APAD-Learning Academy

Atherosclerotic Peripheral Arterial Disease-Learning Academy;

Tying together the common etiology and medical treatment of atherosclerosis in the peripheral arteries.

*Nothing to Disclose  Charles S. Powell, MD, FACS

GOALS

- As CV SPECIALISTS ONE OF THE MOST IMPORTANT ACTIONS WE CAN TAKE IS TO COMMIT TO IMPROVING THE HEALTH OF THE Atherosclerotic Patients IN OUR REGION

- WE WANT REFERRING PROVIDERS TO RECOGNIZE OUR DEDICATION TO THEIR EDUCATION AND OVERALL IMPROVEMENT IN HEALTH STATUS OF THE REGION

- Be Known for our excellent interventional care if patients fail medical Rx
Healthcare Spending Outpaces Growth of The Economy

Health care spending has grown much faster than the rest of the economy in recent decades.

American Heart Association News, 02/17/2017
Seven Heart-Healthy* Habits Could Save Billions in Medicare Costs;

- Stop cigarette smoking
- Increase physical activity
- Improve dietary habits
- Lower BMI
- Control HBP
- Treat elevated Cholesterol
- Control DM

*(Blood Vessel-Healthy too!)*
Wellness program: Vidant Healthsteps for Patients with APAD

- Initial assessment
- 6 minute walk test
- ABI and EKG
- Exercise therapy, walking on treadmill or track
- Risk factor treatment education
- Nutritional counseling
- Psychological counseling
- Stop smoking counseling

**Limitations: not covered by insurance/medicare; most patients in the region cannot return regularly for therapy (3X PER WEEK)

Decision Memo for Supervised Exercise Therapy (SET) for Symptomatic Peripheral Artery Disease (PAD) (CAG-00449N); Finally CMS Will Pay!

- The Centers for Medicare & Medicaid Services (CMS) proposes that the evidence is sufficient to cover supervised exercise therapy (SET) for beneficiaries with intermittent claudication (IC) for the treatment of symptomatic peripheral artery disease (APAD).

- The beneficiary (“aka the patient”) must receive information regarding cardiovascular disease and APAD risk factor reduction, which could include education, counseling, behavioral interventions, and outcome assessments.
Regional Model of Care for APAD
Vidant/BSOM/Eastern AHEC

APAD Learning Academy Session I. Atherosclerosis, Location, Etiology and Risk Factor Management

- Future Sessions-Atherosclerosis Related
- II. Non Dyslipidemia Risk Factor Management (Diet, DM, HBP, Smoking, Exercise)
- III. Carotid, Subclavian & Vertebral Dz.
- IV. Renal and Mesenteric disease
- V. Aortic and Lower extremity disease

Eventually add sessions on Acute limb ischemia, AAA and DVT/PE
All will be archived on AHEC website and approved for CME credit
Session I. Atherosclerosis; Location, Etiology and Risk factor Management

- Objectives:
  - Identify all of the common arteries which can harbor atherosclerotic disease and the likely symptoms they may produce.
  - Discuss the theories of atherosclerotic plaque formation.
  - Identify atherosclerotic risk factors and their treatment.
  - Review basic cholesterol (lipid) metabolism as it relates to atherosclerosis and treatment
  - Identify the adverse effects caused by the atherosclerotic risk factors on the arterial wall.
  - Describe generally the Adult Treatment Protocol (ATP) ATP III and IV guidelines and the European Society of Cardiology (ESC) guidelines for treatment of atherosclerosis risk.

Atherosclerotic Disease in the Right Coronary Artery

![Image of atherosclerotic disease in the right coronary artery]
Atherosclerotic Internal Carotid Stenosis

Atherosclerotic Left Subclavian Stenosis
Atherosclerotic Celiac & Superior Mesenteric Stenosis

Figure 1A. Aortogram with Pigtail catheter demonstrating a celiac trunk stenosis (white arrow) and the occlusion of superior mesenteric artery (SMA) (black arrow). 1B. SMA angiogram after recanalization of the origin of the SMA and predilation of the occluded segment with a 4 mm x 2 cm balloon (black arrow). 1C. Final SMA angiogram shows a good result.

Bilateral Renal Artery Stenosis
Atherosclerotic Aorto-Iliac Occlusion

Atherosclerotic Superficial Femoral Arterial Occlusion
### Implications For APAD Patients

- APAD is a manifestation of systemic atherosclerosis and is associated with increased morbid CV events
- It has defined risk factors which are treatable with medication AND lifestyle changes
- It is poorly understood by patients

ATHEROSCLEROSIS in any arterial bed mandates the same aggressive risk factor treatment as CAD

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### Survival in Patients with Combined CAD and PAD

The Cholesterol Timeline-Lipids and Atherosclerosis

- 1784: Cholesterol discovered in gallstones
- 1900: Fatty streak noted in arteries of cholesterol fed rabbits
- 1950's: Aqueous transport of **INSOLUBLE** cholesterol & fatty acids by lipoproteins (LP) defined by density: VLDL, LDL, IDL, HDL-Chylomicrons
- 1970: Measurement of LP fractions
- 1973: Familial hyperlipidemia discovered to be caused by reduced or defective LDL receptors & associated with increased CVD risk
- 1973: HMG Co-A reductase discovered to be regulator of cholesterol synthesis
- 1987: Approval of lovastatin, the first “statin”; blocks HMG Co-A reductase & reduces serum cholesterol
- 1994: 4 S study proves the efficacy of statins in reduction of CVD events
- 2008: Jupiter study, statins lower CVD events even in low risk population
- 2017: Yellow II study shows statins cause lipid efflux & thickening of the fibrous capsule of coronary atherosclerotic plaque

East Carolina Heart Institute

National Cholesterol Education Panel (NCEP); Adult Treatment Protocol I (ATP I); *Arch Intern Med* 1988;148:36-69

1988: Total cholesterol levels are classified as follows:
- less than 200 mg/dL--“desirable blood cholesterol”;
- 200 to 239 mg/dL--borderline-high blood cholesterol;
- greater than or equal to 240 mg/dL--high blood cholesterol.

Lipoprotein analysis was done on a selective basis

**Dietary therapy was the primary cholesterol-lowering treatment.**
Step I and II Diets for Cholesterol Management; Early 1990’s

- **Step I.**
  - Saturated fat 8% to 10% of total calories
  - 30% or less calories from total fat.
  - Cholesterol intake less than 300 mg/day

- **Step II.**
  - Saturated fat intake to less than 7% of calories
  - Cholesterol intake less than 200 mg/day

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NCEP ATP II 1993

*JAMA, June 16, 1993:Vol169, no. 23,pp. 3016-23*

- Target LDL <130 in pts at high risk for CVD
  - Few Physicians actually complied even in pts at high risk.

**Main focus was screening and risk factor management for CAD and “other forms of atherosclerosis”**

Major statin prevention trials would be published shortly after these recommendations.
**ATHEROGENESIS:**
Endothelium and Subendothelial Space

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NORMAL ARTERIAL WALL

- Internal elastic membrane
- Tunica intima
- Smooth muscle
- Tunica adventitia
- External elastic membrane

SUBENDOTHELIAL SPACE

- Endothelium
- Basal membrane
- Proteoglycan-rich layer
- Internal limiting membrane
- Muscular elastic layer
- Internal elastic lamina

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Factors Effecting Normal vs. Abnormal Endothelial Function
Rutherford Text of Vascular Surgery, 8th Ed.

**Normal endothelium**

- Cytokines
- Oxidized LDL
- ROS
- Low shear stress
- Thrombin
- Hypoxia, ischemia
- Infection (virus, bacteria)

**Endothelial dysfunction**

- Endothelin
- Angiotensin II
- PAF, TXA₂
- von Willebrand factor
- PAI-1
- Growth factors
- Cell adhesion molecules
- Cytokines

**Effects**

- Secretion/expression
- POI₂, NO
- Thrombomodulin
- Antithrombin III
- Tissue plasminogen activator
- Urokinase
- Heparin-like molecules

- Vasodilation
- Decreased leukocyte adhesion
- Antiaggregant and anticoagulant properties
- Inhibition of SMC migration and proliferation
- Semi-selective barrier

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**Vascular constriction**

- Leukocyte recruitment
- Proaggregant and proinflammatory properties
- Stimulation of SMC migration and proliferation
- Increased permeability
- Increased LDL oxidation
Theories of Atherogenesis

- Lipid Hypothesis-
  - Response to Injury
    - High Shear Stress
    - Branch points & Bifurcations
  - Response to Retention
    - Low Shear Stress
    - Carotid bifurcation

Ox-LDL and Cascade of Atherosclerosis Producing Events
Complexity Defined-LIPIDS & ATHERO SCLEROSIS

- “What oxidizes LDL?”
- About 3,270,000 results (0.64 seconds)
- “What gets us into trouble is not what we don’t know. It’s what we know for sure that just ain’t so.” – Mark Twain

The Atheromatous Plaque: LIPID CORE & FIBROUS CAPSULE
Plaque Rupture; The Morbid Event

How Do We Handle Fat in the Body?

- Pathways of Lipid Metabolism
- Exogenous- via the gut and chylomicrons
- Endogenous-via the liver
Lipid Metabolism; Exogenous, Endogenous and Reverse Transport Paths

Exogenous pathway:
- Dietary fat
- Chylomicrons
- Bile acids and cholesterol
- Chylomicron remnants return to cholesterol pool in liver-reformatted for recirculation or excretion

Endogenous pathway:
- Dietary cholesterol
- Lipoprotein lipase
- Free fatty acids
- Lipoprotein lipase
- Free fatty acids

Exogenous Lipid Pathway - LACTEALS

Chylomicrons-lymphatic duct
- Deliver Cholesterol & FA’s to cells; Sterols, energy, cell membrane, prostaglandins
- Chylomicron remnants return to cholesterol pool in liver-reformatted for recirculation or excretion
**LDL Receptors**

- Western diet rich in fat/cholesterol/sugars
- Increases cholesterol in cell
- Turns off (down regulates) LDL-receptors
- Leads to increased serum LDL
- Familial Hypercholesterolemia led to discovery of LDL receptors
HDL is **Antiatherogenic**
- APO A, C, E

HDL absorbs cholesterol from cells/plaque & redistributes it to other cells or returns it to the liver cholesterol pool

LDL is **Atherogenic**
- APO B 48 & 100

VLDL and Chylomicrons deliver FA's and cholesterol to the tissues

Recirculate to liver as LDL & chylomicron remnants; Both found in high concentrations in atheromatous plaque
### Normal levels Cholesterol, Non HDL Cholesterol, HDL, LDL, Triglycerides (mg/dl)

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>HDL</th>
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<tbody>
<tr>
<td>&lt;200 mg/dl</td>
<td>Low &lt;40</td>
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<tr>
<td></td>
<td>High &gt;60</td>
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<tr>
<th>Non HDL cholesterol</th>
<th>Triglycerides</th>
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</thead>
<tbody>
<tr>
<td>non HDL = TC – HDL</td>
<td>Normal &lt;150</td>
</tr>
<tr>
<td>&lt;130 mg/dl</td>
<td>Borderline 150-199</td>
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<tr>
<td></td>
<td>High 200-499</td>
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<td>Very high &gt; 500</td>
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<table>
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<th>LDL</th>
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<tbody>
<tr>
<td>Optimal &lt;100</td>
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<tr>
<td>Near optimal 100-129</td>
</tr>
<tr>
<td>Borderline high 130-189</td>
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<tr>
<td>Very high &gt;190</td>
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### Definition of Dyslipidemia

A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency.

This may be manifested by:
- Elevated total cholesterol
- Elevated LDL or Triglycerides
  - or
- DECREASE in HDL
**ATPIII-IV Recommendations: PRIMARY Prevention of Atherosclerosis 2001&2013**

- LDL > 190 mg/dl
- +Diabetes + Age 40-75 with LDL between 70-189 mg/dl
- No Diabetes + Age 40-75 with LDL between 70-189 mg/dl **AND** a 10 y risk of ASCVD events > 7.5% estimated by a Pooled Cohort Risk Calculator (PCR)

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**Pooled Cohort Risk (PCR)**

- PCR are for **Primary Prevention** in pts up to age 75 that may have elevated CV risk but no established atherosclerotic disease; (dyslipidemia, diabetes, hypertension, smoking)
- For **Secondary Prevention**: The presence of atherosclerosis in any arterial bed qualifies for moderate to maximal intensity statin therapy & other risk modification
Variables in ACC/AHA PCR equations:
- Gender
- Race (AA vs. non-AA)
- Age
- Total cholesterol
- HDL cholesterol
- Systolic blood pressure
- Using antihypertensive medication (yes/no)
- Diabetes (yes/no)
- Smoker (yes/no)

Jonathon Firnhaber presentation '17
11.1% 10y risk of MI or Stroke


- **ATP III**
  - Treat to LDL target with statins
  - goal: (mg/dl)
    - <130
    - <100
    - <70

- **ATP IV**
  - Does not target LDL level
  - Use High, moderate or low intensity statin dose based on risk & presenting level of LDL

Notably, the American Association of Clinical Endocrinology the National Lipid Association & the ESC refused to endorse the new recommendation not to target LDL level.
How the Statin Era Began-The First Statin RCT
Scandinavian Simvastatin Survival Study (4S)-1994


- Double Blind, randomized, placebo controlled
  Men and Women 35-70 y.o.
  Prior MI or Angina
  Cholesterol 212-309 mg/dl

- 20 or 40 mg Simvastain daily

4S Results-5 y
*Lancet* 1994;344:1383-1389

- Compared with Placebo, Simvastatin:
  - Improved survival; 30% risk reduction (RR) p=.0003
  - Reduced coronary mortality; 42% (RR) * p<.00001
  - Reduced major coronary events; 34% (RR)* ("")
  - Reduced need for PTCA and CABG; 37% (RR)* ("")
  - Improved event-free survival; 26% (RR)* ("")

- Substantially reduced TC and LDL
4S
Changes in Serum Cholesterol & Lipoprotein Levels

Simvastatin vs placebo, at study end

TC LDL HDL TGs

% Change

Simvastatin vs Placebo

The Lancet, Vol 344, November 19, 1994

East Carolina Heart Institute

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein


- Randomized 17,802 apparently healthy men and Women from 80,000 screened
- Excluded DM, HBP Pts.
- Entry criteria LDL<130mg/dl; hsCRP> 2.0
  - Target LDL <70 and hsCRP <2.0
  - Rosuvastatin 20mg/day vs. Placebo
- Results:
  - Rosuvastatin reduced LDL by 50%; hsCRP by 37%
  - Reduced MI, Stroke, Death

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin. (JUPITER)
The AURORA trial was conducted in order to investigate whether statins would demonstrate a reduction in cardiovascular events in a hemodialysis population. Patients were randomized to rosuvastatin 10mg daily or placebo. The treatment group had 42.9% lower LDL compared to baseline, compared to the placebo group with a 1.9% reduction. Despite this difference in lipid levels, there was no significant difference in the primary outcome (a composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) or any secondary outcomes.
Newer Investigations

- YELLOW II STUDY

Intracoronary Imaging, Cholesterol Efflux, and Transcriptomes After Intensive Statin Treatment; The YELLOW II Study; JACC Volume 69, Issue 6, February 2017

- 85 pts undergoing PCI for culprit lesion AMI
- Obstructive non-culprit lesion ID’d and studied with optical coherence tomography (OCT)
- 40mg Rosuvastatin/day for 8-12 weeks vs. standard therapy; and restudy both groups with OCT
- Monocytes pre and post to study Cholesterol Efflux Capacity (CEC) and gene expression
Compared to standard therapy:

- Fibrous Cap Thickness (FCT) increased 100.9 vs. 108.6 (micrometers)
- Cholesterol Efflux Capacity (CEC) increased 0.81 vs. 0.84
The Future: Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors

- PCSK9 binds to LDL receptor blocking LDL uptake and increasing serum LDL.
- PCSK9 AB’s result in 47% reduction in serum LDL.
- Expensive.
- Given by subq injection.

Practical Prescribing Advice From Front Line Practitioners

- James Powell MD
  1. I treat APAD patients similarly to those with CAD and prior strokes.
  2. I prefer to treat these patients aggressively.
  3. The best statin for that patient is the one that they can take. I use this same principle to include the best statin is the one that the patient can afford (still an issue in our patients).
  4. With some of the newer guidelines, one can wonder why we still check lipids once someone is on high-dose statins. However, I tell the residents that when you drive down the road, you still need to look at the speedometer, even when you are on cruise control. I still check lipids and I still try to get folks as low as they can go if they merit aggressive therapy.

- Pete Wagner MD
  1. Guidelines are guidelines not policies or rules.
  2. Anyone with ASCVD: CAD, APAD, cerebrovascular disease I treat as high risk. For these patient:
  3. I use the highest dose of a statin that the patient tolerates. Ideally Atorvastatin or Rosuvastatin. This is often the limiting factor. I don’t use Simvastatin - too many drug to drug interactions. Tolerance is the key and statins are not very "clean" when it comes to side effects. Setting numeric goals therefore is problematic.
  4. I check NMR lipid profiles shooting for an LDL-particle number < 1000
  5. If high dose statin is not tolerated I try to get them on any statin which sometimes requires creativity i.e. low dose pravastatin (WOS trial showed statin benefit even without achieving LDL goal), or Rosuvastatin 5 mg every other day...
  6. If statins are not tolerated the new injectable biologics show promise.
What About Particle Analysis?

- Statins have shifted the paradigm for management of APAD and fewer interventions may be needed.
- Patients with Atherosclerosis in any arterial bed require maximal lipid therapy to prevent MI and other morbid events.
- Moderate to intensive statin therapy is beneficial even in patients with lower LDL levels.
- Low HDL and High Triglycerides qualify as Dyslipedemia and should be managed appropriately.
- The newer PCSK9 inhibitors hold immense promise in those refractory or intolerant of statins.