Peripheral Artery Disease

• Underlying cause is atherosclerosis
  – Diffuse and progressive process
  – Variable distribution
  – Variable clinical presentation

• All dependent on the regional circulation involved
  – Size of affected artery
  – Structure of affected artery
  – Local and regional flow
  – Changes in microcirculatory alterations
  – End organ damage

Atherosclerosis is a Systemic Disease

- Carotid TIA/Stroke
- PAD
- Claudication/CLTI/ALI
- CAD ACS
1) LDL moves into subendothelium 2) LDL oxidized by macrophages/smooth muscle cells 3) Release of growth factors/cytokines 4) attracts additional monocytes 5) Monocytes transform to macrophages 6) Macrophages ingest LDL to make foam cells 7) Foam cell accumulation and 8) Smooth muscle cell proliferation result in plaque growth

Peripheral Artery Disease

- Atherosclerosis locates in predictable regions in the arterial tree with flow instabilities
  - Large to medium sized arteries
  - Branch points
  - Bifurcations
  - Vessel curvature
- Carotid arteries – (Considered part of PAD in Canada)
- Aorta and its branches – (PAD in US)
  - Iliac arteries
  - Lower extremity arteries

Peripheral Artery Disease

- Atherosclerosis in the various beds begins early in life
- Progression of early subclinical atherosclerosis (PESA)
- Screened patients age 40-54 years age with no cardiovascular history
  - Duplex ultrasound to examine carotid and aorta/iliofemoral arteries for plaque
  - CT to examine the coronary arteries for calcification
- They screened a total of 4066 patients over 4.5 years
  - 2573 men
  - 1493 women
- Males were more likely to have plaque formation in all beds

Prevalence of Subclinical Atherosclerosis by Vascular Territory PESA Group

MALE

- Carotid Arteries: 36% (Presence of plaque)
- Coronary Arteries: 25% (Coronary calcification)
- Abdominal Aorta: 26% (Presence of plaque)
- Ilio-Femoral Arteries: 53% (Presence of plaque)

FEMALE

- Carotid Arteries: 24% (Presence of plaque)
- Coronary Arteries: 5% (Coronary calcification)
- Abdominal Aorta: 22% (Presence of plaque)
- Ilio-Femoral Arteries: 29% (Presence of plaque)
Peripheral Artery Disease (PAD)

- The presence of a stenosis or occlusion in the aorta or arteries of the limbs
- Usually caused by atherosclerosis
- Associated with an increased risk of death, myocardial infarction, and stroke
- May impair walking or cause critical limb ischemia
Peripheral Artery Disease

• Claudication – calf/buttock pain when ambulating
  – Often described by blocks walked prior to pain onset
  – Pain stops quickly with rest
  – Is reproducible at same distance

• Chronic Limb Threatening Ischemia (CLTI)
  – Pain in foot at rest
  – Non healing pedal ulcers
  – Pedal gangrene

• Acute Limb Ischemia
  – Acute arterial obstruction and limb threat
Heterogeneity in Biology

Hyperlipidemia, Smoking, Hypertension, Inflammation, Stress, Diabetes

Intimal/subintimal Disease

Low ABI ≤ 0.9

Renal Dysfunction, Diabetes (Calcium & Phosphate Regulation, Osteogenesis, Local Cellular Dysfunction)

Medial Calcification

High ABI ≥ 1.3

Pathology of PAD vs CAD Events

• Both CAD and PAD are luminal thrombosis as primary issue
• CAD - Acute Coronary Syndrome
  – Primarily due to luminal thrombosis associated with atherosclerosis
  – Plaque rupture of thin capped fibroatheroma (2/3)
  – Pathological intimal thickening with plaque erosion (1/3)
• PAD – Chronic Limb Threatening Ischemia
  – Primarily due to luminal thrombosis not associated with atherosclerosis
  – Study examining the limbs of amputees for CLTI
  – 70% of the arteries showed >70% stenosis
N = 239 arteries in CLTI

- 70% arteries ≥70% luminal stenosis

- ¼ of arteries had significant atherosclerosis without thrombi
- ¾ of arteries had stenosis associated with thrombi
- ¾ of arteries had thrombi associated with significant atherosclerosis
- ¼ of arteries had thrombi associated with insignificant atherosclerosis
Risk Factors for PAD

- Smoking
- Diabetes
- Hypertension
- Hypercholesterolemia
- Chronic renal insufficiency
- C-Reactive Protein

Smoking and PAD

- Stronger risk factor for PAD than CAD (Edinburgh Artery Study)

- Smoking, Type II Diabetes, hypertension, and hypercholesterolemia
  - Accounted for 75% of PAD risk
  - In males in Health Professional Follow-up Study

Joosten MM et al.  JAMA 2012;308:1660-67
**Figure 1** Incidence (%) of peripheral arterial disease (□) and coronary artery disease (■) in never smokers (pack-years = 0), moderate smokers (0 < packyears ≤ 25) and heavy smokers (packyears > 25).
Diabetes and PAD

• Diabetes increases risk of PAD
  – Rates of claudication 3.5 times with than without diabetes
  – Adversely modifies the clinical course of PAD

• Diabetes most common cause of amputation in US
  – 45-70% of all nontraumatic amputations

## Population Characteristics of Ischemic Amputations

### Table 1. Population Characteristics of Ischemic Amputations in Minnesota, 2005-2008\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Amputations (n = 4,302)</th>
<th>Minor Amputations (n = 2,470)</th>
<th>Major Amputations (n = 1,831)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>67 (56-79)</td>
<td>65 (54-76)</td>
<td>70 (59-81)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>65.4</td>
<td>67.5</td>
<td>62.5</td>
</tr>
<tr>
<td>Urban county residence, %</td>
<td>65.1</td>
<td>66.0</td>
<td>63.9</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>72.3</td>
<td>79.4</td>
<td>62.8</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>7 (4-12)</td>
<td>6 (4-10)</td>
<td>9 (6-14)</td>
</tr>
<tr>
<td>Inpatient charges, median (IQR), $</td>
<td>32,129 (17,980-57,761)</td>
<td>27,377 (16,087-47,737)</td>
<td>39,512 (21,414-73,174)</td>
</tr>
<tr>
<td>Inpatient hospitalization costs, median (IQR), $</td>
<td>12,434 (7,402-21,714)</td>
<td>10,609 (6,525-18,127)</td>
<td>15,246 (8,992-26,912)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

\(^a\) A minor amputation is any amputation below the ankle, and a major amputation is any amputation at or above the ankle; 1 amputation was at an unspecified site.
Dyslipidemia and PAD

- Abnormalities in lipid profile more common in PAD
  - Higher LDL
  - Lower HDL

- Relative risk for PAD increases for each 10 mg/dl increase in total cholesterol

Dyslipidemia and PAD

• Importantly these risk factors are additive

• The figures in the next slide from Health Professionals Followup Study show the individual and then additive risk of PAD with smoking, diabetes, hypertension, and dyslipidemia

Joosten MM et al. JAMA 2012;308:1660-67
PAD According to Individual & Joint Clinical Risk Factors

Joosten MM et al. JAMA 2012;308:1660-67
Risk Factors and PAD

- There are several modifiable risk factors in PAD
  - Smoking cessation
  - Diabetes management
  - LDL cholesterol reduction
  - Hypertension control

- Improvements in these can reduce events and prolong life in patients with PAD