Angina or “Heart Pain”
Well described 600 BCE

- From a cemetery in Cambridge
Classic Heart Attack Symptoms

- Wheezing
- Chest Pain
- Shortness of Breath
- Nausea
- Anxiety
- Vomiting
- Sweating
- Light Headedness
- Cough
Chest Pain Variants

- Localized just under breastbone, or in larger area of mid-chest; or entire upper chest.
- Common combination mid-chest, neck and jaw.
- Mid-chest and inside arms. Left arm and shoulder more frequent than right.
- Upper abdomen where most often mistaken for indigestion.
- Larger area of chest, neck, jaw and inside arms.
- Lower center neck to both sides of upper neck; and jaw from ear to ear.
- Inside right arm from armpit to below elbow; inside left arm to waist. Left arm and shoulder more frequent than right.
- Between shoulder blades.
Do you know your heart attack symptoms?
Heart Attack Warning Signs

**Women**
- Lightheadedness or dizziness
- Upper back pressure
- Chest pressure
- Shortness of breath
- Pain in one or both arms, the back, neck, jaw or stomach
- Fainting or extreme fatigue

Women might not experience the chest pain that is often noted as the most common sign of heart attack. Some women who have had heart attacks say they thought they had the symptoms associated with the flu.

**Men**
- Cold sweat or nausea
- Chest pressure or pain
- Shortness of breath
- Pain in one or both arms, the back, neck, jaw or stomach

If you have any of these symptoms for more than 5 minutes and are unsure of the cause, call 9-1-1.

Treatments work best if given within 1 hour of when heart attack symptoms begin.

Marshfield Clinic®
**Figure A** is an overview of a heart and coronary artery showing damage (dead heart muscle) caused by a heart attack. **Figure B** is a cross-section of the coronary artery with plaque buildup and a blood clot.
Pt RB

Age 38
1ppd Smoker
Father had MI @ Age 46
Total Chol 189
LDL 138
HDL 25
Coronary Angio Suite
All roads lead to Rome
Coronary Catheters
Death is Chasing Them
Current Concepts in Atherosclerosis

Richard C. Padgett, MD
Oregon Heart and Vascular Institute
Oregon Cardiology, PC
Eugene, Springfield, Florence, Reedsport & Coos Bay
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

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

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

(Adapted from Levy et al.)

## Major Risk Factors for CAD

### Modifiable risk factors
- Hypertension
- Dyslipidemia
- Diabetes
- Cigarette smoking
- Obesity
- Physical inactivity

### Nonmodifiable risk factors
- Family history
- Age
- Gender
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.)

Anatomy of the Atherosclerotic Plaque

- **Lumen**
- **Lipid Core**
- **Fibrous cap**
- **Intima**
- **Media Elastic laminæ**
- **Internal**
- **External**
- **Shoulder**
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

Survival of patients with mild vs severe CAD

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.)

IVUS Demonstration
Angiography Cannot Account for Coronary Remodeling
Transition to Acute Coronary Syndrome
Atherosclerosis Begins in Childhood

(Adapted from Berenson et al.)

One in Six Teenagers Has Atheromas

(Adapted from Tuzcu et al.)

IVUS in 262 heart transplant donors

Prevalence of coronary atherosclerosis (% 0.5 mm threshold)

Mean donor age (years)

<20  20 - 29  30 - 39  40 - 49  ≥50

17%  37%  60%  71%  85%

Tuzcu EM et al, in press.
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

0% 2% 4% 6% 8% 10% 12%

No risk factors 1 risk factor 2 risk factors 3 or 4 risk factors

1% 6% 3% 7% 8% 2.4% 11% 7.2%

(Adapted from Berenson et al.)

Small Increases in Cholesterol Lead to Dramatic Increases in CAD Death

(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

“Awaiting overt signs and symptoms of coronary disease before treatment is no longer justified.”

“In some respects, the occurrence of symptoms may be regarded more properly as a medical failure than as the initial indication for treatment.”

—William B. Kannel, MD
Department of Medicine
Boston University Medical Center

Kannel WB in Atherosclerosis and Coronary Artery Disease, 1996.
The CVD Pandemic: Annual Incidence

> 15 Million Fatal Heart Attacks Each Year

Source:
World Heart Federation

Incidence rates based on 1995 data
Adapted from American Heart Association: Heart and Stroke Statistical Update, 1998.
Cardiovascular Disease

- Every 33 seconds, someone dies of a heart attack
- For 60% this is their first sign of Heart Disease
- The number-one killer in the United States since 1900, except during the 1918
- It has killed more Americans than all wars, infectious disease and cancer…Combined
But Who is at Risk?

Jim Fixx, 53
- Not Overweight
- Very Fit
- Non-Smoker

Sir Winston Churchill, 91
- Overweight
- Not Fit
- Heavy Smoker
80.6% of American adults have one or more risk factor for heart attack!
Most heart attack is preventable
Heart attack remains the #1 killer

Eradication of Heart Attack
dream or reality?

Traditional approach has failed
140 Million Americans Have Average or High Cholesterol
76.5 Million Americans Have High CRP
Analogy of Smoking and Lung Cancer

Of course smoking is a strong risk factor for lung cancer but in a town where almost everyone smokes, smoking has no predictive value for lung cancer.

Too many people have risk factors specially when average cholesterol or high CRP is considered as risk factors.
Screening for Atherosclerosis
Risk Factors vs Disease

Numerous Risk Factors
- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
...
Over 200 risk factors have been reported.

Examples of Arterial Structure Tests
- Carotid IMT and Plaque Measured by Ultrasound
- Aortic and Carotid Plaque Detected by MRI
- Coronary Calcium Score Measured by CT
- Ankle Brachial Index

Examples of Arterial Function Tests
- Brachial Vasoreactivity Measured by Ultrasound
- Vascular Compliance Measured by Radial Tonometry
- Microvascular Reactivity Measured by Fingertip Tonometry
Which is High Tech?

Which is more Expensive?
AEHA
The Association for Eradication of Heart Attack

Leading the Way to Eradicate Heart Attacks

Era of Screening
Regular Screening & Interventions
Get in SHAPE
Screening for Heart Attack Prevention and Education

Era of Polypill
Chronic Prophylactic Drug Therapy
Combined Aspirin, Statin, ACE,

Era of Vaccine
Prevention and Stabilization of Atherosclerosis by Vaccination and Immune Modulation Strategies

The Burden of Sudden Heart Attacks Today
19 million deaths every year

$280 Billion / Year only in the USA

AEHA Calls for a Marriage between Fitness and Screening Centers to Proliferate SHAPE Compatible Clinics and Help Fight the Epidemic of Obesity, Diabetes, and Coronary Heart Disease

Shifting Cardiovascular Healthcare to Out of Hospital
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\(^c\)

\(^a\) Cameron J, et al. *FEBS J.* 2008;275:4121-4133.\(^{[2]}\)
PCSK9: 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.\(^c\)

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The PCSK9 Lead

Incidence of CHD Among Black Patients With or Without PCSK9^{142X} or PCSK9^{679X} Allele

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

The Role of PCSK9 in the Regulation of LDLR Expression
Impact of a PCSK9 mAb on LDLR Expression
Mechanism of Action (cont)

Image courtesy of Sergio Fazio, MD, PhD.
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 binding</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>
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<tr>
<td></td>
<td>Humanized monoclonal antibody</td>
<td>LGT209</td>
<td>Novartis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Modified binding protein</td>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>2</td>
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<tr>
<td></td>
<td>Humanized monoclonal antibody</td>
<td>LY3015014</td>
<td>Eli Lilly</td>
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<tr>
<td>PCSK9 synthesis</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

---

PCSK9-Mediated Degradation of LDLR

PCSK9 Inhibition Using Monoclonal Antibodies

### 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)

- **TC**: LS mean (SE)
- **Non-HDL-C**: Median (Q1-Q3)

*P < .05; **P < .01; †P < .001; ‡P < .0001.

Summary

PCSK9 mAbs are clearly leading the way.

PCSK9 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 PCSK9 in the blood is bound. Higher doses may prolong the duration of action by binding newly released PCSK9.

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