Atherosclerosis – A Spectrum of Disease:
February 12, 2015
Richard Cameron Padgett, MD
Executive Medical Director, OHVI
Pt RB

Age 38
1ppd Smoker
Father had MI @ Age 46
Total Chol 189
LDL 138
HDL 25
Death is Chasing Them (video)
Current Concepts in Atherosclerosis

Richard C. Padgett, MD

Oregon Heart and Vascular Institute
Oregon Cardiology, PC
Eugene, Springfield & Florence
Which Patient needs Treatment

- 60 yo with a 2cm lung mass c/w lung Ca
- 60 yo with a 2cm lung mass and weight loss
- 60 yo with a 2 cm lung mass and Bronchial obstruction
Which Patient needs treatment

- 60 yo with “minor” luminal irregularities
- 60 yo with “mild” coronary artery disease
- 60 yo with “diffuse” coronary artery disease
- 60 yo with 95% stenosis of RCA
- 60 yo with multi-vessel CAD requiring CABG
Lesion Severity: A Poor Predictor of Survival

From the Coronary Artery Surgery Study (CASS) as reported by Little et al.

Vascular Disease: Scope of the Problem

• Vascular disease—and CAD in particular—is the leading cause of death in the US and other Western nations

• By 2020, cardiovascular disease will become the most common cause of death worldwide

• Due to the high initial mortality of vascular disease, the target of clinical practice must be aggressive risk factor management

Atherosclerosis: A Systemic Disease

Most CAD patients have concomitant *symptomatic* peripheral or cerebrovascular disease

- CAD + cerebrovascular disease: 32%
- CAD + peripheral disease: 35%
- CAD only: 33%

From a prospective analysis of 1886 patients aged ≥62 years, 810 patients were diagnosed with CAD as defined by a documented clinical history of MI, ECG evidence of Q-wave MI, or typical angina without previous MI. (Adapted from Aronow et al.)

Coronary Artery Disease (CAD): The Diagnosis Often Comes Too Late

Myocardial infarction (MI) or death as initial presentation of CAD

<table>
<thead>
<tr>
<th></th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>62%</td>
</tr>
<tr>
<td>Women</td>
<td>46%</td>
</tr>
</tbody>
</table>

(Adapted from Levy et al.)

## Major Risk Factors for CAD

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Nonmodifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Obesity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Family history</td>
<td>Gender</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
</tbody>
</table>

New Risk Factors

- Homocysteine
- Lp(a)
- Small dense LDL
- Fibrinogen
- Hs-CRP Risk factor or Disease Identifier
- Coronary Calcium
CAD Risk Is Incremental

(Adapted from Neaton et al.)

Development of Atherosclerotic Plaque
Conventional Concept
Most Myocardial Infarctions Are Caused by Low-Grade Stenoses

Coronary stenosis severity prior to MI

- >70% Stenosis: 14%
- 50%-70% Stenosis: 18%
- <50% Stenosis: 68%

(Adapted from Falk et al.)

Lesion Severity: A Poor Predictor of Survival

From the Coronary Artery Surgery Study (CASS) as reported by Little et al.

Conventional vs Contemporary
Coronary Remodeling

Progression

Compensatory expansion maintains constant lumen

Expansion overcome: lumen narrows

Normal vessel  Minimal CAD  Moderate CAD  Severe CAD

(Adapted from Glagov et al.)

Angiography Cannot Account for Coronary Remodeling
Angiography Masks Complicated Lesions
Angiography Underestimates Diffuse Disease
What Is the Culprit Lesion?

- 58-year-old male with chronic stable angina
- Positive stress test with small reversible ischemic defect on nuclear scintigraphy

Medical Rx, but 6 weeks later…

- 3-day history of unstable angina, including 30 minutes of rest pain
- Medically “cooled off” followed by angiography
Absence of Correlation Between Angiographic Results and Clinical Outcomes

(Adapted from Brown et al., Circulation, 1993.)

Transition to Acute Coronary Syndrome
Atherosclerosis Begins in Childhood

(Adapted from Berenson et al.)

One in Six Teenagers Has Atheromas

IVUS in 262 heart transplant donors

Prevalence of coronary atherosclerosis (% 0.5 mm threshold)

<table>
<thead>
<tr>
<th>Mean donor age (years)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>17%</td>
</tr>
<tr>
<td>20 - 29</td>
<td>37%</td>
</tr>
<tr>
<td>30 - 39</td>
<td>60%</td>
</tr>
<tr>
<td>40 - 49</td>
<td>71%</td>
</tr>
<tr>
<td>≥50</td>
<td>85%</td>
</tr>
</tbody>
</table>

(Adapted from Tuzcu et al.)

Tuzcu EM et al, in press.
Consistent Evidence of Early Atherosclerosis

(Adapted from Berenson et al and Tuzcu et al.)

CAD: Silent Disease Necessitates Aggressive Risk Factor Management

- IVUS corroborates necroscopy studies, proving that atherosclerosis begins in youth
- CAD progresses silently; the initial presentation is usually MI or sudden death
- Most atheromas are extraluminal, rendering them angiographically silent
- The only reasonable approach is early and aggressive risk factor management

The Correlation Between Atherosclerosis and Risk Factors Begins Early

Risk factors and CAD in young people

Intimal surface involvement (%)

- Fatty streaks: $P = 0.01$ for treatment
- Fibrous plaques: $P = 0.003$ for treatment

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>No risk factors</th>
<th>1 risk factor</th>
<th>2 risk factors</th>
<th>3 or 4 risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
<td>3%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>.6%</td>
<td>.7%</td>
<td>2.4%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

(Adapted from Berenson et al.)

Small Increases in Cholesterol Lead to Dramatic Increases in CAD Death

MRFIT: CAD death and serum cholesterol

Crude death rate per 10,000 person-years

*P < .05 vs total cholesterol < 182 mg/dL

(Adapted from Neaton et al.)

CAD: Not Just a Lipid Disease

- Half of all MIs occur in normolipidemic patients
- **Smoking**
  Accounts for 200,000 cardiovascular deaths annually
- **Diabetes**
  Affects 16 million Americans—and is growing
- **Hypertension**
  Confers as much risk for MI as smoking or dyslipidemia
  - *Systolic hypertension* is an even greater indicator of CAD risk than diastolic hypertension

Conclusions: Critical Lessons in Understanding Atherogenesis

- CAD is a ubiquitous, systemic disease that requires a systemic solution
- Most patients progress to MI or sudden death before a diagnosis of CAD is ever considered
- IVUS demonstrates that remodeling causes angiography to underestimate the extent of disease
- Extraluminal, angiographically silent atheromas are responsible for most acute coronary events, including sudden death

Learning Objectives

- Describe the mechanism of action of PCSK9 in regulation of cholesterol homeostasis
- Discuss the use of PCSK9 monoclonal antibodies for regulating atherogenic lipoprotein metabolism
- Review efficacy and safety data for the various PCSK9 inhibitors for FH as well as severe hypercholesterolemia
LDLR Function and Life Cycle

LDL particle → Endocytosis

Clathrin-coated vesicle → Recycling of LDL-R

Endosome → Lysosome

Hepatocyte → Nucleus (↑SREBP)

Golgi Apparatus

Endoplasmic reticulum

LDL particle → LDL Receptor

theheart.org Medscape Education
The Role of PCSK9 in the Regulation of LDLR Expression
- Third gene involved in autosomal-dominant hypercholesterolemia
- Found in primates, rats, mice, squirrels, other placental mammals, opossums, chickens, frogs and fish, but not in bovines\(^a\)
- Gain-of-function mutations as cause of ADH in 2 French families\(^b\)
- Loss-of-function mutations as cause of low-plasma LDL-C levels and reduced coronary heart disease risk\(^c\)

PCSK9 Structure

- Synthesized primarily by the liver as a 692-amino acid precursor of about 75 kDa (pro-PCSK9)
- Contains signal sequence (aa 1-30), prodomain (aa 31-152), catalytic domain (aa 153-425), and C-terminal domain (aa 426-692)
- Cleavage of prodomain is required for PCSK9 maturation and secretion

Mainly expressed in the liver, its transcription is driven by intracellular cholesterol concentrations (SREBP).

Autocatalytic processing in the endoplasmic reticulum cleaves the prodomain and produces the mature protein that is then transported to the Golgi apparatus and secreted.

The prodomain remains noncovalently attached to the catalytic domain, thus covering the catalytic pocket of PCSK9.

Therefore, PCSK9 capacity to promote LDLR degradation is independent of its catalytic activity.
PCSK9 In and Out of the Cell

- PCSK9 binds the EGF-A domain of LDLR and promotes the degradation of the receptor in the lysosome.
- Since PCSK9 regulates LDLR levels and uses LDLR for its own clearance, it should be expected that LDLR regulates PCSK9 levels.
- PCSK9 may also interact with other members of the LDLR family, such as VLDLR and ApoER2.
- LDLR and PCSK9 can also interact in the secretory pathway.

PCS9: The Case for Inhibition as a Therapeutic Strategy

- The Y142X or C679X variants, occurring in 2.6% of the African American population, are associated with a 30% reduction in LDL-C levels and an 88% reduction in rates of coronary heart disease.\(^a\)
- The R46L variant, occurring in 3.2% of whites, is associated with a 15% reduction in LDL-C levels and a 47% reduction in rates of coronary heart disease.\(^a\)
- Two unrelated adult patients with total PCSK9 deficiency have been identified; both had very low plasma levels of LDL-C (14 mg/dL and 16 mg/dL) and no adverse clinical issues.\(^c\)

The PCSK9 Lead

![Graph showing incidence of CHD among black patients with or without PCSK9 \(142X\) or PCSK9 \(679X\) allele](image)

**Incidence of CHD Among Black Patients With or Without PCSK9 \(142X\) or PCSK9 \(679X\) Allele**

<table>
<thead>
<tr>
<th>No Nonsense Mutation</th>
<th>Nonsense Mutation</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.7%</td>
<td>1.2%</td>
<td>.008</td>
</tr>
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</table>

Impact of a PCSK9 mAb on LDLR Expression
Mechanism of Action (cont)
Summary

- PCSK9 regulates LDLR and is regulated by SREBP
- Absence of PCSK9 action causes extremely low LDL-C
- PCSK9 increases ApoB levels in the absence of LDLR
- PCSK9 on serum LDL-C may control peripheral regulation of LDLR expression
- Partner proteins may interfere with PCSK9 action
- Therapeutic avenues are available beyond the blockade of PCSK9/LDLR interactions
# Anti-PCSK9 Agents in Development

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Class</th>
<th>Agent</th>
<th>Company</th>
<th>Phase</th>
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<tbody>
<tr>
<td><strong>PCSK9 binding</strong></td>
<td>Human monoclonal antibody</td>
<td>REGN727/SAR236553</td>
<td>Regeneron/sanofi</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Human monoclonal antibody</td>
<td>AMG145</td>
<td>Amgen</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Humanized monoclonal antibody</td>
<td>RN316</td>
<td>Pfizer</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LGT209</td>
<td>Novartis</td>
<td>2</td>
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<tr>
<td></td>
<td></td>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Humanized monoclonal antibody</td>
<td>LY3015014</td>
<td>Eli Lilly</td>
<td>1</td>
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<tr>
<td><strong>PCSK9 synthesis</strong></td>
<td>Modified binding protein</td>
<td>BMS962476</td>
<td>BMS/Adnexus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>SX-PCSK9</td>
<td>Serometrix</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>RNA interference</td>
<td>ALN-PCS02</td>
<td>Alnylam</td>
<td>1</td>
</tr>
</tbody>
</table>

*SPC-5001 (antisense) and BMS-844421 (antisense) clinical development have been terminated*
Evolution of Therapeutic Monoclonal Antibodies

- **Mouse mAb**
  - mAbs: rituximab, cetuximab
  - mouse variable
  - mouse constant
  - no repeated dosing

- **Chimeric**
  - mAbs: trastuzumab, bevacizumab
  - all mouse variable
  - human constant
  - time-consuming to create

- **Humanized**
  - mAbs: adalimumab, panitumumab
  - part mouse variable
  - human constant
  - time-consuming to create

- **Fully Human mAb**
  - human variable
  - human constant
  - repeated dosing possible

Potential for immune response to therapeutic antibody

Fab1 (mAb1-Amgen) Binds to PCSK9 at the Catalytic Site and Interacts With Residues From Both the Prodomain and Catalytic Domain

### Changes in LDL-C From Baseline to Week 12 by Treatment Group (mITT Population)

**Phase 2: Randomized Trial of REGN727/SAR236553 (n = 62) or Placebo (n = 15) in Patients With HeFH on Stable Statin Doses ± ezetimibe**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline LDL-C mg/dL (mmol/L)</th>
<th>% Change LDL-C*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>150.8 (3.9)</td>
<td>−10.7 (5.0)</td>
</tr>
<tr>
<td>REGN727 150 mg Q4W</td>
<td>166.7 (4.3)</td>
<td>−28.9 (5.1)†</td>
</tr>
<tr>
<td>REGN727 200 mg Q4W</td>
<td>169.8 (4.4)</td>
<td>−31.5 (4.9)†</td>
</tr>
<tr>
<td>REGN727 300 mg Q4W</td>
<td>139.6 (3.6)</td>
<td>−42.5 (5.1)†</td>
</tr>
<tr>
<td>REGN727 150 mg Q2W</td>
<td>147.2 (3.8)</td>
<td>−67.9 (4.9)†</td>
</tr>
</tbody>
</table>

*LS mean (SE), using LOCF method (12 weeks).
†P < .001 for % change REGN727 vs placebo.

Change in Calculated LDL-C at 2 Weekly Intervals From Baseline to Week 20

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, 12, 16, and 20 in the mITT population, by treatment group.

Changes in TC, non-HDL-C, ApoB, and Lp(a) From Baseline to Week 12 by Treatment Group (mITT Population)

§ LS mean (SE); †median (Q1-Q3).
*P < .05; **P < .01; †P < .001; ‡P < .0001.

Effects of AMG 145 on LDL-C Levels
Study Design

Phase 1b: AMG 145 (n = 43) or Placebo (n = 14),
Multiple Ascending SC Doses in Subjects With Hypercholesterolemia

Dose-escalation cohorts, subjects on low-to moderate-dose statins
- simvastatin 20-80 mg/d.
- atorvastatin 10-40 mg/d, or
- rosuvastatin 5-20 mg/d)

AMG 145 14 mg SC or Placebo QW 6 doses

AMG 145 35 mg SC or Placebo QW 6 doses

AMG 145 140 mg SC or Placebo Q2W 3 doses

AMG 145 280 mg SC or Placebo Q2W 3 doses

AMG 145 420 mg SC or Placebo Q2W 3 doses

Subjects on high-dose statins (atorvastatin 80 mg/d or rosuvastatin 40 mg/d)

AMG 145 140 mg SC or Placebo Q2W 3 doses

Subjects with HeFH

AMG 145 140 mg SC or Placebo Q2W 3 doses

Screening 5-35 days

Multiple-dose Treatment 6 weeks (QW and Q2W cohorts) or 8 weeks (Q4W cohorts)

End of Treatment Interval 6 weeks (QW and Q2W) or 8 weeks (Q4W)

Follow-up

AMG 145: Mean Percentage Change From Baseline in LDL-C

Phase 1b: AMG 145 (n = 43) or Placebo (n = 14), Multiple Ascending Doses in Subjects With Hypercholesterolemia

Hypercholesterolemics Receiving Low- to Moderate-dose Statins

Hypercholesterolemics Receiving High-dose Statins

Subjects With HeFH

PCS\textsubscript{9} mAbs are clearly leading the way.

PCS\textsubscript{9} mAbs significantly lower TC, LDL-C, ApoB, and Lp(a).

Both the degree and duration of lipid and lipoprotein reductions are dose-dependent.

- Further reductions in LDL-C will not occur once all available PCS\textsubscript{9} in the blood is bound. Higher doses may prolong the duration of action by binding newly released PCS\textsubscript{9}.

Every-2-week dosing appears optimal, but every 4 weeks may be reasonable with much higher doses.
References


25. Gumbiner B. Effects of 12 weeks of treatment with RN316 (PF-04950615), a humanized IgG2Δa monoclonal antibody binding proprotein convertase subtilisin kexin type 9, in hypercholesterolemic subjects on high and maximal dose statins. Paper presented at: AHA Scientific Sessions; 2012; Los Angeles, CA.

