Depression in Peripheral Artery Disease: An important Predictor of Outcome

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UCSF VASCULAR SURGERY SYMPOSIUM
SAN FRANCISCO, CA
APRIL 2012

Goals

1. Does depression negatively impact patients with coronary artery disease?

2. Does depression negatively impact patients with peripheral artery disease?
   - Recent data from the VAMC San Francisco

3. Can we do anything about it?

• There are no conflicts of interest

1. Does depression negatively impact patients with coronary artery disease?

2. Does depression negatively impact patients with peripheral artery disease?
   - Recent data from the VAMC San Francisco

3. Can we do anything about it?
Depression and Cardiovascular Disease

- 1-year prevalence of major depressive disorders in the US is 7%; lifetime: 16%
- Depression almost **doubles** the risk of developing **CAD** in otherwise healthy individuals
- After an acute coronary syndrome (ACS), about 20% of patients will suffer from a major depressive disorder
- Depression is 3x more common after ACS


Mortality burden associated with depression in CAD

- Depression is associated with at least a **doubling in risk of cardiac events** over 1-2 years after MI, after adjusting for infarct severity and CV risk factors
  - “Dose-response relationship: the more severe depression, the earlier and more severe cardiac events”.

Van Melle 2004; Frasure-Smith et al 2006; Barth et al, 2004

Mechanisms

- Hypothalamic-pituitary-adrenal axis dysfunction
- Reduced heart rate variability (increased sympathetic activity/reduced vagal)
- Increased platelet activation
- Increased CRP, IL-6, ICAM-1, fibrinogen
- Impaired vascular function
- Lower n-3 PUFA levels
- Lifestyle behaviors: diet, exercise, medication adherence, smoking, social isolation and chronic life stress.

Musselman et al. Arch Gen Psychiatry. 1998

Depression and Cardiovascular Health

- Depression reduces the chance of successful modifications of other cardiac risk factors

Biological Factors

Behavioral Factors

Depression reduces the chance of successful modifications of other cardiac risk factors
Goals

1. Does depression negatively impact patients with coronary artery disease? **YES**

2. Does depression negatively impact patients with peripheral artery disease?
   - Recent data from the VAMC San Francisco

3. Can we do anything about it?

What is the evidence in PAD?

- There is greater incident PAD among patients with depression
  - Atherosclerosis Risk in Communities Studies

<table>
<thead>
<tr>
<th>Level of depression</th>
<th>Cases</th>
<th>Person-years</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>364</td>
<td>39,523</td>
<td>1.66 (1.39-1.98)</td>
</tr>
<tr>
<td>Moderate</td>
<td>278</td>
<td>44,168</td>
<td>1.22 (1.02-1.47)</td>
</tr>
<tr>
<td>Low</td>
<td>208</td>
<td>41,546</td>
<td>Ref.</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>325</td>
<td>36,744</td>
<td>1.44 (1.19-1.74)</td>
</tr>
<tr>
<td>Moderate</td>
<td>256</td>
<td>41,901</td>
<td>1.20 (0.99-1.45)</td>
</tr>
<tr>
<td>Low</td>
<td>186</td>
<td>39,712</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

Wattanakit et al, Vasc Med 2005

Who is more at risk among patients with PAD?

- Significant depressive symptoms are more common in younger women with PAD than in other gender-age groups
  - 444 patients with PAD
  (Dutch vascular outpatient clinics)

Smolderen et al, JVS 2010
Consequences of depression in PAD

1a. Reduced maximal walking distance

- Smolderen et al. J Affec Dis 2008

2. Poorer performance across different domains

- Smolderen, Vasc Med 2011

Consequences of depression in PAD

1b. Worse performance on 6-min walk test

- McDermott et al, J Gen Intern Med 2003

3. Greater annual decline in functional performance

- Ruo et al, Psychosom Med 2007
Consequences of depression in PAD

4. Less functional improvement after endovascular procedures

5. Increased failure of revascularization

6. Increased progression of contralateral PAD in patients undergoing lower extremity revascularization

7. More CV events after revascularization
Our Experience at the VAMC San Francisco

- PAD and CAD share several biological and behavioral risk factors
- Depression has emerged as a key risk factor for CAD, but less is known for the impact of depression on PAD
- Research Questions:
  1. Is depression a risk factor for PAD?
  2. What are the mechanisms involved in an association between depression and PAD?

Research Cohort: The Heart and Soul Study

- Cohort:
  - 1,024 patients with stable CAD recruited from 2000-2002 from university hospitals in San Francisco
- Cohort Goal:
  - To determine how psychological disorders lead to CV events in outpatients with stable CAD (follow-up 7.2 +/- 2.6 years)
- Events:
  - Carefully adjudicated during follow-up
  - CV events
  - Symptomatic PAD

Statistical Considerations

- Predictor: Depressive symptoms
- Outcome: Prevalent PAD
- Incident PAD during 6 years follow-up

Covariates

- Patient characteristics: Age, Sex, Race
- Comorbid conditions: Hypertension, MI or Stroke, Revasc, CHF, DM
- Medications: Aspirin, ACE-inhibitor, B-blocker, Statin, Diuretic
- PAD Risk Factors: Cholesterol, LDL, HDL, Trig, BP, creat
- Inflammation: CRP, IL-6, TNF-a
- Health Behaviors: Smoking, Physical activity, Med adherence, ETOH, BMI

PATIENTS CHARACTERISTICS BY DEPRESSION STATUS

199 participants had depressive symptoms (PHQ>10)

Grenon et al, J Am Heart Assoc. 2012
MEDIATION ANALYSIS

### Association Between Prevalent PAD and Depression

**Prevalent PAD:**
- 12% (24/199) with depressive symptoms
- 7% (60/825) without depressive symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age and sex only</td>
<td>1.79 [1.06, 3.04]</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for age, sex, and race</td>
<td>1.88 [1.10, 3.20]</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, comorbid conditions, and medication use</td>
<td>1.61 [0.95, 2.78]</td>
<td>0.09</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, and PAD risk factors</td>
<td>1.81 [1.06, 3.07]</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, and inflammation</td>
<td>1.77 [1.04, 3.03]</td>
<td>0.04</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, and health behaviors</td>
<td>1.79 [1.13, 2.81]</td>
<td>0.04</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, comorbid conditions, medication use, PAD risk factors, inflammation, and health behaviors</td>
<td>1.89 [0.98, 3.83]</td>
<td>0.11</td>
</tr>
</tbody>
</table>

### Association Between Incident PAD and Depression

**Incident PAD:**
- 7% (13/175) of patients with depressive symptoms
- 5% (37/759) of patients without depressive symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age and sex only</td>
<td>2.99 [1.09, 4.00]</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for age, sex, and race</td>
<td>1.93 [0.99, 3.74]</td>
<td>0.05</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, comorbid conditions, and medication use</td>
<td>1.79 [0.83, 3.55]</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, and PAD risk factors</td>
<td>1.61 [0.82, 3.23]</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, and inflammation</td>
<td>1.75 [0.89, 3.46]</td>
<td>0.10</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, and health behaviors</td>
<td>1.82 [0.92, 3.21]</td>
<td>0.07</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, comorbid conditions, medication use, PAD risk factors, inflammation, and health behaviors</td>
<td>1.33 [0.65, 2.71]</td>
<td>0.48</td>
</tr>
</tbody>
</table>

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**Table:**

<table>
<thead>
<tr>
<th>Model</th>
<th>PAD events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>-4.2</td>
</tr>
<tr>
<td>White</td>
<td>15.5</td>
</tr>
<tr>
<td>PDA</td>
<td>3.2</td>
</tr>
<tr>
<td>Sex</td>
<td>2.7</td>
</tr>
<tr>
<td>Age</td>
<td>4.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>18.4</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>14.0</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>-6.0</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>-9.0</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>-6.6</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>8.6</td>
</tr>
<tr>
<td>Log Triglycerides (mg/dL)</td>
<td>8</td>
</tr>
<tr>
<td>SBP</td>
<td>-2.7</td>
</tr>
<tr>
<td>DBP</td>
<td>-1.1</td>
</tr>
<tr>
<td>Health Behaviors</td>
<td>8</td>
</tr>
</tbody>
</table>

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**Graphs:**

- **PAD Events By Depression Status**
- **Association Between Prevalent PAD and Depression**
- **Association Between Incident PAD and Depression**

Grenon et al, J Am Heart Assoc. 2012
Conclusions

• Depressive symptoms associated with higher PAD
• The association is partially explained by *modifiable* risk factors
  – smoking, physical inactivity
  – inflammation
• Direction of association needs to be further explored
• Need for a high index of suspicion for depression in the setting of PAD
  – Encouraging patients to seek treatment for this condition

Goals

1. Does depression negatively impact patients with coronary artery disease?

2. Does depression negatively impact patients with peripheral artery disease?
   - Recent data from the VAMC San Francisco

3. Can we do anything about it?
AHA Recommendations

Need to screen is imperative

PHQ2 and if questions positive, use PHQ9

PHQ-2

Over the last 2 weeks, how often have you been bothered by any of the following problems

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

- Score ranges from 0-6
- Score of 3 or higher has an 83% sensitivity and 90% specificity for major depressive disorder

PHQ-9

1. Little interest or pleasure in doing things
2. Feeling down, depressed or hopeless
3. Trouble falling or saying asleep, sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about oneself
7. Trouble concentrating on things
8. Moving or speaking slowly
9. Suicidal thoughts

Score of 10 or higher has a sensitivity and specificity of 88% for major depressive disorders

- Kroenke et al. J Gen Intern Med 2001

AHA Recommendations

- Patients with positive screening
  - Evaluated by a professional qualified
  - Evaluated for adherence to their medical care
AHA Recommendations

- Antidepressant safe in patients with CAD and effective for depression.
  - "Since SSRI treatment soon after AMI appears safe, it is relatively inexpensive, and may be effective for post-AMI depression, it seems appropriate to screen and treat."
- Cognitive therapy can be an alternative or can be used in combination
- Exercise important

Do antidepressants improve cardiovascular outcomes in patients with ACS?

- 2 randomized trial
  - SADHART (sertraline)
  - CREATE (citalopram)
- 1 nonrandomized trial
  - ENRICHD (cognitive tx)

ENRICHD Trial (JAMA 2003)

- Patient Population:
  - 2481 post-MI patients with depression (within 28 days)
- Intervention:
  - Cognitive behavior therapy x 6 months +/- SSRI as indicated
- Goal:
  - To determine if mortality and recurrent infarction are reduced by treatment of depression with cognitive therapy supplemented by SSRI
- Endpoints:
  - Primary: Death/recurrent MI
  - Secondary: depression (17-item hamilton Rating Scale for depression)

ENRICHD Trial (JAMA 2003)

- No change in event-free survival
- Improvement in depression and social isolation

Probability of death or non-fatal MI

SADHART Trial (JAMA 2002)

- **Patient Population:**
  - 369 patients s/p ACS with depression

- **Intervention:**
  - Sertraline vs placebo x 6 months

- **Goal:**
  - To evaluate the safety and efficacy of Sertraline in depressed patients s/p MI or unstable angina

- **Endpoints:**
  - Primary: Change in LVEF
  - Secondary: cardiac measures and CV adverse events, depression symptoms.

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SADHART Trial (JAMA 2002)

- Sertraline is safe and effective for the treatment of depression in patients with ACS

**Endpoints: Change in LVEF**

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. of Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Sertraline: 2</td>
<td>Placebo: 5</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Angina</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>Composite end point</td>
<td>32</td>
<td>41</td>
</tr>
</tbody>
</table>

*RR* indicates relative risk; CI, confidence interval.

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CREATE Trial (JAMA 2007)

- **Patient Population:**
  - 284 with CAD and major depression

- **Intervention:**
  - Interpersonal therapy vs none
  - SSRI (citalopram) vs placebo

- **Goal:**
  - To determine the safety of SSRI (citalopram) and interpersonal psychotherapy in reducing depressive symptoms in patients with CAD and major depression

- **Endpoints:**
  - Primary: change in 24-item Hamilton Depression Rating Scale at 3 months
  - Secondary: Beck Depression inventory score
CREATE Trial (JAMA 2007)

• Efficacy of citalopram
• No added value of interpersonal psychotherapy

Do antidepressants improve cardiovascular outcomes in patients with ACS?

• 2 randomized trial
  – SADHART (sertraline)
  – CREATE (citalopram)

• 1 nonrandomized trial
  – ENRICHD (cognitive tx)

1. Psychological and pharmacological interventions after ACS are safe and reduce anxiety and depression.

1. There is insufficient evidence to know whether treatment of depression improve cardiovascular outcomes.


What about Patients with Peripheral Artery Disease?
Goals

1. Does depression negatively impact patients with coronary artery disease?

2. Does depression negatively impact patients with peripheral artery disease?
   - Recent data from the VAMC San Francisco

3. Can we do anything about it? LIKELY

Summary

- Depression is associated with cardiovascular diseases and appears to influence outcomes.

- Need for a high index of suspicion for depression in the setting of PAD — PHQ2

- Referring to qualified professional may help, if not to improve CV outcomes, at least to help with reduction of anxiety and depressive symptoms.

From: The Relationship of Depression to Cardiovascular Disease: Epidemiology, Biology, and Treatment

Hypothetical schema of pathophysiologic alterations associated with depression that likely contribute to increased vulnerability to cardiovascular disease (CVD). Autonomic nervous system innervation of the heart via parasympathetic vagus (X) and sympathetic (postganglionic efferents from cervical and upper thoracic paravertebral ganglia) nerves is shown. CRF indicates corticotropin-releasing factor; ACTH, corticotropin; TNF-α, tumor necrosis factor-α; IL-1, interleukin 1; IL-6, interleukin-6; HRV, heart rate variability; and HPA, hypothalamic-pituitary-adrenocortical axis.
Platelet adhesion to collagen exposed within the denuded area of vascular endothelium has stimulated platelet activation. Activation is accompanied by extrusion of platelet storage granule contents, which recruits other platelets, causes irreversible platelet-platelet aggregation, and forms a fused platelet thrombus. Ca++ indicates intracellular free calcium concentrations; PF4, platelet factor 4; β-TG, β-thromboglobulin; ADP, adenosine diphosphate; and 5-HT, serotonin. Adapted from R&D Systems, Minneapolis, Minn. Used with permission.