor activity <20% normal
- Untreated TC >500 mg/dL (13mmol/l) and TG <300 (3.8 mmol/l) mg/dL and both parents have documented TC >250 mg/dL (6.5 mmol/l)

From Week 26 to Week 78 (Safety Phase):
- Patients continued on maximum tolerated dose of lomitapide established during the efficacy phase.
- Changes in concomitant LLTs were allowed unless dose alteration rules were met.
- An extension study was available for patients who successfully completed the phase 3 study

Cuchel, M. et al. Lancet 2013; 381: 40-46. (published online: 02 Nov 2012);

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Phase 3 Study Results: Change in LDL-C Through Week 78
(Completer Population, N=23)

Mean % Change from Baseline (95%CI)

Efficacy Phase

Safety Phase

Study Week

Mean Dose (LOCF) (mg):

Effect of lomitapide on apheresis (Cuchel et al, 2012)

• 18 of 29 (62%) homozygotes were on apheresis at the start

• 3 of 18 (17%) were able to discontinue apheresis and 3 others (17%) were able to reduce its frequency

Cost of new therapies?
## TESLA: Patient Genotype and LDLR Activity

<table>
<thead>
<tr>
<th>Patient</th>
<th>MutationAllele 1 (Estimated LDLR Function)</th>
<th>MutationAllele 2 (Estimated LDLR Function)</th>
<th>Overall LDLR Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Asp266Glu (15%-30%)</td>
<td>Asp266Glu (15%-30%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 2</td>
<td>1187-10 G&gt;A† (Not determined)</td>
<td>Asp266Glu (15%-30%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Asp224Asn (&lt;2%)</td>
<td>Cys296Tyr (Not determined)</td>
<td>Negative*</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Deletion Exon 4-18 (Not determined)</td>
<td>Cys197Gly (Not determined)</td>
<td>Negative*</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Asp221Gly (&lt;2%)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 6*</td>
<td>Asp227Glu (5%-15%)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 7*</td>
<td>Asp227Glu (5%-15%)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Asp175Asn (Not determined)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
</tbody>
</table>

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*Confirmed by fibroblast culture  
†Mutation at splice acceptor site 10 nucleotides upstream of the first nucleotide of exon 9, 1187  
*True homozygous patient; patients share the same genotype
**TESLA: LDL-C, Apo B, and Lp(a) Based on LDLR Status**

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>Percentage Change from Baseline, %, Mean (SD)</th>
<th>Defective LDLR (n=6)</th>
<th>Negative LDLR (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 12 Q4W Dosing</td>
<td>Week 12 Q2W Dosing</td>
<td></td>
</tr>
<tr>
<td>UC LDL-C</td>
<td>Apolipoprotein B</td>
<td>Lipoprotein (a)</td>
<td>UC LDL-C</td>
</tr>
<tr>
<td>Defective LDLR</td>
<td>(−19.3) p=0.031†</td>
<td>(−16.0) (13.1)</td>
<td>(−16.0) (11.5) p=0.031†</td>
</tr>
<tr>
<td>Negative LDLR</td>
<td>4.4 (10.3)</td>
<td>1.4 (5.6)</td>
<td>11.0 (23.6)</td>
</tr>
</tbody>
</table>

*Signed-rank test; * Lipoprotein (a) was only collected at week 12 for every-4-week dosing. UC = ultracentrifugation; Q4W = every 4 weeks; Q2W = every 2 weeks; LDLR = low-density lipoprotein receptor

**LDL-C reduction in Rosuvastatin HoFH study:**
Rosuvastatin 80: 19%
Atorvastatin 80: 18%

## TESLA: LDL-C, Apo B, and Lp(a) Based on LDLR Status

<table>
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<tr>
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<td>Week 12 Q2W Dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UC LDL-C</td>
<td>Apolipoprotein B</td>
<td>Lipoprotein (a)</td>
<td>UC LDL-C</td>
</tr>
<tr>
<td>Defective LDLR (n=6)</td>
<td>-22.9 (17.5)</td>
<td>-18.3 (14.9)</td>
<td>-10.0 (11.5)</td>
<td>-23.6 (7.6)</td>
</tr>
<tr>
<td>Negative LDLR (n=2)</td>
<td>2.6 (3.7)</td>
<td>-4.5 (3.5)</td>
<td>-16.8 (8.0)</td>
<td>15.3 (34.7)</td>
</tr>
</tbody>
</table>

|                 | Average of Week 4, 8, and 12 Q4W Dosing | Average of Week 4, 8, and 12 Q2W Dosing |  |  |
|                 | UC LDL-C | Apolipoprotein B | Lipoprotein (a)* | UC LDL-C | Apolipoprotein B | Lipoprotein (a) |
| Defective LDLR (n=6) | -19.3 (15.5) | -18.0 (13.1) | -10.0 (11.5) | -26.3 (20.4) | -22.1 (18.7) | -20.0 (12.1) |
| Negative LDLR (n=2) | 4.4 (10.3) | 1.4 (5.6) | -16.8 (8.0) | 11.0 (23.6) | 2.1 (7.9) | -22.7 (11.2) |

† Signed-rank test; * Lipoprotein (a) was only collected at week 12 for every-4-week dosing.
UC = ultracentrifugation; Q4W = every 4 weeks; Q2W = every 2 weeks; LDLR = low-density lipoprotein receptor
TESLA: PCSK9 Levels By Patient
90% reduction

- Decrease Lp(a) unlikely to be via LDLR
- Decrease production?
  How?
- VLDL receptor?
  What is the impact of PCSK antibodies therapy on VLDL receptor?
  ApoE?
- Other pathways?

An unconnected line indicates a missing value between two time points.
A dashed line indicates time between the two dosing periods of the study.

*Defective LDLR function; †Negative LDLR function
PCSK9 = proprotein convertase subtilisin/kexin 9; LDLR = low-density lipoprotein receptor
SUMMARY

• Lipoprotein apheresis involves the extracorporeal removal of LDL and Lp(a) from the circulation

• No outcome RCT studies but enough evidence to support lipoprotein apheresis

• Aortic stenosis and supravalvular diseases

• New therapies needed in HoFH and severe HeFH

• Evidence-based guidelines and treatment targets for lipoprotein apheresis have been published by HEART UK and other organisations
Questions