CHARLES B. NEMEROFF, MD, PHD
Disclosures

- **Research/Grants:** None
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- **Consultant:** None
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- **Advisory Board:** American Foundation for Suicide Prevention (AFSP); CeNeRx BioPharma; National Alliance for Research on Schizophrenia and Depression (NARSAD); NovaDel Pharma, Inc.; PharmaNeuroBoost; serves on the board of directors of AFSP; Mt. Cook Pharma, Inc.; NovaDel Pharma, Inc.
LEARNING OBJECTIVE

Recognize the relationship between depression and heart disease
Nothing vivifies and nothing kills like the emotions.
— Joseph Roux, 1886

Grief is Mortal… that is to say deadly.
— Shakespeare, 1599

Let no one persuade you to cure the headache until he has given you his soul to be cured. For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body.
— Hippocrates, 2000 B.C.

Every affectation of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.
— William Harvey, 1628
DEPRESSION AND CARDIOVASCULAR DISEASE (CVD)

- Increased incidence of depression in ischemic heart disease (IHD) patients
- Depression is a risk factor for morbidity/mortality post-MI
- Depression is a risk factor for development of coronary artery disease (CAD)
- Depression is associated with increased platelet activation, platelet reactivity, cardiac events
- SSRIs are effective antidepressants in IHD without adverse effects of TCAs

PREVIOUSLY IDENTIFIED RISK FACTORS FOR CORONARY ARTERY DISEASE

- Genetic factors
- Diabetes
- Hypertension
- Thrombocyte dysfunction
- Hyperlipidemia
- Smoking
- Obesity

**RELATIONSHIP BETWEEN DEPRESSION AND ISCHEMIC HEART DISEASE (IHD)**

- 2,832 participants in National Health Examination Follow-up Study
  - Ages 45-77 with no IHD
- Baseline assessment with depression subscale of General Well-Being Schedule
  - Depressed affect 11.5%
  - Moderate hopelessness 10.8%
  - Severe hopelessness 2.9%
- Follow-up
  - Mean 12.4 years
  - 189 cases of fatal IHD
- Depressed affect and hopelessness may have causal role in occurrence of both fatal and non-fatal IHD

DEPRESSION FOLLOWING MYOCARDIAL INFARCTION (MI) IMPACT ON 6-MONTH SURVIVAL

Nancy Frasure-Smith, PhD; Francois Lesperance, MD; Mario Talajic, MD

JAMA 1993;270:1819-1825.
MORTALITY AND DEPRESSION POST-MI

- N = 222 patients who met criteria for MI
- Prospective evaluation of impact of depression after control for significant clinical predictors in the data set
- 12 patients died due to cardiac cause
- Depression was significant predictor of mortality at 6 months
- MDD in patients hospitalized following MI is an independent risk factor for mortality at 6 months and it’s impact is at least equivalent to that of left ventricular dysfunction and history of previous MI

6 MONTHS AND 18 MONTHS CORONARY FATALITIES AFTER ACUTE MI

N = 222, * p < .05; Adjusted RR at 6 months = 3.10 (1.90-4.30)

LONG-TERM SURVIVAL AFTER MI IN RELATION TO BDI SCORE DURING HOSPITALIZATION

BDI = Beck Depression Inventory

Subsequent mortality in post-MI patients with major depression\(^1\)
- Mean relative risk: 4.1 (range: 2.3-7.5)
- Much of mortality risk occurs in first 6 months post-MI
- Mortality risk proportionate to severity of depression
- Presence of other risk factors (e.g., low LVEF), even minor symptoms of depression (BDI < 10) contribute significant additional mortality risk\(^2\)

Administration of the first two questions of PHQ-9 should be standard screener for all patients hospitalized for UA or MI

UA = unstable angina

DEPRESSION AS A RISK FACTOR FOR MORTALITY AFTER CORONARY ARTERY BYPASS SURGERY

James A. Blumenthal, Heather S. Lett, Michael A. Babyak, William White, Peter K. Smith, Daniel B. Mark, Robert Jones, Joseph P. Mathew, Mark F. Newman, for the NORG Investigators*

DEPRESSION AS A RISK FACTOR FOR MORTALITY AFTER CABG

- N = 817 patients undergoing CABG between 1989-2001
- 122 deaths in mean follow-up of 5.2 years
- 310 patients (38%) met criteria for depression (CES-D ≥ 16)
- 213 patients (26%) met criteria for mild depression (CES-D = 16-26)
- 97 patients (12%) met criteria for moderate to severe depression (CES-D ≥ 27)
- Survival analyses controlling for age, sex, number of grafts, DM, smoking, LVEF and previous MI showed that patients with depression that persisted from baseline to 6 months had higher rates of death than those with no depression
  - Adjusted HR 2.2, p = .015

DEPRESSION AND CORONARY ARTERY DISEASE

DEPRESSION AND ANXIETY AS PREDICTORS OF 2-YEAR CVE IN PATIENTS WITH STABLE CAD

- **Design**
  - 2-year follow-up
  - N = 804 patients with stable CAD (649 men)
  - Assessed using the BDI-II, the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), and the Structured Clinical Interview for DSM-IV (masked to self-reports)
  - Assessments done 2 mos after acute coronary syndromes

- **Results**
  - 57 (7.1%) met criteria for MDD
  - 43 (5.3%) met criteria for GAD
  - 11 (1.4%) were comorbid for MDD and GAD
  - 220 (27.4%) had elevated BDI-II scores (≥ 14)
  - 333 (41.4%) had elevated HADS-A scores (≥ 8), with 21.1% overlap

Background

- Recent studies suggest that the use of antidepressants may be associated with increased mortality in patients with cardiac disease.
- Because depression has also been shown to be associated with increased mortality in these patients, it remains unclear if this association is attributable to the use of antidepressants or to depression.

Methods:
- N = 1006 patients, 18 years or older
- Diagnosed with clinical heart failure and an ejection fraction of 35% or less between March 1997 and June 2003
- Patients were followed annually
- Depression status was assessed by BDI scale
- Use of antidepressants was also assessed
- Main outcome of interest was long-term mortality

Results:
- 30.0% met criteria for depression (BDI > 10)
- 24.2% were taking an antidepressant
- 42.7% of the patients died

Overall, use of antidepressants (unadjusted HR, 1.32; 95% CI, 1.03-1.69) or SSRIs only (unadjusted HR, 1.32; 95% CI, 0.99-1.74) was associated with increased mortality.

However, the association between antidepressant use and increased mortality no longer existed after depression and other confounders were controlled for (HR, 1.24; 95% CI, 0.94-1.64).

Nonetheless, depression remained associated with increased mortality (HR, 1.33; 95% CI, 1.07-1.66).

Similarly, depression (HR, 1.34; 95% CI, 1.08-1.68) rather than SSRI use (HR, 1.10; 95% CI, 0.81-1.50) was independently associated with increased mortality after adjustment.

Conclusion: Depression (defined by a BDI score > 10), but not antidepressant use, is associated with increased mortality in patients with heart failure.

Study objectives:
- Determine role of major depression in risk for MI
- Psychotropic medication as a risk factor

Study participants: 64 with MIs/1,551 without heart disease

Odds ratio for MI:
- Major depression: 4.54
- Dysphoria: 2.07

Conclusions:
- Depression and dysphoria increase MI risk
- Risk associated with psychotropics related to depression

DEPRESSION
Association with Acute MI

- Depressed patients are 4 times as likely to have an MI
- Depressed patients have a relative risk of 1.71 ($p = .005$) for MI and 1.59 ($p < .001$) for death from all causes

Depressed post-MI patients more likely to drop out of exercise programs

Depressed smokers 40% less likely to quit smoking over a 9-year period

Depressed CAD patients less likely to adhere to low-dose aspirin therapy

CHANGE IN DEPRESSION AS A PRECURSOR OF CVE

Sylvia Wassertheil-Smoller, PhD; William B. Applegate, MD; Kenneth Berge, MD; Chee Jen Chang, PhD; Barry R. Davis, MD, PhD; Richard Jr, Grimm, MD, PhD; John Kostis, MD; Sara Pressel, MS; Eleanor Schron, RN, MS

CHANGE IN DEPRESSION AS A PRECURSOR OF CVE

- **Design:**
  - N = 4,367 men and women, 60 years or older, 16 clinical centers at Systolic Hypertension in the Elderly Program
  - Cohort study data from randomized DBPC trials of antihypertensive treatment
  - Depressive symptoms assessed semiannually with the Center for Epidemiological Studies-Depression (CES-D) scale
  - Average follow-up of 4.5 years
  - Randomized to active antihypertensive drug therapy or PBO
  - Follow-up CES-D scores and no outcome events during the first 6 mos

- **Main outcome measure:**
  - All-cause mortality, fatal or nonfatal stroke, or myocardial infarction

CHANGE IN DEPRESSION AS A PRECURSOR OF CVE

- **Results:**
  - Baseline depressive symptoms were not related to subsequent events; however, an increase in depression **was** prognostic.
  - Cox regression analyses with CES-D scale as time-dependent variable, indicated 25% ↑ risk of death per 5-unit ↑ in CES-D score: (RR, 1.25; 95% CI, 1.15 to 1.36)
  - ↑ in CES-D score was independent predictor in both PBO and active drug groups and strongest as a risk factor for stroke among women: (RR, 1.29; 95% CI, 1.07 to 1.34)

- **Conclusions:**
  - Among elderly persons, a significant and substantial excess risk of death, stroke, or MI was associated with ↑ in depressive symptoms, which may be marker for subsequent major disease events.
  - Further studies of causal pathways are needed before widespread screening for depression in clinical practice is to be recommended.

DEPRESSION IS A RISK FACTOR FOR CAD IN MEN
THE PRECURSORS STUDY

Daniel E. Ford, MD, MPH; Lucy A. Mead, ScM; Patricia P. Chang, MD; Lisa Cooper-Patrick, MD, MPH; Nae-Yuh Wang, MS; Michael J. Klag, MD, MPH
Objective and methods:
- To determine if clinical depression is independent risk factor of incident CAD
- Prospective, observational study
- N = 1,190 male medical students at Johns Hopkins between 1948-1964
- Info collected on family history, health behaviors, and depression

Results

- Incidence of depression at 40-yr follow-up = 12%
- Men who developed depression drank more coffee but did not differ in baseline blood pressure, serum cholesterol levels, smoking, physical activity, obesity, or family history of CAD
- In multivariate analysis, the men who reported depression were at significantly greater risk for subsequent CHD (RR, 2.12; 95% CI, 1.24-3.63) and MI (RR, 2.12 and 95% CI, 1.11-4.06)

Conclusion

- Clinical depression appears to be an independent risk factor for incident CAD for several decades after the onset of depression

DEPRESSION IS A RISK FACTOR FOR THE DEVELOPMENT OF CARDIOVASCULAR ILLNESS

- Multiple large-scale studies have prospectively followed subjects without CAD
  - Depression is significant independent risk factor for CAD morbidity and mortality
  - Adjusted RR: range of 1.5 to 2-fold
  - RR for depression similar to smoking

INTERPLAY BETWEEN DEPRESSION AND CAD

- 13 studies have prospectively followed > 40,000 healthy subjects for a mean of 10 years, range of 4-37 years
- Depression was found to be significant independent risk factor for development of CAD morbidity and mortality
- Adjusted RR:
  - Major depression: 4-4.5x
  - Subsyndromic depression: 1.5-2x

DEPRESSION PREDICTS MORTALITY FOLLOWING CARDIAC VALVE SURGERY

P. Michael Ho MD, Frederick A. Masoudi MD, MSPH, John A. Spertus MD, MPH, Pamela N. Peterson MD, A. Laurie Shroyer PhD, Martin McCarthy, Jr PhD, Frederick L. Grover MD, Karl E. Hammermeister MD, and John S. Rumsfeld MD, PhD

DEPRESSION PREDICTS MORTALITY FOLLOWING CARDIAC VALVE SURGERY

**Methods**
- N = 648 patients undergoing valve surgery
- Prospective cohort study at 14 VA hospitals

**Results**
- 29.2% (189/648) were depressed at baseline
- Depressed patients were younger, more class III/IV symptoms, more likely required emergent surgery, preoperative intravenous nitroglycerin, or intraaortic balloon pump
- Unadjusted 6-mos mortality = 13.2% for depressed vs. 7.6% for nondepressed patients, \( p = .03 \)
- Depression remained significantly associated with mortality
  - OR, 1.90; 95% CI, 1.07 to 3.40, \( p = .03 \)
- Findings consistent across subgroups undergoing aortic valve replacement, mitral valve replacement, and valve replacement without coronary artery bypass graft

Conclusion

- Preoperative depression is an independent risk factor for mortality following cardiac valve surgery
- Depression screening should be incorporated into preoperative risk stratification
- Future studies are warranted to determine if preoperative or postoperative interventions to treat depression can improve outcomes

### MULTIVARIABLE PREDICTORS OF 6-MOS MORTALITY S/P CARDIAC VALVE SURGERY

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>3.42</td>
<td>1.84-6.38</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Depression</td>
<td>1.90</td>
<td>1.07-3.40</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.89</td>
<td>1.04-2.42</td>
<td>.04</td>
</tr>
<tr>
<td>Age (per 10-yr increment)</td>
<td>1.83</td>
<td>1.28-2.64</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.39</td>
<td>1.14-1.70</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

INSIGHTS INTO CAUSAL PATHWAYS FOR ISCHEMIC HEART DISEASE
ADVERSE CHILDHOOD EXPERIENCES STUDY
Maxia Dong, MD, PhD; Wayne H. Giles, MD, MS; Vincent J. Felitti, MD; Shanta R. Dube, MPH; Janice E. Williams, PhD; Daniel P. Chapman, PhD; Robert F. Anda, MD, MS
Objectives:

- Assess relation of adverse childhood experiences (ACEs) including abuse, neglect, and household dysfunction to risk of ischemic heart disease (IHD)
- Examine mediating impact on relation of IHD risk factors and psychological factors associated with ACEs

Methods and results:

- Retrospective cohort survey data from 17,337 health plan members from ’95-’97

Methods and results:
- 9/10 categories of ACEs significantly increased the risk of IHD by 1.3-1.7x vs. persons with no ACEs
  - OR for IHD in persons with 7 ACEs = 3.6
    - (95% CI, 2.4 to 5.3)
- ACE-IHD relation was mediated more strongly by individual psychological risk factors associated with ACEs vs. traditional risk factors
- Observed significant association between increased likelihood of IHD and depressed affect and anger
  - OR 2.1, 95% CI 1.9-2.4, and 2.5, 2.1 to 3.0 respectively

Conclusions:

- Dose-response relation of ACEs to IHD and relation between almost all individual ACEs and IHD
- Psychological factors appear to be more important than traditional risk factors in mediating the relation of ACEs to risk of IHD
- Findings provide further insights into potential pathways by which ACEs may increase the risk of IHD in adulthood

VASCULAR LESION

Primary Hemostasis
- Platelet adhesion and aggregation

Coagulation
- Fibrin formation

Fibrinolysis
- Clot dissolution
The blood clot, or thrombus (red), captured in this micrograph has formed at the site of an atherosclerotic plaque in a coronary artery and has occluded the vessel. Some clots dissolve before they cause a heart attack or stroke, but they can foster trouble in another way—by stimulating plaque expansion.

EXAGGERATED PLATELET REACTIVITY IN MAJOR DEPRESSION

Dominique L. Musselman, MD; Aaron Tomer, MD; Amita K. Manatunga, PhD; Bettina T. Knight, BSN; Maryfrances R. Porter; Suha Kasey, BS; Ulla Marzec; Laurence A. Harker, MD; Charles B. Nemeroff, MD, PhD

EXAGGERATED PLATELET REACTIVITY IN MAJOR DEPRESSION
Before and After Orthostatic Challenge

Hypothesis: patients suffering from ischemic heart disease (IHD) and depression concurrently may have abnormal platelet activation resulting in an increased risk of thrombosis.

Methods: Platelet factor 4 (PF4) and β-thromboglobulin (β-TG) were measured in young healthy control subjects, in nondepressed patients with IHD, and in depressed patients with IHD.

Results: Mean PF4 and β-TG plasma levels in the IHD group with depression were found to be significantly higher than those of the control and IHD groups. This increase was not related to age, gender, racial difference, aspirin use, or severity of cardiac disease.

Conclusions: In depressed patients with IHD there is greater platelet activation, and may indicate an increased risk of thrombotic complications.

PLATELET ACTIVATION
ISCHEMIC HEART DISEASE
AND DEPRESSION


IHD = ischemic heart disease; D = depression
Platelet factor 4 (PF-4) and beta-thromboglobulin (β-TG) studied in 12 depressed post-MI patients and 12 matched non-depressed post-MI patients.

- PF-4 was significantly higher in the depressed group than in the non-depressed group.
- β-TG was increased in the depressed subgroup, but the difference was not statistically significant.

EXAGGERATED PLATELET REACTIVITY IN MAJOR DEPRESSION Before and After Orthostatic Challenge


**Annexin V Ab (Mean Immunofluorescence ± SD)**

- **Depressed Patients (n = 12)**
- **Controls (n = 8)**

TRICYCLICS AND THE HEART

- Tricyclic antidepressant (TCA) overdose
  - Often fatal, usually cardiovascular death
- Therapeutic levels in the healthy heart
  - Orthostatic hypotension only
- Therapeutic levels in the diseased heart
  - Heart failure
  - Conduction disease
  - Arrhythmia
EFFECT OF SSRIs AND TCAs ON HEART RATE VARIABILITY IN DEPRESSED PATIENTS

* Coefficient of variation; standard duration of R-R interval distribution at rest divided by mean

Study design

- DSM-III-R major depression (17-item HAM-D > 15) plus ischemic heart disease
- 2-week lead-in single-blind placebo phase
- 6-week double-blind randomization phase
- Paroxetine 20-30 mg/day (n = 41)
- Nortriptyline 25-125 mg/day to achieve plasma concentration 80-120 ng/mL (n = 40)

SADHAT: SERTRALINE ANTIDEPRESSANT HEART ATTACK TRIAL

- Multicenter pilot study to evaluate:
  - Preliminary efficacy and safety of sertraline in patients with acute coronary syndrome
  - Feasibility of conducting large clinical trial
- Entry criteria required confirmed MI within previous month and diagnosis of MDD
- 16 weeks of sertraline 50-200 mg (flexible)
- Outcome measures: HAM-D, CGI, Q-LES, BDI
- Other measures: Vital signs, ECG, Holter Monitor, radionuclide ventriculography (MUGA)

SADHAT
Improvement in Depression

SERTRALINE TREATMENT OF MAJOR DEPRESSION IN PATIENTS WITH ACUTE MI OR UNSTABLE ANGINA

SADHART Principal Investigators

- Brian Baker, MD; David Barton, MD; Bradley Bart, MD; Peter Berman, MD; David Brewer, MD; Kevin Browne, MD; John Burks, MD; Robert Campagna, MD; Peter Clemmensen, MD; David Colquhoun, MD; Clinton Corder, MD; Eric Eichhorn, MD; Mitchell Finkel, MD; Les Forman, MD; Andrew Gaffney, MD; Alexander Glassman, MD; David Goldberg, MD; Veeraindar Goli, MD; Wayne Goodman, MD; Richard Gray, MD; John Griffin, MD; Torben Haghfelt, MD; Mark Kelemen, MD; Helmut Klein, MD; Michael Koren, MD; Charles Landau, MD; Lidia Lidagoster, MD; Frank McGrew, MD; Andre Natale, MD; Frank Navetta, MD; Charles Nemeroff, MD; Gerard O’Donnell, MD; Sebastian Palmeri, MD; Kevin Rapepport, MD; David Sane, MD; Peter Schwartz, MD; Dennis Sprecher, MD; Joshua Straus, MD; J. Robert Swenson, MD; Karl Swedberg, MD; Louis Van Zyl, MD; Richard Veith, MD; William Wainwright, MD; Richard Weisler, MD; Tom Wise, MD
SADHART: SERTRALINE ANTIDEPRESSANT HEART ATTACK RANDOMIZED TRIAL

Recent MI or unstable angina
Major depression
Multicenter (30-40 international sites)

14-day run-in

Sertraline 50-200 mg/day
Placebo

Primary endpoint (safety): Change from baseline in resting LVEF
Secondary endpoint (efficacy): Change in HAM-D score in subgroups

LVEF = Left ventricular ejection fraction; HAM-D = Hamilton Depression Rating scale
11,546 MI or unstable angina charts reviewed

3,355 charts eligible and agreed to interview

556 met major depression and inclusion and exclusion criteria

369 sign consent and are randomized

186 sertraline

183 placebo

8,191 excluded for medical or psychiatric reasons or refused interview

187 refused or ineligible after 2 weeks of placebo

SADHART: STUDY DESIGN

- Multicenter study (USA, Canada, Australia, Denmark, Sweden, Italy, Germany)
- Primary safety and clinical endpoints were obtained at wk 164

SADHART: INCLUSION CRITERIA

- Male or female, aged 21 years or older
- In past 30 days meets criteria for a dual cardiac/psychiatric diagnosis:
  - Either acute MI or unstable angina and
  - Major depression (using DSM-IV criteria based on a structured interview)

SADHART: OUTCOME VARIABLES

- Primary
  - Change from baseline in resting left ventricular ejection fraction (LVEF) by radionuclide ventriculography

- Secondary
  - Treatment-emergent events - rehospitalization, reinfarction, total mortality, stroke, worsened angina, and CHF
  - Antidepressant response (CGI-I and HAM-D) in 3 patient groups:
    - Total patient sample (ITT)
    - Patients with ≥ 2 prior episodes of MDD, HAM-D ≥ 18, and CGI-I ≥ 3 (end of washout)

RELATIVE RISK (95% CI) FOR CARDIOVASCULAR EVENTS
Sertraline vs. Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.39 (0.08 – 1.39)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.70 (0.23 – 2.16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.98 (0.14 – 6.93)</td>
</tr>
<tr>
<td>Worsened Angina</td>
<td>0.85 (0.53 – 1.38)</td>
</tr>
<tr>
<td>Congestive Heart failure</td>
<td>0.70 (0.23 – 2.16)</td>
</tr>
<tr>
<td>Composite*</td>
<td>0.77 (0.51 – 1.16)</td>
</tr>
</tbody>
</table>

* Composite consists of combination of 5 individual events

SADHART: WEEK 16 HAM-D CHANGE SCORES

**Total ITT Sample**
- Sertraline (Mean Dose 68.8 mg/day): -8.4
- Placebo (Mean Dose 70.5 mg/day Equivalent): -7.6
  - $p = .140$

**Prior Depression Subgroup**
- Sertraline: -9.8
- Placebo: -7.6
  - $p = .009$

**More Severe Depression Subgroup**
- Sertraline: -12.3
- Placebo: -8.9
  - $p = .012$

† Dose range 50-200 mg/day

**EFFICACY IN POST MI DEPRESSION**

Week 24 Responder* Rates for Sertraline vs. Placebo

- **Total ITT Sample**
  - Sertraline: 67% (186/281)
  - Placebo: 53% (183/349)
  - *Responder: CGI-I ≤ 2

- **Any Recurrent Depression**
  - Sertraline: 72% (96/134)
  - Placebo: 51% (90/177)

- **Two Prior Episodes Plus HAM-D > 18**
  - Sertraline: 78% (50/65)
  - Placebo: 45% (40/89)

*Responder: CGI-I ≤ 2

$p = .01$

$p = .003$

$p = .001$
EFFECTS OF ANTIDEPRESSANT MEDICATION ON MORBIDITY AND MORTALITY IN DEPRESSED PATIENTS AFTER MYOCARDIAL INFARCTION

C. Barr Taylor, Marston E, Youngblood; Diane Catellier, et al.

Arch Gen Psychiatry 2005;62:792-798.
### ENRICHED MEDICAL OUTCOMES AMONG DEPRESSED PATIENTS

**ENRICHED Study Group. JAMA 2003;289:3106-3116.**

<table>
<thead>
<tr>
<th></th>
<th>No drug n = 1,481</th>
<th>SSRI n = 353</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>All-cause mortality</td>
<td>15.3%</td>
<td>7.4%</td>
<td>.0004</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>9.8%</td>
<td>4.5%</td>
<td>.0003</td>
</tr>
</tbody>
</table>
SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND MYOCARDIAL INFARCTION

William H. Sauer, MD; Jesse A. Berlin, ScD; Stephen E. Kimmel, MD, MS. Circulation 2001;104:1894-1898.
Background

- Depression is an independent risk factor for myocardial infarction (MI)
- Selective serotonin reuptake inhibitors (SSRIs) may reduce this risk through attenuation of serotonin-mediated platelet activation in addition to treatment of depression itself

Methods and results

- Case-control study of 653 first MI and 2,990 controls
- Smokers 30-65 yrs of age, 68 hospitals in 8-county area during a 28-month period
- After adjustment, OR for MI among current SSRI users compared with nonusers was 0.35
  - (95% CI 0.18, 0.68; p = .01)
- Non-SSRI antidepressant users had a nonsignificant reduction in MI risk with wide confidence intervals
  - (adjusted odds ratio 0.48, CI 0.17, 1.32; p = .15)
- However, analysis of this group was limited by the small number of exposed subjects

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND MYOCARDIAL INFARCTION

- **Results**
  - During mean follow-up of 29 months, 457 fatal and nonfatal CVEs occurred.
  - The risk of death or recurrent MI was significantly lower in patients taking SSRIs, as were the risk of all-cause mortality and recurrent MI, vs. patients who were not treated with SSRIs.

- **Conclusions:**
  - Use of SSRIs in depressed patients who experience an acute MI might reduce subsequent cardiovascular morbidity and mortality.
  - A controlled trial is needed to examine this important issue.

NSAIDs AND SSRIs
Increased Risk of GI Bleeding

* Adjusted for sex, age, year, antecedents of upper gastrointestinal disorders, smoking status, and use of aspirin, anticoagulants, or steroids

UGI BLEEDING: RISK OF SSRIs COMPARED WITH OTHERS

SSRI receptor avidity
- Age on entry
- Female
- Diabetic
- Hx of UGI bleed
- NSAID use
- ASA use
- Glucocorticoid use
- Anticoagulant use
- H2 RA/PP inhibitor

Hazard Ratio (95% CI)

ugi = upper gastrointestinal
