Depression as a *New Risk Factor for Coronary Heart Disease*

Implications for Minority Health

April 28, 2009

James A. Blumenthal, Ph.D.

Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, NC
Disclosure Information

No Conflicts of Interest
Cameron Indoor Stadium
Home of Duke "Blue Devils"
Carolina Hurricanes: 2006 Stanley Cup Champions!
Health Disparities

- Preventable differences in the indicators of health of different population groups
- Differences in the incidence, prevalence, mortality and burden of disease and other adverse health outcomes
- Includes ethnic or racial differences in treatment approaches and clinical outcomes
Outline of Presentation

• Epidemiology of CHD
• Definitions and assessment of depression
• Health consequences of depression
• Depression as a CHD risk factor
  – Healthy persons
  – CHD patients
• Interventions
  – Pharmacologic
  – Psychological
  – Exercise
Primary Causes of Death in the U.S.

- Cardiovascular Diseases
- Malignant Neoplasms
- Respiratory Disorders
- Neuropsychiatric Disorders
- Unintentional Injuries
- Diabetes Mellitus
- Infectious Diseases
Cardiovascular Disease

- 36.2% of deaths in Whites
- 33.6% of death in African Americans
- 24.9% of death in Native Americans
- 34.8% of death in Asians
- 39.6% of death in Hispanics

Cardiovascular death rates in white and African American men and women.

Ferdinand, 2006.
Annual rate of first myocardial infarction by age among African American and white men and women

Ferdinand, 2006. (Adapted from American Heart Association)
Rates of premature coronary artery disease death by ethnic group and age

Ferdinand, 2006.
CHD and Stroke Mortality Rates by Race and Ethnicity in the United States in 1997

Cooper et al, 2000
Proportions of African American and white subjects in the Dallas Heart Study with coronary artery disease risk factors.

Ferdinand, 2006; Adapted from J Am Coll Cardiol.
Differences in the Clinical Features and Outcomes in African Americans and Whites with Myocardial Infarction

Mehta et al, 2006
Proportion of subjects in the Atherosclerosis Risk in Communities Study with 0, 1, 2, or ≥3 risk factors from among obesity, hypertension, diabetes, smoking, hypercholesterolemia, hypertriglyceridemia, and low HDL cholesterol.

Ferdinand, 2006.
Probability of surviving free of coronary heart disease in women aged 25 to 74 years according to ethnic group and age at baseline

Gillum et al, 1997. Probability of surviving free of coronary heart disease in men aged 25 to 74 years according to ethnic group and age at baseline. Solid lines represent African-American persons, and dashed lines represent white persons.
Years of potential life lost to total heart disease at <75 years of age in African American and white men and women.

Ferdinand, 2006.
Ferdinand, 2006. (Top) Percentage of African American and white population aged 40 to 59 years and ≥60 years screened for dyslipidemia (1999–2000).

(Bottom) Percentage of African Americans and whites treated for dyslipidemia who met lipid goals (1988–1994). Based on data from the Third National Health and Nutritional Examination Survey [NHANES III].
Median and interquartile range (25th and 75th percentile) high-sensitivity C-reactive protein (CRP) levels according to ethnic group in women in the Women’s Health Study not using hormone replacement therapy (top) and using hormone replacement therapy (bottom). Adapted from Am J Cardiol. Ferdinand, 2006.
Death rates for coronary heart disease by sex and race in the United States from 1980 to 1997

Cooper et al, 2000.. *Rates are age-adjusted to 2000 standard.
Differences in the Clinical Features and Outcomes in African Americans and Whites with Myocardial Infarction

Table 1  Differences in baseline characteristics in African Americans versus whites

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whites</th>
<th>African Americans</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30755</td>
<td>1664</td>
<td></td>
</tr>
<tr>
<td>Age (mean [SD] y)</td>
<td>61.1 (12.2)</td>
<td>57.0 (12.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>27.4</td>
<td>34.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>42.8</td>
<td>61.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16.3</td>
<td>27.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>42.7</td>
<td>56.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Elevated cholesterol (%)</td>
<td>39.2</td>
<td>30.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>48.9</td>
<td>43.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior angina (%)</td>
<td>37.3</td>
<td>38.9</td>
<td>.217</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>17.6</td>
<td>18.3</td>
<td>.497</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>2.5</td>
<td>2.7</td>
<td>.638</td>
</tr>
<tr>
<td>Prior congestive heart failure (%)</td>
<td>2.0</td>
<td>2.8</td>
<td>.020</td>
</tr>
<tr>
<td>Prior angioplasty (%)</td>
<td>7.1</td>
<td>6.7</td>
<td>.443</td>
</tr>
<tr>
<td>Prior coronary bypass surgery (%)</td>
<td>6.2</td>
<td>2.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class ≥III (%)</td>
<td>1.6</td>
<td>2.2</td>
<td>.015</td>
</tr>
<tr>
<td>Presenting heart rate (mean [SD], beats/min)</td>
<td>75.3 (17.4)</td>
<td>79.1 (17.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presenting systolic BP (mean [SD], mm Hg)</td>
<td>128.4 (23.7)</td>
<td>134.3 (24.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presenting diastolic BP (mean [SD], mm Hg)</td>
<td>76.6 (15.6)</td>
<td>80.3 (15.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Mehta et al, 2006
Differences in the Clinical Features and Outcomes in African Americans and Whites with Myocardial Infarction

Table 2 Differences in the treatments received in African Americans versus whites

<table>
<thead>
<tr>
<th>Drug therapies</th>
<th>Whites</th>
<th>African Americans</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30755</td>
<td>1664</td>
<td></td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>93.2</td>
<td>93.7</td>
<td>.424</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>80.8</td>
<td>82.6</td>
<td>.070</td>
</tr>
<tr>
<td>Calcium-channel blockers (%)</td>
<td>34.9</td>
<td>37.7</td>
<td>.033</td>
</tr>
<tr>
<td>ACE inhibitors (%)</td>
<td>26.3</td>
<td>32.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Digitalis (%)</td>
<td>17.1</td>
<td>12.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glycoprotein IIb-IIIa antagonist (%)</td>
<td>17.0</td>
<td>13.6</td>
<td>.062</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization (%)</td>
<td>74.3</td>
<td>75.0</td>
<td>.504</td>
</tr>
<tr>
<td>Angioplasty (%)</td>
<td>35.8</td>
<td>30.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary artery bypass surgery (%)</td>
<td>13.8</td>
<td>9.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme.

Mehta et al, 2006
Death rates from heart disease in 2001

Mensah et al, 2005
Years of Potential Life Lost before age 75 due to heart disease in 2001

Mensah et al, 2005
Age-specific death rates for diseases of the heart (A) and stroke (B) by race/ethnicity and sex, United States, 2001.

Mensah et al, 2005
Death rates for diseases of the heart and stroke by race/ethnicity and sex in the United States: 1980 to 2001

Mensah et al, 2005
## 2006 NC Heart Disease Report Card

<table>
<thead>
<tr>
<th>Heart disease deaths per 100,000 population</th>
<th>1997 - 2001</th>
<th>Ratio</th>
<th>2000-2004</th>
<th>Ratio</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>257.8</td>
<td></td>
<td>237.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>249.6</td>
<td>1.0</td>
<td>228.1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>African American or Black</td>
<td>308.7</td>
<td>1.2</td>
<td>281.9</td>
<td>1.2</td>
<td>C</td>
</tr>
<tr>
<td>American Indian</td>
<td>312.3</td>
<td>1.3</td>
<td>266.0</td>
<td>1.2</td>
<td>C</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>83.1</td>
<td>0.3</td>
<td>68.5</td>
<td>0.3</td>
<td>A</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>78.5</td>
<td>0.3</td>
<td>81.6</td>
<td>0.3</td>
<td>A</td>
</tr>
</tbody>
</table>

http://www.schs.state.nc.us/SCHS/data/minority.cfm
Burden of Disease in the U.S.

IHD = ischemic heart disease; CVD = cerebrovascular disease; CHD = coronary heart disease; MDD = unipolar major depressive disorder


DALY = Death and Disability Adjusted Life Years
Definition of Depression

• Mood state: transient feeling: “down”, sad, unhappy, dissatisfied
• Clinical Condition: constellation of persistent symptoms
  – Major depression
  – Minor depression
  – Bipolar depression
  – Dysthymia
DSM-IV Criteria for MDD

- Depressed mood
- Markedly diminished interest or pleasure in nearly all activities most of the day
- Significant weight loss, or change in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death, suicidal ideation
ASSESSMENT METHODS

• INTERVIEW
  – SCID
  – DIS
  – CIDI
  – HAM-D*
  – PHQ-9**

• SELF-REPORT QUESTIONNAIRES*
  – BDI
  – CES-D
  – ZUNG

• To assess symptom severity NOT to diagnose MDD
** Screening instrument-not for diagnosis
Sample Items from Beck Depression Inventory
(BDI > 10 at least mild to moderate symptoms)

1. ▪ 0 I do not feel sad.
   ▪ 1 I feel sad.
   ▪ 2 I am sad all the time and I can’t snap out of it.
   ▪ 3 I am so sad or unhappy that I can’t stand it.

13. ▪ 0 I make decisions about as well as before.
   ▪ 1 I put off making decisions more than I used to.
   ▪ 2 I have greater difficulty in making decisions than before
   ▪ 3 I can’t make decisions at all any more
Is Screening Appropriate?

- Thombs et al. JAMA 2008; 300: 2161-2171
- Examined benefits of depression screening
  - 11 studies screening accuracy
  - 6 depression treatment trials
- Concluded that there is “[no] evidence for or against the recommendations that depression be evaluated or that screening for depression be considered as part of standard care in patients with CVD.” (p 2169)
- Suggested that routine screening “is not supported by the evidence”
Epidemiology of Major Depression in the United States

• Lifetime prevalence: 16.6%
• 12-month prevalence: 10%
• Twice as likely in women compared to men
• Up to 25% in adolescents with >50% recurrence in adulthood
• Up to 50% in cardiac populations

Lifetime Prevalence of Depression By Ethnicity

Riolo et al, 2005
Hasin et al, 2005
Diagnostic Patterns in Psychiatric Patients

Minsky et al, 2003
Diagnostic Patterns in Psychiatric Patients

Minsky et al, 2003
Personal Cost of Depression

- Lower quality of life
- Increased risk of
  - Addictions
  - Divorce/separation
  - Shame and stigma
  - Unemployment

Weissman et al. JAMA. 1996;276:293.
Consequences of Depression

• Shorter survival in elderly and seriously ill
• Increased risk of
  – Heart disease\(^1\) and stroke\(^2\)
  – Osteoporosis\(^3\)
  – Diabetes\(^4\)

Why Focus on Depression in Cardiac Patients?

- 2\textsuperscript{nd} major cause of early death and disability in industrialized countries (following CHD)
- Associated with poor compliance and increased health care costs
- Highly prevalent in CHD patients
- Associated with worse clinical outcomes
## Prevalence of Depression in Hospitalized CHD Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study Details</th>
<th>Sample Size</th>
<th>Major Depression</th>
<th>Elevated Depression Symptoms / Minor Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>(Frasure-Smith et al, 1993, 1999)</td>
<td>n=222</td>
<td>12–16%</td>
<td>17–20%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>(Lespérance et al, 2000)</td>
<td>n=430</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>CHF</td>
<td>(Jiang et al, 2001)</td>
<td>n=374</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>Catheterization</td>
<td>(Hance et al, 1996)</td>
<td>n=200</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>(Connerney et al, 2001)</td>
<td>n=309</td>
<td>20%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Prevalence of Depression following MI

- 24 studies; 14,326 patients
- Structured Interview: 19.8%
- BDI: 31.1%
- HADS > 8%

Thombs et al, 2006
Depressive Symptoms in Cardiac Patients

- Caucasian 79%
- African American 15%
- Native American 5%
- Asian 1%

Waldman et al., AHJ 2009
Prevalence of Depression in CAD Patients Undergoing Cardiac Catheterization

- BDI > 10: 28%
- Receiving anti-depressants: 10%
- Total sample depressed: 38%
- BDI scores > 10
  - Caucasian: 27%
  - African American: 34%
- Receiving anti-depressant medication
  - Caucasian: 21%
  - African American: 11.7% *

Waldman et al., AHJ, 2008

P = .016
Unrecognized Depression in Patients with Acute Coronary Syndrome

Amin et al, 2006
Meta Analysis: Primary Risk Factor

Regulies R. Depression as a Predictor for Coronary Heart Disease

- Cohort studies with depression as the exposure and MI or CHD as outcome
- Study design, sample size, depression, outcome, N, Relative Risk abstracted
- 11 studies met inclusion criteria
- RR for the development of CHD was 1.64
- RR for clinical depression was 2.69
Figure 2. Individual and overall relative risks (most-adjusted) for coronary heart disease in depressed subjects

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Relative Risk (random) 95% CI</th>
<th>Relative Risk (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Traditional Risk Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.05 [1.04, 1.06]</td>
<td></td>
</tr>
<tr>
<td>HT Stage 2</td>
<td>1.92 [1.42, 2.59]</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.71 [1.39, 2.10]</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.47 [1.04, 2.08]</td>
<td></td>
</tr>
<tr>
<td>LDL &gt; 160</td>
<td>1.74 [1.36, 2.23]</td>
<td></td>
</tr>
<tr>
<td>HDL &lt; 35</td>
<td>1.46 [1.15, 1.85]</td>
<td></td>
</tr>
<tr>
<td>02 Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed Mood</td>
<td>1.49 [1.16, 1.92]</td>
<td></td>
</tr>
<tr>
<td>Clinical Depression</td>
<td>2.69 [1.63, 4.43]</td>
<td></td>
</tr>
</tbody>
</table>
Depression in Cardiac Patients: Recent Meta Analyses

• Barth et al. Psychosom Med 66: 802-813; 2004
• van Melle et al. Psychosom Med 66: 814-822; 2004
Depression and All Cause Mortality

Comparison: 01 Depression versus no depression
Outcome: 01 All-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Depression n/N</th>
<th>No depression n/N</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bush (34)</td>
<td>5 / 46</td>
<td>12 / 221</td>
<td>2.12 [0.71, 6.35]</td>
<td>7.3</td>
<td>2.12 [0.71, 6.35]</td>
</tr>
<tr>
<td>Irvine (18)</td>
<td>15 / 98</td>
<td>17 / 203</td>
<td>1.98 [0.94, 4.15]</td>
<td>16.6</td>
<td>1.98 [0.94, 4.15]</td>
</tr>
<tr>
<td>Kaufman (33)</td>
<td>14 / 87</td>
<td>19 / 231</td>
<td>2.14 [1.02, 4.48]</td>
<td>17.3</td>
<td>2.14 [1.02, 4.48]</td>
</tr>
<tr>
<td>Lauzon (35)</td>
<td>13 / 191</td>
<td>15 / 359</td>
<td>1.67 [0.78, 3.60]</td>
<td>19.3</td>
<td>1.67 [0.78, 3.60]</td>
</tr>
<tr>
<td>Lesperance (32)</td>
<td>8 / 35</td>
<td>13 / 187</td>
<td>3.97 [1.50, 10.46]</td>
<td>6.3</td>
<td>3.97 [1.50, 10.46]</td>
</tr>
<tr>
<td>Mayou (12)</td>
<td>4 / 25</td>
<td>24 / 318</td>
<td>2.23 [0.71, 6.99]</td>
<td>6.1</td>
<td>2.23 [0.71, 6.99]</td>
</tr>
<tr>
<td>Silverstone (29)</td>
<td>8 / 48</td>
<td>1 / 60</td>
<td>11.80 [1.42, 98.04]</td>
<td>1.5</td>
<td>11.80 [1.42, 98.04]</td>
</tr>
<tr>
<td>Strik (36)</td>
<td>1 / 63</td>
<td>4 / 143</td>
<td>0.56 [0.06, 5.12]</td>
<td>4.8</td>
<td>0.56 [0.06, 5.12]</td>
</tr>
</tbody>
</table>

Total (95% CI)

Test for heterogeneity chi-square = 6.57 df = 8 p = 0.58
Test for overall effect z = 5.59 p < 0.00001

Van Melle et al., Psychosom Med, 2004
Methods Used in Montreal Studies of Psychosocial Aspects of Acute Coronary Syndromes

• Samples
  – Post-MI: Study I (N=222); Study II (N=678)
  – Unstable Angina: Study III (N=430)
  – 30.8% women; no age limits
• Baseline psychosocial interviews during admission (depression, anxiety, anger, social support)
• Primary measure of depression: the Beck Depression Inventory
• Usual care
• 5-year follow-up for events

Frasure-Smith, Lespérance, et al
Depression and 1-Year Post-MI Cardiac Mortality

Survival Free of Cardiac Mortality, Cumulative %

- Not Depressed (BDI < 10)
- Depressed (BDI ≥ 10)

Odds Ratio = 3.4 (1.8 – 6.7)

P< 0.001

Frasure-Smith et al,
Depression and 4-Year Post-MI Cardiac Mortality

Survival Free of Cardiac Mortality, Cumulative %

Time After Discharge for MI, Days

Not Depressed (BDI < 10)

Depressed (BDI > 10)

Lespérance, et al, 2000

N=896
Long-Term Survival Impact of Increasing Levels of Post-MI Depression (BDI Score)

Survival Free of Cardiac Mortality, Cumulative %

Time After Discharge for MI, Days

Lespérance, et al, 2000

N=896
Depression and 1-Year Cardiac Prognosis in Unstable Angina

Survival Free of Cardiac Mortality or Non-Fatal MI, Cumulative %

Not Depressed (BDI < 10)

Depressed (BDI ≥ 10)

Odds Ratio = 4.7 (1.9 – 11.3)
P < 0.001

Lespérance et al, 2000

N = 430
Depression and Heart Failure

• 204 HF outpatients
• Assessments
  – Depression assessed by BDI
  – Disease severity assessed by NT-proBNP
  – Follow-up = 3yrs
  – Endpoint: Deaths and hospitalizations
• Results
  – 54 deaths
  – 126 hospitalizations

Sherwood et al. 2007 Arch Int Med
Depression Risk: BDI: HR = 1.56 (CI 1.07-2.29)
Risk for Anti-depressant use: HR = 1.75 (CI = 1.14 - 2.68)
Depression and Survival After CABG Surgery

- 817 patients undergoing CABG at DUMC between May 1989 and May, 2001
- Presurgical data obtained from medical records
- Mortality assessed every year by searching hospital records, making follow-up calls, and searching the national death records
- Assessed for depression using the CES-D
  - before surgery
  - 6-months after surgery
- Patients were followed for up to 12.2 years (median 5.2 yrs) to assess all-cause mortality
Depression Prevalence at Baseline

<table>
<thead>
<tr>
<th>Depression Level</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (%) (CESD 16-26)</td>
<td>26</td>
</tr>
<tr>
<td>Moderate-Severe (%) (CESD ≥27)</td>
<td>12</td>
</tr>
</tbody>
</table>
Survival Curves by Severity of Baseline Depression

Figure 1. Survival curves by severity of baseline (pre-surgical) depression, adjusted for age, LVEF, diabetes, gender, number of surgical grafts, and history of MI. The hazard ratio associated with CES-D ≥ 27 was 2.8 (95% CI: 1.8-5.1, p < .001).
# Crude Death Rate by Course of Depression

<table>
<thead>
<tr>
<th>Baseline</th>
<th>6 months</th>
<th>Variable</th>
<th>Death/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed</td>
<td>Depressed</td>
<td>Persistent</td>
<td>15/78 (19%)</td>
</tr>
<tr>
<td>Non-Depressed</td>
<td>Depressed</td>
<td>New Onset</td>
<td>5/36 (14%)</td>
</tr>
<tr>
<td>Depressed</td>
<td>Non-Depressed</td>
<td>Remitted</td>
<td>11/108 (10%)</td>
</tr>
<tr>
<td>Non-Depressed</td>
<td>Non-Depressed</td>
<td>Never</td>
<td>34/333 (10%)</td>
</tr>
</tbody>
</table>
Figure 2. Survival curves by six-month course of depression, adjusted for age, LVEF, diabetes, gender, number of surgical grafts, and history of MI. The hazard ratio associated with Persistent Depression was 2.3 (95% CI: 1.2-4.6, p = .01). The hazard ratio for the New Onset Depression category was 2.4 (95% CI: 0.8-7.2, p = .12).
Summary of Studies of Depression as a Secondary Risk for CHD events

• A number of prospective studies with objective CHD measures
• Consistent association in various CHD groups (post-MI, unstable angina, CHF, and CABG) and various investigative teams
• Risk increased 2-4 fold
• Dose-related increase in risk
• Risk independent of age and a variety of other cardiac risk factors
Alternate Explanations for Prognostic Impact of Depression in CHD

- Impact not explained by cardiac disease severity.
- Impact not explained by age, gender, or other demographic characteristics.
- Impact not explained by differential medication use.
- Impact not explained by overlap of cardiac and depressive symptoms (fatigue, sleep difficulties, etc.).
POTENTIAL MECHANISMS

- Adherence
- Lifestyle: Smoking, Alcohol Consumption, Physical Inactivity
- Metabolic Syndrome
- Autonomic Nervous System Dysregulation
- Platelet activity
- Inflammation
Potentially Useful Treatments for Depression in CHD Patients

- Anti-depressants (SSRIs)
- Brief, structured psychotherapies with active therapist involvement
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Psychotherapy (IPT)
- Exercise
SADHART
Sertraline Anti-depressant heart Attack Randomized Trial

- Multi-site RCT of placebo vs SSRI for post-ACS patients with MDD
- Primary endpoint: \( \Delta \) LVEF; Safety and Efficacy trial (JAMA, 2002)
Sertraline Antidepressant Heart Attack Randomized Trial (SADHART)

Recent MI
Major depression
Multicenter (30-40 international sites)
369

14-day run-in

Sertraline 50-200 mg/day  Placebo

Safety endpoints: Change from baseline in resting LVEF
Efficacy endpoints: Change from baseline in total HAM-D score

Secondary endpoints: 1) EKG, HRV and arrhythmia analysis
2) Platelet function
3) Composite clinical endpoint
### SADHART: Antidepressant Efficacy Results

#### Table 6. Antidepressant Efficacy Results*

<table>
<thead>
<tr>
<th></th>
<th>Sertraline</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>186</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>CGI-I score, mean (SD)†</td>
<td>2.57 (0.06)</td>
<td>2.75 (0.07)</td>
<td>.049</td>
</tr>
<tr>
<td>HAM-D change score, mean (SD)‡</td>
<td>−8.4 (0.41)</td>
<td>−7.6 (0.41)</td>
<td>.14</td>
</tr>
<tr>
<td>CGI-I responder, No. (%)</td>
<td>125 (67)</td>
<td>97 (53)</td>
<td>.01</td>
</tr>
<tr>
<td>Any recurrent MDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>96</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>CGI-I score, mean (SD)†</td>
<td>2.49 (0.09)</td>
<td>2.80 (0.09)</td>
<td>.02</td>
</tr>
<tr>
<td>HAM-D change score, mean (SD)‡</td>
<td>−9.8 (0.59)</td>
<td>−7.6 (0.61)</td>
<td>.009</td>
</tr>
<tr>
<td>CGI-I responder, No. (%)</td>
<td>69 (72)</td>
<td>46 (51)</td>
<td>.003</td>
</tr>
<tr>
<td>More severe (2 prior episodes plus HAM-D score ≥18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>50</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>CGI-I score, mean (SD)†</td>
<td>2.41 (0.13)</td>
<td>2.98 (0.12)</td>
<td>.002</td>
</tr>
<tr>
<td>HAM-D change score, mean (SD)‡</td>
<td>−12.3 (0.88)</td>
<td>−8.9 (0.98)</td>
<td>.01</td>
</tr>
<tr>
<td>CGI-I responder, No. (%)</td>
<td>39 (78)</td>
<td>18 (45)</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Patients with no follow-up data are included in the analysis by imputing no change. CGI-I indicates Clinical Global Impression Improvement Scale; MDD, major depressive disorder; and HAM-D, Hamilton Depression Scale.
†For repeated measures of analysis of CGI-I, weeks 2, 6, 10, 16, and 24 are used. CGI-I at week 0 is used as a covariate in the model. Responders have CGI-I scores of ≤2 (much or very much improved) at endpoint.
‡For repeated-measures analysis of HAM-D, weeks 6, 10, and 16 are used.

Glassman, O’Connor, et al, JAMA, 2002;288:701-709
Relative Risk of Death and Urgent Rehospitalizations

Glassman, O’Connor, et al, JAMA, 2002;288:701-709
<table>
<thead>
<tr>
<th>Event</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>0.39 (0.08 – 2.00)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.70 (0.23 – 2.17)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.49 (0.09 – 2.65)</td>
</tr>
<tr>
<td>Worsened Angina</td>
<td>0.70 (0.36 – 1.32)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>0.62 (0.21 – 1.85)</td>
</tr>
<tr>
<td>Composite</td>
<td>0.68 (0.43 – 1.09)</td>
</tr>
</tbody>
</table>
ENRICHED
Enhancing Recovery in Coronary Heart Disease

- Multi-site RCT of CBT (with SSRI) vs usual care for post MI patients with depression and/or low social support
- Primary endpoint: Mortality and Morbidity; Survival trial (JAMA, 2003)
Participant Selection

33,780 Screened

32,246 Met MI Criteria

1,534 Did not meet MI criteria

22,967 Medically ineligible
6,698 Did not meet criteria for depression or low social support

2481 Randomized

1243 Usual Care

1238 Psychosocial Intervention
Baseline to 6-Month Changes in Social Support and Depression

ESSI Score  Hamilton Depression Score

Intervention Effect

Intervention Usual Care

ESSI reported for patients with low social support only.
Hamilton depression score reported for depressed patients only.
Kaplan-Meier Survival Curves

Log Rank Chi-Square: 0.02

$P = .89$
Hazard Ratios for Prespecified Subgroups

Overall
Women
Men
Minority
Nonminority

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0

Intervention Better  Usual Care Better
Effect of Antidepressant Use on All-Cause Mortality

Taylor et al., Arch Gen Psychiatry, 2004
CREATE
The Canadian Cardiac Randomized Evaluation of Anti-depressant and Psychotherapy Efficacy Trial

– 2 by 2 (IPT/Clinical mgt and Citalopram/placebo)
– Primary endpoint: HAM-D; Depression trial (JAMA, 2007)
CREATE Trial

• 284 CAD patients
  – MDD
  – HAMD ≥ 20
• 12 weeks of treatment
• 2 X 2 factorial design
  – IPT/clinical management
  – Citalopram/placebo
• 1° Outcome: HAM-D
• 2° Outcome: BDI-II
CREATE Study: 12-week Change in HAM-D

Δ HAMD

- IPT (+CM) P = .06
- Clinical Mgt
- Drug P = .005
- Placebo
Primary Care Treatment for Depression

Miranda & Cooper, 2004
Physician Visits and Prevalence of Depression

Rates of MDD (per 100 in US)

Skaer et al, 2000; Sclar et al, 2008
Rates of MDD and antidepressant prescription (per 100 in US)

Skaer et al, 2000; Sclar et al, 2008

Physician-Diagnosed Depression and Antidepressant Prescriptions
Treatment of Depression in Patients with Ischemic Heart Disease

% Receiving Antidepressant Treatment

Waldman et al., Am Heart J, 2008
Predictors of Antidepressant use

Waldman et al., AHJ, 2008
Criticisms of Waldman et al.

• Coyne et al.
  – Careless prescription practices

• Thombs
  – Depression screening imprecise
  – Ineffective treatments for depression
  – African Americans may be skeptical of psychiatric treatment
Ethnic Differences in Suicide

Figure 1
Rates of completed suicide between 1986 and 2004 among Tennessee Medicaid/TennCare enrollees, by sex and race

Ray et al, 2007
Antidepressant Treatment and Suicide

% Receiving Antidepressant Treatment

- 1-year preceding suicide
- 90 days preceding suicide

Ray et al, 2007
Possible Explanations

• Depression is under-diagnosed in African Americans
• Physicians are less likely to prescribe treatment for African Americans
• African Americans may be more reluctant to accept pharmacologic treatment
• Psychopharmacologic treatment may be less effective in African Americans
• All of the above
Anxiety and Mortality

Riolo et al, 2005
Ethnic Differences in Suicide

Median age for suicide:
• Whites: 44 years
• Blacks: 34 years
• “Others”: 35 years

Garlow et al, 2005
Response to Citalopram

Lesser et al, 2007
Ethnic Differences in Efficacy and Side Effects of Prozac

Schnittker, 2003
Ethnic Differences in Willingness to use Prozac

Schnittker, 2003
General Findings from RCTs of Depression in Cardiac Patients

• Depression can be reduced
  – SSRIs
  – CBT
  – Clinical management as good/better compared to IPT

• No evidence that treating depression results in better medical outcomes
  – CBT = Education
  – SSRIs may be beneficial (non-RCTs)
Mechanisms: Implications for Treatment

Intervening here does not necessarily*…

...target mediating factors

Depression  Mechanism  CAD outcome
General Findings from RCTs of Depression in Cardiac Patients

- Depression can be successfully reduced
  - Medications (SSRIs)
  - Cognitive Behavior Therapy (CBT)
- Not clear that depression is recognized as often in African Americans and other minorities
- No evidence that treating depression results in better medical outcomes, especially in women and minorities
- More RCTs including adequate representation of women and minorities are needed
- Alternative treatments (e.g., exercise) should be considered.
Exercise: Efficient, Direct Intervention

Psychotherapy *
Antidepressants *
Exercise*

Depression

Adherence *
Lifestyle **
Metabolic Syndrome *
Platelet **
HPA axis *
ANS *
Inflammation *

CAD outcome
Effects of Exercise Training on Older Patients with Major Depression

- 156 men and women with MDD
- > 50 yrs
- Sedentary
- Randomized to 4 months of
  - Aerobic exercise
  - Anti-depressant medication
  - Combination of exercise and medication

Blumenthal et al., Arch Int Med., 1999
Changes in Depression

**HAM-D Score**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Ex</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Comb</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

**BDI Score**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Ex</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Comb</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

* Different from Baseline, p < .001
Recovery Rate

Criterion: No DSM-IV Dx after 16 weeks
Exercise and Mortality following AMI: The ENRICHD Experience

- 2078 AMI patients (1175 men; 903 women) in ENRICHD trial
- Patients with depression/low support and MI <28 days
- Assessment of exercise performed 6 months after AMI
- Follow-up: 4 yrs (Mean = 2.0 yrs)

Blumenthal et al., MSSE, 746-755; 2004
Assessment of Exercise

In the past 6 months, have you engaged in regular exercise?

Yes: 982 (47%)
No: 1,097 (53%)
Depression and Exercise Following Acute MI

Baseline Six Months Beck Depression Score

Exercise
No Exercise

0 2 4 6 8 10 12 14 16 18 Beck Depression Score

Baseline
Six Months
Clinical Events

• Mortality (N = 187)
  • 5.6% among exercisers
  • 12.95% among non-exercisers

• Morbidity (N = 179)
  • 6.5% among exercisers
  • 10.5% among non-exercisers

• Exercise Main Effect: No evidence of Mediation or Moderation
Exercise and Mortality Following Acute MI
Conclusions

• Depression is a risk factor for healthy persons and CHD patients
• Data are limited, but the risk appears comparable for African Americans and Caucasians
• There are a number of plausible behavioral and physiologic mechanisms that could explain this relationship
• Depression can be successfully treated
• However, depression--especially among African Americans--can be under-recognized and appears to be under-treated
• As yet, there is no evidence that treating depression improves survival, BUT....
Conclusions (Continued)

• Treating depression is very important to improve quality of life
• Alternative treatments (i.e., exercise) show promising results.
• More well-controlled Randomized Clinical Trials (RCTs) are needed that include adequate numbers of women and minorities!
"Well, I see my time is about up..."
SAY, WHY DO WE FALL FROM THE TREE AND DIE ANYWAY?
Well, the way I understand it, when fall comes, changes begin to occur in the cells where our stem is attached to the branch ...
AND THE VESSELS WHICH SUPPLY US WITH NOURISHMENT BECOME PLUGGED WITH GUMS, CAUSING US TO WITHER AND FALL FROM THE TREE.
THAT ISN'T GOING TO HAPPEN TO ME! I JOG!