PCSK9 inhibition in familial hypercholesterolemia: A revolution in treatment

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A case of severe hypercholesterolemia

Mrs. TDK

50 year old female. Well. Non smoker and no other risk factors for cardiovascular disease. Serum cholesterol measured because of positive family history of coronary artery disease, her father having undergone coronary bypass surgery at age 52. On examination she had arcus cornealis as well as marked thickening of her tendo-Achilles.
Mrs TDK, a case of severe hypercholesterolemia

Fasting lipid profile

Total cholesterol: 15.6 mmol/L
Triglycerides: 1.34 mmol/L
HDL-cholesterol: 1.8 mmol/L
LDL-cholesterol 13.2 mmol/L
## Heterozygous vs Homozygous FH

<table>
<thead>
<tr>
<th>Heterozygous FH</th>
<th>Homozygous FH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>Prevalence 1:300 000 -1000 000</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>LDL-cholesterol</td>
</tr>
<tr>
<td>5.0-12 mmol/L</td>
<td>12-20 mmol/L</td>
</tr>
<tr>
<td>(190-500mg/dL)</td>
<td>(500–1000 mg/dL)</td>
</tr>
<tr>
<td>CHD onset usually age 30-60 yrs</td>
<td>CHD onset in early childhood</td>
</tr>
<tr>
<td>Most patients respond to drug therapy, but individual response quite variable</td>
<td>Poorly responsive to lipid-lowering drug therapy</td>
</tr>
</tbody>
</table>

Nordestgaard B.G. et al. *Eur Heart J* 2013;34:3478-3490
Diagnostic definition of homozygous familial hypercholesterolemia

- Genetic confirmation of 2 mutant alleles at the LDL receptor, APOB, PCSK9, or ARH adaptor protein gene locus

OR

- An untreated LDL cholesterol of 13 mmol/L (>500 mg/dL) or treated LDL cholesterol 7.8 mmol/L (≥300 mg/dL) or treated non-HDL cholesterol 8.5 mmol/L (≥330 mg/dL) together with either:
  - Cutaneous or tendonous xanthoma before age 10 years
    OR
  - Elevated LDL cholesterol levels before lipid-lowering therapy consistent with heterozygous FH in both parents*

* Except in the case of ARH
Phenotypic variability in FH

**LDL cholesterol**

- mmol/L
- mg/dL

**Clinical diagnosis**

- Homozygous FH
- Heterozygous FH
- Common or polygenic hypercholesterolemia

**Mutation diagnosis**

- Homozygous LDL-receptor negative
- Homozygous LDL-receptor defective or homozygous LDLRAP1/ARH
- Homozygous APOB defect/PCSK9 gain of function
- Compound heterozygous LDL-receptor APOB/PCSK9

Adapted from Cuchel M, *Eur Heart J* 2014;35:2146-57
FH

Cholesterol (mmol/L)

Heterozygous FH

Normal

Homozygous

Compound heterozygous FH

Adapted from Cuchel M, *Eur Heart J* 2014;35:2146-57
Therapy for severe FH

- Pharmacotherapy
  - lipid modifying drugs

- Extracorporeal removal of LDL
  - LDL apheresis

- Surgical therapy
  - portacaval shunt
  - partial ileal bypass

- Methods to restore LDL receptor activity
  - liver transplantation
  - gene therapy

Gidding S. The agenda for FH; Circulation 2015;132:2167-2192
Despite the absence of randomised clinical trial in subjects with FH, since their introduction in the late 1980’s statins have become the mainstay of therapy.
Cholesterol Synthesis

Acetyl CoA

HMG CoA

HMG CoA reductase

Mevalonic Acid

STATINS

Dolichols

Farnesyl pyrophosphate

Ubiquinones Heme

Squalene

Cholesterol

Compensatory increase in Synthesis of Hepatic LDL Receptors

High Dose Simvastatin and Atorvastatin in Homozygous FH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>% LDL-C Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>80 mg/d</td>
<td>- 25%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>160 mg/d</td>
<td>- 31%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg/d</td>
<td>- 20%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>80 mg/d</td>
<td>- 33%</td>
</tr>
</tbody>
</table>

Low-density lipoprotein-cholesterol levels in homozygous autosomal dominant hypercholesterolemia patients after LLT

Prior to LLT

After LLT

LDL-C levels (mmol/L)

Two null alleles
One null and one defective allele
Two defective alleles
Mechanisms of action of high dose statins in HoFH

Receptor defective HoFH

- Upregulation of LDL receptors

Receptor negative HoFH

- Reduction in hepatic apo-B lipoprotein synthesis

Mean percentage reduction in LDL-C for patients with HoFH receiving ezetimibe plus statin

**Entire Study Cohort (n=48)**

- **Statin-80:** -7.0%
- **Ezetimibe + Statin 80:** -27.5%

**Genotype Confirmed HoFH (n=35)**

- **Statin-80:** -5.6%
- **Ezetimibe + Statin 80:** -26.6%

Gagne C. Circulation 2002;105:2469-2475
Reduction in LDL-C in FH with combination lipid-lowering therapy

Adapted from Nordestgaard B.G. et al. Eur Heart J 2013;34:3478-3490 and Hovingh G.K et al. Eur Heart J 2013;34, 962–971
Mrs TDK, a case of severe hypercholesterolemia

Treated with Rosuvastatin 40mg daily x 3 months

Lipid profile

- Total cholesterol: 9.4 mmol/L
- Triglycerides: 1.20 mmol/L
- HDL-cholesterol: 1.9 mmol/L
- LDL-cholesterol: 7.0 mmol/L
Mrs TDK, a case of severe hypercholesterolemia

Ezetimibe 10mg daily added

Lipid profile

Total cholesterol: 7.6 mmol/L
Triglycerides: 1.30 mmol/L
HDL-cholesterol: 1.8 mmol/L
LDL-cholesterol: 5.2 mmol/L
Cross-sectional study was conducted in outpatient lipid clinics of 3 Academic Centers and 2 regional hospitals. Patient records of known HeFH patients were retrieved and data were reviewed on the use of lipid-lowering medication, plasma lipids and lipoproteins, safety laboratory results and reasons for not achieving treatment goals.

Pijlman AH, Atherosclerosis 2010;209:189-94
SAFEHEART study: Proportion of FH patients at LDL-C target

**CVD (+) / LDL-C Target <1.8 mmol/L (70 mg/dL)**

**CVD (-) / LDL-C Target <2.6 mmol/L (100mg/dL)**
Current/Emerging therapies for severe FH

- While statins and ezetimibe constitute first-line therapy, they provide less than optimal LDL-C reduction in severe FH
- in particular HoFH requires combination therapy: high-dose statin, ezetimibe, with or without apheresis

**Therapies for severe FH:**

**New therapies**
- Mipomersen (apoB inhibitor)
- Lomitapide (MTP inhibitor)
- PCSK9 inhibitors

**Emerging therapies**
- PPAR delta agonists
- Acetyl CoA carboxylase inhibitor (Gemcabene)
- ACL/AMP kinase modulator (ETC-1002 or Bempedoic acid)
- ANGPTL3 inhibitors
- Others e.g. CETP–inhibitors, probucol
- AAV-8 LDLR gene replacement therapy

Stein EA, Raal FJ. *Curr Cardiol Reports* 2015;17:1-11
PCSK9

(Proprotein convertase subtilisin/kexin type 9)

- PCSK9 is a serine protease that is an extracellular regulator of LDL receptors.

- PCSK9 binds to the EGF-A extracellular domain of the LDLR. After binding and internalisation, PCSK9 directs the LDLR to lysosomal degradation rather than for recycling.

EGF = epidermal growth factor
Catabolism of LDL, the role of PCSK9 and antibody to PCSK9

In 2003 Marianne Abifadel from Lebanon described two gain-of-function mutations in the PCSK9 gene which resulted in a FH phenotype.

First subjects treated with PCSK9 mAb in SAD studies

First MAD phase 1b trials with PCSK9 mAb started including FH, non-FH, statin Rx

Phase 2 trials in-progress published for REGN727 including FH, Q2W/Q4W dosing

Phase 3 trials complete for 2 mAbs, BLA* filed and CVD outcome trials started

Phase 2 trials published for AMG145 including HoFH, Statin intol, Q2W/Q4W

1st publications MAD in FH, nonFH on statin or diet

Early data on CVD benefit

Marketing approval USA/Europe

*BLA – Biologics licensing application; SAD – single ascending dose, MAD – multiple ascending dose
## Pharmaceutical approaches targeting PCSK9

<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Compound</th>
<th>Development stage</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAbs</td>
<td>Highly selective</td>
<td>IV or subcutaneous admin.</td>
<td><strong>Alirocumab</strong>/ REGN7272/ SAR236553</td>
<td>FDA approved July 24, 2015</td>
<td>Sanofi/Regeneron</td>
</tr>
<tr>
<td></td>
<td>Less dosing frequencies</td>
<td>High cost</td>
<td><strong>Evolocumab</strong>/ AMG145</td>
<td>FDA approved Aug 27, 2015</td>
<td>Amgen</td>
</tr>
<tr>
<td></td>
<td>No serious adverse reactions</td>
<td>Short shelf life</td>
<td><strong>Bococizumab</strong>/ RN-316/ PFO4950615</td>
<td>Development stopped in Nov 2016</td>
<td>Pfizer/Genentech</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SAR236553</strong></td>
<td>Phase II</td>
<td>Genentech/Roche</td>
</tr>
<tr>
<td>Mimetic peptides</td>
<td>Highly selective</td>
<td>Injection administration</td>
<td><strong>SX-PCK9</strong>/ EGF-A peptide</td>
<td>Preclinical</td>
<td>Serometrix</td>
</tr>
<tr>
<td></td>
<td>Easier production than mAbs</td>
<td></td>
<td></td>
<td>Preclinical</td>
<td>Merck &amp; Co</td>
</tr>
<tr>
<td>Adnectin</td>
<td>Selective</td>
<td>Short half-life</td>
<td><strong>BMS-962476</strong></td>
<td>Phase I completed</td>
<td>BMS-Adnexus</td>
</tr>
<tr>
<td></td>
<td>Easier &amp; less costly production than mAbs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>siRNA</td>
<td>Highly selective</td>
<td>IV or subcutaneous administration</td>
<td><strong>Inclisiran</strong>/ ALN-PCS (IV)</td>
<td>Phase I completed</td>
<td>Medicines Company</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>ALN-PCSsc (sub)</strong></td>
<td>Phase II, III recruiting</td>
<td>Alnylam Pharmaceuticals;</td>
</tr>
<tr>
<td>Small molecules</td>
<td>Oral administration</td>
<td>Less selective</td>
<td><strong>SBC-1 &amp; SBC-1</strong></td>
<td>Preclinical completed</td>
<td>Shifa Biomedical Corp</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Greater likelihood of side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDL

Endocytosis

Recycling of LDL-R

LDL receptor

mAb

LDL

LDL-R synthesis

Clathrin-coated vesicle

Endoplasmic reticulum

Nucleus

SREBP

Hepatocyte

Lysosome

Golgi apparatus

PCSK9 processing/export

siRNA or ASO

Mean percent change from baseline in LDL-C values among healthy volunteers in single-dose studies

Subcutaneous administration of Alirocumab

Subcutaneous administration of Alirocumab
INHIBITION OF PCSK9 in FH

1. How effective is PCSK9-inhibitor therapy in FH?

1. In patients with HoFH with either no (<2%) or little (2-25%) LDL-receptor activity will PCSK9 inhibition be effective?
With each doubling of statin dose only results in a further 6% reduction in cholesterol.
Statin therapy and upregulation of PCSK9

SREBP2 = Sterol regulatory element-binding protein -2

Serum PCSK9 levels in subjects with heterozygous and homozygous familial hypercholesterolemia

Raal FJ. J Am Heart Assoc 2013;2:e000028
**RCTs (Phase III trials) with PCSK9 inhibitors published or presented**

<table>
<thead>
<tr>
<th>RCT</th>
<th>Study Design</th>
<th>Net LDL-C reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESCARTES</td>
<td>Long-term efficacy &amp; safety</td>
<td>-49 to -62</td>
</tr>
<tr>
<td>LAPLACE-2</td>
<td>Combination therapy with statins</td>
<td>-63 to -75</td>
</tr>
<tr>
<td>GAUSS-2</td>
<td>Statin intolerance</td>
<td>-37 to -39</td>
</tr>
<tr>
<td>MENDEL-2</td>
<td>Monotherapy</td>
<td>-39 to -40</td>
</tr>
<tr>
<td>RUTHERFORD 2</td>
<td>Heterozygous FH</td>
<td>-60 to -66</td>
</tr>
<tr>
<td>TESLA/TAUSSIG</td>
<td>Homozygous FH</td>
<td>-31</td>
</tr>
<tr>
<td>ODYSSEY MONO</td>
<td>Comparison with ezetimibe in pts with hypercholesterolemia at mod CV risk</td>
<td>-32</td>
</tr>
<tr>
<td>ODYSSEY COMBO II</td>
<td>Comparison with ezetimibe</td>
<td>-30</td>
</tr>
<tr>
<td>ODYSSEY FH I and II</td>
<td>Heterozygous FH</td>
<td>-51 to -58</td>
</tr>
<tr>
<td>ODYSSEY long-term</td>
<td>Combination with statins</td>
<td>-62</td>
</tr>
<tr>
<td>ODYSSEY ALTERNATIVE</td>
<td>Statin intolerance</td>
<td>-30</td>
</tr>
<tr>
<td>ODYSSEY High FH</td>
<td>Severe heterozygous FH</td>
<td>-39</td>
</tr>
<tr>
<td>ODYSSEY COMBO I</td>
<td>On top of maximally tolerated statins ± other lipid-lowering drugs in high risk patients</td>
<td>-24 to -49</td>
</tr>
<tr>
<td>ODYSSEY OPTIONS I and II</td>
<td>Comparison of different strategies to further reduce LDL-C in high-risk pts. not a goal</td>
<td>-20 to -37</td>
</tr>
</tbody>
</table>
**ODYSSEY FH I and FH II Studies**

HeFH patients on maximally tolerated statin with or without other LLT

LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) (history of CVD) or
≥ 2.6 mmol/L (≥100 mg/dL) (no history of CVD)

Assessments

- W0
- W4
- W8
- W12
- W16
- W24
- W36
- W52
- W64
- W78

**Double-Blind Treatment Period (78 Weeks)**

- Alirocumab 75 mg Q2W SC with potential ↑ to 150 mg Q2W SC
  (single 1-mL injection using prefilled pen for self-administration)

- Per-protocol dose ↑ possible based on prespecified LDL-C level

- N=323 (FH I); N=167 (FH II)
- N=153 (FH I); n=72 (FH II)

**Placebo Q2W SC**

- OLE/8 week FU

**Primary efficacy endpoint**

- Dose ↑ if LDL-C > 1.8 mmol/L (>70 mg/dL) at W8

**Pre-specified analysis**

- Pre-specified analysis: Efficacy: All patients to W52
- Safety: Baseline-W78 (at least W52)

OLE=Open Label Extension
FU=Follow-up

FH I and FH II - Results over 52 Weeks

Achieved LDL-C over time on background of maximally tolerated statin with or without other LLT

LDL-C, LS mean (SE), mmol/L

Time (weeks)

Dose ↑ if LDL-C > 1.8 mmol/L at W8

Placebo FH I

Placebo FH II

Alirocumab FH I

Alirocumab FH II

Kastelein JP et al. Eur Heart J 2015;36:2996-3003
The Rutherford-2 Study

Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder

**Design:**
A 12-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study

**Objective:**
To evaluate the efficacy and safety of evolocumab (AMG 145) 140 mg Q2W and 420 mg QM administered subcutaneously in a large cohort of HeFH patients unable to achieve an LDL-C < 2.6 mmol/L despite statin therapy with or without ezetimibe

Study design

Screening Period with Placebo Injection

Randomization

Evolocumab 140 mg SC Q2W
N = 111\(^a\)

Evolocumab 420 mg SC QM
N = 110

Placebo SC Q2W
N = 55\(^a\)

Placebo SC QM
N = 55

End of Study

Max. 6 weeks

Day 1
Week 2
Week 4\(^b\)
Week 6\(^b\)
Week 8
Week 10
Week 12
Week 14\(^c\)

\(^a\) N’s are number of patients randomized. One patient in each of the placebo Q2W and evolocumab Q2W groups did not receive any doses of the study drug and were not included in the analyses

\(^b\) Injections at weeks 4 and 6 were done at home

\(^c\) Week 14 was a follow-up call for Q2W patients to capture adverse events and concomitant medications

Mean percentage change from baseline in LDL cholesterol in the four groups.

Mean LDL-C baseline = 4 mmol/L

Placebo monthly (n=55)
Placebo every 2 weeks (n=54)
140 mg evolocumab every 2 weeks (n=110)
420 mg evolocumab monthly (n=110)

Evolocumab every 2 wks
Evolocumab monthly

Rutherford-2

B

Percent changes from baseline in LDL-C

Baseline  Week 2  Week 4  Week 6  Week 8  Week 10  Week 12

- Negative  - Defective  - Unclassified  - No mutation identified

The TESLA Part B Study

- **Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities Part B**
- **Design**
  A 12-week randomized, double-blind, placebo-controlled multicenter phase 3 study
- **Objective**
  To evaluate the efficacy and safety of evolocumab in patients with HoFH

Study design

Study drug administration

*Randomization stratified by screening LDL-C (<10.9 mmol/L or ≥10.9 mmol/L).
†Week 2 and week 10 study visits were optional.

Primary endpoint: Percent change from baseline in Ultracentrifugation LDL-C at week 12

Percent change in UC LDL-C from baseline to week 12

Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values.

Baseline
Week 4
Week 6
Week 8
Week 12

Study drug administration

Study Week

Placebo (N = 16)
Evolocumab 420 mg QM (N = 33)

Absolute difference = 2.5 mmol/l (100mg/dL)

### LDL-C lowering by type of mutation

**Percent Change from Baseline in UC LDL-C at Week 12, Mean (SE)**

<table>
<thead>
<tr>
<th>Mutation status</th>
<th>N</th>
<th>Placebo</th>
<th>Evolocumab 420 mg QM</th>
<th>Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>49</td>
<td>7.9 (5.3)</td>
<td>-23.1</td>
<td>-30.9 (6.4)*</td>
</tr>
<tr>
<td>LDLR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective/any†</td>
<td>28</td>
<td>11.2 (5.1)</td>
<td>-29.6 (3.4)</td>
<td>-40.8 (6.1)†</td>
</tr>
<tr>
<td>Defective/defective</td>
<td>13</td>
<td>15.1 (7.3)</td>
<td>-31.8 (5.8)</td>
<td>-46.9 (9.4)‡</td>
</tr>
<tr>
<td>Negative/Defective</td>
<td>9</td>
<td>3.5 (5.8)</td>
<td>-21.0 (4.0)</td>
<td>-24.5 (7.0)#</td>
</tr>
<tr>
<td>Unclassified</td>
<td>22</td>
<td>3.8 (11.7)</td>
<td>-17.9 (8.8)</td>
<td>21.7 (13.9)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td></td>
<td>7.2 (0.0, 9.9)</td>
<td>-39.2 (-48.8, -14.6)</td>
<td>-</td>
</tr>
<tr>
<td>Negative/negative</td>
<td>1</td>
<td>-</td>
<td>10.3</td>
<td>-</td>
</tr>
<tr>
<td>LDLR heterozygous</td>
<td>1</td>
<td>-</td>
<td>-55.7</td>
<td>-</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>2</td>
<td>10.8, 13.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>ARH</td>
<td>1</td>
<td>-</td>
<td>3.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are least squares (LS) mean for groups with sufficient data; otherwise actual value at week 12. LS mean is from the repeated measures model, which includes treatment group, screening LDL, scheduled visit and the interaction of treatment with scheduled visit as covariates. *Adjusted P-value < 0.001; †Receptor defective in at least one of two affected alleles. ‡Nominal P-value < 0.001; #Nominal P-value = 0.013; ‖Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group).
## TESLA: Safety and Tolerability

<table>
<thead>
<tr>
<th>Adverse events (AE), n (%)</th>
<th>Placebo QM</th>
<th>Evolocumab 420 mg QM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 16</td>
<td>N = 33</td>
</tr>
<tr>
<td>Treatment emergent AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious or leading to discontinuation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Common treatment emergent AEs*</td>
<td>10 (63)</td>
<td>12 (36)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (6)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle-related SMQ</td>
<td>1 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Potential injection site reactions†</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal laboratory tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK &gt;5 x ULN</td>
<td>1 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>ALT or AST &gt;3 x ULN</td>
<td>1 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Anti-evolocumab antibodies‡</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reported in >1 patient in one or both arms. †Searched using high-level term grouping, which includes injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria. ‡Excludes 1 patient with positive binding antibody test at BL. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; QM, monthly; SMQ, Standard MedDRA Queries; ULN, upper limit of normal.
TAUSSIG Study: LDL-C change between baseline and 48 weeks

Mean change in LDL cholesterol (%)

Study week

Baseline 4 8 12 16 20 24 36 48

All patients (n=106)
No apheresis (n=72)
Apheresis (n=34)

Raal FJ et al. Lancet Diabetes Endocrinol 2017;5:280-290
TAUSSIG Study: LDL-C change between baseline to week 12, by underlying genetic abnormality

- LDLR unclassified (-25%)
- LDLR defective (-20%)
- LDLR neg/neg (5%)
- PCSK9 GoF/LDR Negative (-65%)
- ARH (-15%)
- Apolipoprotein B (-47%)
<table>
<thead>
<tr>
<th></th>
<th>After ≥12 weeks of 420 mg evolocumab every month</th>
<th>After 12 weeks of 420 mg evolocumab every 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value at baseline, mmol/L</td>
<td>9.35 (3.35)</td>
<td>9.35 (3.35)</td>
</tr>
<tr>
<td>Change from baseline, mmol/L</td>
<td>-1.77 (2.05)</td>
<td>-2.57 (2.14)</td>
</tr>
<tr>
<td>Percentage change from baseline</td>
<td>-20.1% (21.7)</td>
<td>-27.3% (21.1)</td>
</tr>
</tbody>
</table>
## TAUSSIG: Safety and Tolerability

<table>
<thead>
<tr>
<th>Adverse events (AE), n (%)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 106</td>
</tr>
<tr>
<td>Treatment emergent AEs</td>
<td>82 (77%)</td>
</tr>
<tr>
<td>Serious or leading to discontinuation</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
<tr>
<td>Common treatment emergent AEs*</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Muscle-related AEs</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Potential injection site reactions†</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Abnormal laboratory tests</td>
<td></td>
</tr>
<tr>
<td>CK &gt;5 x ULN</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>ALT or AST &gt;3 x ULN</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Anti-evolocumab neutralising antibodies</td>
<td>0</td>
</tr>
</tbody>
</table>
Mrs TDK - A case of severe hypercholesterolaemia

Addition of Evolocumab 140 mg Q2W subcutaneously

**Lipid profile**

- Total cholesterol: 4.2 mmol/L
- Triglycerides: 1.21 mmol/L
- HDL-cholesterol: 1.9 mmol/L
- LDL-cholesterol: 1.8 mmol/L
Cumulative LDL-Cholesterol lowering effects of statin, ezetimibe and a PCSK9-inhibitor

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13.2</td>
</tr>
<tr>
<td>Statin</td>
<td>7.0</td>
</tr>
<tr>
<td>Plus Ezetimibe</td>
<td>5.2</td>
</tr>
<tr>
<td>Plus PCSK9-inhibitor</td>
<td>1.8</td>
</tr>
</tbody>
</table>

- Statin: 47% reduction
- Plus Ezetimibe: 26% additional reduction
- Plus PCSK9-inhibitor: 65% additional reduction
Index case:

Dutch

CABG age 52
Died age 90

Dutch

Died age 74
Alzheimer’s disease

TC 15.6 mmol/L
LDL 13.2 mmol/L
Age 50

TC 16.0 mmol/L
Died aged 62
MI

TC 8.0 mmol/L
Age 45

14
TC 6.4 mmol/L
LDL 4.6 mmol/L

17
TC 5.6 mmol/L
LDL 4.0 mmol/L

11
TC 6.4 mmol/L
LDL 4.6 mmol/L

= C.1690A>C (N564H)
2458 - 2466 del

Dutch

Died age 90

Dutch

Died age 74
Alzheimer’s disease

Index case:
FH

Age 50

TC 15.6 mmol/L
LDL 13.2 mmol/L

Died aged 62
MI

TC 16.0 mmol/L

Age 45

TC 8.0 mmol/L

14
TC 6.4 mmol/L
LDL 4.6 mmol/L

17
TC 5.6 mmol/L
LDL 4.0 mmol/L

11
TC 6.4 mmol/L
LDL 4.6 mmol/L

Dutch

CABG age 52
Died age 90

Died age 74
Alzheimer’s disease

Dutch

FH Amsterdam

= C.917C>T (S306L)
FH Amsterdam
FH Amsterdam

FH
Age 50
CABG age 52
Died age 62
MI

FH
Died age 74
Alzheimer’s disease

FH
Age 50
TC 15.6 mmol/L
LDL 13.2 mmol/L

TC 16.0 mmol/L
Died aged 62
MI

TC 8.0 mmol/L

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11
TC 6.4 mmol/L
LDL 4.6 mmol/L

= C.1690A>C (N564H)
2458 - 2466 del

= C.917C>T (S306L)
FH Amsterdam
LDL levels in FH

From a lethal disorder to a manageable dyslipidaemia

Adapted from Kastelein JJP. Nat Rev Cardiol. 2014;11:629-631
Initiation of high-intensity statin monotherapy is standard of care

Ezetimibe is added when patient is not at LDL-C threshold

Bile acid sequestrants, ? fibrates and niacin are added alone or in combination for those not at LDL threshold

Add a PCSK9 inhibitor

Apheresis for patients on maximally tolerated therapy and LDL-C > 7.8 mmol/L or CAD and LDL-C > 5.2 mmol/L. Mipomersen and lomitapide for HoFH

Severe FH patients

Statin

Cholesterol absorption inhibitor

? Fibrate

Bile acid sequestrant

? Niacin

PCSK9 inhibitor

Apheresis

Mipomersen

Lomitapide

A CURE FOR FH?

WITH THE ARRIVAL OF NOVEL DRUGS; GENE THERAPY ETC, WE HOPE SO
FH exposes people to very high cholesterol from birth, thus reaching a threshold for CHD earlier in life.

Cumulative exposure (cholesterol yrs) by age: FH vs unaffected (healthy) individuals

CHD = Coronary heart disease

Adapted from Horton et al. J Lipid Res. 2009;50:S172-S177
LDL cholesterol burden


Age (years)

Cumulative LDL-C (mmol)

Homozygous FH

Heterozygous FH

Without FH

Start high dose statin

Start low dose statin

Threshold for CHD

12.5 years

15 years

28 years

48 years

53 years

Female sex

Smoking

Hypertension

Diabetes

↑ Triglycerides

↓ HDL-C

↑ Lipoprotein(a)
The Role of PCSK9 Inhibitors

- Inhibition of PCSK9 with fully human mAbs is a very promising, and very effective, approach to reducing LDL cholesterol further in:
  - Severe heterozygous FH or non-FH patients who have not responded adequately to statin +/- ezetimibe therapy alone
  - The 70-95% of HoFH patients with defective LDLR activity
  - Patients with progressive coronary artery disease despite high dose statin +/- ezetimibe therapy
  - Patients unable to tolerate statins or effective doses of statins
    - “statin intolerance”

Adapted from Stein EA, Raal FJ. *Endocrinol Metab Clin N Am* 2014;43:1007-33