Is There A Magic Bullet?
The Use of Exercise for Treating Depression and Cardiovascular Disease
Department of Psychiatry and Behavioral Sciences
Grand Rounds November 13, 2014

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Disclosure Information

No Conflicts of Interest
"Our next award is for spectacular failure."
Quotes from Vince Lombardi
Former Coach of Green Bay Packers

• The greatest accomplishment is not in never falling, but in rising again after you fall.
• The measure of who we are is what we do with what we have.
• Winners never quit and quitters never win.
Be more concerned with your character than your reputation, because your character is what you really are, while your reputation is merely what others think you are.
What if there was one prescription that could prevent and treat dozens of diseases, such as diabetes, hypertension and obesity—and improve mental health?"

“That would be a Magic Bullet!”
Some Purported Health Benefits of Regular Exercise

- **BRAIN**
  - Reduces stress and improves mood
  - Decreases risk of depression
  - Decreases anxiety
  - Improves concentration
  - Increases oxygen and nutrients to the brain

- **BREASTS**
  - Decreases risk of breast cancer in women

- **LUNGS**
  - Improves respiratory capacity
  - Improves ability to extract oxygen from the air

- **LIVER AND PANCREAS**
  - Increases rate of metabolism
  - Reduces risk of type 2 diabetes

- **COLON**
  - Decreases risk of colon cancer

- **BLOOD VESELS**
  - Increases levels of good cholesterol (HDL)
  - Lowers resting blood pressure
  - Decreases risk of atherosclerosis
  - Improves circulation

- **HEART**
  - Decreases risk of heart disease
  - Strengthens the heart
  - Increases volume of blood pumped to the body

- **BONES**
  - Increases bone density
  - Strengthens bones
  - Decreases risk of osteoporosis

- **JOINTS**
  - Increases range of motion
  - Reduces the pain and swelling of arthritis

- **MUSCLES**
  - Increases muscle strength and tone
  - Improves muscle endurance and coordination
Exception
He’ll Never
Regret

Arnold Lemerand of Southgate, Minn., who was
told by his doctor not to
lift heavy objects, gets a
hug from Phillip Roth, 5,
after he saved the boy’s
life by lifting an 1,800-
pound cast-iron pipe off of
his head. Lemerand, 56,
was told by his doctor to
avoid strenuous work
after suffering a heart at-
tack six years ago.

(AP Laserphoto)
Clinical Practice Guideline
Number 17
Cardiac Rehabilitation

M.H. Department of Health and Human Services
Public Health Service
Agency for Health Care Policy and Research
Research Triangle Park, NC 27709
Cardiac Rehabilitation

- Most insurance carriers cover for:
  - Angina
  - Post bypass and angioplasty
  - Post MI
  - Valve Surgery
  - Post-transplant
  - Heart failure

- 20-36 exercise sessions over 2-4 months
Cardiac Rehabilitation After Myocardial Infarction: Combined Experience of Randomized Clinical Trials (Oldridge et al. JAMA 1988)

- 10 RCTs
- 4347 patients
- Pooled OR = 0.76 for all-cause mortality
- OR = 0.75 CV death
- OR = 1.15 for non-fatal re-infarction (ns)
Exercise is Good For You?

Endurance exercise kills! Beware.
Cheboygan Times-Standard
On Saturday, a teenage girl training for an IronMan Triathlon dies

Runner dies after London Marathon

A 22-year-old runner who was taken ill after completing the London Marathon has
died, race organisers have said.

Triathlete died of a heart attack
He collapsed at Cohasset event
By Mac Daniel, Globe Staff | July 10, 2007

Soldier collapses, dies during Country Music Marathon

The Associated Press. April 26, 2009

Triathlon athletes have twice the risk of sudden cardiac death, study shows

Los Angeles Times

According to a new study published this week at the American College of Cardiology
Conference in Orlando, Florida, triathlon athletes are dying more frequently than
marathon runners.
Jim Fix (1932-1984)

- Avid runner
- Author, The Complete Book of Running
- Leading force in starting America’s Fitness Boom
- Started running at age 35.
  - Weight 240 pounds
  - Smoked 2 packs of cigarettes per day.
- Ten years later, he was 60 pounds lighter and smoke-free.
- But he died at age 52 of a massive MI. Had extensive CAD
Cardiovascular Rehabilitation Programs

Safety of Exercise Training

- 167 randomly selected programs (1980 - 1984)
- 51,303 patients
- 2 million exercise hours
- 21 cardiac arrests (3 fatal)
- 8 nonfatal MIs

VanCamp SP, Peterson RA. JAMA 1986;256:1160.
Cardiovascular Rehabilitation Programs

Complications

• 1 cardiac arrest per 111,996 hours
• 1 AMI per 293,900 hours
• 1 fatality per 783,976 hours

VanCamp SP, Peterson RA. JAMA 1986;256:1160.
Exercise Side Effects

Vulnerable Joints: Knee

X-ray of the normal knee

X-ray of a knee with osteoarthritis
Vulnerable Joints II: Hip

- Normal joint space
- Narrowed joint space from loss of cartilage
- Bone spurs

Figure 1
Figure 2
Summary of Benefits of Exercise in Cardiac Patients

- Improved functional capacity
- Improvement in CVD risk factors
  - Blood pressure
  - Lipids
  - Glucose metabolism/insulin resistance
- Increased survival
- Safe for most participants (with adherence to appropriate exercise prescription)
- Psychological benefits?
• Not modifiable
  – Genetics
  – Gender
  – Age

• Modifiable
  – High blood pressure
  – High cholesterol
  – Diabetes
  – Obesity
  – Smoking
  – Stress/Depression?
ABC News: “Lay Had History of Heart Disease, but Did the Stress Do It?”
According to ABC News, “it's hard to prove a direct cause-and-effect link. The American Heart Association lists stress as a possible risk factor for heart attacks.”
“It's hard to know,” said doctors.

- "The reason that the [AHA] and others have not made depression and stress a risk factor for death after myocardial infarction is that the whole concept of stress is very hard to define."
- "What is stressful for one person may not be stressful for another person."

Dr. Brian Olshansky
Director of cardiac electrophysiology, University of Iowa Hospitals.
Historical Perspective on Psychosocial Prognostic Factors in Health Psychology

• The example of the Type A behavior pattern
Type A behavior—
a pattern common to
group who are prone
to coronary attacks.  
Standing in line
ties these people
up in knots.
Rushed
Competitive
Job involvement
ON YR MRK, GT SET, GO!

Rapid pace
“I've got twenty-five to seven, Hank. What have you got?”

Time urgency/time pressure
“It always takes Howard a couple of days to relax.”
Western Collaborative Group Study

• Prospective cohort study
• >3500 middle aged white males
• Rated as Type A/B based upon SI
• 113 men had CHD initially (80 classified as Type A)
• Followed for ~ 10 yrs (M=8.5 yrs)
• 257 developed CHD (178 classified as Type A)
WCGS; Friedman et al., 1971
The review panel accepts the available body of scientific evidence as demonstrating that type A behavior ... is associated with an increased risk of clinically apparent CHD in employed, middle-aged U.S. citizens.

This risk is greater than that imposed by age, elevated values of systolic blood pressure and serum cholesterol, and smoking and appears to be of the same order of magnitude as the relative risk associated with the latter three of these other factors.”

### SOME MAJOR STUDIES OF TYPE A AND CORONARY HEART DISEASE (CHD)

<table>
<thead>
<tr>
<th>Study*</th>
<th>Type of People</th>
<th>Duration</th>
<th>Type A Measure</th>
<th>Type A-CHD Connection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Collaborative Group Study</td>
<td>3,200 CHD-free middle-aged men</td>
<td>8 yrs.</td>
<td>Structured Interview</td>
<td>Yes</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td>1,600 CHD-free middle-aged men and women</td>
<td>8 yrs.</td>
<td>Framingham Type A Scale (self-report)</td>
<td>Yes, in women and white-collar men</td>
</tr>
<tr>
<td>French-Belgian Cooperative Heart Study</td>
<td>3,200 CHD-free European men</td>
<td>5 yrs.</td>
<td>Bortner Rating Scale (self-report)</td>
<td>Yes</td>
</tr>
<tr>
<td>Belgian Heart Disease Prevention Trial</td>
<td>1,900 CHD-free middle-aged European men</td>
<td>5 yrs.</td>
<td>Jenkins Activity Survey (self-report)</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrent Coronary Prevention Project</td>
<td>800 male CHD patients</td>
<td>5 yrs.</td>
<td>Videotaped Structured Interview</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiple Risk-Factor Intervention Trial</td>
<td>1) 12,700 high-risk but CHD-free men</td>
<td>7 yrs.</td>
<td>Jenkins Activity Svy.</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2) 3,100 of these men</td>
<td></td>
<td>Jenkins Structured Interview</td>
<td>No</td>
</tr>
<tr>
<td>Multicenter Post-Infarction Program</td>
<td>500 male, female CHD patients</td>
<td>3 yrs.</td>
<td>Jenkins Activity Svy.</td>
<td>No</td>
</tr>
<tr>
<td>Aspirin Myocardial Infarction Study</td>
<td>2,300 male, female CHD patients</td>
<td>3 yrs.</td>
<td>Jenkins Activity Svy.</td>
<td>No</td>
</tr>
<tr>
<td>Honolulu Heart Study</td>
<td>2,100 CHD-free men</td>
<td>8 yrs.</td>
<td>Jenkins Activity Svy.</td>
<td>No</td>
</tr>
</tbody>
</table>
“We’ll feel pretty silly if it’s downgraded to a tropical storm.”
Why Focus on Depression in Cardiac Patients?

- 2nd major cause of early death and disability in industrialized countries (following CHD)
- Depression is highly prevalent in CHD populations
- Depression is associated with poor compliance and increased health care costs
- Depression is associated with impaired quality of life
- Depression is associated with worse clinical outcomes
## Prevalence of Depression in Hospitalized CHD Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sample Size (n)</th>
<th>Major Depression</th>
<th>Elevated Depression Symptoms / Minor Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>222</td>
<td>12–16%</td>
<td>17–20%</td>
</tr>
<tr>
<td>(Frasure-Smith et al, 1993, 1999)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>430</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>(Lespérance et al, 2000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>374</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>(Jiang et al, 2001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheterization</td>
<td>200</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>(Hance et al, 1996)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>309</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>(Connerney et al, 2001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Unrecognized Depression in Patients with Acute Coronary Syndrome

% Unrecognized Depression during hospitalization

OR = 6.73, P = .001

Amin et al., 2006
Prevalence of Depression in CAD Patients Undergoing Cardiac Catheterization

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

Waldman et al., AHJ, 2008

P = .016
Evidence from Observational Studies: Montreal Heart Institute Studies of Depression

- **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, and colleagues*
Beck Depression Inventory

- 21-items reflect attitudes and symptoms of depression often displayed by depressed individuals
- Usually self-administered
- Good reliability and validity*
  - Coefficient alpha = 0.86 (internal consistency)
  - Correlation coefficient 0.72 (with clinical ratings in psychiatric patients)
- Clinical cutoffs
  - $BDI-I \geq 10$; $BDI-II \geq 14$

Sample Items from Beck Depression Inventory

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.

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
Depression and 1-Year Post-MI Cardiac Mortality

Survival Free of Cardiac Mortality, Cumulative %

Time After Discharge for MI, Days

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

Lespérance, et al, 2000
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

N=896

BDI < 4
BDI 4 to 9
BDI 10 to 18
BDI ≥ 19

Lespérance, et al, 2000
Depression and 1-Year Cardiac Prognosis in Unstable Angina

Lespérance et al., 2000

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

Not Depressed (BDI < 10)

Depressed (BDI ≥ 10)

Odds Ratio = \(4.7 (1.9 - 11.3)\)

\(P < 0.001\)

Time After Discharge for Unstable Angina, Days

\(N = 430\)
Depression in Cardiac Patients: Meta Analyses

• Barth et al. Psychosom Med 66: 802-813; 2004
• van Melle et al. Psychosom Med 66: 814-822; 2004
• Meijer et al. Gen Hosp Psychiat 33:203-216 2011
van Melle et al. Psychosom Med 2004

• **Scope**
  – 1975-2003

• **Articles:** 236 publications
  – 36 met criteria; 22 studies

• **Results**
  – All cause: OR 2.38
  – Cardiac: OR 2.59

• **Cohort effect:** Older studies > more recent studies
  – OR (<1992) = 3.22
  – OR (>1992) = 2.01
### Comparison: Depression versus no depression

#### Outcome: 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></td>
<td>7.3</td>
<td>2.12[0.71,6.35]</td>
</tr>
<tr>
<td>Carney (30)</td>
<td>28 / 358</td>
<td>11 / 408</td>
<td></td>
<td>18.8</td>
<td>3.06[1.50,6.24]</td>
</tr>
<tr>
<td>Irvine (18)</td>
<td>15 / 98</td>
<td>17 / 203</td>
<td></td>
<td>18.6</td>
<td>1.98[0.94,4.15]</td>
</tr>
<tr>
<td>Kaufman (33)</td>
<td>14 / 87</td>
<td>19 / 231</td>
<td></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></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></td>
<td>6.3</td>
<td>3.97[1.50,10.46]</td>
</tr>
<tr>
<td>Mayou (12)</td>
<td>4 / 26</td>
<td>24 / 318</td>
<td></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></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></td>
<td>4.8</td>
<td>0.56[0.06,5.12]</td>
</tr>
</tbody>
</table>

**Total (95%CI):**

*96 / 952* vs *116 / 2130*

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

OR = 2.38[1.76,3.22]
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)
Worsening Depression is a Risk Factor
Sherwood, Blumenthal, Hinderliter et al. JACC, 2011;57:418-23

• 147 HF outpatients
• Assessed for depression using BDI at baseline and 1 year
• Followed for up to 7 years (range 4-7 yrs)
• Primary outcome: death or CV hospitalization
• Results: 1 point increase in BDI scores associated with 7% increased risk of CV event (death or CV hospitalization)
• HR=1.07 (CI=1.02 to 1.12; p < .007)
Blumenthal, Babyak, et al. JAMA 2012; eFigure available at http://www.jama.com).
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>Condition</th>
<th>Prevalence (%)</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 6-month Course of Depression

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).
AHA Science Advisory

Depression and Coronary Heart Disease
Recommendations for Screening, Referral, and Treatment

A Science Advisory From the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research

Endorsed by the American Psychiatric Association

Judith H. Lichtman, PhD, MPH, Co-Chair; J. Thomas Bigger, Jr, MD; James A. Blumenthal, PhD, ABPP; Nancy Frasure-Smith, PhD; Peter G. Kaufmann, PhD; François Lespérance, MD; Daniel B. Mark, MD, MPH; David S. Sheps, MD, MSPH; C. Barr Taylor, MD; Erika Sivarajan Froelicher, RN, MA, MPH, PhD, Co-Chair

Abstract—Depression is commonly present in patients with coronary heart disease (CHD) and is independently associated with increased cardiovascular morbidity and mortality. Screening tests for depressive symptoms should be applied to identify patients who may require further assessment and treatment. This multiplicity consensus document reviews the evidence linking depression with CHD and provides recommendations for healthcare providers for the assessment, referral, and treatment of depression. (Circulation. 2008;118:40-6.)

Key Words: AHA Scientific Statement ■ depression ■ coronary disease ■ psychosocial factors ■ assessment; patient outcomes

Over the past 40 years, more than 60 prospective studies have examined the link between established indices of depression and prognosis in individuals with known coronary heart disease (CHD). Since the first major review articles were published in the late 1990s, there have been more than 100 additional narrative reviews of this literature, as well as numerous meta-analyses examining the role of depression on cardiovascular morbidity and mortality. Despite differences in samples, duration of follow-up, and assessment of depression and depressive symptoms, these studies have demonstrated relatively consistent results.

Depression is 3 times more common in patients after an acute myocardial infarction (AMI) than in the general community. Assessments conducted in the hospital indicate that 15% to 20% of patients with myocardial infarction (MI) meet Diagnostic and Statistical Manual of Mental Disorders criteria for major depression (duration since admission, no assessment of functional impairment), and an even greater proportion show an elevated level of depressive symptoms. Prevalence rates of depression have been shown to be higher among women in the general population and among cardiac patients, with recent evidence suggesting that young women may be at particularly high risk for depression after AML. Prevalence estimates in patients hospitalized for unstable angina, angioplasty, bypass surgery, and valve surgery are similar to those in patients with AML with slightly higher levels reported in patients with congestive heart failure. Less is known about the prevalence of depression in outpatient samples; however, available studies suggest that both major depression and elevated depressive symptoms are also considerably higher among people with CHD living in the community as compared with individuals...
AHA Scientific Advisory

- Screening for Depression
- Referral for diagnosis and management
- Monitor for: adherence to medical care, drug efficacy, and safety (CV and mental health)
- Coordination of care
- Suggest one possible screening tool: PHQ 9

Lichtman et al., Circulation, Oct 2008
**PHQ 9**

Patient Health Questionnaire

Initial screen items 1 & 2

Referral based on Full scale > 10

---

### Appendix: Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "x" to indicate your answer)

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself— or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed. Or the opposite— being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead. or of hurting yourself in some way

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
</table>

Add columns: **| | | **

**TOTAL:**

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

© MacArthur Foundation Initiative on Depression and Primary Care
Depression and Coronary Heart Disease
Recommendations for Screening, Referral, and Treatment
A Science Advisory From the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research
Endorsed by the American Psychiatric Association

Judith H. Lichtman, PhD, MPH, Co-Chair
James A. Blumenthal, PhD, ABPP
François Lespérance, MD
C. Barr Taylor

Depression Screening and Patient Outcomes
Letters to the Editor

Perceived Social Support Predicts Outcomes Following Myocardial Infarction: A Call for Screening?

In Response

Learning from history: A commentary on the American Heart Association Science Advisory on depression screening

Treating depression in patients with heart disease: Is the glass half empty or half full?
Screening is Controversial


• Blumenthal JA, O’Connor C. No Laughing Matter. *J Am Coll Cardiol* 2010; 55:836

• Ziegelstein RC, Thombs BD, Coyne CJ, de Jonge P. In Reply *J Am Coll Cardiol* 2010; 55:836-7
Issues

• Time
• Cost
• Precision
• Benefit
• Harm
Issues

- Time: Requires <3 minutes to administer and score
- Cost
- Precision
- Benefit
- Harm
Issues

• Time
• Cost: $1 + 3 minutes of time
• Precision
• Benefit
• Harm
Issues

• Time
• Cost
• Precision: PHQ-9 $\geq 10$ Sensitivity = 88% and Specificity = 88% for MDD; Patients with MDD ~7x more likely to score PHQ-9 $\geq 10$ compared to patients without diagnosis of MDD
• Benefit
• Harm

Issues

- Time
- Cost
- Precision
- Benefit: Identify patients with compromised QoL, at risk for adverse cardiac events, and may benefit from treatment
- Harm
Issues

- Time
- Cost
- Precision
- Benefit

- Harm: ? Unaware of any data to indicate that assessment of depression in cardiac patients is harmful.
Depression as a Risk Factor for Poor Prognosis Among Patients With Acute Coronary Syndrome: Systematic Review and Recommendations
A Scientific Statement From the American Heart Association

Judith H. Lichtman, PhD, MPH, Co-Chair; Erika S. Froelicher, RN, MA, MPH, PhD, FAHA, Co-Chair; James A. Blumenthal, PhD, ABPP; Robert M. Carney, PhD; Lynn V. Doering, RN, DNSc, FAHA; Nancy Frasure-Smith, PhD; Kenneth E. Freedland, PhD; Allan S. Jaffe, MD; Erica C. Leifheit-Limson, PhD; David S. Sheps, MD, MSPH, FAHA; Viola Vaccarino, MD, PhD, FAHA; Lawson Wulsin, MD; on behalf of the American Heart Association Statistics Committee of the Council on Epidemiology and Prevention and the Council on Cardiovascular and Stroke Nursing

Background—Although prospective studies, systematic reviews, and meta-analyses have documented an association between depression and increased morbidity and mortality in a variety of cardiac populations, depression has not yet achieved formal recognition as a risk factor for poor prognosis in patients with acute coronary syndrome by the American Heart Association and other health organizations. The purpose of this scientific statement is to review available evidence and recommend whether depression should be elevated to the status of a risk factor for patients with acute coronary syndrome.

Methods and Results—Writing group members were approved by the American Heart Association’s Scientific Statement and Manuscript Oversight Committees. A systematic literature review on depression and adverse medical outcomes after acute coronary syndrome was conducted that included all-cause mortality, cardiac mortality, and composite outcomes for mortality and nonfatal events. The review assessed the strength, consistency, independence, and generalizability of the published studies. A total of 53 individual studies (32 reported on associations with all-cause mortality, 12 on cardiac mortality, and 22 on composite outcomes) and 4 meta-analyses met inclusion criteria. There was heterogeneity across studies in terms of the demographic composition of study samples, definition and measurement of depression, length of follow-up, and covariates included in the multivariable models. Despite limitations in some individual studies, our review identified generally consistent associations between depression and adverse outcomes.

Conclusions—Despite the heterogeneity of published studies included in this review, the preponderance of evidence supports the recommendation that the American Heart Association should elevate depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome.

Key Words: AHA Scientific Statements ■ acute coronary syndrome ■ coronary heart disease ■ depression ■ risk factors
• The goal of this scientific statement is to review current evidence on the role of depression as a risk factor for adverse medical outcomes among adults recovering from ACS in order to make a recommendation as to whether depression should be elevated to the status of a risk factor among patients with ACS by the American Heart Association (AHA).

Lichtman et al. Circulation, 2014; p 1351
Studies Included

- All-cause mortality $n = 32$
- Cardiac mortality $n = 12$
- Composite outcome $n = 22$
Characteristics of Studies

• **Most studies:**
  - $\geq 25\%$ depressed patients
  - $< 20\%$ lost to follow-up
  - Self-report measures (e.g., BDI-I)
  - Outcome events adjudicated independently
Conclusions

• Despite heterogeneity (in methods), the preponderance of evidence supports the recommendation that the AHA should elevate depression to the status of a risk factor for adverse medical outcomes in patients with ACS

(Circulation p.14, March 25, 2014)
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.).
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
Exercise vs Pills to Treat Depression

DILBERT

COMPANY CONCIERGE

I DON'T HAVE TIME FOR MY DOCTOR APPOINTMENT.

GO IN MY PLACE AND TELL HIM YOU'RE HAVING TROUBLE SLEEPING AT YOUR DESK.

AND DON'T LET HIM SWEET-TALK YOU ABOUT DIET AND EXERCISE. I WANT PILLS!

Scott Adams
Typical Guidelines for Treating MDD with Antidepressants

• Acute phase treatment 6-12 weeks
  – 60% response rate
• Responders (eg, remission), continuation 4-9 months
  – 40% relapse rate
• Maintenance phase 9 months and longer
Antidepressant Medications

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)
- Not powered to examine clinical endpoints
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><strong>All randomized patients</strong></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><strong>Any recurrent MDD</strong></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><strong>More severe (2 prior episodes plus HAM-D score ≥18)</strong></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 co-variate in the model. Responders have CGI-I scores of ≤2 (much or very much improved) at end point.

‡For repeated-measures analysis of HAM-D, weeks 6, 10, and 16 are used.

Glassman, O'Connor, et al, JAMA, 2002;288:701-709
SADHART-CHF
Sertraline against depression and heart disease in chronic heart failure
Randomized Trial

- Multi-site RCT of placebo vs SSRI for CHF patients with MDD
- Primary endpoint: $\Delta$ HDRS; Composite cardiovascular status
- Safety and Efficacy trial – also examined survival and cardiac events (JACC, 2010)
SADHART-CHF
O’Connor, Jiang, et al. JACC 2010;56:692-9

- Sertraline + NFS 50 mg/day N=234
- Matching Placebo + NFS N=235

12-weeks

- Completers N=138
  Mean Days: 86.1 +/- 5.7
  Median (25th, 75th): 85 (83, 88)
- Dropouts N=96
  Mean Days: 36.7 +/- 26.2
  Median (25th, 75th): 31.5 (14, 56)
- Completers N=152
  Mean Days: 86.2 +/- 5.3
  Median (25th, 75th): 85 (83, 87)
- Dropouts N=83
  Mean Days: 34.7 +/- 26.1
  Median (25th, 75th): 31.0 (13, 5)

Reasons for dropout, N (%)
- Withdrew consent, 7 (3)
- Loss to follow-up, 5 (2.1)
- Adverse event, 27 (11.5)*
- Withdrawn by clinical team, 15 (6.4)
- Noncompliance, 26 (11.1)
- Other, 5 (2.1)
- Death, 11 (4.7)

*P=.03

N included in Primary Analysis = 234
N included in Primary Analysis = 235
SADHART-CHF: Changes in HDRS From Baseline to Week 12

Mean change
Sertraline: -7.1
Placebo: -6.8

O' Connor, Jiang, Kuchibhatla, et al. Safety and Efficacy of Sertraline for Depression in Patients With Heart Failure: Results of the SADHART-CHF Trial. JACC 2010
SADHART-CHF: Survival Results

O’Connor, Jiang, et al. JACC, 2010

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=</th>
<th>235</th>
<th>213</th>
<th>198</th>
<th>192</th>
<th>183</th>
<th>179</th>
<th>176</th>
<th>174</th>
<th>174</th>
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</thead>
<tbody>
<tr>
<td>Sertraline N=</td>
<td>234</td>
<td>206</td>
<td>193</td>
<td>186</td>
<td>181</td>
<td>172</td>
<td>170</td>
<td>167</td>
<td>166</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms: Implications for Treatment

Intervening here does not necessarily*…

…target mediating factors

Depression  Mechanism  CAD outcome
"Comparing the mode of treatment by which the mind and body are to be preserved...moderate exercise reduces to order, according to their affinities, the particles and affections which are wandering about the body"

- Plato...Dialogues circa 400 BC
“Jogging ain’t never helped nobody but chicken thieves, moonshiners, and Yankees.”

-Granny of “The Beverly Hillbillies” circa 1959
Meta Analyses

- Lawlor and Hopker
  - *BMJ*, 2001
  - 14 studies
- Mead, et al.
  - *Cochrane Review* 2009
  - 25 studies
- Rimer, et al.
  - *Cochrane Review* 2012
  - 32 studies
Two arms (N=13*)
  - Ex v Wait list (n=3); Ex v placebo (n=6); Ex v CBT (n=2); CBT+Ex v CBT (n=2); Ex v light (n=1)

Three arms (N=11)
  - Ex v sert+Ex vs sert (n=1); Ex v WL v Placebo (n=3); Ex v UC v CBT (n=2); Ex v CBT v Ex+CBT (n=1); Ex v low CBT v hi CBT (n=1); Ex v placebo v CBT (n=1); hi int resis v low int resis v UC (n=1); run v resis v WL (n=1)

Four arms (N=2)
  - Ex v 4 controls (n=1); sup Ex v home Ex v sert v placebo (n=1)

Five arms (N=1)

Six arms (N=1)

*Mead, Morley, et al. Exercise for Depression, Cochrane Database, 2009; issue 3
### Exercise v Control

#### 23 trials (N=907 participants)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment N</th>
<th>Mean(SD)</th>
<th>Control N</th>
<th>Mean(SD)</th>
<th>Std. Mean Difference, 95% CI</th>
<th>Weight</th>
<th>Std. Mean Difference, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Knupper 2007</td>
<td>20</td>
<td>11.2 (4)</td>
<td>18</td>
<td>15.5 (6.1)</td>
<td>-0.22 [-1.49, -0.16]</td>
<td>5.9%</td>
<td></td>
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<tr>
<td>Gneh 1978</td>
<td>3</td>
<td>7 (6.6)</td>
<td>2</td>
<td>16.5 (2.12)</td>
<td>-1.35 [-3.71, 1.22]</td>
<td>1.3%</td>
<td></td>
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<tr>
<td>M. Neil 1991</td>
<td>10</td>
<td>11.1 (3)</td>
<td>10</td>
<td>14.7 (0.7)</td>
<td>-0.92 [-1.97, -0.68]</td>
<td>4.9%</td>
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<tr>
<td>Bonnet 2005</td>
<td>5</td>
<td>24.46 (0.3)</td>
<td>6</td>
<td>16.5 (5.8)</td>
<td>1.31 [0.09, 2.53]</td>
<td>2.7%</td>
<td></td>
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<tr>
<td>Nudie 1985</td>
<td>5</td>
<td>5.46 (4.23)</td>
<td>7</td>
<td>21.4 (5.26)</td>
<td>-2.59 [-3.76, -1.62]</td>
<td>2.8%</td>
<td></td>
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<tr>
<td>Epstein 1985</td>
<td>7</td>
<td>9 (0.34)</td>
<td>10</td>
<td>16.3 (7.44)</td>
<td>-0.77 [-1.78, 0.24]</td>
<td>3.8%</td>
<td></td>
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<tr>
<td>Hove-Hemmer 1981</td>
<td>6</td>
<td>9.8 (6.93)</td>
<td>6</td>
<td>16.2 (6.42)</td>
<td>-0.77 [-1.96, 0.41]</td>
<td>3.3%</td>
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<tr>
<td>Singh 2005</td>
<td>18</td>
<td>8.5 (5.5)</td>
<td>19</td>
<td>14.4 (4)</td>
<td>-1.00 [-1.69, -0.31]</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Nathanson 2005</td>
<td>21</td>
<td>14.4 (4.12)</td>
<td>28</td>
<td>17.5 (4.23)</td>
<td>-0.73 [-1.31, -0.14]</td>
<td>5.2%</td>
<td></td>
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<tr>
<td>Doan 1987</td>
<td>13</td>
<td>5.03 (6.44)</td>
<td>11</td>
<td>15.25 (6.3)</td>
<td>-1.19 [-2.08, -0.31]</td>
<td>4.2%</td>
<td></td>
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<tr>
<td>Fremont 1987</td>
<td>18</td>
<td>10 (5.3)</td>
<td>16</td>
<td>8 (7.1)</td>
<td>-0.23 [-0.45, 0.09]</td>
<td>4.9%</td>
<td></td>
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<tr>
<td>Nathan 2001</td>
<td>43</td>
<td>12.6 (7.92)</td>
<td>43</td>
<td>13.7 (6.82)</td>
<td>0.57 [0.09, 0.26]</td>
<td>5.0%</td>
<td></td>
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<tr>
<td>Reuter 1984</td>
<td>5</td>
<td>5.1 (4.75)</td>
<td>9</td>
<td>18.56 (7.7)</td>
<td>-2.00 [-3.19, -0.23]</td>
<td>3.3%</td>
<td></td>
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<tr>
<td>Setaro 1985</td>
<td>25</td>
<td>62 (6.31)</td>
<td>25</td>
<td>65.38 (6.56)</td>
<td>-0.14 [-2.07, 0.81]</td>
<td>5.1%</td>
<td></td>
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<tr>
<td>Singh 1997</td>
<td>17</td>
<td>9.8 (4.2)</td>
<td>15</td>
<td>13.8 (5.2)</td>
<td>-1.75 [-2.59, -0.92]</td>
<td>4.4%</td>
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<tr>
<td>Dos 2002</td>
<td>17</td>
<td>9.8 (3.6)</td>
<td>18</td>
<td>14 (4.9)</td>
<td>-1.16 [-1.94, -0.37]</td>
<td>4.5%</td>
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<tr>
<td>Chen 2004</td>
<td>7</td>
<td>15.3 (8.8)</td>
<td>7</td>
<td>29.1 (6.7)</td>
<td>-2.29 [-3.73, -0.84]</td>
<td>2.7%</td>
<td></td>
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<tr>
<td>Veits 1992</td>
<td>26</td>
<td>13.94 (6.5)</td>
<td>28</td>
<td>17.79 (8.64)</td>
<td>-0.52 [-1.03, 0.02]</td>
<td>5.5%</td>
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<td>Kien 1995</td>
<td>14</td>
<td>1.03 (0.34)</td>
<td>9</td>
<td>0.62 (0.51)</td>
<td>0.24 [-0.54, 1.11]</td>
<td>4.3%</td>
<td></td>
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<tr>
<td>Blumenthal 2007</td>
<td>51</td>
<td>9.2 (6.1)</td>
<td>49</td>
<td>11.1 (7)</td>
<td>-0.29 [-0.58, 0.01]</td>
<td>5.8%</td>
<td></td>
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<tr>
<td>Blumenthal 1999</td>
<td>55</td>
<td>8.73 (6.06)</td>
<td>48</td>
<td>7.81 (5.49)</td>
<td>0.14 [-0.25, 0.52]</td>
<td>5.9%</td>
<td></td>
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<tr>
<td>Tsang 2005</td>
<td>46</td>
<td>3.19 (2.12)</td>
<td>34</td>
<td>6.15 (4.66)</td>
<td>-1.56 [-2.07, -1.06]</td>
<td>5.5%</td>
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<tr>
<td>Mattissen 1983</td>
<td>24</td>
<td>12.1 (7.1)</td>
<td>19</td>
<td>22.8 (11.4)</td>
<td>-1.14 [-1.79, -0.48]</td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 476 / 433 = 109.0% **SMD = -0.82; Large clinical effect**

Test for overall effect: Z = 5.15; P < 0.00001

---

SMD = Standardized Mean Difference; CI = Confidence Interval; df = Degrees of Freedom; P = Significance Level
Exercise v Cognitive Therapy
6 Trials (N=152 participants)

SMD= -0.17: No difference
Risk of Bias

• Allocation concealment (N=8)
• Incomplete outcome data (N=7)
• Blinding (N=7)
• Other (N=1) (premature stopping)
• None (N=3)
3 Studies with Best Methodology

SMD = 0.42 (moderate clinical effect)*

*=ns
Exercise seems to improve depressive symptoms in people with a diagnosis of depression, but when only methodologically robust trials are included, the effect sizes are only moderate and not statistically significant.
Exercise v Antidepressants
2 trials (N=201 participants)

SMD = -0.04: no difference
SMILE Study

To assess the effectiveness of aerobic exercise for the treatment of major depression in older adults

Blumenthal et al., Arch Int Med, 1999
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
SMILE Study Design

Baseline Assessment (N = 156)

Randomization

Medication (N = 48)

Exercise Only (N = 53)

Combination (N = 55)

Post-treatment Assessment (N = 133)
Exercise Training

- 3 sessions per week for 16 weeks
- 10 minutes warm-up period of stretching and exercise bicycle
- 30 minute period of continuous walking or jogging at 70-85% heart rate reserve
- 5 minutes of cool down exercise
Medication

• 16 weeks of Sertraline (Zoloft)
• 50-200mg q.d.
• Visit with study psychiatrist at weeks 2, 6, 10, 14, and 16
Combined Exercise/Medication

- 3 exercise sessions per week for 16 weeks
- 50-200mg Sertraline q.d. for 16 weeks
Post-treatment Aerobic Fitness adjusted for pretreatment levels

* Different from Medication, p < .05
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>10</td>
</tr>
<tr>
<td>Comb</td>
<td>18</td>
<td>12</td>
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</tbody>
</table>

* Different from Baseline, p < .001

## BDI Score

<table>
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<th>Treatment Group</th>
<th>Before treatment</th>
<th>After treatment</th>
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<tbody>
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<td>Med</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Ex</td>
<td>20</td>
<td>12</td>
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<tr>
<td>Comb</td>
<td>22</td>
<td>18</td>
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</table>

* Different from Baseline, p < .001
### Recovery Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
<th>Count/Total</th>
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<tbody>
<tr>
<td>Med</td>
<td>36/48</td>
<td></td>
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<tr>
<td>Exercise</td>
<td>32/53</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>33/55</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>101/156</td>
<td></td>
</tr>
</tbody>
</table>

Criterion: No DSM-IV Dx after 16 weeks
Weekly Course of HAM-D Scores

HAM-D = 22
at Baseline

HAM-D = 15
at Baseline

Combined
Exercise
Med

Combined
Exercise
Med

Week
Fitted Score
4
8
12
16
20
24
0 1 2 3 4 6 8 12 16
Six Month Follow-up

Major Depression

Relapse

Babyak et al., *Psychosom Med*, 2000
Prediction of MDD at Six Month Follow-up

OR

0.5
1.0
1.5
2.0
2.5

Exercise
Med
Age
Baseline HRSD
4 month HRSD

Babyak et al., Psychosom Med, 2000
Limitations

• Short term study
• No placebo control group
• Confound of social support
• Dose of exercise?
• Mechanisms?
• Impact on physical health?
SMILE II

• Randomized to Exercise or Pill Conditions
• 4 Groups:
  – Exercise (Home based or Supervised)
  – Pill (Sertraline or Placebo)
• Treatment duration: 4 months
• Eligibility: MDD and HAM-D ≥ 13
• N = 202
• Primary endpoint: HAM-D and Recovery

Blumenthal et al, Psychosom Med, 2007
457 patients screened

Completed baseline assessments and randomized (N = 202)

135 did not meet depression criterion
47 withdrew consent
40 psychiatric comorbidity
13 contraindication to exercise
15 poor assessment adherence
1 Already exercising
1 currently in psychiatric treatment
3 sertraline contraindicated

Home Based Exercise N = 53
-3 withdrew
-2 withdrawals completed post-tx assessment
-1 completer with no post-tx assessment
50 completed treatment

Supervised Exercise N = 51
-10 withdrew
-5 withdrawals completed post-tx assessment
-1 completer with no post-tx assessment
41 completed treatment

Sertraline N = 49
-7 withdrew
-4 withdrawals completed post-tx assessment
-1 completer with no post-tx assessment
42 completed treatment

Placebo N = 49
-14 withdrew
-8 withdrawals completed post-tx assessment
-1 completer with no post-tx assessment
35 completed treatment
Improvement in Aerobic Fitness

Aerobic Capacity

Exercise Duration

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>VO₂ (mL/kg/minute)</th>
<th>Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Sup.</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Med.</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Plac.</td>
<td>26</td>
<td>9</td>
</tr>
</tbody>
</table>

Ex v Placebo, p = .0005
Med v Placebo , p = .554
Ex v Med, p = .005

Ex v Placebo, p = .0001
Med v Placebo , p = .523
Ex v Med, p = .0005
Absence of Depression after Treatment

No DSM Dx of Depression and HRSD < 8: All Patients

No DSM Dx of Depression and HRSD < 8: Immediate responders removed

Probability of Recovery

Absence of Depression after Treatment

P = .057

P = .016
Hamilton Depression Score after Treatment

HAMD: All patients

Score After Treatment

Treatment Group

P = .231

HAMD: Immediate responders removed

Score After Treatment

Treatment Group

P = .048
SMILE II One Year Follow up

- 172 (85%) patients available for follow up
- 66% fully remitted
- 36% taking anti depressants
- 49% reporting at least some exercise
- Median 103 min/wk for those engaged in exercise
- 17% receiving psychotherapy
- Difference in patient reporting 0 min of exercise compared to 180 min/wk of exercise was 3.1 pts on HAMD

Hoffman et al. 2011
Exercise: Efficient, Direct Intervention

Depression

Lifestyle

Adherence

Metabolic Syndrome

Platelet

HPA axis

ANS

Inflammation

Psychotherapy *
Antidepressants *
Exercise *

CAD outcome
What About Exercise in Cardiac Patients with Depression?

• Non-randomized observational studies with and without comparison groups
  – The Oshsner Studies

• Randomized Controlled Trials
  – HF-ACTION
  – UPBEAT
Benefits of Cardiac Rehabilitation

Depression

- Young (age <55; n=104)
  - Before Rehab: 23%
  - After Rehab: 4%
  - p<0.0001

- Elderly (age >70; n=260)
  - Before Rehab: 19%
  - After Rehab: 6%
  - p<0.0001

Lavie, Milani: Arch Int Med 2006;166:1878-1883
Cardiac Rehabilitation and Depression

HF-ACTION: A Randomized Controlled Trial Investigating Outcomes of Exercise Training
## History of HF-ACTION

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Concept Letter</td>
</tr>
<tr>
<td>1999-2001</td>
<td>Grant Funded!</td>
</tr>
<tr>
<td>2002</td>
<td>1st Patient Enrolled</td>
</tr>
<tr>
<td>April 2003</td>
<td>Presentations AHA Meeting</td>
</tr>
<tr>
<td>2008</td>
<td>JAMA 2009</td>
</tr>
<tr>
<td>2009</td>
<td>JAMA 2012</td>
</tr>
<tr>
<td>2012</td>
<td>Secondary analysis: Depression JAMA 2012</td>
</tr>
<tr>
<td>2013</td>
<td>Additional papers</td>
</tr>
</tbody>
</table>

- **3 Submissions**
- **1st Patient Enrolled April 2003**
- **Presentation AHA Meeting**
- **Primary Publication JAMA 2009**
- **Secondary analysis: Depression JAMA 2012**
- **Additional papers**
Initial Site Locations (n=50) (Later Expanded to 82, with 5 in Canada, 6 in France)
Hypotheses

• Exercise training would be associated with improved clinical outcomes relative to usual care
  – All cause mortality and all cause hospitalization
  – CV mortality and CV hospitalizations

• Exercise training would be associated with reduced depression relative to usual care
  – 3 months
  – 1 year
Sample Characteristics in HF-ACTION

- NYHA Class (III or IV) : 38%
- Age: 65 yrs
- Women: 28%
- African American: 38%
- BDI-II scores ≥ 14: 28%
- 14% on SSRI anti-depressants
  - 10% BDI-II <14
  - 23% BDI-II ≥14
Study Design

Chronic heart failure, NYHA Class II-IV, LVEF ≤ 35%, optimal HF medical therapy, capable of exercising

Pre-randomization CPX and ECHO

Randomization 1:1
(Stratified by center and HF etiology)

N = 2331
Median Follow-up 2.5 years

Usual Care

Exercise Training

Whellan DJ. Am Heart J 2007;153:201-211.
2331 Randomized

1159 assigned to Exercise

1158 with complete Beck Depression Inventory-II (BDI-II)

821 with BDI-II < 14

17 Lost to follow-up
24 Withdraw consent

490 (60%) ≥ 1 Hospitalization
26 (3%) Deaths
516 (63%) Total Events

1172 assigned to Usual Care

1164 with complete Beck Depression Inventory-II (BDI-II)

848 with BDI-II < 14

532 (63%) ≥ 1 Hospitalization
25 (3%) Deaths
557 (66%) Total Events

316 with BDI-II ≥ 14

7 Lost to follow-up
13 Withdraw consent

222 (70%) ≥ 1 Hospitalization
10 (3%) Deaths
232 (73%) Total Events

821 used in primary analysis

337 used in primary analysis

848 used in primary analysis

316 used in primary analysis
Treatment Groups

- **Usual Care**
  - Optimized medical treatment
  - Patient education
  - Regular phone calls to assess health status + physical activity

- **Exercise Training**
  - Optimized medical treatment
  - Patient education
  - Supervised facility-based training—3 months
  - Unsupervised home training—up to 18 months
  - Select mode of exercise (bike or treadmill for home use)
  - Regular phone calls to confirm adherence
A Priori Adherence Classification

SUPERVISED
• Non-adherer: < 15 min/week
• Poor: 15-44 min/week
• Partial: 45-89 min/week
• Full: ≥ 90 min/week

HOMEBASED
• Non-adherer: < 15 min/week
• Poor: 15-69 min/week
• Partial: 70-119 min/week
• Full: ≥ 120 min/week
## Adherence to Exercise Protocol

<table>
<thead>
<tr>
<th>Supervised</th>
<th>Home-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full:</strong> 41%</td>
<td><strong>Full:</strong> 38%</td>
</tr>
<tr>
<td>Partial: 30%</td>
<td>Partial: 14%</td>
</tr>
<tr>
<td>Poor: 16%</td>
<td>Poor: 15%</td>
</tr>
<tr>
<td>Non-adherent: 7%</td>
<td>Non-adherent: 8%</td>
</tr>
<tr>
<td>Zero: 0.6%</td>
<td>Zero: 11%</td>
</tr>
<tr>
<td>Missing: 5%</td>
<td>Missing: 16%</td>
</tr>
</tbody>
</table>
## Median Change in 6-Minute Walk and Cardiopulmonary Exercise (CPX) Tests

<table>
<thead>
<tr>
<th></th>
<th>Baseline to 3 months*</th>
<th>Baseline to 12 months*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual Care</td>
<td>Exercise Training</td>
</tr>
<tr>
<td><strong>6-minute walk distance (m)</strong></td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td><strong>CPX exercise duration (min.)</strong></td>
<td>0.3</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Peak VO₂ (mL/min/kg)</strong></td>
<td>0.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Complete case analysis
All-Cause Mortality or All-Cause Hospitalization

(Primary) HR 0.93 (95% CI: 0.84, 1.02), $P = 0.13$

*Adjusted HR 0.89 (95% CI: 0.81, 0.99), $P = 0.03$

* Adjusted for key prognostic factors
Unadjusted Kaplan-Meier Curves of the Primary Endpoint by Quartiles of MET-hr/wk
QoL Endpoint: Predicted KCCQ Overall Score

Overall treatment effect $p=0.001$

- The 2-point difference in early change between treatment arms was significant $p=0.0005$
## Serious Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Usual Care N=1172</th>
<th>Ex Training N=1159</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one CV event *</td>
<td>40%</td>
<td>37%</td>
</tr>
<tr>
<td>At least one ICD firing</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>Hospitalized after physical activity</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Hospitalized for fracture of hip/pelvis</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Deaths identified as possibly occurring within 3 hours of physical activity</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

* Worsening HF, MI, unstable angina, serious adverse arrhythmia, stroke, TIA
Assessment of Depression

- Beck Depression Inventory-II (BDI-II)
- Administered at baseline and every 3 months for 1 year
- Primary endpoint: BDI-II at 3 months
- Secondary endpoint BDI-II at 12 months
- Hypotheses:
  - BDI-II lower at 3 months and 12 months in AE compared to UC
  - BDI-II at baseline associated with clinical endpoints
  - Change in BDI-II related to primary medical endpoint
Depression in HF-ACTION

- 28% (N=653) had BDI-II scores ≥ 14
- 28% women
- 33% African American
- 14% on SSRI anti-depressant
  - 10% BDI-II <14
  - 23% BDI-II ≥14
Changes in Depressive Symptoms

Beck Depression Inventory II Score

Usual Care
Exercise

Months

Beck Depression Inventory II Score

0 3 6 9 12

Usual Care
Exercise

0 3 6 9 12

Months
# Mean BDI-II Scores by Treatment Group and Depression Severity

## All Subjects

<table>
<thead>
<tr>
<th>Time</th>
<th>Exercise</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>8.9</td>
<td>9.7</td>
</tr>
<tr>
<td>12 months</td>
<td>8.9</td>
<td>9.5</td>
</tr>
</tbody>
</table>

## Depressed (BDI-II ≥14)

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.6</td>
<td>18.0</td>
</tr>
<tr>
<td>15.8</td>
<td>17.3</td>
</tr>
</tbody>
</table>
Usual Care

- Guideline-based treatment
- Close monitoring including biweekly phone calls
- 23% on anti-depressants
- 48% engaged in regular exercise up to twice a week
Exercise Volume and Depression Scores at 3-Months
Exercise Volume and Depression Scores at 12 Months
**STAGE 1**

Single-center trial

**STAGE 2**

Multi-center validation of original study

**STAGE 3**

Randomized controlled trials

---

**Intermediate end points**

- **Anatomic**
  - *Examples:*
    - Carotid IMT/plaque
    - Coronary calcification

- **Pathophysiologic**
  - *Examples:*
    - Myocardial ischemia
    - Endothelial dysfunction
    - BNP

**Hard end points**

- *Examples:*
  - Cardiac death
  - Myocardial infarction

---

Rozanski et al. JACC, 2005
UPBEAT STUDY
Understanding Prognostic Benefits of Exercise and Antidepressant Medication

• RCT in cardiac patients with depression
  – Exercise
  – Sertaline
  – Placebo

• Examine changes in symptoms of depression and biomarkers of risk (e.g., FMD, HRV, platelets)

• Methods published in Clinical Trials, 2007; 4:558-559.

• Results published in JACC, 2012; 60:1053-63
1680 Inquiries

1115 Not eligible
- 281 Not scheduled
  - 123 Schedule would not allow
  - 86 Expressed no longer interested
  - 32 No response to follow-up calls
  - 40 Other
- 183 Screened out
  - 50 BDI < 7
  - 55 No longer interested
  - 54 Medical contraindications
  - 10 Other Psychiatric
  - 14 Medication use

565 Initially Eligible

284 Available for further screening

101 randomized

37 Exercise
- 1 Withdrew due to family problems and time constraints
- 36 completed protocol
  - 1 imputed for ITT analysis

40 Medication
- 2 withdrew due to side effects
- 1 withdrew due to illness but completed assessments
- 36 completed protocol
  - 1 did not complete protocol but provided assessment data
  - 3 imputed for ITT analysis

24 Placebo
- 1 withdrew for unknown reasons
- 23 completed protocol
  - 1 imputed for ITT analysis
Changes in Depression

HAM-D

BDI-II

Panel A
Groups
Mean HAM-D at 16 Weeks
0 5 10 15
Exercise Sertraline Placebo

Panel B
Groups
BDI Rank at 16 Weeks
20 30 40 50 60 70 80
Exercise Sertraline Placebo

Median BDI Score=5
Median BDI Score=7.5
Median BDI Score=6
Changes in Biomarkers

HRV  BRS  FMD

SDNN at 16 Weeks

Exercise  Sertraline  Placebo

BRS at 16 Weeks

Exercise  Sertraline  Placebo

FMD at 16 Weeks (minutes)

Exercise  Sertraline  Placebo
Is There a Magic Bullet?

Conclusions

• Depression is common in CHD patients
• Depression is now considered to be a risk factor for cardiac patients
• Interventions to treat depression are modestly effective
• Exercise training may be just as effective in reducing depression as medication in patients who are at least willing to consider exercise as a potential treatment option.
Is There a Magic Bullet

Conclusions (Continued)

• Exercise may not only reduce depression but may also improve cardiovascular biomarkers and reduce risk for fatal and non-fatal cardiac events.

• Mechanisms for the benefits of exercise remain uncertain.

• Effective interventions to treat depression in CHD patients are needed!
Is Exercise a Magic Bullet?

What Do You Think?
“Well, I see my time is about up...”