Atherosclerosis – A Spectrum of Disease: February 13, 2018
Richard Cameron Padgett, MD
Executive Medical Director Oregon Heart & Vascular Institute
Pt RB

Age 38
1ppd Smoker
Father had MI @ Age 46
Total Chol 189
LDL 138
HDL 25
Death is Chasing Them
New technology to treat Aortic Stenosis

Richard C. Padgett, MD
Executive Medical Director
Aortic Stenosis
An Increasing Burden

Burden of Valve Diseases in the US

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year 2000</th>
<th>Year 2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>2.5 millions</td>
<td>4.6 millions</td>
</tr>
<tr>
<td>MR</td>
<td>2.7 millions</td>
<td>4.8 millions</td>
</tr>
</tbody>
</table>
Aortic Stenosis: Natural History

- Latent period
- Onset of severe symptoms
- Average age at death
- Average survival (yr)

Chart showing survival percentage over age (yr) with key events.
# Aortic Stenosis

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Live expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>5 years</td>
</tr>
<tr>
<td>Syncope</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>

Therapy: Valve replacement for severe aortic stenosis  
Operative mortality (elderly) $\sim$ 4-24%  
Morbidity $\sim$ 3-11%  
Event rate in asymptomatic severe AS $\sim$ 1%/year
Standard Therapies are Inadequate

- Despite frequent BAV, **standard therapy did not alter the dismal course of disease for inoperable patients** in The PARTNER Trial.
  - 50% died within 1 year
  - 68% died within 2 years
Worse Prognosis than Many Metastatic Cancers

- 5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis

- Using constant hazard ratio. Data on file, Edwards Lifesciences LLC. Analysis courtesy of Murat Tuzcu, MD, Cleveland Clinic
Absolute Reduction in Mortality in Inoperable Patients

The Edwards SAPIEN valve significantly improves survival

24.7% absolute reduction in mortality

Despite expert care and frequent BAV, standard therapy failed to alter the dismal natural course of disease
ANIMATION

Transfemoral Deployment of Edwards SAPIEN Transcatheter Heart Valve in Calcified Aortic Valve
To ensure the success of the hybrid approach, the multidisciplinary team approach has developed

- Facilitates joint pre-operative decision-making and intra-operative collaboration between surgery and cardiology
A Dedicated Heart Team

Requires marriage of OR & Cath Lab staff

- Cardiothoracic Surgeon Learns: Large bore catheter technology and wire techniques
- Interventional Cardiologist Learns: Structural heart & aortic stenosis
- OR and Cath Lab staff both have to learn new equipment and processes
Summary JS

- 85 y.o. male
- STS 10%
- EuroSCORE 3%
- NYHA III
- Creatinine 1.2  BUN 14
- Hgb 12.9
- PLT 130  BNP 422

Clinical History

- Increasing fatigue and exercise intolerance
- Work-up for total knee replacement; echocardiogram shows progression of aortic stenosis, now severe.
- Alzheimer's dementia.
- CAD - moderate
- Chronic kidney disease.
- Hypertension
- Hyperlipidemia,
- Diabetes/ Diabetic neuropathy.
- Obesity.
- History of osteomyelitis of the ankle/ foot.
- BPH./ prostate cancer
- Arthritis.
- Gout.
- Suspected carrier of methicillin-resistant Staph aureus.
Simultaneous rhythm with occasional Premature ventricular complexes with subsequent sinus beat after PVC. Conducting with prolonged PR and subsequent 2nd degree AV block. Probable Mobitz 1 as new PR is shorter than prior PRs.

Left axis deviation
Abnormal ECG

When compared with ECG of 18-MAY-2015 15:14,
No significant change was found
Confirmed by MUNKENBECK, MD. FRANCES (14835) on 7/9/2015 8:08:32 AM

JS EKG
Echocardiography – JS

• TTE performed on 6/12/2015

**Required Measurements**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Velocity</td>
<td>4.29 m/s</td>
</tr>
<tr>
<td>Mean Gradient</td>
<td>44.4 mmHg</td>
</tr>
<tr>
<td>Annulus Diameter</td>
<td>21 mm</td>
</tr>
<tr>
<td>AVA</td>
<td>0.80 cm</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Findings**

• Severe aortic stenosis
• Mild aortic regurgitation.
• Trace mitral regurgitation
• Trace tricuspid regurgitation
PROCEDURE: Attempted TEE

DISCUSSION: Patient underwent an attempted TEE. Because of an obstruction just distal to the pharynx, we were unable to pass the probe. The patient tolerated the procedure poorly. If in the future, a TEE is required, then consideration of a GI endoscopy to confirm patency and perhaps even general anesthesia.
3Mensio – area 473.0 (26 Valve)
Annulus 75%
Area 4.49 cm²
Avg. Diameter 23.9 mm
Perimeter 68.1 mm
Ostial heights

Lt: 12.5

Rt: 13.6
DL access
JS access
Deployment angle  RAO 3  Cranial 2
## JS  Peripheral Sizing

### Minimal Luminal Diameters

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Iliac</td>
<td>8.0 mm</td>
<td>Common Iliac</td>
</tr>
<tr>
<td>Prox external Iliac</td>
<td>8.8 mm</td>
<td>Prox external Iliac</td>
</tr>
<tr>
<td>Mid external iliac</td>
<td>9.0 mm</td>
<td>Mid external iliac</td>
</tr>
<tr>
<td>Common Femoral</td>
<td>8.8 mm</td>
<td>Common Femoral</td>
</tr>
</tbody>
</table>
This patient is suitable for transfemoral TAVR with Sapien XT
- Concern of calcium extending into LVOT
- Plan B - Dr. Koh – support only

<table>
<thead>
<tr>
<th>Annulus Diameter Measurement</th>
<th>THV Valve Size Proposed</th>
<th>Femoral Access Side Proposed</th>
<th>Smallest Vessel Diameter Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.7 cm</td>
<td>26 mm</td>
<td>Right</td>
<td>8.0 mm</td>
</tr>
</tbody>
</table>
First TAVR @ OHVI  Sept 12th 2012
Sacred Heart Medical Center Riverbend
Oregon Heart & Vascular Institute, Springfield OR
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.

Atherosclerosis: A Systemic 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

Men: 62%
Women: 46%

(Adapted from Levy et al.)

## Major Risk Factors for CAD

### Modifiable risk factors

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Cigarette smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>Obesity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Physical inactivity</td>
</tr>
</tbody>
</table>

### Nonmodifiable risk factors

<table>
<thead>
<tr>
<th>Family history</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<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

Age-adjusted CAD death rates

Deaths per 10,000 patient-years

Serum cholesterol quintile (mg/dL)  Systolic BP quintile (mm Hg)

245+  221-244  203-220  182-202  <182  <118  118-124  125-131  132-141  142+

(Adapted from Neaton et al.)

Anatomy of the Atherosclerotic Plaque

- Lumen
- Lipid Core
- Fibrous cap
- Shoulder
- Intima
- Media
- Elastic laminae
- Internal
- External
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.)

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.)

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

(Date 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., Arch Intern Med, 1992.
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 are 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!
Eradication of Heart Attack

dream or reality?

• Most heart attack is preventable
• Heart attack remains the #1 killer

Traditional approach has failed
140 Million Americans Have Average or High Cholesterol
76.5 Million Americans Have High CRP

Correlates of Elevated C-Reactive Protein Among Adults in the United States: Findings From the 1999-2000 National Health and Nutrition Examination Survey
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
- 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: Leading the Way to Eradicate Heart Attacks

The Burden of Sudden Heart Attacks Today

Regular Screening & Interventions

Era of Screening

$280 Billion / Year only in the USA

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

Learn about the AEHA Vaccine Initiative Mission 2020

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
PCS K9

- 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\(^c\)

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PCS\textsuperscript{k}9: 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.\textsuperscript{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.\textsuperscript{a}
- Two unrelated adult patients with total PCS\textsuperscript{k}9 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.\textsuperscript{c}

\textsuperscript{b} Zhao Z, et al. \textit{Am J Hum Genet}. 2006;79:514-523.\textsuperscript{[11]}
The PCSK9 Lead

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>
</tbody>
</table>

LDLR Function and Life Cycle
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><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>
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<tr>
<td></td>
<td></td>
<td>LGT209</td>
<td>Novartis</td>
<td>2</td>
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<tr>
<td></td>
<td>Humanized monoclonal antibody</td>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Modified binding protein</td>
<td>BMS962476</td>
<td>BMS/Adnexus</td>
<td>1</td>
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<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>SX-PCSK9</td>
<td>Serometrix</td>
<td>Preclinical</td>
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<tr>
<td><strong>PCSK9 synthesis</strong></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**
- mouse variable
- mouse constant
- no repeated dosing

**Chimeric**
- mAbs: rituximab, cetuximab
- all mouse variable
- human constant
- time-consuming to create

**Humanized**
- mAbs: trastuzumab/bevacizumab
- part mouse variable
- human constant
- time-consuming to create

**Fully human mAb**
- mAbs: adalimumab/panitumumab
- human variable
- human constant
- repeated dosing possible

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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)

Change From Baseline to Week 12, %

TC § Non-HDL-C § ApoB § Lp(a) ¶

LS mean (SE); ¶median (Q1-Q3).

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

PCS9 mAbs are clearly leading the way.

PCS9 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.