Modern Lipid Management: New Drugs, New Targets, New Hope

Kirk U. Knowlton, M.D
Director of Cardiovascular Research
Co-Chief of Cardiology
Why lower LDL-C in those without evidence of CAD (primary prevention)
West of Scotland Coronary Prevention Study (WOSCOPS)

- Men between 45 and 64 with LDL-C >155
- No known Coronary Heart Disease
- Treated with Pravastatin
- LDL-C decreased
- Decreased nonfatal MI or CHD death

The air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

- Men (age 45-73) and women (age 55-73) without evidence of CHD.

- Lipid entry criteria-average levels
  - TC, 80-264mg/dL
  - LDL-C 130-190 mg/dL
  - HDL-C <45 -47
  - Triglycerides, <400 mg/dL
- Treated with lovastatin 20 mg QD

Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA)

- Men and women, Age 40-79 with HTN and at least 3 other CHD risk factors
- Atorvastatin 10mg

Lancet 5 April 2003
Jupiter Trial

• Men and women with LDL<130
• hsCRP>=2

Secondary Prevention
Multiple studies have demonstrated the reduction in MACE in individuals with previous Cardiovascular events or known CAD

- Heart Protection Study of cholesterol lowering with simvastatin
- 2013 ACC/AHA Guidelines “The Expert Panel found extensive and consistent evidence supporting the use of statins for the prevention of ASCVD in ... all secondary-prevention individuals without New York Heart Association class II–IV heart failure who were not receiving hemodialysis”

The Lancet 6 July 2002
Treat to LDL-C
Statin intolerance

What to do?
Ezitemibe-IMPROVE-IT Trial

- Patients >50 years of age
- Within 10 days of an acute myocardial infarction or unstable angina
- Ezitemibe/simvastatin
  - 40 mg simvastatin initially
  - Increased to 80 mg if LDL-C >79
- Versus Placebo/simvastatin
Anacetrapid

- HDL cholesterol was higher by 43 mg per deciliter (104% increase)
- the mean level of non-HDL cholesterol was lower by 17 mg per deciliter (18% decrease)
- “Merck, the last big firm standing in the once-hyped CETP field, has opted against filing for approval of anacetrapib.”
  - “best option is to cut its losses and move on.”
  - Fierce Biotech October 2017
PCSK9 inhibition
Overview

- The discovery of PCSK9 and its role in lipoprotein metabolism
- Major clinical trials of inhibitors of PCSK9
- Discussion about low implementation of PCSK9 inhibitors
- Is there a need for PCSK9 inhibitors at Intermountain and directions for the future
Evidence for a third genetic locus causing familial hypercholesterolemia: a non-LDLR, non-APOB kindred

L. Haddad, I. N. M. Day, S. Hunt, R. R. Williams, S. E. Humphries, and P. N. Hopkins

Centre for Cardiovascular Genetics, Department of Medicine, University College London Medical School, The Rayne Institute, 5 University Street, London WC1E 6JJ, United Kingdom, and Cardiovascular Genetics, Department of Internal Medicine, University of Utah, 410 Chipeta Way, Room 167, Salt Lake City, UT 84108

Not a mutation in the LDL Receptor or APOB
Submitted June 4, 1998
Large Utah, multigenerational family, FH3, with familial hypercholesterolemia that lacked linkage to LDL-receptor.
A Third Major Locus for Autosomal Dominant Hypercholesterolemia Maps to 1p34.1-p32

Mathilde Varret,1,* Jean-Pierre Rabès,1,* Bruno Saint-Jore,1 Ana Cenarro,6 Jean-Christophe Marinoni,1 Fernando Civeira,6 Martine Devillers,1 Michel Krempf,4 Monique Coulon,1 Rochelle Thiart,7 Martha J. Kotze,7 Helena Schmidt,8 Jean-Claude Buzzi,2 Gert M. Kostner,6 Stefano Bertolini,9 Miguel Pocovi,6 Alberto Rosa,10 Michel Farnier,5 Maria Martinez,2 Claudine Junien,1,* and Catherine Boileau1,*

Submitted October 27, 1998

The French group first documented that the mutation was in PCSK9 that caused FH3

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Marianne Abifadel1,2, Mathilde Varret1, Jean-Pierre Rabès1,3, Delphine Allard1, Khadija Ouguerram4, Martine Devillers1, Corinne Cruaud5, Suzanne Benjannet6, Louise Wickham6, Danièle Erlich1, Aurélie Derre1, Ludovic Villégé1, Michel Farnier7, Isabel Beucler1, Eric Bruckert1, Jean Chambaz10, Bernard Chanu11, Jean-Michel Lece112, Gerald Luc12, Philippe Moulin13, Jean Weissenbach1, Annick Prat6, Michel Krempf6, Claudine Junien1,3, Nabil G Seidah6 & Catherine Boileau1,3

It was later learned that these mutations resulted in an activating mutation in PCSK9-resulting in hyperlipidemia
Adenoviral-mediated expression of Pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype

Kara N. Maxwell and Jan L. Breslow*

Laboratory of Biochemical Genetics and Metabolism, The Rockefeller University, 1230 York Avenue, New York, NY 10021

7100–7105 PNAS May 4, 2004 vol. 101 no. 1
Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9


Departments of *Molecular Genetics, †Biochemistry, and ‡Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390-9046

Communicated by Joseph L. Goldstein, University of Texas Southwestern Medical Center, Dallas, TX, March 2, 2005 (received for review February 8, 2005)

PNAS April 12, 2005 vol. 102 no. 15:5374 –5379

• Knockout of the gene resulted in
  • No evidence of perinatal lethality
  • Healthy appearing mice
  • Decreased plasma cholesterol
  • Potentiation of the statin response
Mechanism of PCSK9:
(proprotein convertase subtilisin/kexin type 9)
What does it do?
Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.


88 percent reduction in the risk of CHD in African Americans with the mutation (P = 0.008 for the reduction; hazard ratio, 0.11; 95 percent confidence interval, 0.02 to 0.81; P = 0.03) in the Atherosclerosis Risk in Communities (ARIC) study
Despite having no immunodetectable circulating PCSK9 and an LDL-C of only 14 mg/dL, II.2 is an apparently healthy, fertile, normotensive, college-educated woman with normal liver and renal function tests (including urinalysis) who works as an aerobics instructor.
Clinical studies with inhibition of PCSK9
Two major approaches being tested

- Monoclonal antibody against PCSK9
- RNA inhibiting therapeutic strategy using anti-sense oligonucleotides.
Low-Density Lipoprotein Cholesterol-Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia

The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial

Frederick Raal, MB, BCh, MMed, PhD; Rob Scott, MD; Ransil Somaratne, MD; Ian Bridges, MSc; Gang Li, PhD; Scott M. Wasserman, MD; Evan A. Stein, MD, PhD

Circulation, 126 (2012), pp. 2408-2417

Alirocumab/Praluent
• 2341 patients on maximum tolerated statin
• Randomly assigned 2:1 ratio
• Every 2 week injection for 78 weeks
• Post hoc analysis – lower MACE, HR 0.52
• Injection site reactions, myalgias, neurocognitive events, and ophthalmologic events
• Randomized 4465 patients on standard therapy
• Open label trial
• Significant reduction in LDL
• Suggestion of improved MACE
• Probably safe- but blinded study needed
FDA approved Praluent

FDA News Release

FDA approves Praluent to treat certain patients with high cholesterol

First in a new class of injectable cholesterol-lowering drugs

For Immediate Release  July 24, 2015
Then Repatha - prior to clinical outcomes from blinded randomized trials

FDA News Release

FDA approves Repatha to treat certain patients with high cholesterol

For Immediate Release August 27, 2015
Original Investigation

Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance
The GAUSS-3 Randomized Clinical Trial

Steven E. Nissen, MD; Erik Stroes, MD, PhD; Ricardo E. Dent-Acosta, MD; Robert S. Rosenson, MD; Sam J. Lehman, MBBS, PhD; Naveed Sattar, MD, PhD; David Press, MD; Eric Bruckert, MD; Richard Celsa, MD; Norman Lepor, MD; Christie M. Ballantyne, MD; Ioanna Gouni-Berthold, MD; Mary Elliott, MS; Danielle M. Brennan, MS; Scott M. Wasserman, MD; Ranil Somaratne, MD, MBA; Rob Scott, MD; Evan A. Stein, MD, PhD; for the GAUSS-3 Investigators

JAMA.2016;315(15):1580-1590

- Statin intolerant-rigorous protocol
- Randomized for 24 weeks

Figure 3. Mean Percent Change in Low-Density Lipoprotein Cholesterol Level During Randomized Treatment With Ezetimibe or Evolocumab, GAUSS-3 Trial

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Evolocumab</th>
<th>Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>73</td>
<td>73</td>
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<tr>
<td>4</td>
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<td>127</td>
</tr>
<tr>
<td>22</td>
<td>117</td>
<td>117</td>
</tr>
</tbody>
</table>

Ezetimibe dose, 10 mg daily; evolocumab dose, 140 mg 3 times monthly (420 mg total dosage). GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3. Error bars indicate 95% CIs.
27,564 patients with LDL-C>70 who were receiving statins
Randomized, double blind, placebo controlled
Evolocumab 140 mg every two weeks or 420 mg monthly
Significant reduction in LDL
Improved MACE, though not overwhelming at this time point
Only adverse event was injection site reaction, 2.1 vs. 1.6%
27,564 patients with LDL-C>70 who were receiving statins

Randomized, double blind, placebo controlled

Evolocumab 140 mg every two weeks or 420 mg monthly

Significant reduction in LDL

Improved MACE, though not overwhelming at this time point

Significance driven by MI, revascularization, and stroke.

No significant difference in death

Only adverse event was injection site reaction, 2.1 vs. 1.6%

Primary efficacy end point (the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization)

Key secondary efficacy end point (the composite of cardiovascular death, myocardial infarction, or stroke)
Fourier results released
Why has the uptake on the monoclonal antibodies been so slow?

• **COST $$$$$**
  - Initially $14,000 for one year of therapy and must be used chronically
  - Cost for generic statins as little as $10
  - Estimated $16 billion for therapy of familial hypercholesterolemia
  - Statin intolerant another $20 billion
  - Prescription requires a lengthy prior authorization process that is different for each insurance provider.
Why has the uptake on the monoclonal antibodies been so slow?

- Adding PCSK9 inhibitors to statins was estimated to prevent 2,893,500 more MACE compared with adding zetimibe at an ICER (incremental cost ratio) of $450,000/QALY.
- Reducing annual drug costs by 71% (to $4215) would be needed for PCSK9 inhibitors to be cost effective at a threshold of $100,000/QALY.
On the other hand...

- Gregg Fonarow and colleagues found that the current price of evolocumab ($14,523) in addition to standard background therapy to treat patients with atherosclerotic CVD surpassed “generally accepted cost-effectiveness thresholds.”

- They used $150,000 acceptable QALY and found that Evolocumab would need to cost an annual net price of $9,669
  - JAMA Cardiology August 2017
Two major approaches being tested

- Monoclonal antibody against PCSK9
- RNA inhibiting therapeutic strategy using anti-sense oligonucleotides.
Anastasia Khvorova, NEJM January 2017

The cost to generate the molecule is, “expected to be in the low hundreds of dollars per gram on a commercial scale. With a yearly dose of 300 to 500 mg, the manufacturing cost for this class of drugs is on par with that of small molecule drugs and is probably much lower than that of monoclonal antibodies.”
Anastasia Khvorova, NEJM January 2017
• Open label
• Phase I
• 4-8 patients in each dose cohort
• Randomized 3:1
• 1 patient with elevation in GGT

PCSK9 levels

LDL-C levels
Phase II
501 patients randomized
Double Blind, Placebo Controlled
Multiple-ascending dose
Single dose, and two dose regimens
Patients with high risk CV disease
Side effects were similar between placebo and control except injection site reactions in 4-7% of Inclisiran injections

*N Engl J Med 2017; 376:1430-1440 April 13, 2017*
Fourier-AHA Late breaking trials.
November 2017

Evolocumab in patients with peripheral artery disease
Evolocumab has greater benefit in patients with:
- MI within last 2 years
- 2 or more events.
- multi-vessel disease
Canakinumab

Inhibits inflammation by blocking IL-1 beta
Decreases MACE, but small amount given cost of $60,000/year/patient
Reduction in hsCRP after first dose predicts more benefit

**CANTOS: Primary Cardiovascular Endpoints**
- Placebo SC q 3 months
- Canakinumab 150/300 mg SC q 3 months

**MACE**

<table>
<thead>
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<th>Follow-up Years</th>
<th>Cumulative Incidence (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
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<tr>
<td>2</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
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**HR 0.85**
95% CI 0.76-0.96
P = 0.007

**MACE - Plus**

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**HR 0.83**
95% CI 0.74-0.92
P = 0.0006

35 - 40% reductions in hsCRP and IL-6
No change in LDL-C

**CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE)**

- 25% reduction in risk for those achieving hsCRP < 2 mg/L
- 5% reduction in risk for those achieving hsCRP ≥ 2 mg/L
  (No change in LDL cholesterol)

No. at risk:
- Placebo:
  - 3182
  - 3014
  - 2653
  - 2525
  - 2258
  - 1067
  - 195
- Canakinumab:
  - hsCRP ≥ 2.0 mg/L:
    - 2868
    - 2724
    - 2674
    - 2258
    - 1067
    - 195
  - hsCRP < 2 mg/L:
    - 3484
    - 3553
    - 3214
    - 2890
    - 1411
    - 243

AHA late breaking clinical trials, 2017