Treatment of severe Familial Hypercholesterolemia
PCSK9 inhibitors

2nd Severe FH Course: Recognize, Diagnose and Treat Severe Familial Hypercholesterolemia
December 2-3, 2018
Muscat, Oman

Dr. Khalid Al-Waili, MD, FRCPC, DABCL
Senior Consultant Medical Biochemist & Lipidologist
Sultan Qaboos University Hospital
Disclosures

• Received honorariums for giving lectures for AstraZeneca and Pfizer.

• Attended conferences sponsored by Sanofi Amgen, Pfizer and Abbott.
Background

- Cardiovascular Disease (CVD) remains the biggest killer worldwide.

- Reducing levels of low-density lipoprotein (LDL) cholesterol is a cornerstone of the prevention of CVD.

- Despite the proven efficacy of statins in lowering CV events, many patients fail to reach recommended LDL-C goals.
Putting Into Perspective the Hazards of Untreated Familial Hypercholesterolemia

Figure. Cumulative probability of developing coronary artery disease (CAD) in men (left) and women (right) with heterozygous familial hypercholesterolemia (FH) as compared with unaffected relatives or the general population (non-FH). Relative risk (Rel Risk), as the ratio of cumulative CAD risk in FH divided by non-FH, is shown below each curve.

Paul N. Hopkins, J Am Heart Assoc. 2017;6:e006553
Are Statins Enough?

- Statins are effective, potent, inexpensive and generally well tolerated

- Residual Risk
Achieving LDL-c target with Statins

Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia

5-Year SAFEHEART Registry Follow-Up

Leopoldo Perez de Isla, MD, Rodrigo Alonso, MD, Gerald F. Watts, MD, Nelva Mata, MD, Adriana Saltijeral Cerezo, MD, Ovidio Muñiz, MD, Francisco Fuentes, MD, José Luís Díaz-Díaz, MD, Raimundo de Andrés, MD, Daniel Zambón, MD, Patricia Rubio-Marin, MD, Miguel A. Barba-Romero, MD, Pedro Saenz, MD, Juan F. Sanchez Muñoz-Torrero, MD, Ceferino Martinez-Faedo, MD, José P. Miramontes-Gonzalez, MD, Lina Badimón, MD, Pedro Mata, MD, for the SAFEHEART Investigators
Although plasma low-density lipoprotein cholesterol (LDL-C) concentration decreased at follow-up, LDL-C goals, as defined by recent international recommendations on familial hypercholesterolemia (FH), were reached in <10% of cases. Nevertheless, there was an increase in the percentage of subjects who reached recommended goals at follow-up compared with at study entry, whether the patient had a history of atherosclerotic cardiovascular disease (CVD [+] or had no such history (CVD [-]).
Despite a high percentage receiving maximal lipid-lowering therapy, most familial hypercholesterolemia (FH) patients still have high low-density lipoprotein cholesterol (LDL-C) levels and did not achieve the recommended LDL-C target for patients (A) with or (B) without cardiovascular disease (CVD). There is a clinical need for new lipid-lowering treatments in combination with current therapy to reach lower LDL-C levels in an effort to prevent the development of premature atherosclerotic cardiovascular disease.
• Proprotein convertase subtilisin/kexin type 9 (PCSK9)

• the 9th member of the proprotein convertase family of proteins that activate other proteins

• involved in the degradation of low-density lipoprotein (LDL) receptors in the liver.
The Role of PCSK9 in the Regulation of LDL Receptor Expression

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Marianne Abifadel1,2, Mathilde Verrel1, Jean-Pierre Babic1,3, Delphine Allard1, Khadija Ouquerna1, Martine Dreffler1, Corinne Grasuad1, Susanne Benjamin6, Louise Winkham6, Danièle Edlich1, Aurélie Decro1, Ludovic Villéger1, Michel Farnier7, Isabelle Benedet5, Éric Broderet1, Jean Chambaz6, Bernard Charn1,11, Jean-Michel Locard5, Gerald Loch3, Philippe Mias10, Jean Veisenbach9, Annick Prat6, Michel Kremp6, Claudine Junier1,2, Nabil G. Seidah5 & Catherine Boileau1,2

PCSK9 GOF alleles: increased LDL levels

2003
1. PCSK9 **GOF** alleles: increased LDL levels  
2. PCSK9 **LOF** alleles: decreased LDL levels
PCSK9, LDL levels and coronary heart disease

1. PCSK9 GOF alleles: increased LDL levels 2003
2. PCSK9 LOF alleles: decreased LDL levels 2005-2006
3. PCSK9 LOF alleles: protect against CHD 2006

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**BRIEF COMMUNICATIONS**

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

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**LETTERS**

Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9

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**ORIGINAL ARTICLE**

Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

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![Image of graphs showing LDL cholesterol levels and frequency of PCSK9 alleles.](image-url)
PCSK9, LDL levels and coronary heart disease

1. PCSK9 **GOF** alleles: increased LDL levels 2003
2. PCSK9 **LOF** alleles: decreased LDL levels 2005-2006
3. PCSK9 **LOF** alleles: protect against CHD 2006
4. PCSK9 **LOF** alleles: no obvious adverse events 2006

A Spectrum of PCSK9 Alleles Contributes to Plasma Levels of Low-Density Lipoprotein Cholesterol

Ingrid K. Kotowski,1,4,5 Alexander Pertseridou,1,3 Amy Luke,1 Richard S. Cooper,2 Gloria L. Vega,1,2 Jonathan C. Cohen,1,2,3,4,5 and Helen H. Hobbs1,2,3,4

The American Journal of Human Genetics Volume 78 March 2006

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noncarriers</th>
<th>Carriers of PCSK9null</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation status — no. of subjects (%)</td>
<td>9223 (96.8)</td>
<td>301 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>54±6</td>
<td>54±6</td>
<td>0.56</td>
</tr>
<tr>
<td>Male sex — %</td>
<td>45</td>
<td>46</td>
<td>0.84</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.9±4.9</td>
<td>26.8±4.5</td>
<td>0.51</td>
</tr>
<tr>
<td>Total cholesterol — mg/dl</td>
<td>214±40</td>
<td>194±37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides — mg/dl</td>
<td>133±87</td>
<td>135±80</td>
<td>0.79</td>
</tr>
<tr>
<td>LDL cholesterol — mg/dl</td>
<td>117±37</td>
<td>116±33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol — mg/dl</td>
<td>51±17</td>
<td>52±17</td>
<td>0.64</td>
</tr>
<tr>
<td>Hypertension — %</td>
<td>25.0</td>
<td>24.6</td>
<td>0.87</td>
</tr>
<tr>
<td>Diabetes — %</td>
<td>8.0</td>
<td>7.3</td>
<td>0.68</td>
</tr>
<tr>
<td>Smoking — %</td>
<td>24.6</td>
<td>25.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Carotid-artery intima-media thickness — mm</td>
<td>0.73±0.18</td>
<td>0.71±0.16</td>
<td>0.005</td>
</tr>
<tr>
<td>Coronary heart disease — no. of subjects</td>
<td>1089</td>
<td>19</td>
<td>0.003</td>
</tr>
<tr>
<td>Stroke — no. of subjects (%)</td>
<td>267 (2.9)</td>
<td>9 (0.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Death — no. of subjects (%)</td>
<td>988 (10.7)</td>
<td>25 (8.3)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 2. The R466L-Encoding Allele of PCSK9 and Cardiovascular Risk Factors among 9524 White Subjects in the Study.
PCSK9, LDL levels and coronary heart disease

1. PCSK9 \text{GOF} alleles: increased LDL levels  
   \text{2003}

2. PCSK9 \text{LOF} alleles: decreased LDL levels  
   \text{2005-2006}

3. PCSK9 \text{LOF} alleles: protect against CHD  
   \text{2006}

4. PCSK9 \text{LOF} alleles: no obvious adverse events\text{2006}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{LDL levels vs. Risk of CHD}
\end{figure}
PCSK9, LDL levels and coronary heart disease

1. PCSK9 GOF alleles: increased LDL levels 2003
2. PCSK9 LOF alleles: decreased LDL levels 2005-2006
3. PCSK9 LOF alleles: protect against CHD 2006
4. PCSK9 LOF alleles: no obvious adverse events 2006
5. Clinical trials: monoclonal antibody to PCSK9 2012

Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial

Evan A. Stein, Don Gips, Jean Bergeron, Daniel Gaudet, Robert Woloz, Richard Dufour, Richard Wu, Robert Fardy

The New England Journal of Medicine

ORIGINAL ARTICLE

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

Evan A. Stein, M.D., Ph.D., Scott Melliis, M.D., Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Stahl, Ph.D., Douglas Logan, M.D., William B. Smith, M.D., Eleanor Lisbon, M.D., M.P.H., Maria Gutierrez, M.D., Cheryle Webb, M.D., Richard Wu, Ph.D., Yunling Du, Ph.D., Therese Kranz, R.N., M.B.A., Evelyn Gasparino, B.S., and Gary D. Swerdelg, M.D., Ph.D.
Impact of a PCSK9 mAb on LDL Receptor Expression

## Impact of Statin Therapy on PCSK9 Levels

<table>
<thead>
<tr>
<th>Statin</th>
<th>PCSK9 Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 80 mg (1)</td>
<td>+47%</td>
</tr>
<tr>
<td>Atorvastatin 40 mg (2)</td>
<td>+34%</td>
</tr>
<tr>
<td>Rosuvastatin 20 mg (3)</td>
<td>+28% (men)</td>
</tr>
<tr>
<td></td>
<td>+35% (women)</td>
</tr>
<tr>
<td>Controls (4)</td>
<td>+45%</td>
</tr>
<tr>
<td>Statin therapy</td>
<td></td>
</tr>
<tr>
<td>Stain-ezetimibe therapy</td>
<td>+77%</td>
</tr>
<tr>
<td>Titration of atorva 5 to 80 mg/d</td>
<td>+30%</td>
</tr>
<tr>
<td>Titration of rosvuva 5 to 40 mg/d</td>
<td>+37%</td>
</tr>
</tbody>
</table>

1. Welder et al. J Lipid Res 2010; 51: 2714-2721
4. Dubuc et al. J Lipid Res 2010; 51: 140-149
Statins Also Upregulate the Expression of PCSK9

SREBP2 = sterol regulatory element-binding protein 2
PCSK9 inhibition with mAbs in clinical trials reduces LDLC by 60% on top of standard therapy.
>70% decrease in LDL-C and 90-100% of patients reach predefined levels with 150 mg Q2W + 80 mg atorvastatin.

SAR236553 + atorva 80 mg resulted in 73% reduction in mean LDL-C vs 17% for atorva 80 mg only.
SAR236553 + stable dose of atorva 10 mg resulted in 66% LDL-C reduction.
SAR236553 was generally well tolerated.

- p<0.0001 vs Placebo + A80

**% of LDL-C change**
- Placebo + Atorvastatin 80 mg
- SAR236553 150 mg Q2W + atorvastatin 10 mg (N=29)
- SAR236553 150 mg Q2W + atorvastatin 80 mg (N=30)

**% of patients at predefined LDL-C target**
- Placebo + A80
- SAR236553 + A10
- SAR236553 + A80
Most heFH Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

Proportion of patients reaching LDL-C goal† at Week 24

FH I  FH II

<table>
<thead>
<tr>
<th>% patients</th>
<th>Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH I</td>
<td>72.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>FH II</td>
<td>81.4%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

P < 0.0001

†Very high-risk: <1.81 mmol/L (70 mg/dL); high-risk: <2.59 mmol/L (100 mg/dL). LLT = lipid-lowering therapy.

Intent-to-treat (ITT) Analysis
Most of These High CV-Risk Patients Receiving Alirocumab on Background Statin Achieved LDL-C Goal

Proportion of Patients Reaching LDL-C $<1.8$ mmol/L (70 mg/dL) at Week 24
All patients on background of maximally-tolerated statin

- Alirocumab: 77.0%
- Ezetimibe: 45.6%

P < 0.0001

Intent-to-treat (ITT) analysis
Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia Undergoing Lipoprotein Apheresis: the ODYSSEY ESCAPE Trial


†Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA; Medical Department II – Grosshadern, University of Munich, Munich, Germany; Metabolic Leader, LLC, Scarborough, MA, USA; Division of Endocrinology, Metabolism, and Diabetes, Anschutz Health and Wellness Centre, Anschutz Medical Campus, Aurora, CO, USA; Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA; Extracorporeal Treatment and Lipoprotein Apheresis Center, Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Apherese Zentrum Passau, Passau, Germany; Apheresis Center Rostock, Rostock, Germany; Apheresis Centre, Nehologisches Zentrum Göttingen GbR, Göttingen, Germany; Mayo Clinic, Rochester, MN, USA; Charité, Universitätsmedizin Berlin-Campus Virchow-Klinikum, Berlin, Germany; Cardiology, Hartford Hospital, Hartford, CT, USA; Medizinische Klinik und Poliklinik IV, LMU Klinikum der Universität München, Munich, Germany; Medical Department, Sanofi-Aventis Deutschland GmbH, Berlin, Germany; Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

†These joint authors contributed equally to this manuscript

Pre-apheresis LDL-C Over Time

Apheresis rate varied from Week 7 onwards

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab 150 mg Q2W (n=41)</th>
<th>Placebo (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>-53.7 (2.3)</td>
<td>1.6 (3.1)</td>
</tr>
<tr>
<td>Week 18</td>
<td>-42.5 (4.7)</td>
<td>3.9 (6.3)</td>
</tr>
</tbody>
</table>

LDL-C % change from baseline, LS mean (SE), %:

Raw mean values are provided for baseline. SE, standard error.

Time-Averaged Cholesterol Concentrations†
(Kroon Formula†)

Time-averaged concentrations are widely regarded to provide the best estimate of the physiologically effective plasma cholesterol concentrations during long-term treatment with lipoprotein apheresis. Data labels are expressed in both measurements.


Standardized Apheresis Treatment Rates from Week 7–18

An apheresis rate of 0 indicates that the patient skipped all planned aphereses and an apheresis rate of 1 indicates that the patient received all planned aphereses between Week 7 and Week 18 (apheresis rate of 0.75: the patient received 75% of planned aphereses).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*
Study Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

RANDOMIZED DOUBLE BLIND

Follow-up Q 12 weeks
LDL-C Levels

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Evolocumab (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 70 mg/dL</td>
<td>87%</td>
<td>18%</td>
</tr>
<tr>
<td>≤ 40 mg/dL</td>
<td>67%</td>
<td>0.5%</td>
</tr>
<tr>
<td>≤ 25 mg/dL</td>
<td>42%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>
Primary Endpoint

Hazard ratio, 0.85 (95% CI, 0.79–0.92)
P<0.001

Cumulative Incidence (%)

Placebo
Evolocumab

No. at Risk
Placebo 13,780 13,278 12,825 11,871 7610 3690 686
Evolocumab 13,784 13,351 12,939 12,070 7771 3746 689
Key Secondary Efficacy Endpoint

![Graph showing cumulative incidence and hazard ratio.](image)
## Safety: Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evolocumab (N=13,769)</th>
<th>Placibo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events — no. of patients (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10,664 (77.4)</td>
<td>10,644 (77.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>3410 (24.8)</td>
<td>3404 (24.7)</td>
</tr>
<tr>
<td>Thought to be related to the study agent and leading to discontinuation of study regimen</td>
<td>226 (1.6)</td>
<td>201 (1.5)</td>
</tr>
<tr>
<td><strong>Injection-site reaction</strong></td>
<td>296 (2.1)</td>
<td>219 (1.6)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>420 (3.1)</td>
<td>393 (2.9)</td>
</tr>
<tr>
<td>Muscle-related event</td>
<td>682 (5.0)</td>
<td>656 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>8 (0.1)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Cataract</td>
<td>228 (1.7)</td>
<td>242 (1.8)</td>
</tr>
<tr>
<td>Adjudicated case of new-onset diabetes†</td>
<td>677 (8.1)</td>
<td>644 (7.7)</td>
</tr>
<tr>
<td>Neurocognitive event</td>
<td>217 (1.6)</td>
<td>202 (1.5)</td>
</tr>
<tr>
<td><strong>Laboratory results — no. of patients/total no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase level &gt;3 times the upper limit of the normal range</td>
<td>240/13,543 (1.8)</td>
<td>242/13,523 (1.8)</td>
</tr>
<tr>
<td>Creatine kinase level &gt;5 times the upper limit of the normal range</td>
<td>95/13,543 (0.7)</td>
<td>99/13,523 (0.7)</td>
</tr>
</tbody>
</table>

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.
The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher, Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402
Treatment Assignment

Post-ACS patients (1 to 12 months)
Run-in period of 2−16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin
At least one lipid entry criterion met
Randomization
Alirocumab SC Q2W
Placebo SC Q2W

Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

# LDL-C: ITT and On-Treatment Analyses

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

HR 0.85
(95% CI 0.78, 0.93)
P=0.0003
All-Cause Death

ARR† 0.6%

HR 0.85
(95% CI 0.73, 0.98)
P=0.026*

*Nominal P-value
†Based on cumulative incidence
2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Ulf Landmesser\(^1\)\(^*,\)\(^†\), M. John Chapman\(^2\)\(^†\), Jane K. Stock\(^3\), Pierre Amarenco\(^4\), Jill J.F. Belch\(^5\), Jan Borén\(^6\), Michel Farnier\(^7\), Brian A. Ference\(^8\), Stephan Gielen\(^9\), Ian Graham\(^10\), Diederick E. Grobbee\(^11\), G. Kees Hovingh\(^12\), Thomas F. Lüscher\(^13\), Massimo F. Piepoli\(^14\), Kausik K. Ray\(^15\), Erik S. Stroes\(^12\), Olov Wiklund\(^16\), Stephan Windecker\(^17\), Jose Luis Zamorano\(^18\), Fausto Pinto\(^19\), Lale Tokgözoglu\(^20\), Jeroen J. Bax\(^21\), and Alberico L. Catapano\(^22\)
Priority Patient Groups for PCSK9 Inhibition

- Patients with clinical ASCVD and substantially elevated LDL-C levels.

Patients should be on maximally tolerated statin therapy (ideally with concomitant ezetimibe), or unable to tolerate three or more statins.

- Familial hypercholesterolaemia (FH) patients without clinical ASCVD but with substantially elevated LDL-C levels

Patients should be on maximally tolerated statin therapy plus ezetimibe

Patients with Clinical ASCVD: When to Consider a PCSK9 Inhibitor

Two LDL-C thresholds:

>3.6 mmol/L (>140 mg/dL)

>2.6 mmol/L (>100 mg/dL) with additional indices of risk severity

- Familial hypercholesterolaemia
- Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor such as marked hypertension
- Severe and/or extensive ASCVD, (refer to Box 3)
- Rapid progression of ASCVD, i.e. repeated ACS, unplanned coronary revascularizations, or ischaemic strokes within 5 years of the index event

Patients with FH: When to Consider a PCSK9 Inhibitor

Two LDL-C thresholds:
- >4.5 mmol/L (>180 mg/dL)
- >3.6 mmol/L (>140 mg/dL) with additional indices of risk severity

Patients with familial hypercholesterolaemia without clinically diagnosed ASCVD on maximally tolerated statin plus ezetimibe therapy

- Check for additional indices of risk severity
  - Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor (e.g. marked hypertension)
  - Lipoprotein(a) >50 mg/dL
  - Major risk factors: smoking, marked hypertension
  - >40 years of age without treatment
  - Premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives
  - Imaging indicators (refer to text)

No additional indices of risk severity
- LDL-C >4.5 mmol/L (>180 mg/dL)

Additional indices of risk severity
- LDL-C >3.6 mmol/L (>140 mg/dL)*

Consider a PCSK9 inhibitor

* Confirmed on two consecutive occasions

2018
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHa/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
# Recommendations for Primary Severe Hypercholesterolemia

**[LDL-C ≥190 mg/dL (≥4.9 mmol/L)]**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>3. In patients 20 to 75 years of age with a baseline LDL-C ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≥300 mg/dL (≥3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.</td>
</tr>
</tbody>
</table>

**Value Statement:**

**Uncertain Value (B-NR)**

6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.
Recommended Use of PCSK9I’s

- Based on current guidelines, available evidence, and economic considerations:
  - Patients with FH or ASCVD and statin resistance (on max dose) for additional LDL lowering is a reasonable strategy.
    - Discuss with patient costs vs clinical benefit
  - In FH patients to avoid apheresis
  - 2nd line to addition of ezetimibe for statin intolerant patients
  - No evidence to support use of PCSK9I’s as monotherapy or for arbitrary reduction of statin dose
    - In complete statin intolerance, PCSK9I monotherapy should be considered only after careful risk assessment and patient preference
Questions ?