NEW RESEARCH ON PERIPHERAL ARTERIAL DISEASE (PAD) RISK FACTORS

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Research and Consulting
Disclosures

Honorarium:
• Cardiovascular Systems Inc.

Consultant:
• Cardiovascular Systems Inc.

Purchased Research:
• Boston Scientific India
• Medtronic
PAD REMAINS UNDERDIAGNOSED & UNDERTREATED

MAJORITY OF PAD ASYMPTOMATIC

- Asymptomatic: 75%
- CLI: 15%
- IC: 10%

KNOWLEDGE OF PAD RISK FACTORS HELPS IDENTIFY PATIENTS WITH PAD

AGE
SMOKING
DIABETES
HYPERTENSION
HIGH CHOLESTEROL
CHRONIC KIDNEY DISEASE
RACE
FAMILY HISTORY

PAD PREVALENCE INCREASES WITH AGE

Source: Mozaffarian D. Circulation. 2015;131:e29-e322
## RELATIVE RISKS

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RELATIVE RISK*</th>
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<tbody>
<tr>
<td>AGE</td>
<td>2X-3X PER DECADE</td>
</tr>
<tr>
<td>SMOKING</td>
<td>2X-5X</td>
</tr>
<tr>
<td>DIABETES</td>
<td>2X-4X</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>1X-2X</td>
</tr>
<tr>
<td>HIGH CHOLESTEROL</td>
<td>1X-2X</td>
</tr>
<tr>
<td><strong>CHRONIC KIDNEY DISEASE</strong></td>
<td>2X-3X</td>
</tr>
<tr>
<td>RACE-AFRICAN AMERICAN</td>
<td>2X</td>
</tr>
<tr>
<td>FAMILY HISTORY</td>
<td>2X</td>
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</tbody>
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*Numbers are rounded.

RELATIVE RISK INCREASES WITH ADVANCED AGE

MULTIVARIATE ADJUSTED ODDS RATIO OF PAD BY AGE

Source: Savji 2013.
SMOKING—STRONGEST MODIFIABLE RISK FACTOR

- Significant independent association between PAD & smoking
- Confers significantly higher risk for PAD than CAD (5X vs 1.7X)
- Smoking increases disease severity & progression
- Smoking increases risk of amputation & death
- Dose response to amount & duration of smoking
- Elevated risk continues after cessation—even after 20 years
- Second-hand smoke increases risk 1.7X with dose response to amount and duration of exposure

PAD IN DIABETICS—MORE AGGRESSIVE & MORE SEVERE

- Increases risk of moderate & severe PAD (CLI)
- CLI develops suddenly in DM
- DM increases risk of amputation
- DM increases risk of mortality
- Duration of DM increases PAD risk & severity
- Each 1% increase in blood glucose increases PAD risk by 28x—importance of glucose control
- DM disease distribution & characteristics: more diffuse disease, more distal and more calcification

CLI RISK FACTORS

AGE
RACE

RELATIVE RISK INCREASES:
DIABETES 6X-7X VS 2-4X PAD
CVD (MI, STROKE, CHF) RR 2X

HYPERTENSION 2X-3X
CHRONIC RENAL FAILURE 2X
SMOKING RR 2X

PAD IN WOMEN

- **MYTH-PAD IS A MALE DISEASE—OLD DEFINITION OF PAD AS IC & WOMEN RARELY HAVE IC**

- **HIGHER INCIDENCE & PREVALENCE IN FEMALES IN SOME STUDIES (BERGER, ERASO HIRAMOTO & SAVJI)**
  - ESPECIALLY IN OLDER AGE GROUPS, AA AND/OR THOSE W/ DM OR CKD

- **SOME EVIDENCE OF HIGHER CLI INCIDENCE & PREVALENCE IN FEMALES (NEHLER)**

- **SMOKING GREATER IMPACT ON WOMEN: 12X (<15 CIGS/DA) 21X (> 15 CIGS/DA)**

- **CKD PARTICULARLY IMPORTANT RF FOR WOMEN IN ALL RACIAL/ETHNIC GROUPS**
  - MODERATE & SEVERE RENAL INSUFFICIENCY INCREASES RISK OF PAD (1.6X & 3.2X)

RACE AND PAD

- AFRICAN AMERICANS (AA)—HIGHER INCIDENCE & PREVALENCE PAD

- AA—MAY HAVE HIGHER INCIDENCE & PREVALENCE CLI (IN MEDICARE)

- ASIANS (IN US): LOWEST PREVALENCE OF PAD

- NATIVE AMERICANS: ONE OF THE HIGHEST PREVALENCES—ESPECIALLY OLDER WOMEN

- DIFFERENT DISEASE DISTRIBUTION—MORE DISTAL DISEASE IN BLACKS AND SE ASIANS

NEWER PAD RISK FACTORS

MULTIPLE RISK FACTORS—CUMULATIVE EFFECT
SEDENTARY LIFESTYLE
GENETIC

SEDENTARY LIFESTYLE AND RISK OF PAD

- NUMEROUS STUDIES SHOW THAT PHYSICAL ACTIVITY REDUCES RISK OF CAD

- PAD & PHYSICAL ACTIVITY—NOT WELL STUDIED

- PHYSICAL ACTIVITY REDUCED ODDS OF PAD BY 36%
  - AFTER MULTIVARIATE ADJUSTMENT FOR AGE, SEX, RACE AND OTHER RF

- GREATER FREQUENCY REDUCED PAD RISK
  - ODDS REDUCED BY 26% FOR 1X WEEK TO 45% FOR ACTIVITY > 3X WEEK

- GREATER INTENSITY REDUCED RISK: WALKING OR BICYCLING OR O.63 BUT RUNNING OR FELL TO 0.39

- RESULTS UNCHANGED EVEN AFTER EXCLUDING SUBJECTS WITH PHYSICAL ACTIVITY LIMITATIONS (IC, ANGINA, NEUROPATHY) OR PREVIOUS CAD

Source: Stein RA 2014.
RESEARCH ON MULTIPLE RISK FACTORS

● BERGER 2013 MULTIVARIATE ANALYSIS
  ● 5 RF: SMOKING, DM, HTN, HIGH CHOLESTEROL & SEDENTARY LIFESTYLE

● ERASO 2014 MULTIVARIATE ANALYSIS
  ● 4 RF: SMOKING, DM, HTN, CKD,

Source: Eraso 2014 and Berger 2013.
MULTIPLE RISK FACTORS INCREASE PAD ODDS

Source: Eraso 2014.
AFRICAN AMERICANS—PARTICULARLY SUSCEPTIBLE TO MULTIPLE RISK FACTORS

RELATIVE ODDS OF PAD BY RACE AND NUMBER OF RISK FACTORS

Source: Eraso 2014.
WOMEN PARTICULARLY SUSCEPTIBLE TO MULTIPLE RISK FACTORS

RELATIVE ODDS OF PAD BY SEX AND NUMBER OF RISK FACTORS

Source: Eraso 2014.
FAMILY HISTORY OF PAD INCREASES THE RISK

- **SIGNIFICANT INDEPENDENT ASSOCIATION WITH PAD**  \( RR = 2X \)
- **STRONGER ASSOCIATION IN YOUNGER AGE < 68**  \( RR = 2.5X \)
- **RISK OF PAD SIMILAR FOR PARENTAL & SIBLING HISTORY OF PAD**
- **RISK OF PAD INCREASES W/ NUMBER OF RELATIVES W/ HISTORY OF PAD**
- **FAMILY HISTORY OF CAD INCREASES RISK OF PAD, BUT LESS IMPACT THAN FAMILY HISTORY OF PAD**

**Both genetic & environmental factors**

PAD & CAD share genetic variants

PAD also has unique genetic variants

Source: Khaleghi M 2014.
GENETIC FACTORS AND RISK OF PAD

- DATA ON ETHNIC & FAMILIAL PAD RISKS, AS WELL AS ON EARLY ONSET PAD INDICATE ROLE FOR GENETIC VARIANTS

- FEWER GENETIC VARIANTS HAVE BEEN DISCOVERED FOR PAD THAN CAD

- MAY REFLECT STRONGER ENVIRONMENTAL CONTRIBUTION TO PAD, FOR EXAMPLE SMOKING OR DIABETES

- MAY ALSO REFLECT PAD COMPLEXITY AND HETEROGENEITY
  - 2 SUBTYPES: PROXIMAL & DISTAL ASSOCIATED W/ DISTINCT RISK FACTOR & COMORBIDITY PROFILES
  - PROXIMAL W/ FEMALE, SMOKING, HTN & DYSLIPIDEMIA
  - DISTAL W/ MALE, OLDER AGE & DM

# GENE POLYMORPHISMS ASSOCIATED WITH PAD

<table>
<thead>
<tr>
<th>PRO-ATHEROTHROMBOTIC</th>
<th>PRO-ATHEROSCLEROTIC</th>
<th>NOVEL</th>
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<tbody>
<tr>
<td>Factor II</td>
<td>CONNEXIN 37</td>
<td>SLC2A10</td>
</tr>
<tr>
<td>P2Y12</td>
<td>APO E &amp; APO B</td>
<td>PAOD1</td>
</tr>
<tr>
<td>FIBRINOGEN β</td>
<td>IL-6 PROMOTER</td>
<td>LSQ-1</td>
</tr>
<tr>
<td>MTHFR 677T</td>
<td>E-SELECTIN</td>
<td>CHRNA3 (nicotinic receptors)</td>
</tr>
<tr>
<td></td>
<td>ICAM-1</td>
<td></td>
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<tr>
<td></td>
<td>MCP-1</td>
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<tr>
<td></td>
<td>MMP-1</td>
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<td>ACE D</td>
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<tr>
<td></td>
<td>CDKN2b &amp; CDKN2a (9p21)</td>
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Table adapted from Katwal.
# USING PAD RISK FACTORS TO FIND PATIENTS—SCREEN HIGH RISK GROUPS

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>PREVALENCE</th>
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<tbody>
<tr>
<td>DIABETIC FOOT ULCER (DFU)</td>
<td>50-80</td>
</tr>
<tr>
<td>CORONARY ARTERY &amp; CEREBROVASCULAR DISEASE</td>
<td>40*</td>
</tr>
<tr>
<td>CHRONIC KIDNEY DISEASE 65+</td>
<td>30-40**</td>
</tr>
<tr>
<td>DIABETES AGE 50+</td>
<td>30-40</td>
</tr>
<tr>
<td>VENOUS ULCERS</td>
<td>27</td>
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*CAD/CVD Patients who have been hospitalized.

**40% in CKD + DM

CONCLUSIONS PAD RISK FACTORS

- Knowledge of risk factors can be employed to identify high risk patients for further diagnostic testing.

- Smoking is the strongest PAD risk factor.

- Women have PAD as often as men especially at older ages. Multiple risk factors increase the relative risk much more than for men.

- African Americans—higher prevalence of PAD and impacted by presence of multiple risk factors.

- Multiple risk factors significantly increase the risk—10x-12x.

- Diabetes increases PAD severity & risk of mortality & amputation.
CONCLUSIONS PAD RISK FACTORS II

- SEDENTARY LIFESTYLE INCREASES THE RISK—PHYSICAL ACTIVITY REDUCED RISK BY 36%

- FAMILY HISTORY INCREASES RISK 2X

- GENETIC VARIATIONS PLAY A SIGNIFICANT ROLE—MORE RESEARCH NEEDED TO BE ABLE TO CREATE SCREENING TESTS OR DEVELOP INDIVIDUAL TREATMENT PROGRAMS SUCH AS THOSE FOR CANCER

- CERTAIN HIGH RISK PATIENT GROUPS INCLUDING DFU, CAD & CVD, DM AGE 50+, CKD AGE 65+ AND POSSIBLY VENOUS ULCERS WITH HIGH PREVALENCE OF PAD REPRESENT CANDIDATES FOR SCREENING/DIAGNOSTIC TESTING
THANK YOU!

CAT ISLAND * BEAUFORT, SC
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