Depression and Coronary Artery Disease: Cause, Effect or Coincidence?

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  Canada
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- Montreal Heart Institute Research Foundation
- The Pierre David Fund
Depression and Coronary Artery Disease: Cause, Effect or Coincidence?

- History of progress in this field
- Prevalence of depression in CAD patients
- Evidence that depression increases risk of cardiac events in CAD patients
- Evidence of primary risk (depression increases risk of developing CAD)
- Mechanisms
- Potential treatments and RCT results
Coronary Artery Disease (CAD) = Coronary Heart Disease (CHD) = Ischemic Heart Disease (IHD)

http://www.nhlbi.nih.gov/health

http://www.academy.de/linksection/cva
Acute Coronary Syndromes

Vulnerable Atherosclerotic Plaque

Vasospasm → Platelet Function

Incomplete

70% Unstable Angina (increasing)

Non-Q Wave

CONTINUUM

Complete

30% Myocardial Infarction (declining)

Q Wave
McGill University 1979

Raymond H. Prince, MD, MSc, pioneer in Transcultural Psychiatry, father of the Ischemic Heart Disease (IHD) Life Stress Monitoring Program (1977-1981)
Sample Items from the Schedule of Recent Experiences

<table>
<thead>
<tr>
<th>Health</th>
<th>Life Change Units (LCUs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Illness (in bed a week or hospitalization)</td>
<td>62</td>
</tr>
<tr>
<td>Change in heavy physical work or exercise</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recently out of work</td>
</tr>
<tr>
<td>Recently fired from work</td>
</tr>
<tr>
<td>Retirement</td>
</tr>
<tr>
<td>Change in work responsibilities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal and Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of spouse</td>
</tr>
<tr>
<td>Divorce</td>
</tr>
<tr>
<td>Held in jail</td>
</tr>
</tbody>
</table>

*Hawkins, Davies and Holmes, 1957*
Timing of Stressful Life Events During the 2 Years Prior to Sudden Cardiac Death

Rahe et al. *Arch Int Med*, 1974

Prior CAD (n=65)

No Prior CAD (n=61)

Year - Quarters Prior to Death

YEAR ONE

YEAR TWO

SUDDEN DEATH
What is in the black box connecting increasing stressful life events and cardiac events?
What is in the black box connecting increasing stressful life events and cardiac events?
If we intervene to change distress will we alter post-MI prognosis?
Goal: reduction of *psychological distress*

Primary Outcome: 1-year cardiac mortality

461 men post-Myocardial Infarction (MI)

Randomized to

- 1-Year Program (telephone distress monitoring and home nursing visits)
- Usual Care
1-Year Cardiac Mortality in the IHD Life Stress Monitoring Program (n=461 men)

Hazards Ratio = 0.5, P=0.07

Frasure-Smith and Prince, Psychosom Med, 1985
5-Year Cardiac Mortality Impact of In Hospital Psychological Distress (GHQ ≥ 5) in Men Receiving Usual Care (n=229)

Frasure-Smith, Am J Cardiol, 1991
### Percent Cardiac Death over 5 Years among Male Post-MI Patients (usual care; n=229)

<table>
<thead>
<tr>
<th>Distress Symptom</th>
<th>“Worse than usual”</th>
<th>“No worse than usual”</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Cannot concentrate</td>
<td>33.0%</td>
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<td>0.03</td>
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<td>Not playing a useful part in things</td>
<td>36.8%</td>
<td>17.1%</td>
<td>0.003</td>
</tr>
<tr>
<td>Not enjoying activities</td>
<td>29.0%</td>
<td>17.6%</td>
<td>0.03</td>
</tr>
<tr>
<td>Feeling unhappy and depressed</td>
<td>36.5%</td>
<td>15.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Not doing things well</td>
<td>55.8%</td>
<td>17.3%</td>
<td>0.0001</td>
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McGill University

Université de Montréal

1988-1989
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Sociologists are anthropologists who can do math.
Sociologists are anthropologists who can do math.

What is depression?

http://www.texastmscenter.com/depression.html
What is Depression?

- It is not feeling sad or down for a day or two
- It changes and interferes with usual daily activities
- It has physiological correlates: sleep and appetite changes, fatigue, slowing of thoughts or body movements
- It usually recurs
  - after 1 episode, 50% recurrence
  - after 2, 70%
  - after 3 or more, 90% (Solomon et al, 1997)
- There is no gold standard, no laboratory test
American Psychiatric Association DSM-IV Criteria for Major Depression

1. Sadness

2. Loss of interest

3. Decrease in appetite

4. Insomnia

5. Psychomotor agitation or retardation

6. Loss of energy

7. Feelings of worthlessness

8. Lack of concentration

9. Life not worth living

Major Depression
- Symptoms 1 or 2
- Total of 5 symptoms
- Daily at least 2 weeks
- Impairment

Not due to
- Substance abuse
- Medical condition
- Bereavement (< 2 mos)
Joint Program in Mental Health Research of the FRSQ-CQRS

*Emotions and Prognosis Post Infarct (EPPI): A Study of Potential Pathophysiological Links*

$120,959 (Canadian).
N. Frasure-Smith; F. Lespérance, M. Talajic

1991-1993
Location, location, location

- Environment and Resources
  - Important patient flow
  - Support from key leaders in cardiology: Martin Juneau, Mario Talajic, Jean-Lucien Rouleau, Stanley Nattel
  - Mixing McGill scientific track record and MHI excellence in clinical services in psychosomatic medicine (Dr Robert Leroux)
EPPI Methods

- 222 Post-MI patients (22% women, no age limits)
- Interviewed in hospital, 6 and 12 months
- DSM Criteria for depression: Diagnostic Interview Schedule (DIS)
- Depression Symptoms: BDI-I
- Long-term follow-up for events using Medicare data and chart searches
HR = 4.3; p = 0.013

Adjusted for Killip class, left ventricular dysfunction and previous MI

Frasure-Smith, Lespérance, Talajic, JAMA 1993
Prevalence of Major Depression In Hospitalized CHD Patients (~20%)
Sample Items from 21-item 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
About 1 in 3 hospitalized CHD patients have major depression, which is about 3 times as common as in the general community.

What Do We Know about Depression in CAD Patients?

- No matter how you measure it, depression is common in CAD patients
- Is it a “normal reaction” to CAD?
Post-MI Depression 1 Year Later

- No Evidence of Depression in Hospital: 86%
- Some Depression (BDI > 10 but not meeting criteria): 52%
- Major Depression in Hospital: 31%

Lespérance, Frasure-Smith et al, Psychosom Med, 1996
Depression (BDI $\geq 10$) and 1-Year Cardiac Prognosis

Post-MI (n=896)

- Odds Ratio $= 3.7 (1.7 - 8.0)$
- $P = 0.001$

- Adjusted for Age, Killip Class, Non-Q wave MI, Left Ventricular Ejection Fraction, Smoking and Sex

Unstable Angina (n=430)

- Odds Ratio $= 6.7 (1.4 - 18.6)$
- $P < 0.001$

- Adjusted for Left Ventricular Ejection Fraction, Number of Diseased Vessels, and ECG Evidence of Ischemia

Frasure-Smith, Lespérance et al, Psychosom Med 1999

Lespérance, Frasure-Smith et al, Arch Int Med 2000
Long-Term Survival Impact of Increasing Levels of Post-MI Depression (BDI Score)

N=896

BDI < 5
BDI 5 - 9
BDI 10 - 18
BDI ≥ 19

Lespérance, Frasure-Smith et al, Circulation 2002
Multivariate Age- and Sex-Adjusted Baseline Predictors of 5-Year Post-MI Cardiac Mortality

Thrombolysis 0.6 (0.3 – 0.9)
Revascularization 0.5 (0.3 – 0.9)

2.3 (1.4 – 3.6) LVEF < 35%
2.1 (1.3 – 3.2) Diabetes
2.0 (1.3 – 3.1) Previous MI

Depression Symptoms

3.1 (1.6 – 6.3) BDI >18
3.2 (1.8 – 5.6) BDI 10 -18
1.8 (1.0 – 3.2) BDI 5 - 9
(all vs BDI < 5)

Lespérance, Frasure-Smith et al, Circulation 2002
Meta-analysis of Depressive Symptoms as a Risk Factor for Short/ Medium Term Post-MI Mortality (3 months to 2 years)

Published 1988- end 2002
- Bush 2001
- Frasure-Smith 1999
- Jenkinson 1993
- Ladwig 1991
- Lane 2001
- Mayou 2000
- Romanelli 2002

Subtotal: OR=2.24 (1.39 – 3.60)

Test for heterogeneity ns

Barth et al, Psychosom Med, 2004
What do we know about depression in CAD patients?

- Depression is highly prevalent
- Largely consistent evidence that depression is associated with worse prognosis independent of disease severity
- What about anxiety?
What about Anxiety?

Generalized Anxiety Disorder
- Continuous, Excessive Worry
- Muscle Tension
- Sleep Problems
- Restlessness/Agitation
- Concentration Difficulty
- Fatigue
- Irritability

Major Depression
- Sadness
- Worthlessness
- Loss of interest/pleasure
- Appetite Disturbance
- Suicidality

What about Anxiety?
What about Anxiety?

- Diagnostic criteria of GAD and MDD overlap
- High rates of comorbidity between mood and anxiety disorders
  - Estimates vary, usually between 25 to more than 50%
- In non-medically ill, comorbid anxiety/depression associated with
  - More severe symptoms
  - More chronic course
  - More impairment
- Evidence of a common genetic substrate
- Antidepressants are useful for treating both GAD and MDD

Gorman 1996; Zimmerman et al, 2003; Cameron et al, 2004; Fava et al, 2006; Kendler et al, 1992; Schmitt et al, 2005
Epidemiological Study of Acute Coronary Syndromes And the Pathophysiology of Emotions (ESCAPE)

- 804 stable CAD patients 2 months post acute coronary syndrome
- Self-reports of Symptoms
  - Depression: BDI-II
  - Anxiety: Anxiety sub-scale of the HADS
- SCID for DSM-IV
  - Major Depression
  - Generalized Anxiety Disorder
- Followed 2 years (Medicare data and chart searches)
  - MACEs=cardiac death, MI, survived cardiac arrest, non-elective revascularization

Frasure-Smith and Lespérance, Arch Gen Psychiatry, 2008
Prevalence of Depression and Anxiety in Stable CAD Patients in ESCAPE (n=804)

Depression

- Low Level of Depression Symptoms: 72%
- Elevated Depression Symptoms, not MDD: 21%
- MDD: 7%

Anxiety

- Low Level of Anxiety Symptoms: 59%
- Elevated Anxiety Symptoms, not GAD: 36%
- GAD: 5%
Baseline Measures of Depression and Anxiety and MACEs over 2 years in 804 Stable CAD Patients

<table>
<thead>
<tr>
<th></th>
<th>Covariate Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current MDD</td>
<td>2.27 (1.15 – 4.47)</td>
<td>0.022</td>
</tr>
<tr>
<td>Elevated Depression</td>
<td>1.61 (1.03 – 2.50)</td>
<td>0.038</td>
</tr>
<tr>
<td>Symptoms (BDI-II ≥ 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current GAD</td>
<td>2.29 (1.07 – 4.88)</td>
<td>0.040</td>
</tr>
<tr>
<td>Elevated Anxiety</td>
<td>1.45 (0.95 – 2.22)</td>
<td>0.084</td>
</tr>
<tr>
<td>Symptoms (HADS-A ≥ 8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, education, smoking, previous cardiac history, ejection fraction, CABG at index, vessels blocked after revascularization, BMI, triglycerides, blood pressure, calcium channel blockers, ACE inhibitors, statins

Frasure-Smith and Lesperance Arch Gen Psychiatry, 2008
Relationship Between DSM-IV Diagnoses of Major Depression and Generalized Anxiety Disorder and MACES over 2 years (cardiac death, MI, survived cardiac arrest, non-elective revascularization)

Frasure-Smith and Lespérance Arch Gen Psychiatry, 2008
What about Anxiety?

- Prevalence of GAD or elevated anxiety symptoms at least as high as MDD or elevated depression symptoms in stable CAD patients
- Increase in risk of cardiac events associated with GAD is comparable to the increase in risk with MDD
- Comorbid GAD/MDD does not appear to add to this risk, but sample may not have been large enough
- Additional epidemiological research is warranted
What about depression as a risk factor for developing CAD?

Fewer prospective studies in samples initially free of CAD than in CAD patients

- Require very large samples
- Difficult to establish freedom from CAD
- Require lengthy follow-up for event occurrence
Meta Analysis of Depression as a Predictor of CAD

- Anda, 1993
- Aromaa, 1994
- Barefoot, 1996
- Ferketich, 2000 women
- Ferketich, 2000 men
- Ford, 1998
- Mendes de Leon, 1998 women
- Mendes de Leon, 1998 men
- Pratt, 1996
- Schwartz, 1998
- Sesso, 1998
- Wassertholl-Smoler, 1995
- Whooley, 1998

- All Studies (n=13)
- Depressive Mood Only (n=10)
- Clinical Depression only (n=3)

RR = 1.64 (95% CI, 1.29 – 2.08)

Decreased Risk  
Increased Risk
Biologically Plausible Mechanisms Linking Depression with CAD?

“I think you should be more explicit here in step two.”
Biologically Plausible Mechanisms Linking Depression with CAD?

- Behavioural
  - Reduced compliance with medications and risk factor modification
  - Quality of medical care
    - Over/under-reporting of somatic symptoms
    - Delayed/ excessive treatment seeking
Therapeutic Advances in Cardiovascular Disease

% Mortality Risk Reduction Associated with Major Therapeutic Advances in Cardiovascular Disease


J.S. Kooner, Imperial College, London
Heart and Soul Study: Depression and Medication Nonadherence in Stable CAD Patients

Did not take as prescribed ≥ 75% of time

Forgot to take > once per week

Stopped completely

Proportion of Nonadherent* Acute Coronary Syndrome Patients in Relation to Baseline Level of Depression (n=274)

*aspirin taken < 80% of days according to MEM device over 90 days

Rieckmann N et al, JACC, 2006

Exploring the Treatment-Risk Paradox in Coronary Disease

Finlay A. McAlister, MSc, MD; Antigone Oropoules, MSc; Colleen M. Norris, PhD; Michelle M. Graham, MD; Ross T. Tsuyuki, MSc, PharmD; Merrill Knudson, MD; William A. Ghali, MD, MPH; for the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators

Background: The cause of the “treatment-risk paradox” reported for patients with coronary disease is unknown; however, determining the factors that contribute to this paradox is essential to properly design quality improvement interventions.

Methods: Prospective cohort study enrolling consecutive patients with angiographically proved coronary disease between February 1, 2004, and November 30, 2005, in Alberta.

Results: One month after an angiogram, statins were being taken by 2436 (62.9%) of 3871 patients (mean age, 64 years). High-risk patients were less likely to be taking statins than lower-risk patients (55.8% vs 63.5%; crude odds ratio [OR], 0.72 [95% confidence interval [CI], 0.57-0.92]; risk ratio [RR], 0.88 [95% CI, 0.79-0.97]), but this treatment-risk paradox was completely attenuated by adjusting for exertional capacity and depressive symptoms (OR, 0.98 [95% CI, 0.75-1.28]; RR, 0.99 [95% CI, 0.89-1.09]). These results were robust across drug classes: while high-risk patients were less likely to be taking angiotensin-converting enzyme inhibitors, aspirin, and statins (25.8% vs 32.3%; crude OR, 0.73 [95% CI, 0.56-0.95]; RR, 0.80 [95% CI, 0.65-0.97]), this association did not persist in the adjusted model (OR, 0.98 [95% CI, 0.72-1.33] [P = .87]; RR, 0.99 [95% CI, 0.79-1.20]).

Conclusions: The treatment-risk paradox reported in administrative database analyses is attributable to clinical factors not typically captured in these databases (such as functional capacity and depressive symptoms). Interventions to address the treatment-risk paradox should recognize that patients with reduced functional capacity, depression, or both are at higher risk for underuse of these beneficial therapies and should target physicians and patients.

Arch Intern Med. 2007;167:1019-1025
Biologically Plausible Mechanisms Linking Depression with CAD?

- Behavioural
- Pathophysiological
  - Autonomic dysregulation (increased risk of ventricular arrhythmias; decreased heart rate variability)
  - Inflammation
  - Endothelial dysfunction
  - Platelet changes
PVCs, depression and 18-month post-MI mortality (n=193)

Frasure-Smith, Lespérance et al, Circulation, 1995
Time to First Appropriate Implantable Cardioverter-defibrillator (ICD) Discharge by Presence of Depression in the TOVA Study

Depression (CES-D ≥ 16; n=115)

No Depression (n=530)

Whang et al, JACC, 2005
Cardiovascular Death-Free Survival in Relation to Baseline Level of Depression Symptoms (BDI-II) in AF-CHF Patients

HR for BDI-II $\geq 14 = 1.59 \ (1.24–2.05) \ P = 0.001^*$

*P for interaction of depression by treatment group = 0.91

Frasure-Smith, Lespérance et al, Circulation, 2009
Elevated Depression Symptoms and Time to Cardiac Events over 5 Years (AF-CHF Study; n=974)

Epidemiological Study of Acute Coronary Syndromes And the Pathophysiology of Emotions (ESCAPE)

Goals

• Confirm the prognostic impact of major depression and elevated depression symptoms in stable CAD patients
• Assess the role of potential mechanisms
  • Markers of inflammation (fasted blood draw)
  • Short-term Heart Rate Variability (30 minute)
  • Genetic polymorphisms

Lespérance, Frasure-Smith, Théroux, Rouleau et al, Dana Foundation, Canadian Institutes of Health Research, Glaxo Smith-Kline
Heart Rate Variability
Heart Rate Variability

- Non-invasive measure of autonomic function
- Decreased HRV predicts mortality in CAD patients
- Decreased HRV reflects
  - Decreased parasympathetic (vagal) activity
  - Increased sympathetic activity
  - Or both
### Adjusted Heart Rate Variability in Post-MI Patients with and without Depression

<table>
<thead>
<tr>
<th>HRV Index</th>
<th>Depressed Patients (N=135)</th>
<th>Nondepressed Patients (N=365)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnULF</td>
<td>$8.52 \pm 0.05$</td>
<td>$8.66 \pm 0.05$</td>
<td>0.03</td>
</tr>
<tr>
<td>lnVLF</td>
<td>$6.32 \pm 0.06$</td>
<td>$6.59 \pm 0.065$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>lnLF</td>
<td>$5.09 \pm 0.07$</td>
<td>$5.34 \pm 0.08$</td>
<td>0.009</td>
</tr>
<tr>
<td>lnHF</td>
<td>$4.41 \pm 0.07$</td>
<td>$4.58 \pm 0.08$</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, diabetes and smoking

*Carney et al, Circulation, 2001*
Mediation model of the effect of depression (DEP) on time to death through heart rate variability (HRV)

Survival Rates for Depressed and Nondepressed Patients

Adjusted Survival Rate vs. Follow-up Time, mo

- Nondepressed
- Depressed

Adjusted for LnVLF Power
Not Adjusted for LnVLF Power

Conclusions: Partial mediation

1) Link between depression and time to death is slightly attenuated by adjustment for HRV

2) Additional mechanisms must be involved.

### Depression symptom levels and heart rate variability

<table>
<thead>
<tr>
<th></th>
<th>Not depressed (BDI-II &lt; 14; n = 491)</th>
<th>At least mild to moderate depression symptoms (BDI-II ≥ 14; n = 191)</th>
<th>p</th>
<th>p adjusted for covariates</th>
</tr>
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<tr>
<td>RR interval</td>
<td>1030 ± 152</td>
<td>997 ± 164</td>
<td>0.013</td>
<td>0.20</td>
</tr>
<tr>
<td>SD of RR intervals (SDNN)</td>
<td>56.9 ± 25.1</td>
<td>56.2 ± 27.7</td>
<td>0.77</td>
<td>0.99</td>
</tr>
<tr>
<td>Low frequency power (ln)</td>
<td>2.92 ± 0.51</td>
<td>2.92 ± 0.54</td>
<td>0.98</td>
<td>0.76</td>
</tr>
<tr>
<td>ms², median (25th, 75th percentile)</td>
<td>176.3</td>
<td>169.7</td>
<td>0.68</td>
<td>0.66</td>
</tr>
<tr>
<td>High frequency power (ln)</td>
<td>2.60 ± 0.50</td>
<td>2.62 ± 0.54</td>
<td></td>
<td></td>
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<tr>
<td>ms², median (25th, 75th percentile)</td>
<td>123.0</td>
<td>122.7</td>
<td></td>
<td></td>
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</table>

Effect size of depression on heart rate variability (high frequency power or root mean square of RR interval)

In healthy samples weighted average = 0.33 (0.18 – 0.49)

In cardiac samples weighted average = 0.28 (0.13 – 0.43)

Rottenberg, Bio Psychiatry, 2007
What May be Different about Depression in CAD?

Atherosclerosis: an Inflammatory Disease of the Arteries

Endothelial Dysfunction
Fatty-Streak Formation
Advanced, Complicated Lesion

What May be Different about Depression in CAD?
Sickness (Cytokine) Model of Depression

- Reduced motor activity
- Fatigue
- Loss of interest
- Loss of appetite

Interferon-induced depression in humans

Sickness Model of Depression in Inflammatory Disorders

Risk factors for inflammatory disorders

Activation of brain pro-inflammatory cytokine signalling

Systemic infection → Peripheral cytokines

Changes in neuronal function

Sickness behaviour
- Attenuation of parasympathetic tone
- Activation of HPA axis
- Reduced appetite
- Altered thermoregulation and energy metabolism
- Flattening of diurnal rhythms
- Decreased social and physical activity
- Increased SWS and reduced REM
- Impaired learning and memory
- Pain
- Fatigue

Decompensation → Clinical depression

Risk factors for mood disorders

Dantzer, R et al. Nat Rev Neurosci, 2008
High cytokine levels in the context of elevated cortisol may disrupt tryptophan/serotonin metabolism leading to depression.


Dantzer, R et al. *Nat Rev Neurosci*, 2008
Inflammatory Markers (cytokines)

sICAM-1 (Soluble intercellular adhesion molecule)

IL-6 (Interleukin-6)

CRP (C-reactive protein)

- Are increased in patients with CAD
- Predict the incidence of CAD, and prognosis in patients with established CAD
- Some evidence that inflammatory markers are increased in depressed non-CAD patients
sICAM-1 (Soluble intercellular adhesion molecule)
sICAM-1 and Levels of Depression Symptoms in Men 2 Months Post- Acute Coronary Syndrome

<table>
<thead>
<tr>
<th></th>
<th>BDI-II &lt; 14; n=450</th>
<th>BDI-II &gt; 14; n=152</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICAM-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (ng/ml; 25\textsuperscript{th} and 75\textsuperscript{th} percentile)</td>
<td>179.1 (156.5 – 210.2)</td>
<td>192.6 (166.9 – 233.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Frasure-Smith, Lespérance, Irwin et al, Biol Psychiatry, 2007*
sICAM-1 in Men 2 Months Post- Acute Coronary Syndrome and Hazards for MACEs over 2 years (cardiac death, survived MI, survived cardiac arrest, emergency revascularization)

<table>
<thead>
<tr>
<th>Per SD increase in sICAM-1</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.24 (1.02 – 1.51)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Frasure-Smith, Lespérance, Irwin et al, Biol Psychiatry, 2007
sICAM-1 in Men 2 Months Post- Acute Coronary Syndrome and Hazards for MACEs over 2 years (cardiac death, survived MI, survived cardiac arrest, emergency revascularization)

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.24 (1.02 – 1.51)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Adjusted for education, marital status, smoking, index CABG, **no. of vessels with > 50% blockage**, BMI, triglycerides, glucose, HDL, diastolic BP, beta-blockers, ACE inhibitors, calcium channel blockers, statins, long acting nitrates

1.19 (0.96 – 1.48) 0.12

*Frasure-Smith, Lespérance, Irwin et al, Biol Psychiatry, 2007*
Comparison of Chemokine and Soluble Adhesion Molecules in Depressed Young Adult Patients (n=15) Compared with Controls (n=15)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Depressed</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1</td>
<td>345 ± 128</td>
<td>486 ± 138</td>
<td>0.005</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>204 ± 37</td>
<td>273 ± 46</td>
<td>0.005</td>
</tr>
<tr>
<td>E-Selectin</td>
<td>31 ± 8</td>
<td>45 ± 22</td>
<td>0.02</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>440 ± 32</td>
<td>459 ± 34</td>
<td>0.69</td>
</tr>
</tbody>
</table>

ng/ml ± SEM

Rajagopalan, Brook, Rubenfire, Pitt, Young and Pitt, Am J Cardiol, 2001
Assessment of Endothelial Function
Attenuation of Brachial Artery Responses to Flow in Depressed Young Adults (n=15 depressed, 15 controls)

Rajagopalan, Brook, Rubenfire, Pitt, Young and Pitt, *Am J Cardiol*, 2001
(N=70 healthy adults; Profile of Mood States)

Cooper et al, Psychosom Med 2010
Patients referred for exercise stress testing and interviewed with the PRIME-MD

Relative uptake ratio (RUR) as a function of depression group

Lavoie, Arsenault et al, Psychosom Med 2010
Infection, ischemia, tissue damage (atherosclerosis)

Macrophage

Release of Cytokines: IL-1, IL-6, TNF-α

Liver

Acute Phase Reactants: CRP
## Markers of Inflammation and Levels of Depression Symptoms in Men Two Months Post-Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>BDI-II &lt; 14; n=450</th>
<th>BDI-II &gt; 14; n=152</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (pg/ml: 25\textsuperscript{th} and 75\textsuperscript{th} percentile)</td>
<td>2.03 (1.41 – 3.14)</td>
<td>2.22 (1.41 – 3.64)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mg/L: 25\textsuperscript{th} and 75\textsuperscript{th} percentile)</td>
<td>1.66 (0.91 – 3.87)</td>
<td>2.02 (1.02 – 4.91)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

*Frasure-Smith, Lespérance, Irwin et al, Biol Psychiatry, 2007*
### Meta-Analysis of Association Between Depression and CRP

*(Howren et al, Psychosom Med, 2009)*

#### TABLE 1. Random Effects Models for All CRP Analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of Studies</th>
<th>Effect Size (d)</th>
<th>p</th>
<th>95% CI</th>
<th>Q (df)</th>
<th>Fail-Safe N</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies</td>
<td>49</td>
<td>0.15</td>
<td>&lt;.001</td>
<td>0.10–0.21</td>
<td>234.79 (58)**</td>
<td>1119</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>17</td>
<td>.009</td>
<td>0.04–0.30</td>
<td>66.71 (13)**</td>
<td>54</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI adjusted</td>
<td></td>
<td>2</td>
<td>.17</td>
<td>-0.02–0.30</td>
<td>65.93 (14)**</td>
<td>216</td>
</tr>
<tr>
<td>BMI unadjusted</td>
<td></td>
<td>9</td>
<td>&lt;.001</td>
<td>0.08–0.21</td>
<td>132.01 (38)**</td>
<td>289</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants adjusted</td>
<td></td>
<td>36</td>
<td>0.14</td>
<td>&lt;.001</td>
<td>171.51 (43)**</td>
<td>359</td>
</tr>
<tr>
<td>Antidepressants unadjusted</td>
<td></td>
<td>7</td>
<td>0.22</td>
<td>0.10–0.23</td>
<td>179.68 (40)**</td>
<td>662</td>
</tr>
<tr>
<td>Statins adjusted</td>
<td></td>
<td>18</td>
<td>0.1</td>
<td>0.08–0.21</td>
<td>62.89 (14)**</td>
<td>67</td>
</tr>
<tr>
<td>Statins unadjusted</td>
<td></td>
<td>32</td>
<td>0.17</td>
<td>0.06–0.44</td>
<td>65.92 (10)**</td>
<td>37</td>
</tr>
<tr>
<td>HRT/contraceptive adjusted</td>
<td></td>
<td>26</td>
<td>0.15</td>
<td>0.06–0.44</td>
<td>65.92 (10)**</td>
<td>37</td>
</tr>
<tr>
<td>HRT/contraceptive unadjusted</td>
<td></td>
<td>29</td>
<td>0.21</td>
<td>0.10–0.37</td>
<td>197.69 (40)**</td>
<td>673</td>
</tr>
<tr>
<td>Clinical intake</td>
<td></td>
<td>12</td>
<td>0.14</td>
<td>0.08–0.21</td>
<td>171.51 (43)**</td>
<td>359</td>
</tr>
<tr>
<td>Self-report</td>
<td></td>
<td>15</td>
<td>0.22</td>
<td>0.10–0.23</td>
<td>179.68 (40)**</td>
<td>662</td>
</tr>
<tr>
<td>Community sample</td>
<td></td>
<td>10</td>
<td>0.17</td>
<td>0.08–0.21</td>
<td>171.51 (43)**</td>
<td>359</td>
</tr>
<tr>
<td>Clinical sample (MDD Only)</td>
<td></td>
<td>9</td>
<td>0.18</td>
<td>0.03–0.33</td>
<td>17.99 (9)*</td>
<td>21</td>
</tr>
</tbody>
</table>

**Note:**
- CRP = C-reactive protein; CI = confidence interval; BMI = body mass index; Meds = medications; HRT = hormone replacement therapy; MDD = major depressive disorder; CAD = coronary artery disease.
- $a$ Total N = 51,234.
- $b$ Reflects the removal of two outliers (51,52).
- $^* p < .05; ^{**} p \leq .001$. 

#### CRP and Depression

**Overall:** 49 studies ES=.15 (0.10 – 0.21)  
Fail safe n=1119

**CAD:** 9 studies ES=.18 (0.03 – 0.33)  
Fail safe n=21
Meta-Analysis of Association Between Depression and IL-6 
(Howren et al, Psychosom Med, 2009)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of Studies</th>
<th>Effect Size ($d$)</th>
<th>$p$</th>
<th>95% CI</th>
<th>$Q$ (df)</th>
<th>Fail-Safe N</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies</td>
<td>61</td>
<td>0.25</td>
<td>&lt;.001</td>
<td>0.18–0.31</td>
<td>281.02 (64)**</td>
<td>2343</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
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</tr>
<tr>
<td>BMI adjusted</td>
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<tr>
<td>BMI unadjusted</td>
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<tr>
<td>Men</td>
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<tr>
<td>Women</td>
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</tr>
<tr>
<td>Antidepressants</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anti-inflammatories</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatories unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins adjusted</td>
<td>14</td>
<td>0.33</td>
<td>.003</td>
<td>0.11–0.55</td>
<td>103.87 (14)**</td>
<td>92</td>
</tr>
<tr>
<td>Statins unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRT/contraceptives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical interview</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical sample (MDD only)</td>
<td>25</td>
<td>0.71</td>
<td>&lt;.001</td>
<td>0.04–0.15</td>
<td>47.80 (18)**</td>
<td>111</td>
</tr>
<tr>
<td>Clinical sample (comorbid CAD-related illness)</td>
<td>12</td>
<td>0.10</td>
<td>.049</td>
<td>0.00–0.20</td>
<td>14.05 (12)**</td>
<td>5</td>
</tr>
<tr>
<td>Clinical sample (comorbid cancer)</td>
<td>7</td>
<td>0.36</td>
<td>.038</td>
<td>0.02–0.70</td>
<td>17.99 (6)*</td>
<td>23</td>
</tr>
</tbody>
</table>

IL-6 and Depression
Overall: 61 studies $ES=0.25$
(0.18 – 0.31)
Fail safe n=2343

CAD: 12 studies $ES=0.10$ (0.00-0.20)
Fail safe n=5

IL = interleukin; CI = confidence interval; BMI = body mass index; Meds = medications; HRT = hormone replacement therapy; MDD = major depressive disorder; CAD = coronary artery disease.

$a$ Total $N = 24,873$.

$b$ Reflects the removal of one outlier (51).

$p < .05; ** p \leq .001; *** p = .30.$
Elevated CRP Levels 2 months Post-ACS and MACEs Over 2 years (cardiac death, survived MI, survived cardiac arrest, emergency revascularization)

- CRP < 2 mg/L
- CRP > 2 mg/L

N=602 men

HR=1.67 (1.07 – 2.62)

\( p = 0.025 \)

Adjusted* HR = 1.68

\( (1.04 – 2.71) \)

\( p = 0.034 \)

*Adjusted for education, marital status, smoking, index CABG, no. of vessels with > 50% blockage, BMI, triglycerides, glucose, HDL, diastolic BP, beta-blockers, ACE inhibitors, calcium channel blockers, statins, long acting nitrates
Elevated BDI-II Scores 2 months Post-ACS and MACEs Over 2 years (cardiac death, survived MI, survived cardiac arrest, emergency revascularization)

Adjusted* HR = 1.72 (1.07 to 2.77)  
$p=0.024$

*Adjusted for education, marital status, smoking, index CABG, no. of vessels with > 50% blockage, BMI, triglycerides, glucose, HDL, diastolic BP, beta-blockers, ACE inhibitors, calcium channel blockers, statins, long acting nitrates
Two-Year MACE-free Survival By Levels of Depression Symptoms (BDI-II) and CRP Post-ACS in Men (p for interaction=0.02)

Frasure-Smith, Lеспérance, Irwin et al, Biol Psychiatry, 2007
Cholinergic Anti-Inflammatory Pathway:
Reflex that Normally Inhibits Inflammation

Pathogens
Ischemia
Tissue Injury

Tracey KJ. JCI, 2007
Cholinergic Anti-Inflammatory Pathway:
Reflex that Normally Inhibits Inflammation

Pathogens
Ischemia
Tissue Injury

Cytokine Release

Tracey KJ. JCI, 2007
Pathogens
Ischemia
Tissue Injury

Cholinergic Anti-Inflammatory Pathway:
Reflex that Normally Inhibits Inflammation

Afferent vagus nerve

Cytokine Release
Cholinergic Anti-Inflammatory Pathway: Reflex that Normally Inhibits Inflammation

Pathogens Ischemia Tissue Injury

Cytokine Release

Efferent vagus nerve

Acetylcholine Release

Afferent vagus nerve
Cholinergic Anti-Inflammatory Pathway: Reflex that Normally Inhibits Inflammation

Pathogens
Ischemia
Tissue Injury

Inhibition of Cytokine Release

Increased vagal activity = increased heart rate variability

Efferent vagus nerve

Acetylcholine Release
Correlations between CRP and 24-hour HRV in Patients with Unstable Angina (n=531 all measures significant*)

*remained significant after adjustment for Troponin level and statin use (stepwise selected)

Lanza et al Am J Cardiol, 2006
Correlations between Inflammation and short-term HRV in the CARDIA Study (healthy, mean age=40)*

IL-6 and Low Frequency Power (n=734)

CRP and Low Frequency Power (n=678)

*Remained significant after adjustment for race, sex, age, education, smoking, physical activity, systolic blood pressure and BMI

Correlations Between Night Time HRV and Morning Inflammatory Markers In Depressed Patients with Coronary Heart Disease (n=44)

<table>
<thead>
<tr>
<th></th>
<th>IL-6</th>
<th></th>
<th>CRP</th>
<th></th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>LnTP</td>
<td>−0.38</td>
<td>0.03</td>
<td>−0.12</td>
<td>0.49</td>
<td>−0.04</td>
</tr>
<tr>
<td>LnVLF</td>
<td>−0.32</td>
<td>0.07</td>
<td>−0.15</td>
<td>0.40</td>
<td>−0.12</td>
</tr>
<tr>
<td>LnLF</td>
<td>−0.32</td>
<td>0.07</td>
<td>−0.17</td>
<td>0.32</td>
<td>−0.04</td>
</tr>
<tr>
<td>LnHF</td>
<td>−0.19</td>
<td>0.31</td>
<td>−0.11</td>
<td>0.54</td>
<td>−0.15</td>
</tr>
</tbody>
</table>

Carney, Freedland, Stein, Miller et al, J Psychosom Res, 2007
Correlations Between Night Time HRV and Morning Inflammatory Markers In Depressed Patients with Coronary Heart Disease (n=44)

<table>
<thead>
<tr>
<th></th>
<th>IL-6</th>
<th>CRP</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>LnTP</td>
<td>−0.38</td>
<td>0.03</td>
<td>−0.12</td>
</tr>
<tr>
<td>LnVLF</td>
<td>−0.32</td>
<td>0.07</td>
<td>−0.15</td>
</tr>
<tr>
<td>LnLF</td>
<td>−0.32</td>
<td>0.07</td>
<td>−0.17</td>
</tr>
<tr>
<td>LnHF</td>
<td>−0.19</td>
<td>0.31</td>
<td>−0.11</td>
</tr>
</tbody>
</table>

• Sample too small for covariate control

• No non-depressed patients

• Other studies of HRV and inflammation correlation have had an unknown combination of depressed and non-depressed subjects

Carney, Freedland, Stein, Miller et al, J Psychosom Res, 2007
Does the correlation between inflammatory markers and HRV differ in depressed and non-depressed CAD patients?

Is there evidence of a difference in the efficiency of the cholinergic anti-inflammatory reflex associated with depression?
<table>
<thead>
<tr>
<th></th>
<th>IL-6&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not depressed (BDI-II &lt; 14; n = 491)</td>
<td>At least mild to moderate depression Symptoms (BDI-II ≥ 14; n = 191)</td>
</tr>
<tr>
<td>RR intervals</td>
<td>−.16 (&lt;0.001)</td>
<td>−.25 (&lt;0.001)</td>
</tr>
<tr>
<td>SD of RR intervals</td>
<td>−.18 (&lt;0.001)</td>
<td>−.21 (0.003)</td>
</tr>
<tr>
<td>SDNN</td>
<td>−.20 (&lt;0.001)</td>
<td>−.25 (&lt;0.001)</td>
</tr>
<tr>
<td>Low frequency power</td>
<td>−.14 (0.002)</td>
<td>−.29 (&lt;0.001)</td>
</tr>
<tr>
<td>High frequency power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not depressed (BDI-II &lt; 14; n = 491)</td>
<td>At least mild to moderate depression symptoms (BDI-II ≥ 14; n = 191)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>RR intervals</td>
<td>−.19 (&lt;0.001)</td>
<td>−.25 (&lt;0.001)</td>
</tr>
<tr>
<td>SD of RR intervals (SDNN)</td>
<td>−.066 (0.15)</td>
<td>−.31 (&lt;0.001)</td>
</tr>
<tr>
<td>Low frequency power&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−.033 (0.47)</td>
<td>−.30 (&lt;0.001)</td>
</tr>
<tr>
<td>High frequency power&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−.009 (0.83)</td>
<td>−.27 (&lt;0.001)</td>
</tr>
</tbody>
</table>

<sup>a</sup>CRP: C-reactive protein
Fig. 1. SD of RR intervals (SDNN).
<table>
<thead>
<tr>
<th></th>
<th>BDI-II &lt; 14</th>
<th></th>
<th>BDI-II ≥ 14</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of Variance in CRP Explained</td>
<td></td>
<td>% of Variance in CRP Explained</td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>&lt;0.0%</td>
<td>0.91</td>
<td>4.1%</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (per SD)</td>
<td>0.4%</td>
<td>0.070</td>
<td>0.1%</td>
<td>0.63</td>
</tr>
<tr>
<td>Female</td>
<td>0.8%</td>
<td>0.035</td>
<td>1.0%</td>
<td>0.14</td>
</tr>
<tr>
<td>Current daily smoker</td>
<td>0.3%</td>
<td>0.20</td>
<td>0.4%</td>
<td>0.33</td>
</tr>
<tr>
<td>Coronary bypass surgery at index</td>
<td>1.3%</td>
<td>0.008</td>
<td>1.4%</td>
<td>0.070</td>
</tr>
<tr>
<td>Body mass index (per SD)</td>
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Cholinergic Anti-Inflammatory Pathway: Reflex that Normally Inhibits Inflammation

Pathogens
Ischemia
Tissue Injury

Afferent vagus nerve

Inhibition of Cytokine Release

Efferent vagus nerve

Acetylcholine Release

Increased vagal activity = increased heart rate variability

Tracey KJ. JCI, 2007
Diffusable Glucocorticoids (HPA Axis) Normally Inhibit Inflammation (reduced inhibition in depression)
Limitations

- No assessment of HPA axis function (cortisol)
- Assessment of elevated depression symptoms rather than major depression because number of participants with MDD too small to permit covariate control
- Cross-sectional data
  - We don’t know whether changes in HRV produce changes in inflammatory markers or vice versa
  - We don’t know whether depression is cause or the consequence of the changes in HRV and inflammation
What do we know about depression in CAD patients?

- Depression is highly prevalent
- Largely consistent evidence that depression is associated with worse prognosis
- Association is not currently better explained in other ways
- Mechanisms unknown, but multiple plausible and interacting mechanisms are likely to exist