Depression and CV Disease
A Depressing Story

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Depression and CV Disease

• HF affects > 5 million people in the US

• 15-20% of patients with HF have depression

• Patients with HF + depression have a worse quality of life and CV risk

• The risk of death for depressed individuals with HF is 2.1

Faris, R. et al
Eur H J 2002;4:541
Rutledge, T et al
Rumsfeld, JS et al
JACC 2003;42:1811
Depression and CV Disease

Effect of MDD on Cardiac Mortality in 2847 individuals age 55-85 years

- Depression increases the risk of CV death in subjects with and without cardiac disease at baseline. The excess in CV mortality was more than twice as high for major depression as for minor depression

Penninx, BWJH et al
Arch Gen Psychiatry
2001;58:221
Depression and CV Disease

- Approximately 50% of patients with MDD have an adequate response to antidepressant therapy and 15% have a partial response— but 20-35% are non-responders, while some become more severely depressed after initiation of therapy.

- Treatment resistant depression is associated with a high risk of CV mortality and morbidity in patients with an ACS.

Carney, R. M. et al
Am J. Psychiatry
2009;166:410
Conclusion: after adjustment for CVD, DM, and poor functional health there was no association between Depression CV risk

Figure 1 (a) Survival functions for symptomatic versus asymptomatic depression (Table 3; Model 2; definition ‘b’), unadjusted and raw. (b) Survival functions for symptomatic versus asymptomatic depression (Table 3; Model 2; definition ‘b’), unadjusted. (c) Survival functions for symptomatic versus asymptomatic depression (Table 3; Model 2; definition ‘b’), adjusted for significant covariates.

Atlantis, E et al
Int J. Geriatric Psychiatry 2010
Depression and CV Disease

- The Diagnoses of Major Depressive Disorder (MDD) requires the presence for at least 2 weeks of at least 5 symptoms including:
  - Sad mood, weight change, sleep abnormality, fatigue, feeling of worthlessness or excessive guilt, indecisiveness or poor concentration, and or recurrent thought of death or suicide

- Simple screening tools such as
  - Patient Health Questionaire (PHQ)
  - Beck Depression Inventory
  - Hospital anxiety and Depression Scale

Will detect most patients with MDD
Depression and CV Disease
Recommendations for Screening and Referral

Table 1. Patient Health Questionnaire: 2 Items*

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

1. Little interest or pleasure in doing things.
2. Feeling down, depressed, or hopeless.

*If the answer is "yes" to either question, then refer for more comprehensive clinical evaluation by a professional qualified in the diagnosis and management of depression or screen with PHQ-9.

Table 2. Patient Health Questionnaire-9 (PHQ-9)* Depression Screening Scales

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

1. Little interest or pleasure in doing things.
2. Feeling down, depressed, or hopeless.
3. Trouble falling asleep, staying asleep, or sleeping too much.
4. Feeling tired or having little energy.
5. Poor appetite or overeating.
6. Feeling bad about yourself, feeling that you are a failure, or feeling that you 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 being so fidgety or restless that you have been moving around a lot more than usual.
9. Thinking that you would be better off dead or that you want to hurt yourself in some way.

*Questions are scored: not at all=0; several days=1; more than half the days=2; and nearly every day=3. Add together the item scores to get a total score for depression severity.

Lichtman. JH et al
Circ 2008;118:1768
Depression and CV Disease

Recommendations for screening and Referral

Lichtman, JH et al
Circ 2008;118:1768
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A systematic review of the evidence on depression screening and treatment in patients with CHD found that the majority of patients who screen positive will not have major depression.

- Treatment of depression in CHD patients only accounts for a small variance in depression in symptom change scores.
- There is no evidence that screening for depression improves CHD outcomes.

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Effect of symptoms of MDD (Beck-Inventory) on clinical outcome in patients with HF

- Worsening symptoms of depression are associated with a poor prognosis in patients with HF
- Routine assessments of symptoms of depression in HF patients may help guide medical management

Sherwood, A. et al
JACC 2011; 57:418
Depression and CV Disease

Cardiologists screen for depression

- Over the past 2 weeks, have you been bothered by any of the following problems:
  
  1. Feeling little interest or pleasure in doing things?
  2. Feeling down, depressed, or hopeless?

Connerney, I et al
JACC 2011;57:424
**Depression and CVD**

**Figure.** Proposed remodeling of mind-heart interactions leads to progressive increases in neuroimmune activation in response to stress. In a state such as depression, there is increased sympathetic activity, decreased parasympathetic activity, and activation of proinflammatory pathways. In response to stress, there is further activation of the sympathetic nervous system and proinflammatory pathways and further withdrawal of parasympathetic activity. This results in an environment that promotes sudden cardiac death and vascular and myocardial injury.

Emani, S. et al
Circ HF 2010;3:715
Depression and CV Disease

Endothelial Function in young Adults with MDD without CV risk factors

MDD in the absence of other CV risk factors is associated with endothelial dysfunction and an increase in inflammatory cytokines
Depression and CV Disease

Vascular Dysfunction in a model of chronic stress and depression (8 weeks of unpredictable chronic mild stress in mice-VCMS)

- Arterial Nitric oxide production was attenuated in VCMS mice-associated with insulin resistance, vascular inflammation, and hypertension

Depression and CV Disease

Effect on Endothelial progenitor cells (EPCs)

- Patients with major depression have a decreased number of CD34+/VEGFR2 + circulating EPCs, independent of psychotropic drugs

Dome, P, et al
Molecular Psych
2009;14:523
Depression and CVD

- Pro-inflammatory cytokines (IL-1β, IL-2 and IFN-γ, and TNF-α, etc.)
  - Upregulation of iNOS in neurons
  - NO spike
    - NO mediated tPA-Plasmin, superoxide and p38 MAPK, etc. Cortical Destruction (MDD) Pathways
  - Work in concert with HPA-induced cortisol and C-peptide, etc.
    - Inhibition of dimethylarginine dimethylaminohydrolase (DDAH)

- Indoleamine 2,3 dioxygenase (IDO)
  - Tryptophan (TRP)
    - Serotonin (S-HT)
    - Quinoline: Cortical Destruction (MDD) Pathway
      - Downregulation of NOS (iNOS, eNOS) in endothelium
      - Abnormalities in vascular tone, platelet activation, endothelial interactions with leukocytes, and myocardial muscle function: CVD pathway

Ehrmann, Deldin, Pitt 2011
Depression and CV Disease

Association between depression and markers of Fibrosis

➢ Depression is associated with an increase in pro collagen I and type 1 collagen which could contribute to the development of HF

Kop. W.J. et al
Brain, Behavioral and Immunity
2010;24:229
Depression and CVD

Relationship between depressive symptoms with visceral adipose tissue and subcutaneous fat in middle aged woman

- Increased visceral fat but not subcutaneous fat was associated with depressive symptoms and may contribute to the increased CV risk associated with depression and CVD

Everson-Rose, SA et al
Psych Med 71:410, 2009
Depression and CV Disease

SADHEART

- Double Blind, placebo controlled randomized trial comparing the safety and antidepressant efficacy of the SSR1 sertraline vs. placebo in 369 patients with an ACS + MDD

Glassman, A.He. et al
Arch Gen Psych 2009;66, 1022
Depression and CV Disease

7 year follow up of SADHART participants

Glassman, A H et al
Arch Gen Psych 2009;66:1022
Depression and CV Disease

SADHART-CHF

Patients with Chronic Heart Failure & with Age ≥45 year-old, a NYHA Class ≥II, and LVEF ≤45%
- Consent for Depression Screen
  - BDI ≥ 10
  - Consent for SADHART Trial Participation

Major Depressive Disorder per DSM-IV criteria via Structured Psychiatric Diagnosis
- Randomization
  - Sertraline
  - Placebo

12-week Acute Treatment Phase*
- open treatment follow-up phase
  - Last Enrolled Patient Completes 180 Days*

*Acute Treatment Phase Endpoints
1. Worsening in clinical status, mortality, hospitalization;
2. Depressive symptoms and cardiac measures;
3. Quality of life

*Long-term Open Treatment Follow-up Endpoints:
Mortality and re-hospitalizations

Jiang, W. et al
AHJ 2008;156:437
Treatment with the SSRI sertraline compared to placebo did not provide greater reduction in depression or CV events in patients with MDD + HF
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Effect of antidepressants on CV risk in patients with heart failure treated with beta-blocker

In 99,335 patients surviving their first hospitalization for HF the use of antidepressants (TCAs and SSRIs) was determined and the risk of total mortality and CV mortality evaluated using propensity adjusted models

- Antidepressants were prescribed to 19,411 patients

Fosbol, E. L. et al
Circ HF Sept 22, 2009
Depression and CVD

Fosbol, E. L. et al
Circ HF Sept 22, 2009
Depression and CVD

Conclusions:

- The use of BBs was associated with a reduction in CV mortality in patients with HF.

- Use of both TCAs and SSRIs were associated with an increased risk of total and CV mortality.

- Coadministration of SSRIs and BBs was associated with a higher risk of mortality compared to coadministration of TCAs and BBs.

Fosbol, E. L. et al
Circ HF Sept 22, 2009
Depression and CVD

Effect of Omega-3 fatty acids + the SSRI sertraline vs. sertraline in patients with Depression + CVD:

- Treatment of patients with MDD and CHD with omega 3 fatty acids + an SSRI did not improve MDD compared to a SSRI alone

Garney, R.M. et al
JAMA 2009;302:1651
Depression and CVD

- Patients with Depression are more likely to have sleep disordered breathing (SDB) compared to controls – with an adjusted odds ratio up to 5.6

- Both Depression and SDB are associated with an increase in inflammatory cytokines and abnormalities in nitric oxide availability

- CPAP decreases cytokine proliferation, nitric oxide dysfunction, depression and CVD

DEW, M.A et al Arch Gen Psych 1981;138:129
Lam, B. et al thorax 2007;62:354
Obstructive Sleep Apnea

Plasma Aldosterone levels in patients with OSA with Resistant Hypertension

- OSA was present in 85% of patients with Resistant Hypertension
- A significant correlation between Plasma Aldosterone and severity of OSA was found in patients with resistant hypertension but not in control subjects

Pratt-Ubunama MN. Et al
Chest 2007;131:453
Obstructive Sleep Apnea

Effect of Diuretic therapy with IV furosemide and Spironolactone 100 mg bid for 3 days

- Diuretic treatment resulted in a significant decrease in Body weight, B.P., and Apnea-hyponea index. (AHI)

Bucca, CB et al
Chest 2007;132:440
Depression and CVD

- Sleep-Disordered Breathing
  - Hypoxia, SNS activation, PNS attenuation, etc.
    - HIF-1, NFκB, and other transcription factors from the *fos* and *jun* families
    - Glucocorticoid and Catecholamine release
    - Inflammatory agent production (intercellular adhesion molecule 1 (ICAM-1) and C-reactive protein (CRP), IL-1β, IL-2 and IFN-γ, and TNF-α, etc.)
    - Nitric Oxide Dysfunction in both the cortical and peripheral tissues
      - MDD via NO mediated cortical destruction
      - CVD via NO deficiency related cardiac abnormalities
      - Other SDB clinical correlates: sleep deprivation, soft palate inflammation, etc.
Depression and CVD

- Inflammatory cytokine proliferation and activation
  - NOS inhibition via ADMA
- Increased sympathetic drive and parasympathetic inhibition with HPA dysfunction
- Endothelial dysfunction and lack of progenitor cells
- Increased platelet aggregability
  All often minimized by CPAP

Ehrmann, D.E. Deldin PJ, Pitt B
Int J. Cardiol 2010
Depression and CV Disease

SDB + MDD
N=40

SDB without MDD
N=40

Controls
N=40

- Determine whether patients with SDB + MDD have an increase in inflammatory cytokines (IL-6, TNF-alpha, IFN-gamma) and a decrease in Nitric oxide availability (ADMA) compared to patients with SDB without MDD and healthy controls.

- Correlate the depression scores of patients with SBD + MDD to the severity of SDB and the extent of inflammation cytokine release and increase in ADMA.

Deldin, P. Dalock, G. Pitt. B
Depression and CV

Randomized study of collaboration care (Nurse + physician) in 214 patients with depression and CV disease (DM or CAD)

Collaborative care improved control of depression and CV disease

Table 3. Clinical and Quality-of-Life Measures.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group</th>
<th>Usual-Care Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement on Patient Global Improvement Scale — no./total no. (%)†</td>
<td></td>
<td></td>
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<tr>
<td>6 mo</td>
<td>64/96 (67)</td>
<td>15/91 (16)</td>
<td>&lt;0.001‡</td>
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<tr>
<td>12 mo</td>
<td>41/92 (45)</td>
<td>16/91 (18)</td>
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<tr>
<td>≥50% decrease in SCL-20 score — no./total no. (%)</td>
<td></td>
<td></td>
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<tr>
<td>6 mo</td>
<td>57/97 (59)</td>
<td>22/96 (23)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>12 mo</td>
<td>56/94 (60)</td>
<td>28/92 (30)</td>
<td></td>
</tr>
<tr>
<td>All three medical measures below guidelines or showing clinically significant change at 12 mo — no./total no. (%)‡</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6 mo</td>
<td>36/97 (37)</td>
<td>19/87 (22)</td>
<td>0.024¶</td>
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<tr>
<td>12 mo</td>
<td>37/102 (36)</td>
<td>18/96 (19)</td>
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<tr>
<td>≥10 mm Hg decrease in systolic blood pressure from baseline at 12 mo — no./total no. (%)</td>
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<td></td>
<td>0.016¶</td>
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<tr>
<td>6 mo</td>
<td>41/101 (41)</td>
<td>25/101 (25)</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>81/90 (90)</td>
<td>46/84 (55)</td>
<td></td>
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<tr>
<td>Satisfaction with care of depression — no./total no. (%)</td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>47/92 (51)</td>
<td>43/92 (47)</td>
<td>&lt;0.001¶</td>
</tr>
<tr>
<td>6 mo</td>
<td>84/97 (87)</td>
<td>53/86 (62)</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>81/90 (90)</td>
<td>46/84 (55)</td>
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<tr>
<td>Satisfaction with care of diabetes, heart disease, or both — no./total no. (%)</td>
<td></td>
<td></td>
<td>&lt;0.001¶</td>
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<tr>
<td>Baseline</td>
<td>73/104 (70)</td>
<td>65/95 (68)</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>87/97 (90)</td>
<td>65/95 (68)</td>
<td></td>
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<tr>
<td>12 mo</td>
<td>79/92 (86)</td>
<td>62/88 (70)</td>
<td></td>
</tr>
<tr>
<td>Quality-of-life score‡**</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>4.2±1.9</td>
<td>4.6±1.8</td>
<td>&lt;0.0011</td>
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<tr>
<td>6 mo</td>
<td>5.8±2.4</td>
<td>5.2±1.8</td>
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<tr>
<td>12 mo</td>
<td>6.0±2.2</td>
<td>5.2±1.9</td>
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Katon, WJ. Et al
NEJM 2010;363:2611
Depression and CV Disease

A positive affect – assessed by measures such as whether a patient smiles during the clinical interview and whether they take pleasure or excitement with aspects of their daily life protects against the development of coronary heart disease while depressive symptoms increased the likelihood of disease independent of age, gender, and CV risk factors (Davidson, K.lo. Et al EHJ, 2010)

- The apparent failure of current antidepressive therapy with TCAs and SSRIs to break the link between MDD and CVD emphasizes the importance of efforts to increase happiness and well being (Pitt, B., Deldin P. EHJ 2010)
Depressive symptoms are frequent in patients with HF and are associated with an increased mortality. Exercise training decreases depressive symptoms and improves mortality.

Katon, WJ. Et al
NEJM 2010;363:2611
Stress and Intern Year

- High responsibility/Low control
- High work volume
  - 80+ hrs/week
  - 30 hr shifts
  - Sleep deprivation

Shem 1978; Jauhar 2008; Duffy 2005; Eyes et al 2006; Shanafelt et al 2002
Incidence of Depression Before and During Medical Internship

- Before Internship: 0.00%
- 3 Months: 5.00%
- 6 Months: 10.00%
- 9 Months: 15.00%
- 12 Months: 20.00%

Intern Assessment Time

PHQ Depression Rate
Depression and CVD

Determination of the Biomarkers linking depression to CVD

- The incidence of depression increases from 4% prior to medical internship to 26% during the year of internship
- Biomarkers including: (blood + saliva)
  - ADMA
  - Circulating EPCs
  - IL-1beta, IL-6, IL-10, hs CRP, TNF-alpha
- Mood and sleep assessment (PHQ-9 + PSQ1)
- Objective sleep (assessment (Activewatch-Light))
  Will be determined in 350-500 medical interns before and during their internship year
Depression and CV Disease

Summary:

- The links between Depression and CFD and between CVD and depression are incompletely understood.

- The current therapy of Depression with TCAs and SSRIs has not reduced the increased CV risk associated with MDD and may in fact have increased the risk in patients with HF.
Depression and CV Disease

Summary:

- Depression is associated with an increase in sleep disordered breathing and sleep apnea.

- The concurrence of Depression and SDB increases inflammatory cytokine activation and abnormalities in Nitric oxide availability.

- Treatment of SDB by CPAP decreases the severity of Depression.

- Further studies are needed to determines the early links between depression and CVD and new therapeutic and behavioral approaches are needed to reduce the CV risk associated with Depression.

Pitt B. 2011