Objectives

- Scope of the problem
- What is plaque?
- Pathogenesis of plaque, the role of inflammation
- What is a vulnerable plaque?
- Can we detect vulnerable plaque? Should we?
- Can we treat plaque? Stent, CABG, lifestyle modifications, aspirin and a statin.
- Is that all you got?
Scope of the Problem

- Cardiovascular disease is still the leading cause of death in the US but we are doing something right.
- Can we do better?

Cardiovascular disease – Remarkable progress

Coronary disease + stroke
~ 60% of CV deaths
Atherosclerosis

- Chronic inflammatory process that develops in "response-to-injury"

- Metabolic
- Physical
- Genetic
- Environmental
- Infectious

Ross R. NEJM 1999

Atherosclerosis

- A chronic inflammatory disease initiated by the accumulation of cholesterol-containing lipoproteins in the artery wall
- In the arterial wall lipoprotein components are generated through oxidative, lipolytic and immunologic reactions
- Starts as a response to arterial wall injury
- Can be unrecognized or asymptomatic for long periods, decades, even a lifetime
- But... can have rapid transition to an unstable or fatal event

Cholesterol

- It's pretty clear that non-HDL cholesterol has a key role in arterial injury and our body's response to that injury
- In most cases, cholesterol itself is not the problem. It's essential for life and has many uses.
- Brown & Goldstein won a Nobel prize for describing cholesterol regulation and homeostasis
- Let's focus on the concepts rather than the gory details
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LDL receptor and cholesterol homeostasis – LDL is recycled and balanced

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LDL receptor and cholesterol homeostasis – Oxidized LDL does not fit. Does it scavenger receptors.

Cellular free radicals, from cellular respiration, smoking, bacon, hypertension, diabetes, hypercholesterolemia.

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Activating Effect of LDL Infiltration on Inflammation in the Artery.
Slide 16

Inflammation

- Normal homeostatic body response to wounds or infection
- Usually self-limited when the threat is resolved
- Chronic inflammation occurs when the irritant(s) cannot be eliminated or when self-limiting mechanisms fail

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Inflammation in atherosclerosis

- There is an increased CHD event rate in patients with chronic inflammatory conditions
- Rheumatoid arthritis, psoriasis, periodontal disease, gout, diabetes, DM...
- Elevated CRP is a strong risk factor for CV events
- CRP is a nonspecific marker in inflammation
- Debate as to whether it plays a role in atherogenesis

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Relation of Number of Complex Coronary Lesions to Serum C-Reactive Protein Levels and Major Adverse Cardiovascular Events at One Year

Goldstein et al., Am J Cardiol 2005;96:56-60
Markers of Inflammation and Cardiovascular Risk

CRP
LDL

Plaque Development
- Endothelial cell (EC) changes recruit circulating monocytes which differentiate into macrophages and become foam cells
- Cytokines released by activated EC and Mø act on SMCs or their precursors to produce extracellular matrix to produce a fibromuscular plaque
- Progressive remodeling leads to a fibrous cap over a lipid-rich core containing OxLDL, cholesterol crystals, cellular debris
- Lateral edges contain inflammatory cells, activated Mø and T cells, natural killer T cells. ROS and proteases can erode the cap

Immune System in Atherosclerosis

Innate Immunity
- Cytokines are released which in turn attract other inflammatory cells
- Circulating monocytes adhere to damaged endothelium and migrate into the vessel wall. They differentiate into macrophages
- Scavenger receptors on the macrophages recognize Ox-PL and engulf them. They eventually become lipidladen macrophages or foam cells which are the primary cell in a fatty streak
- Fatty streaks are an accumulation of foam cells beneath the endothelium. Earliest signs of plaque. May progress or regress. Starts early in life.
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3 year old with a fatty streak

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Immune System in Atherosclerosis

Innate and Adaptive

- Innate: Non-specific, not long-lasting response to injury leading to inflammation: macrophages, PMNs, mast cells...
- Oxidized Phospholipids (OxPL) share structural homology with Pathogen Associated Molecular Patterns (PAMPs) & Pathogen Associated Molecular patterns (PAMhs)
- These are evolutionarily conserved sequences that activate immune cells and vascular cells to generate a non-specific inflammatory response. Endothelial cells are damaged and undergo apoptosis and macrophages are activated to engulf OxPL.

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Immune System in Atherosclerosis

Adaptive Immunity

- T and B cells
- T cells are present in fatty streaks
- T cells make up ~20% of cells in human plaques. Most are CD4+ and most of those are T helper 1 (Th1) cells.
- Th1 cells are a major source of proatherogenic cytokines such as IFNγ and TNFα.
- In general, T cells seem to promote atherosclerosis. TREGs may be an exception.
- T and B cells arise from both the lumen and from neovascularization from the adventitia in more advanced plaque.
Slide 25

* **Immune System in Atherosclerosis**
  
  * Adaptive Immunity
    - Recall that B cells present antigens and make antibodies.
    - Antibodies to OxLDL and other plaque components are found in atheroma.
    - Animal studies suggest that B cells are generally atheroprotective.

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* **Effects of T-Cell Activation on Plaque Inflammation.**

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Slide 27

* **Inflammatory Cells**
  
  * Libby et al., Circ Cell Cardio, 2011.
Stages of Atherosclerosis

Glagov’s Coronary Remodeling Concept

Plaque vascular remodeling
Plaque remodeling

• So do we just keep getting tighter and tighter stenoses?
• In some cases yes they keep getting tighter, but some plaques stabilize, some actually regress, and some can go from 0 to 60 in 3-7 seconds • STEM
• Plaque rupture -> a breach in the fibrous cap
• Many inflammatory cells, particularly macrophages and mast cells can be dumped within plaque. They release proteases which can directly degrade collagen and other connective tissue components of the plaque

Smooth muscle cells produce the arterial extracellular matrix

Structural Integrity of the Plaque’s Fibrous Cap

• Depends on interstitial collagen fibrils (types I & III) synthesized by smooth muscle cells
Acute Coronary Syndromes (ACS)

- Occur upon fibrous cap disruption.
- Large amounts of tissue factor are present in the underlying plaque which is a strong procoagulant.
- Can also occur with endothelial erosion over a fibrous cap. This can result in a platelet-rich thrombus. It’s felt that approximately 50% of ACS are due to this mechanism. Some studies suggest this mechanism is more common in women.

Subclinical ACS

- Infarction occurs when there is thrombotic occlusion of the vessel after fibrous cap disruption.
- Thrombotic occlusion after cap disruption is not a given.
- Approximately 50% of obstructive coronary plaques show histologic evidence of previous rupture and repair. (Harrington, 1997, JACC)
- This seems to be a major mechanism of plaque growth.
Slide 37

Severity of coronary artery stenosis before acute MI

- Vascular biologic state of the plaque more important than the severity of blockage
- Not that the culprit lesion is more prone to rupture

Data from four studies. Smith SC. Circulation 1996

Diameter stenosis (%)

0 10 20 30 40 50 60 70 80 90 100

< 50 > 70

n = 195

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Multiple Complex Coronary Plaques in Patients with Acute Myocardial Infarction


Slide 39

Plaque rupture in a non-critical lesion
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**Calcium Score**

- Does not identify plaques as vulnerable but does identify the presence of atherosclerosis
- If someone has chest pain and has a negative stress test we say, “It’s not your heart.”

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**Plaque vascular remodeling**

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**Identifying vulnerable plaque**

- It’s not just the tight ones
- Athero—Sclerosis
- A more stable plaque has more sclerosis, less athero
Coronary CT Angiography

- Characteristics of high risk plaque
  - Positive remodeling: plaque expands outward initially preserving the lumen
  - Necrotic core: low attenuation
  - Marfan ring sign: low attenuation surrounded by high attenuation
  - Spectral broadening
- Each of these plaque characteristics is more common in patients presenting with an acute coronary syndrome (ACS) than those with stable angina. 

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Coronary CT Angiography

- 3581 patients had coronary CTA: High risk lesions defined as positive remodeling and a necrotic core.
- In serial follow-up, the ACS event rate in patients with these plaque characteristics was 10% versus 3.4% for those without, respectively (p = 0.04)

Slide 48

Positive remodeling and infarcts
Virtual Histology (VH) IVUS

- Gray scale IVUS uses the amplitude of reflected sound
- VH IVUS does post processing to get spectral signatures of tissue types
- Tissues are color coded as four major components
  - Dense calcified: white
  - Necrotic core: red
  - Fibrous tissue: yellow-green
  - Collagen tissue: dark green
  - COOL PICS!!
Slide 55

OCT • Optical Coherence Tomography

- Intra coronary imaging with very high resolution • 50 microns
- Great for plaque size and stent apposition
- Poor depth penetration, poor resolution greater than 2 mm from the probe
- Poor depth means that OCT cannot measure plaque size or burden
- OCT is not reliable for interpreting tissue composition
- Adding fluorescent dyes is being employed to make it more specific

Slide 56

OCT • Optical Coherence Tomography
Not reliable for tissue characterization

- LVOT Stent Registry
- 22 cases with autopsy and OCT on 36 lesions
- Tried to correlate OCT patterns with histology
- OCT was not reliable in classifying lipids, calcium or macrophages
- Luther et al J Am Coll Cardiol 2016

Slide 57

VH-IVUS combined with OCT

- This is being tested to improve on the weakness of each modality
- May be reasonable in research, currently not practical for the cath lab
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Positron emission tomography (PET) inflammation imaging.

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Multimodal approach to atherosclerosis imaging.

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Should we image vulnerable plaque?

- My opinion
- A qualified yes
- We can’t image everyone
- We can image vulnerable plaque
- This advances our understanding of the biology of plaque.
- We can target more aggressive therapies for those patients
- Changes in plaque characteristics are now endpoints of many trials
Effects of statins on plaque morphology evaluated by intravascular imaging.


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% atheroma volume and total atheroma volume decrease while calcification increases.

Vulnerable Plaque or Vulnerable Patient?

- Plaque starts early and is very common.
- Clearly every plaque or every person does not go on to ACS.
- When a high risk plaque is found, it is usually not in isolation.
- Studies show multiple high risk plaques are often present when ACS occurs.
- If plaque is found, it is a good indication to watch for further events.
- Most of these high risk plaques do not meet criteria for a stent.
- In the non-surgical setting, techniques to identify a vulnerable plaque are actually identifying a vulnerable patient.

Coronary Atherosclerosis: Management

<table>
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<tr>
<th>Type</th>
<th>Lat</th>
<th>X-ray</th>
<th>CT</th>
<th>MRI</th>
<th>Angiography</th>
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</table>

- Lat = Lateral
- X-ray = X-ray
- CT = Computed Tomography
- MRI = Magnetic Resonance Imaging
- Angiography = Angiography
Slide 64

Stents and CABG

- Revascularization is essential to restoring blood flow when you are having a heart attack
- If you are not having a heart attack, but have CAD, whether you are symptomatic or asymptomatic, the role of revascularization is less clear
- Revascularization can improve survival in a few situations like decreased ejection fraction with VOD or left main proximal LAD
- For most other situations, it improves symptoms but does not improve survival or prevent heart attacks

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Stents get the road open but it's still snowing!

Slide 66

Targeting inflammatory pathways in atherosclerosis
Are these pathways, “Drugable?”
Trial design: Participants within 30 days of an acute coronary syndrome (ACS) were randomized to darapladib 160 mg daily (n = 6,504) versus placebo (n = 6,522).

Results

Conclusions

• Among patients with recent ACS, darapladib was not associated with a reduction in adverse cardiovascular events compared with placebo.  

O'Donoghue ML, et al. JAMA 2014;312:1006-15

(p = 0.93)

Darapladib
%
16.3
15.6

Placebo
**Slide 70**

**Methotrexate**

- Methotrexate is effective in animal models of CAD and decreases CV events in patients with rheumatoid and psoriatic arthritis.
- Are we just improving the underlying inflammatory disease? Is the benefit from treating the RA more aggressively?

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**Slide 71**

**Inclacumab – P-selectin inhibitor**

- Models suggest P-selectin inhibitor decreases neutrophil and platelet adhesion and macrophage accumulation.
- 590 patients with NSTE-ACS randomized to placebo, low or high dose of inclacumab. (Phase 3 trial)
- PCI completed, change in troponin tracked for 24 hours.
- High dose inclacumab led to a 24% decrease in troponin level at 24 hours and 44% of the peak troponin level after PCI.
- Gutt RJ et al. JAMA 2009.

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**Slide 72**

**Antibodies to oxidized LDL**

- Antibodies to OxLDL and other components of plaque are found in atherosclerotic lesions.
- Can we make a vaccine to prevent or slow plaque?
- A monoclonal OxLDL antibody has been studied in humans. Well tolerated. No change in plasma lipids or CRP. No change in 18FDG uptake in arterial wall.
- (References to paper and studies)
**Slide 73**

**SPARCL – OxPL-apoB substudy**

- Randomized trial of placebo vs 80 mg atorvastatin for secondary stroke prevention
- 4,068 patients with stroke or TIA within past 6 months but no known CAD
- Primary: recurrent stroke, secondary: cardiac event
- Biomarker substudy with Oxidized Phospholipids levels
- Elevated OxPL–apoB levels at baseline predicted recurrent stroke and any CV event over 5 years

**Slide 74**

**New ways to target inflammation**

- TREM: Triggering receptors expressed on myeloid cells
- TREM1 is a receptor expressed in PMNs and monocytes/macrophages
- Activation of TREM1 by LPS in the presence of other cytokines results in increased levels of IL-6 and TNFα and inhibits anti-inflammatory cytokines like IL-10
- TREM1 also regulates migration of myeloid cells to sites of inflammation

**Slide 75**

**TREM-1**

- New known to play a role in septic shock, but also in acute pancreatitis and rheumatoid arthritis
- Recall that OxPL activate scavenger receptors and this leads to amplification of the inflammatory response and plaque growth
- OxPL also shares memory with DAMPs and PAMPs which activate TREM1
- In patients with ACS, plasma TREM1 level was an independent predictor of MACE (from the ACUITY trial)
- TREM1 genotypes were linked to CAD risk in a Russian population
Slide 76

**TREM-1**

- TREM-1 is expressed in human atheroma, highest levels in more infarmed plaques
- A dodecapeptide named LiRs2 strongly inhibits engagement of TREM-1 receptors. In animal models of shock and inflammation LiRs2 significantly attenuates the inflammatory response
- Joffre et al showed that TREM-1 KO mice had markedly reduced atherosclerosis and foam cell formation. Importantly, in Apo E KO mice, LiRs2 did as well – JACC 2016
- A Phase 5 trial of LiRs2 in healthy humans is underway

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**Summary**

- Chronic inflammatory process that develops in “response-to-injury”
- Lipoprotein accumulation and oxidation
- Monocyte and T lymphocyte recruitment
- Leads to plaque progression
- Leads to endothelial dysfunction

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Slide 78

**Summary**

- Molecular and cellular mechanisms that promote weakening of the plaque's fibrous cap
- Inflammation and leukocyte adhesion
- Increased degradation of matrix macromolecules
- Loss of SMC, which synthesize plaque matrix
- Pro-inflammatory cytokines regulate these processes
- Plaque angiogenesis and intra-plaque hemorrhage
- Can we think of new approaches to get better understanding plaque biology?