

Depression and CV Disease

A Depressing Story

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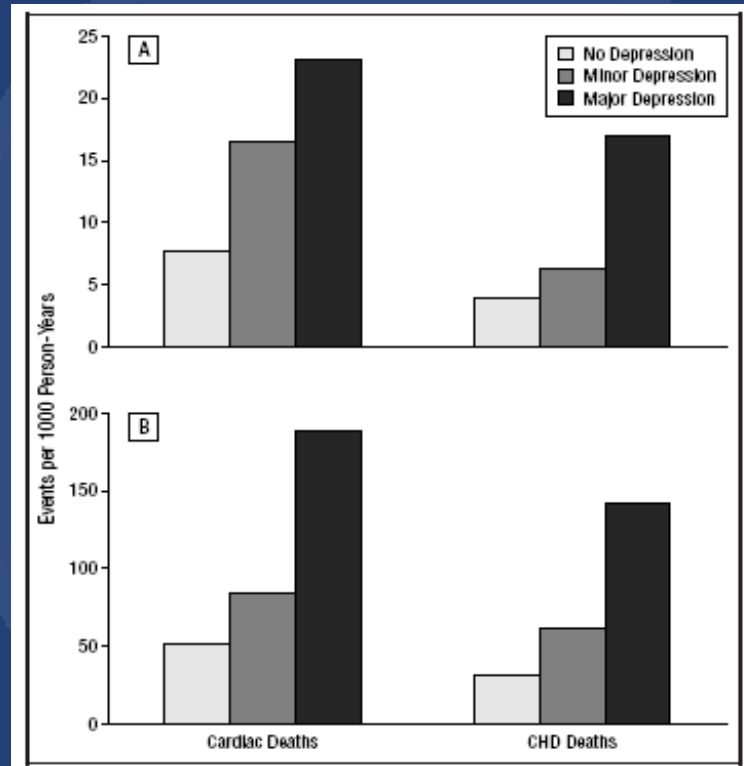
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Depression and CV Disease

- 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

Depression and CV Disease

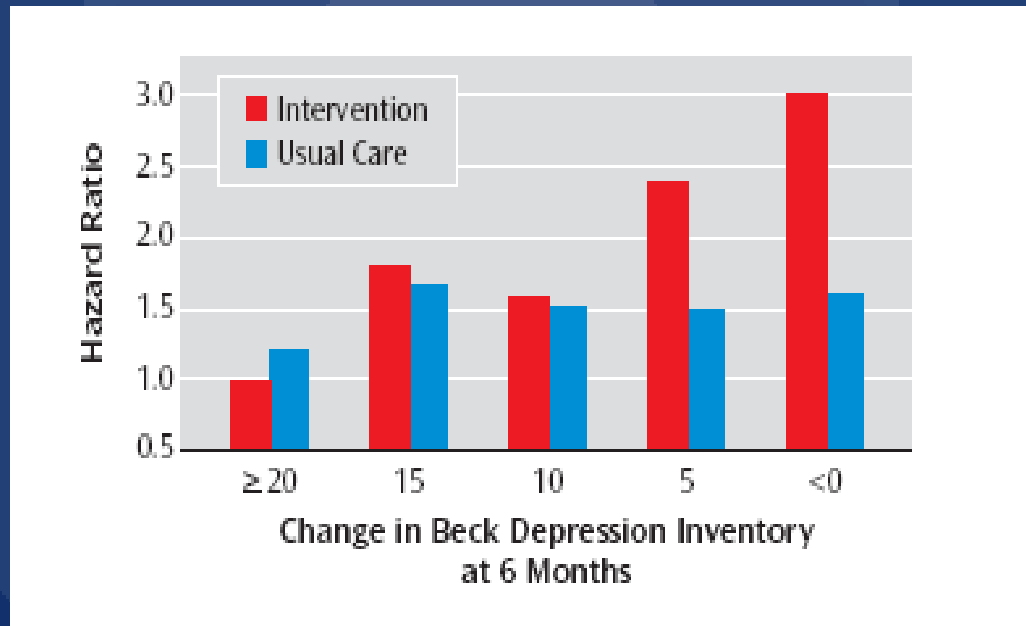
Effect of MDD on Cardiac Mortality in 2847 individuals age 55-85 years



- 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

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

Depression and CVD

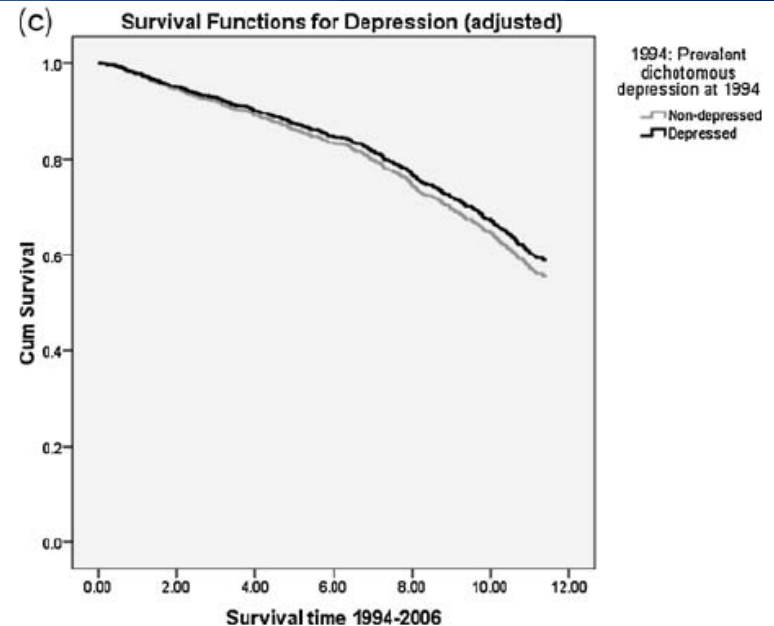
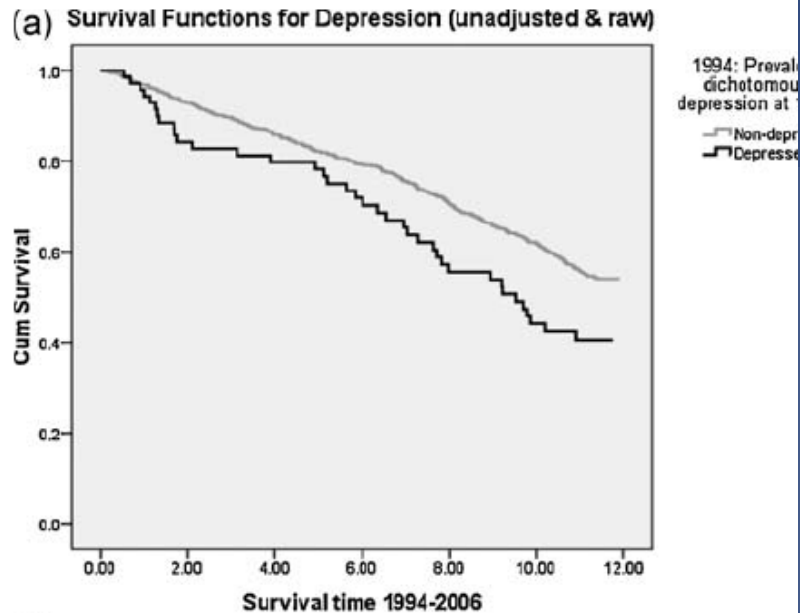


Figure 1 (a) Survival functions for symptomatic *versus* asymptomatic depression (Table 3; Model 2; definition 'b'), unadjusted and raw. (b): Survival functions for symptomatic *versus* asymptomatic depression (Table 3; Model 2; definition 'b'), unadjusted. (c): Survival functions for symptomatic *versus*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

- Conclusion: after adjustment for CVD, DM, and poor functional health there was no association between Depression CV risk

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 Questionnaire (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

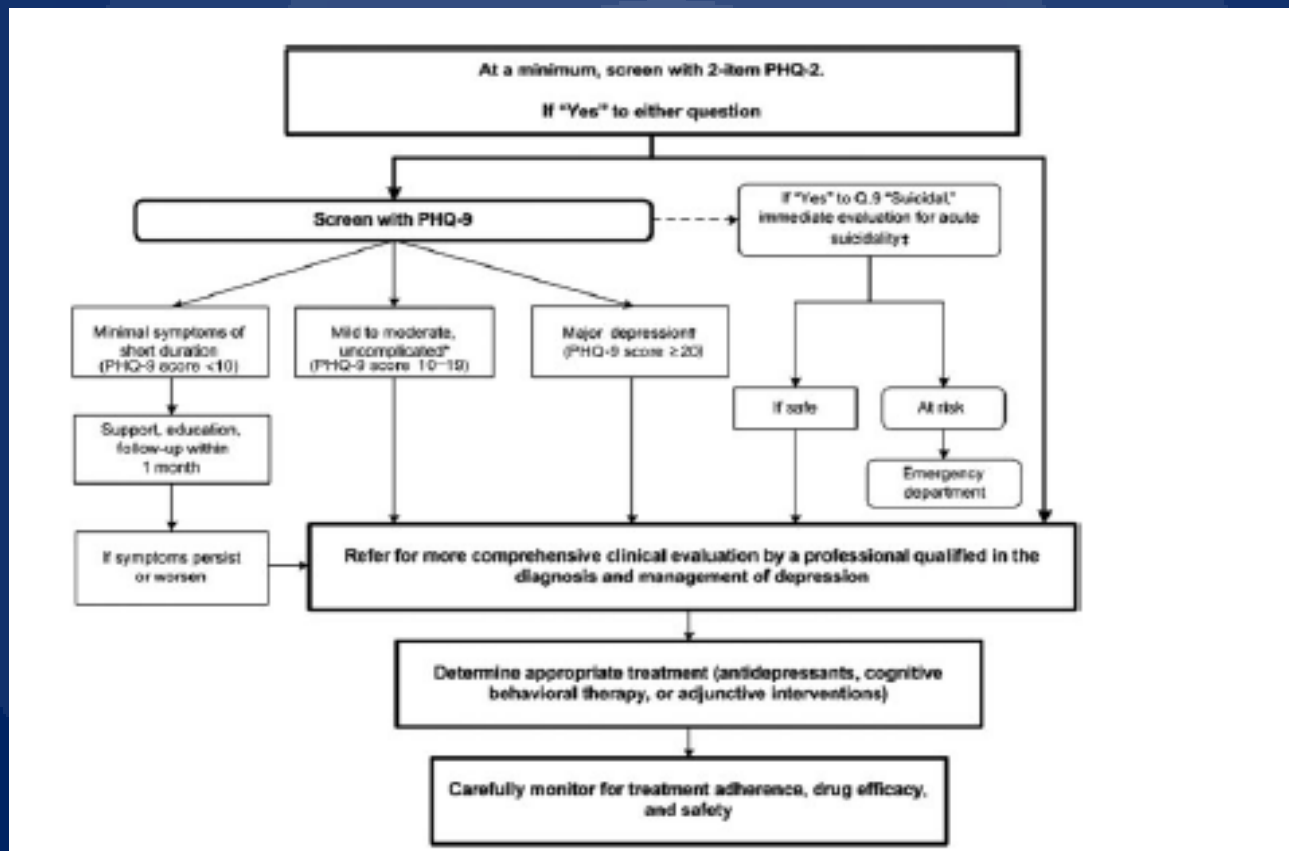
Over the past 2 weeks, how often have you been bothered by any of the following problems?

- (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.

Depression and CV Disease

➤ Recommendations for screening and Referral



Depression and CV Disease

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

Depression and CV Disease

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

Table 2

Multivariate Cox Proportional Hazards Models Assessing the Association of Baseline Depression Symptoms (Beck Depression Inventory Score) and 1-Year Change in Depression Symptoms (Change in Beck Depression Inventory Score) With Composite End Points of Hospitalizations and Death

Planned Model Characteristic	Cardiac Hospitalization or Death (112 Events)		All-Cause Hospitalization or Death (127 Events)	
	p Value	HR (95% CI)	p Value	HR (95% CI)
Age (yrs/10)	0.103	1.17 (0.97–1.41)	0.019	1.25 (1.04–1.51)
Cause (1 = ischemic; 0 = nonischemic)	0.004	1.83 (1.22–2.75)	0.053	1.46 (0.99–2.14)
NT-proBNP (pg/ml/1,000)	0.031	1.17 (1.01–1.36)	0.129	1.12 (0.97–1.29)
LVEF (%)	0.011	0.97 (0.95–0.99)	0.098	0.98 (0.96–1.00)
Baseline depression symptoms (BDI score)	<0.001	1.10 (1.06–1.14)	<0.001	1.09 (1.05–1.13)
1-year change in BDI score	0.007	1.07 (1.02–1.12)	0.023	1.06 (1.01–1.11)
Antidepressant (1 = yes; 0 = no)	0.092	0.63 (0.36–1.08)	0.309	0.78 (0.48–1.26)
Hospitalization in first year (1 = yes; 0 = no)	<0.001	2.40 (1.57–3.66)	<0.001	2.36 (1.59–3.51)

BDI = Beck Depression Inventory; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; other abbreviation as in Table 1.

- 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

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?

Depression and CVD

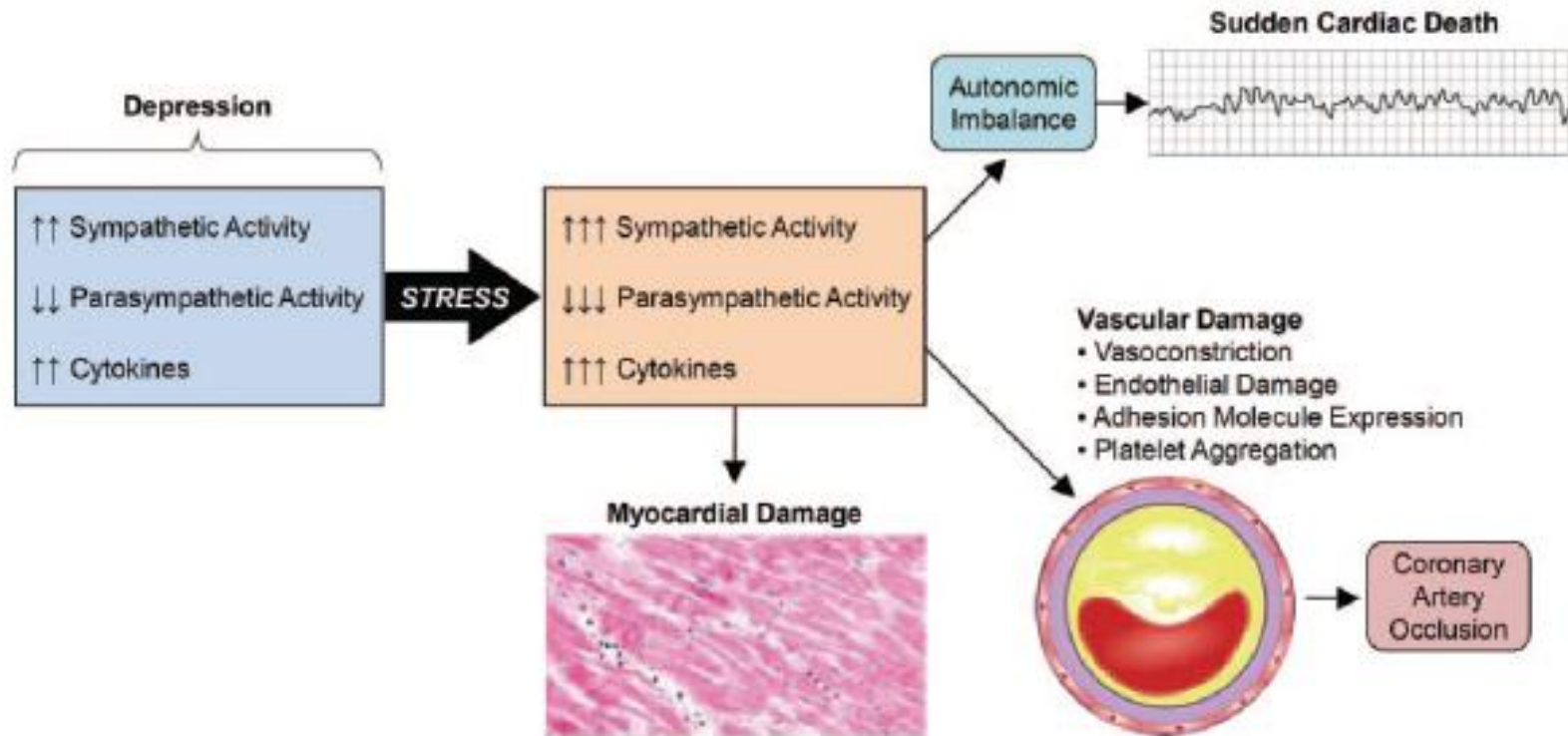


Figure. Proposed remodeling of mind-heart interactions leads to progressive increases in neuroimmune activation in response to stress. In a state such as depression, there is increased sympathetic activity, decreased parasympathetic activity, and activation of proinflammatory pathways. In response to 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.

Depression and CV Disease

Endothelial Function in young Adults with MDD without CV risk factors

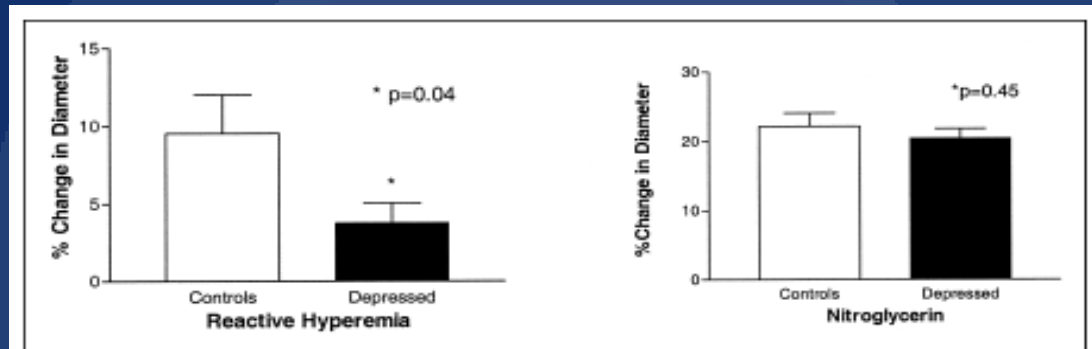


FIGURE 1. Brachial artery responses to flow are attenuated in patients with depression. All values are percent \pm SEM.

TABLE 2 Comparison of Chemokine and Solubilized Adhesion Molecules in Patients with Depression Compared With Controls

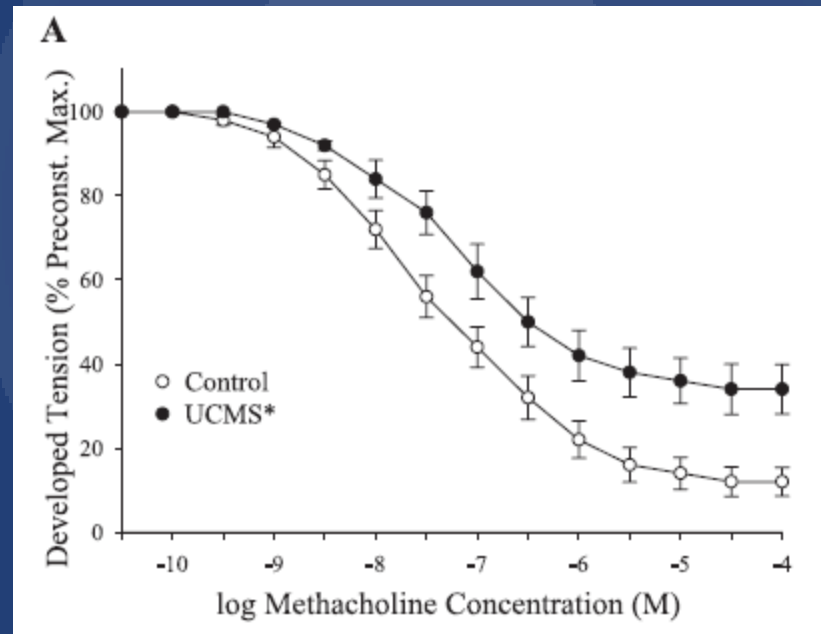
	Controls	Depressed	p Value
MCP-1	345 \pm 128	486 \pm 138	0.005
sICAM-1	204 \pm 37	273 \pm 46	0.005
E-Selectin	31 \pm 8	45 \pm 22	0.02
sVCAM-1	440 \pm 32	459 \pm 34	0.69

All values are expressed as means (ng/ml) \pm SD.

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

Depression and CV Disease

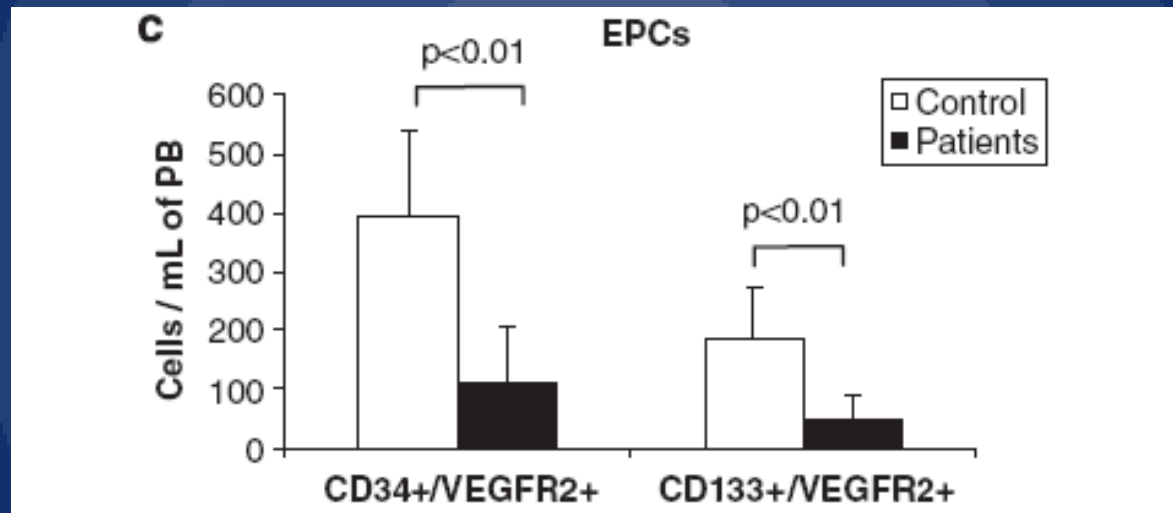
Vascular Dysfunction in a model of chronic stress and depression (8 weeks of unpredictable chronic mild stress in mice-VCMS)



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

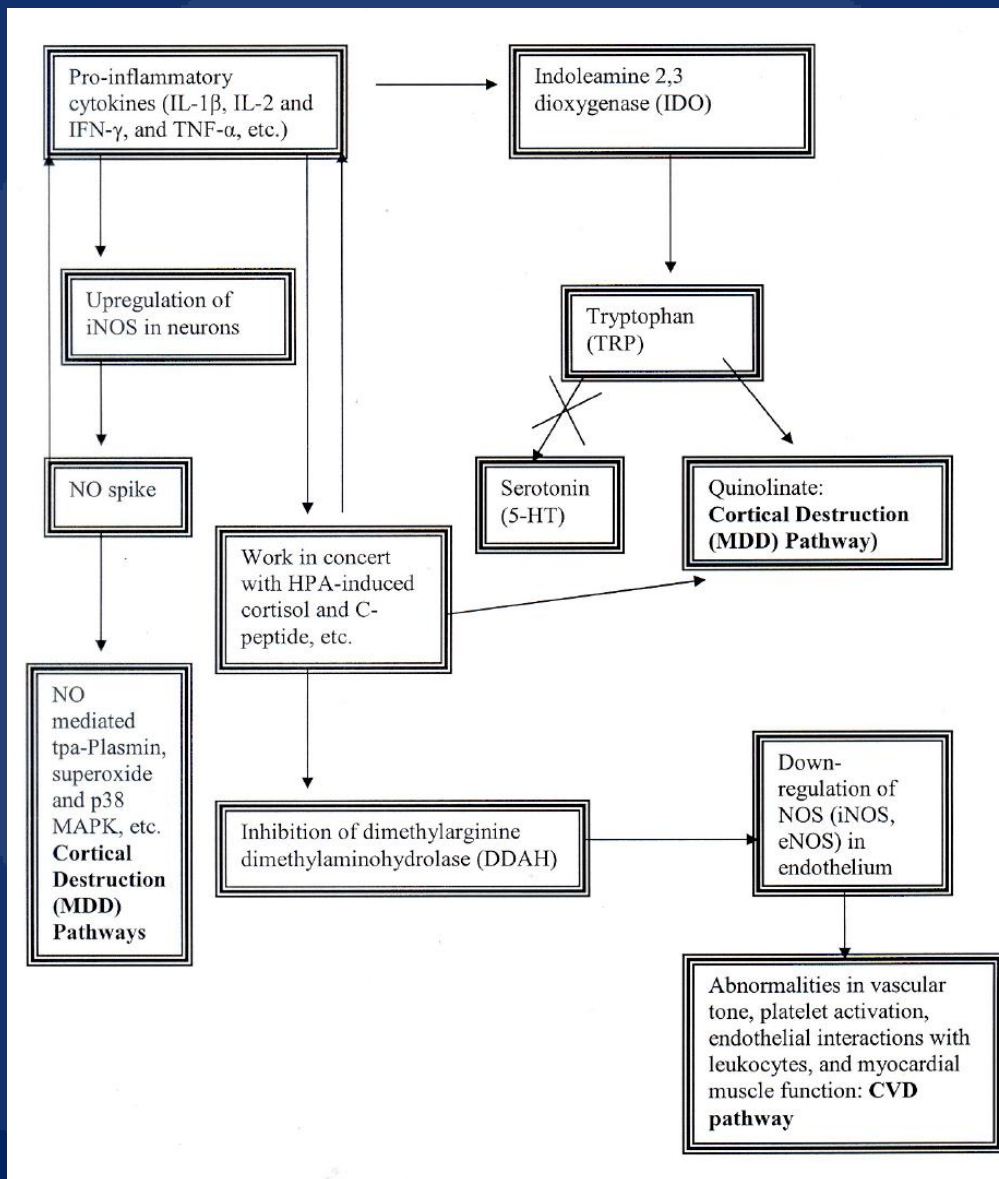
Depression and CV Disease

Effect on Endothelial progenitor cells (EPCs)



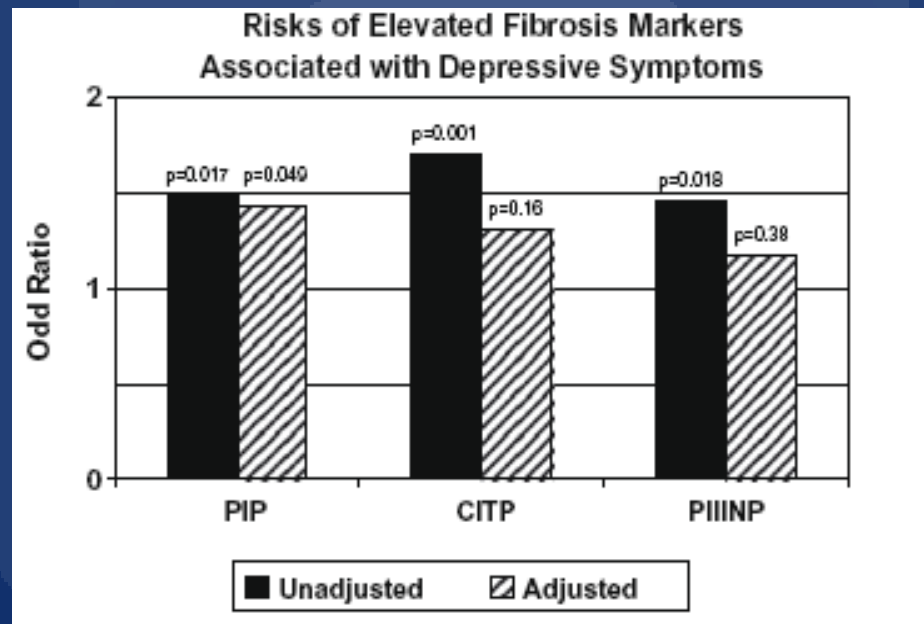
- Patients with major depression have a decreased number of CD34+/VEGFR2 + circulating EPCs, independent of psychotropic drugs

Depression and CVD



Depression and CV Disease

Association between depression and markers of Fibrosis

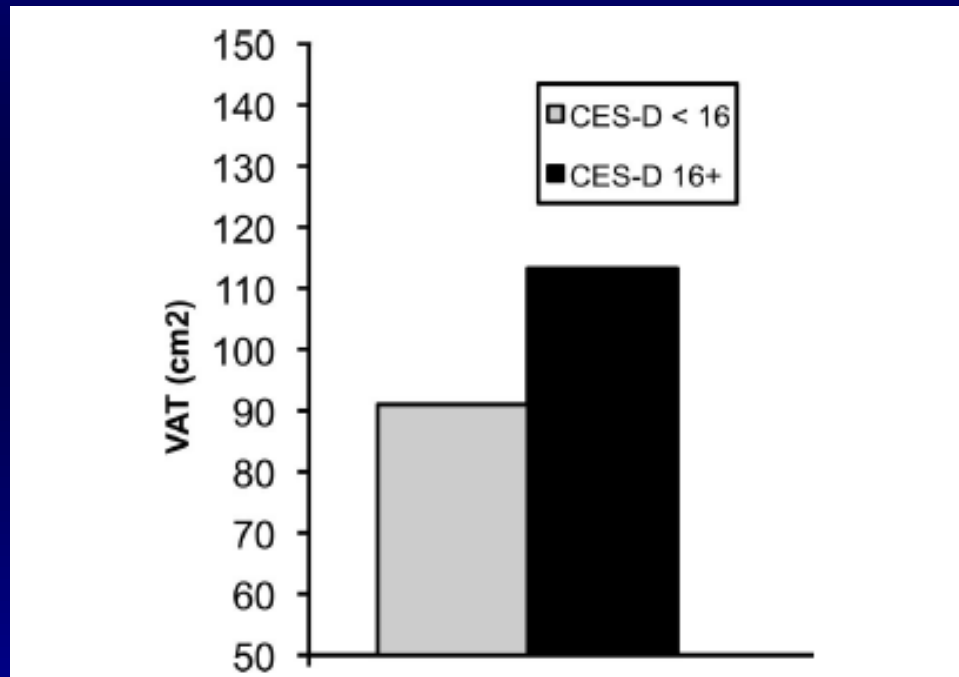


- Depression is associated with an increase in pro collagen I and type 1 collagen which could contribute to the development of HF

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

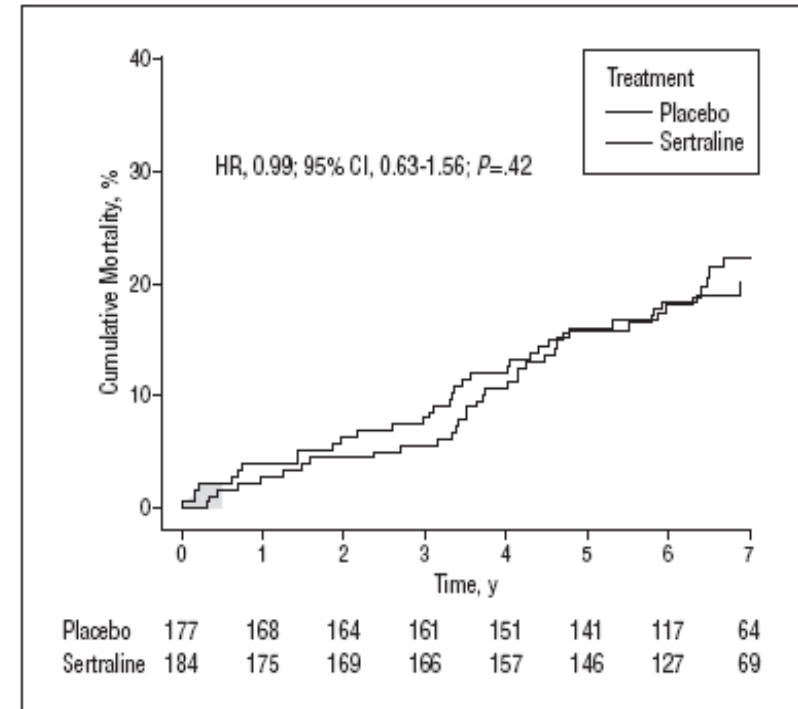
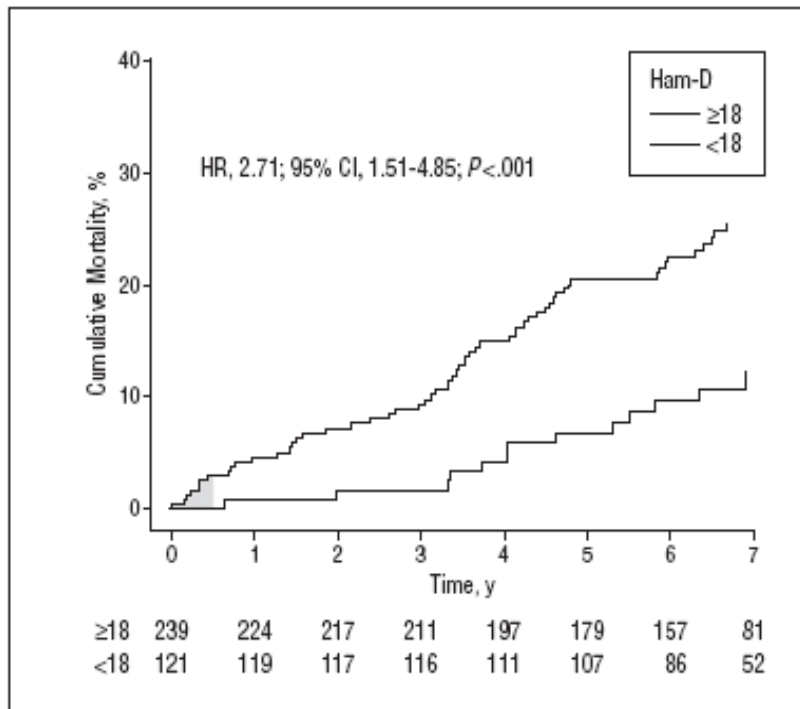
Depression and CV Disease

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

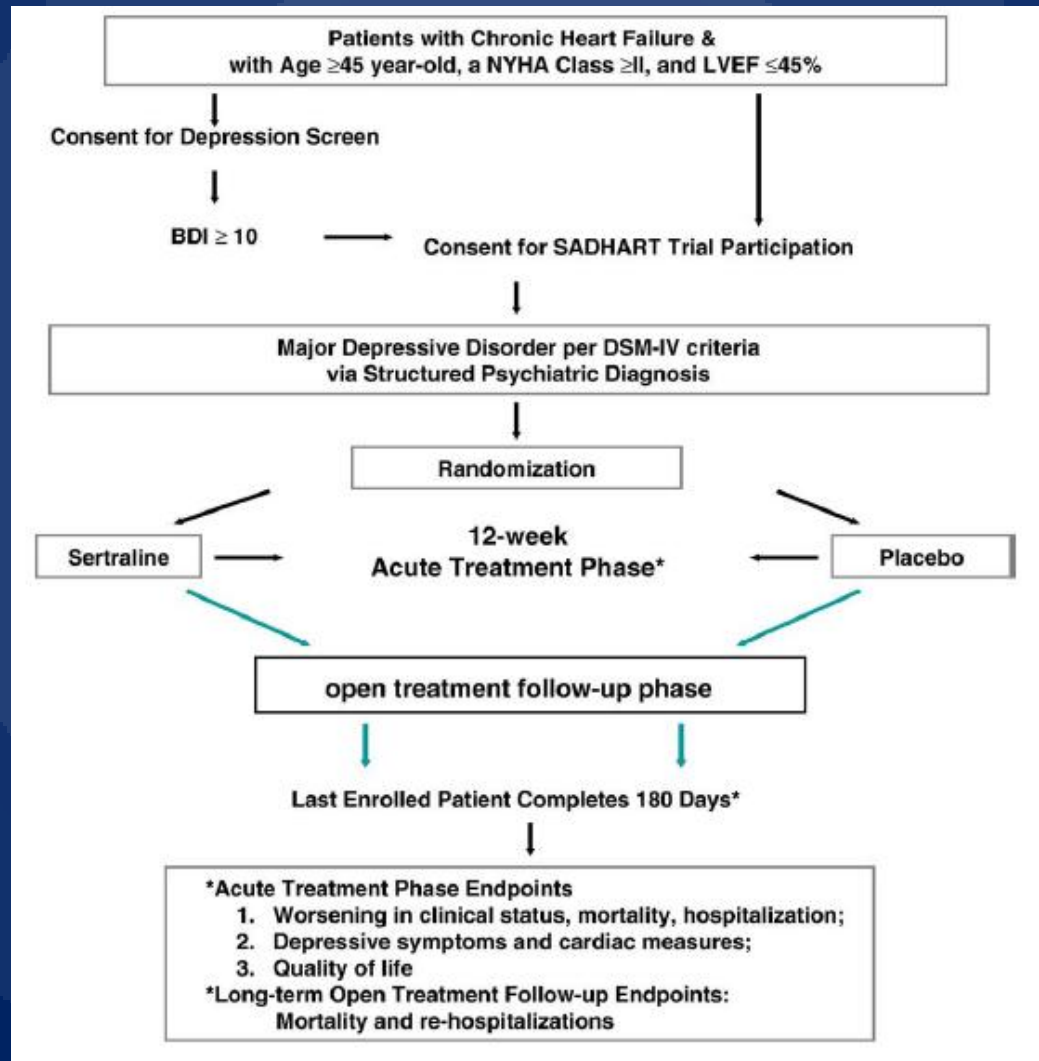
Depression and CV Disease

7 year follow up of SADHART participants



Depression and CV Disease

SADHART-CHF



Depression and CV Disease

Effect of the SSRI-Sertraline in patients with MDD and HF
(SADHEART-CHF)

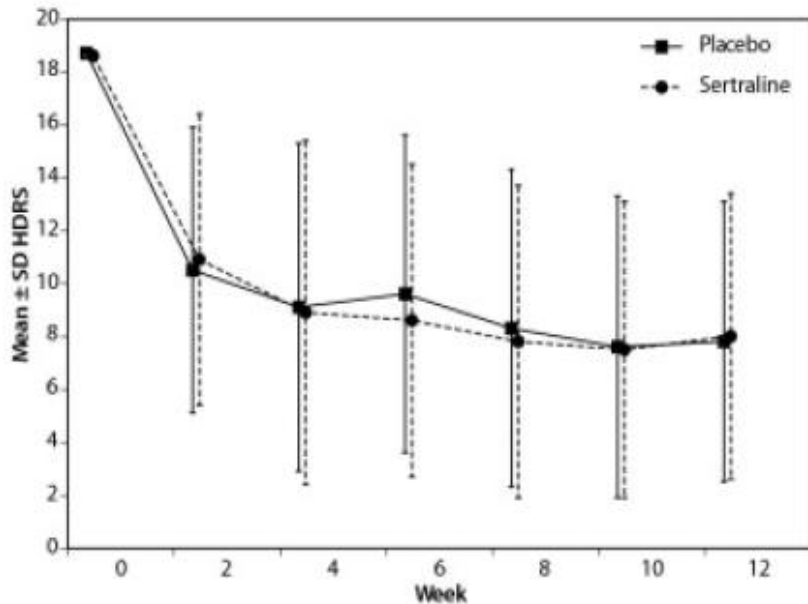


Table 3. Fatal and Nonfatal Events Through 12 Weeks

Event	Sertraline (n = 234)	Placebo (n = 235)	p Value
All-cause mortality	18 (7.7)	15 (6.8)	0.58
Cardiovascular death	16 (6.8)	10 (4.3)	0.59
Nonfatal cardiovascular event	47 (20.1)	55 (23.0)	0.39
Acute myocardial infarction	1 (0.4)	0	0.31
Arrhythmia	4 (1.7)	6 (2.6)	0.53
Cardiac syncope	0	1 (0.4)	0.32
Cerebrovascular accident	2 (0.8)	1 (0.4)	0.56
Exacerbation of heart failure	19 (8.1)	30 (12.8)	0.1
Unstable angina	7 (3.0)	5 (2.1)	0.55
Other nonfatal cardiovascular event	14 (6.0)	12 (5.1)	0.68
All-cause mortality or nonfatal cardiovascular event	65 (29.4)	70 (29.8)	0.63
Heart failure hospitalization or death	37 (15.8)	45 (19.2)	0.34

➤ Treatment with the SSRI sertraline compared to placebo did not provide greater reduction in depression or CV events in patients with MDD + HF

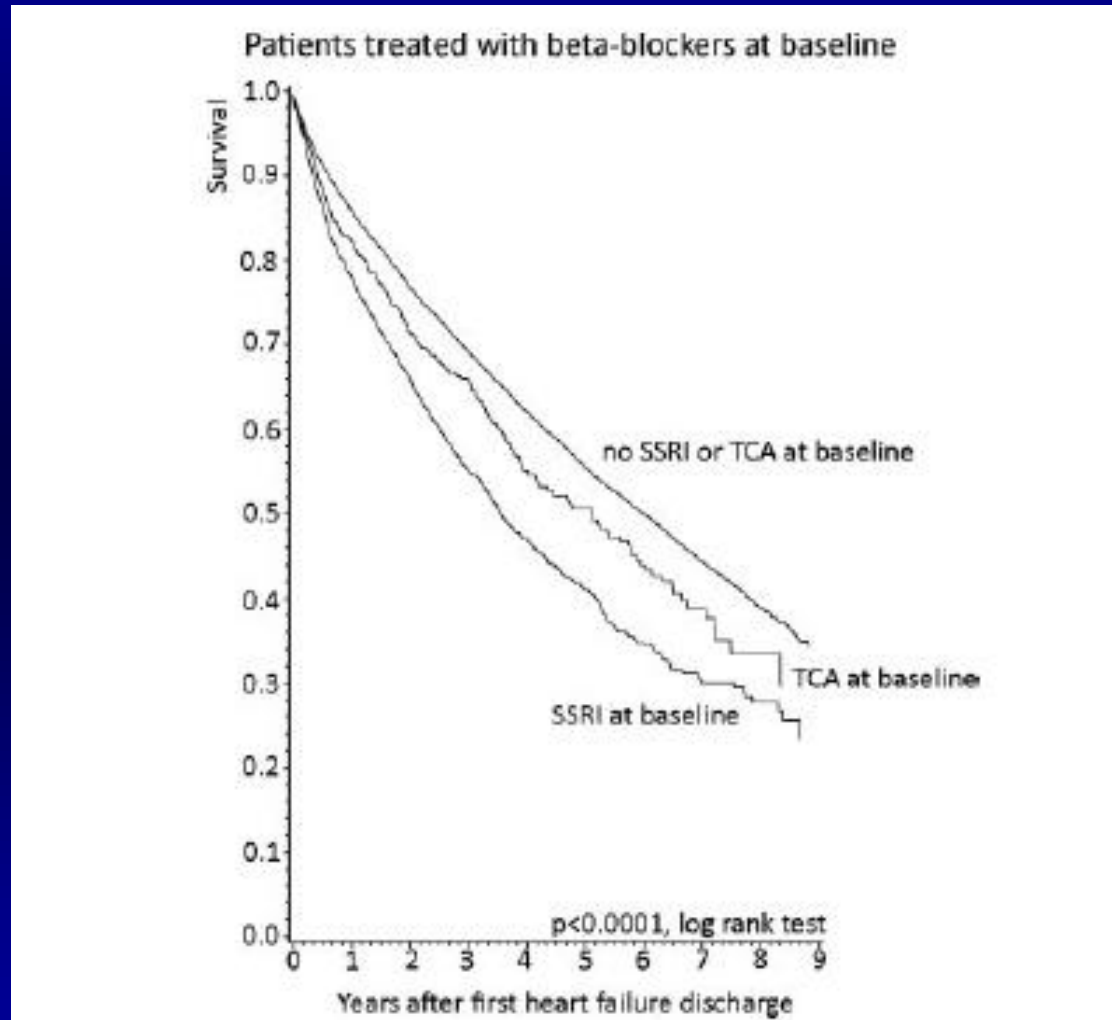
Depression and CVD

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

Depression and CVD



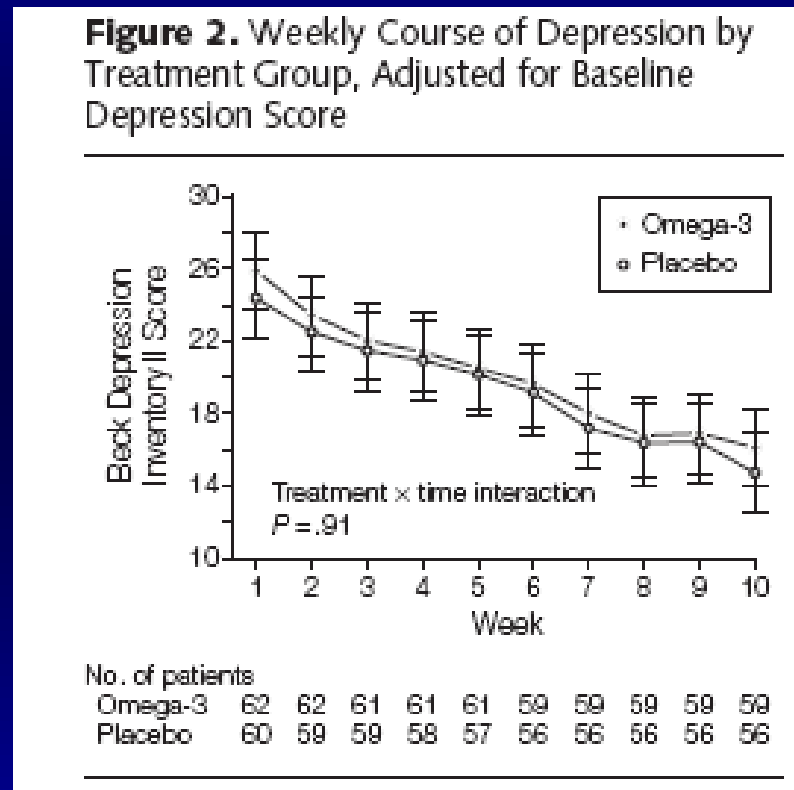
Depression and CVD

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

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

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

Schnoder, C.M. et al Annals of Gen Psych 2005;4:13

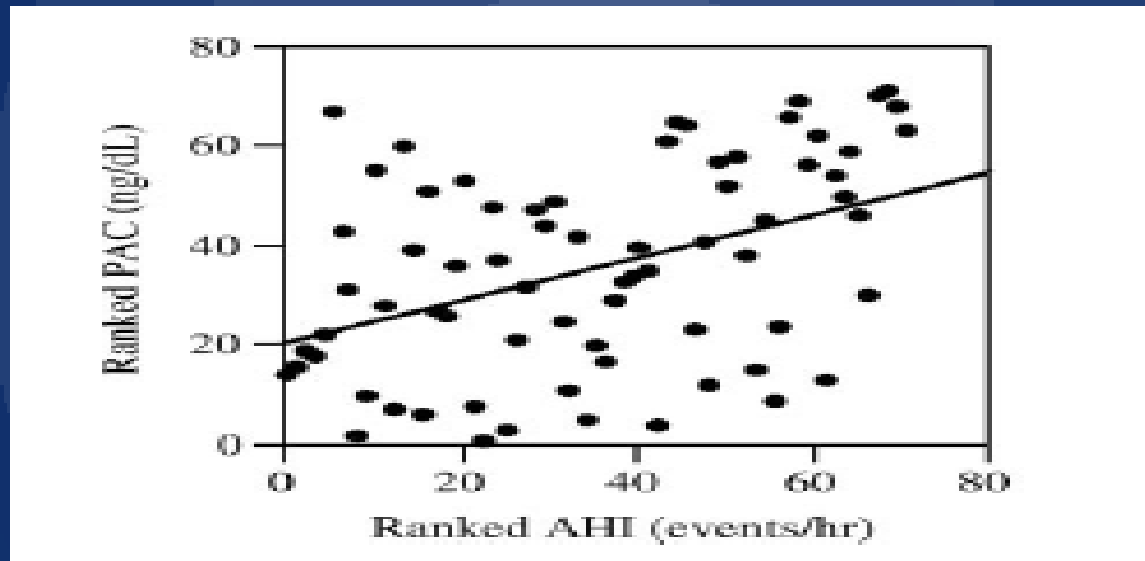
Shrhar, E. et al Am. J Resp and Crit Care Med 2001;163:19

Lam, B. et al thorax 2007;62:354

Sanchez, A.I. et al Psych and Clin Neurosciences 2001;55:641

Obstructive Sleep Apnea

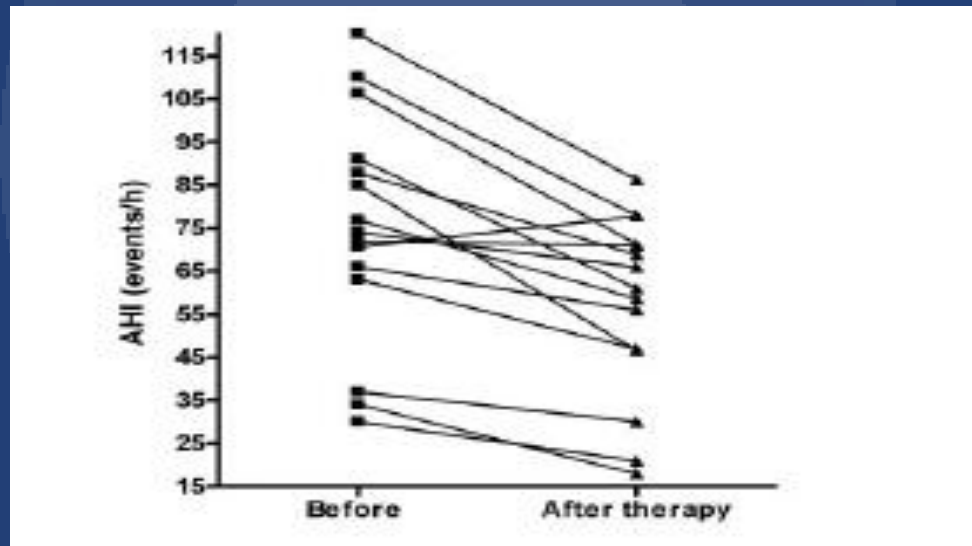
Plasma Aldosterone levels in patients with OSA with Resistant Hypertension



- 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

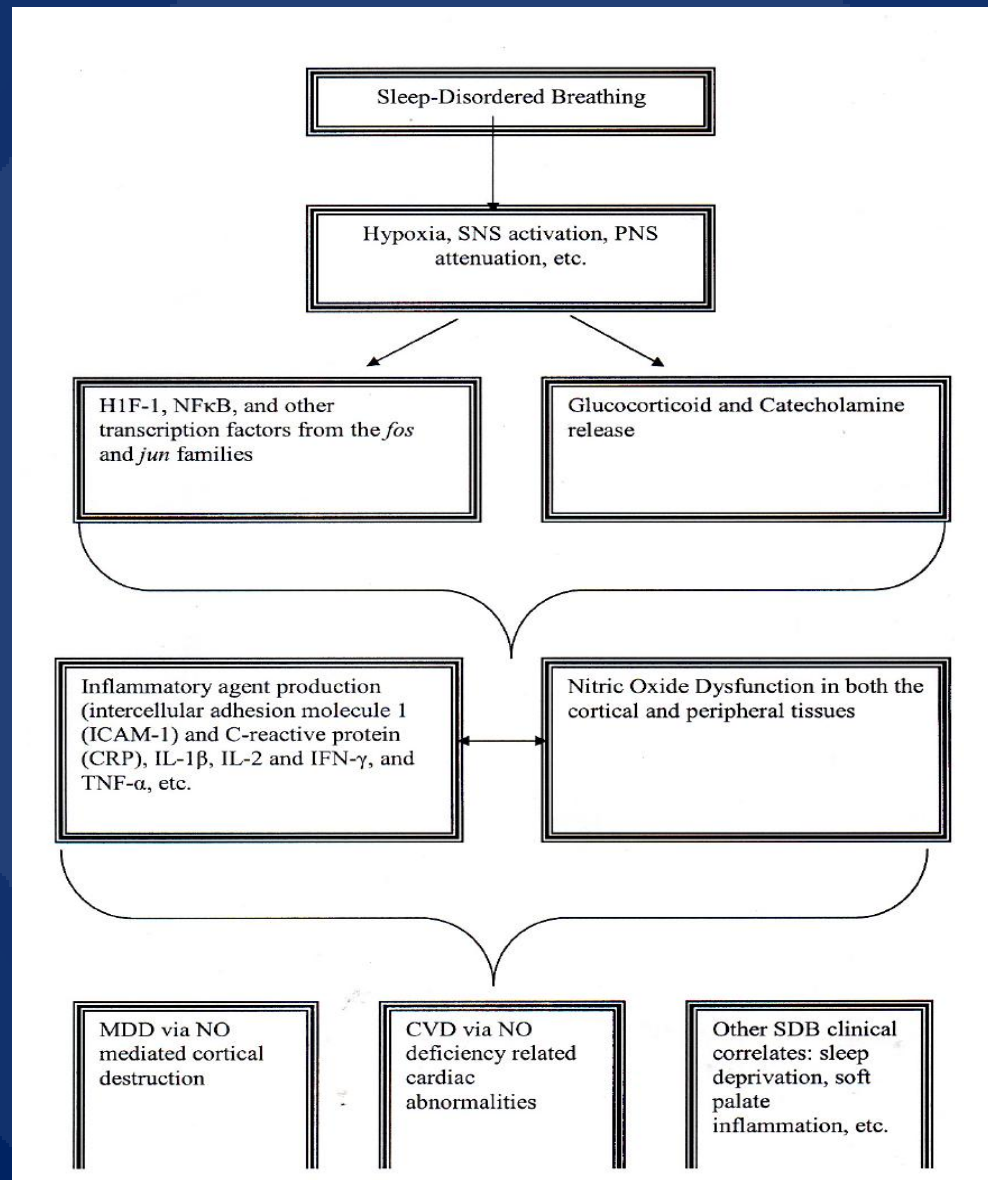
Obstructive Sleep Apnea

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-hypopnea index. (AHI)

Depression and CVD



Depression and CVD



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 SDB +MDD to the severity of SDB and the extent of inflammation cytokine release and increase in ADMA

Depression and CV

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

Outcome	Intervention Group	Usual-Care Group	P Value
Improvement on Patient Global Improvement Scale — no./total no. (%)†			
6 mo	64/96 (67)	15/91 (16)	<0.001‡
12 mo	41/92 (45)	16/91 (18)	
≥50% decrease in SCL-20 score — no./total no. (%)			
6 mo	57/97 (59)	22/96 (23)	<0.001‡
12 mo	56/94 (60)	28/92 (30)	
All three medical measures below guidelines or showing clinically significant change at 12 mo — no./total no. (%)§	36/97 (37)	19/87 (22)	0.024¶
≥1.0 percentage point decrease in glycated hemoglobin level from baseline at 12 mo — no./total no. (%)	37/102 (36)	18/96 (19)	0.006¶
≥10 mm Hg decrease in systolic blood pressure from baseline at 12 mo — no./total no. (%)	41/101 (41)	25/101 (25)	0.016¶
Satisfaction with care of depression — no./total no. (%)			
Baseline	47/92 (51)	43/92 (47)	<0.001¶
6 mo	84/97 (87)	53/86 (62)	
12 mo	81/90 (90)	46/84 (55)	
Satisfaction with care of diabetes, heart disease, or both — no./total no. (%)			
Baseline	73/104 (70)	65/95 (68)	<0.001¶
6 mo	87/97 (90)	65/95 (68)	
12 mo	79/92 (86)	62/88 (70)	
Quality-of-life score***			
Baseline	4.2±1.9	4.6±1.8	<0.001
6 mo	5.8±2.4	5.2±1.8	
12 mo	6.0±2.2	5.2±1.9	

➤Collaborative care improved control of depression and CV disease

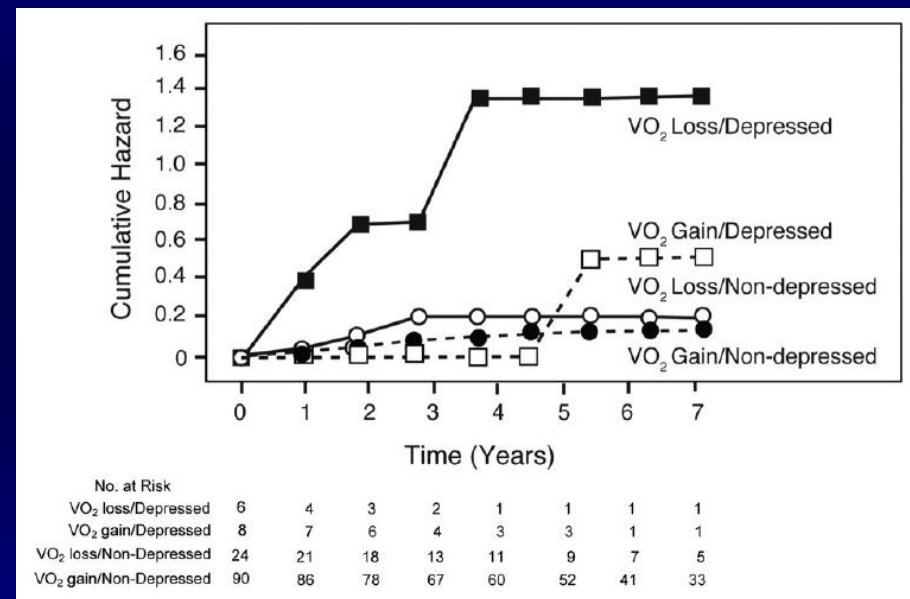
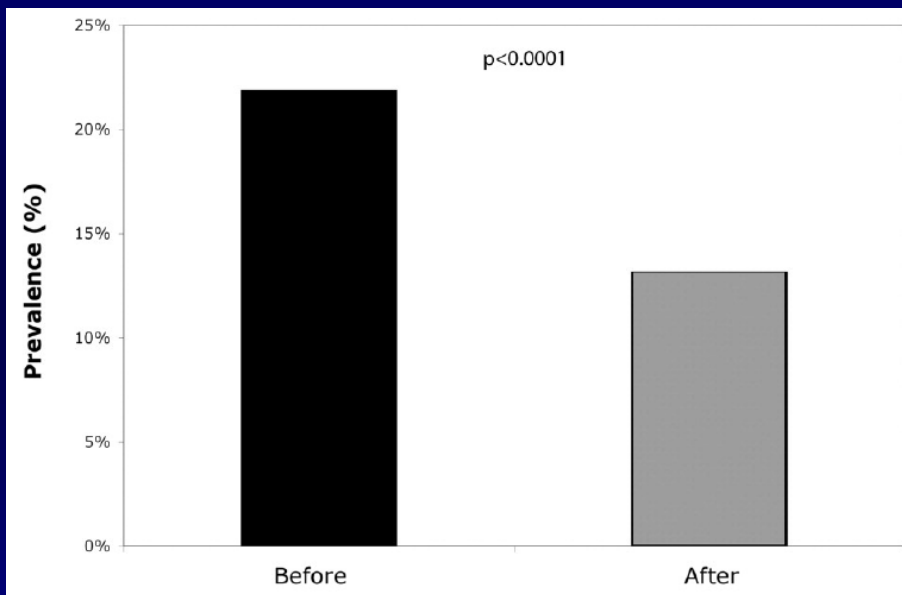
Depression and CV Disease

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.I. et al EHI, 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. EHI 2010)

Depression and CV Disease

Impact of Exercise Training



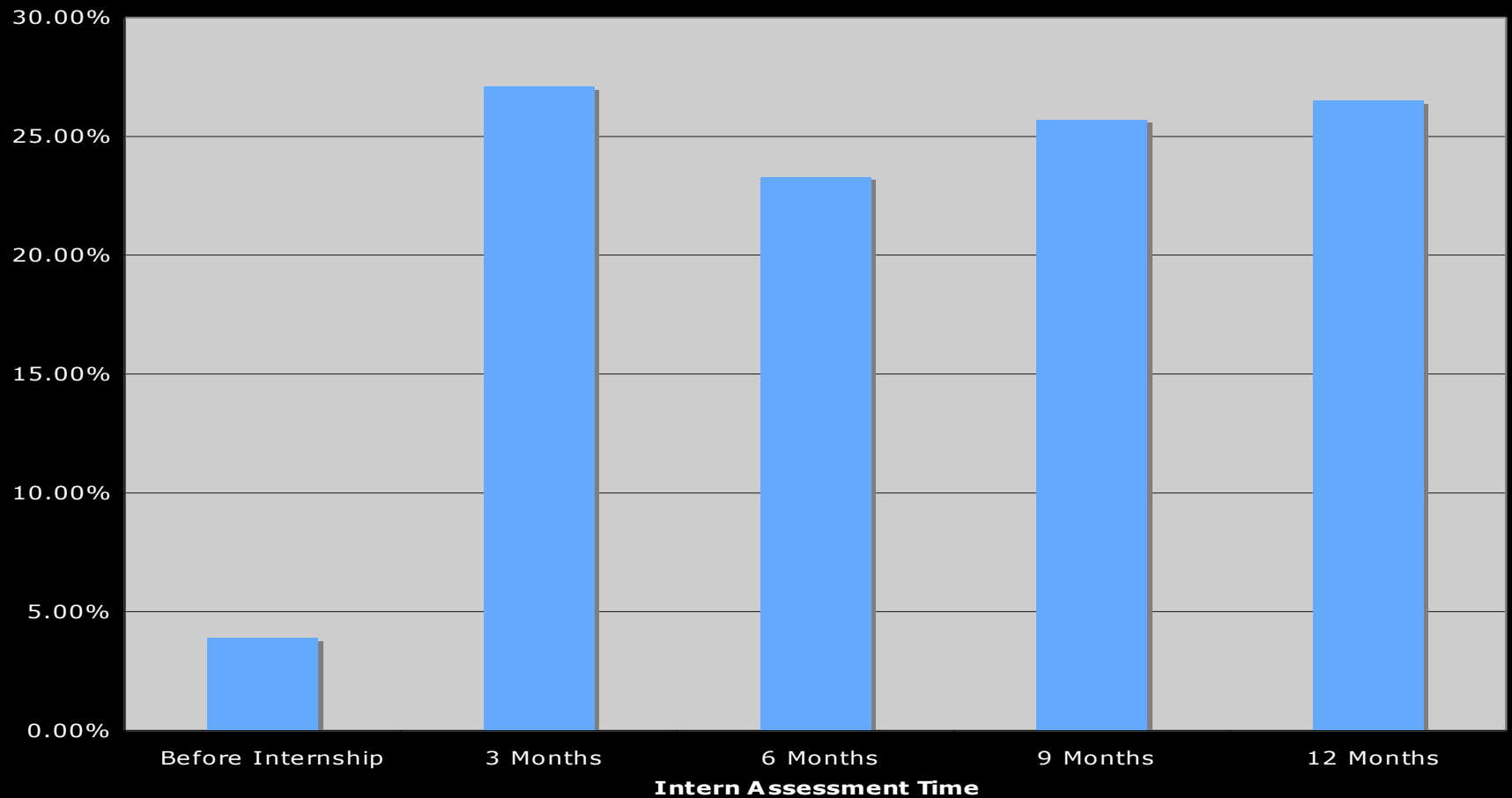
➤ Depressive symptoms are frequent in patients with HF and are associated with an increased mortality. Exercise training decreases depressive symptoms and improves mortality

Stress and Intern Year

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



Incidence of Depression Before and During Medical Internship



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 determine the early links between depression and CVD and new therapeutic and behavioral approaches are needed to reduce the CV risk associated with Depression