SSRIs and Cardiovascular Disease:
How to Help an ‘Achy Breaky Heart’

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Learning Objectives

1. Describe the prevalence and impact of comorbid depression and cardiovascular disease.
2. Review selective serotonin reuptake inhibitors (SSRIs) and the possible mechanisms by which
   they affect the cardiovascular system.
3. Review the available evidence describing cardiovascular risks and benefits with SSRIs.
4. Recommend appropriate, evidence-based options for SSRIs in patients with cardiovascular
   disease, including reasons to use or to avoid them in certain patients.
I. Depressive disorders
   a. Sad, empty or irritable mood plus somatic and cognitive changes significantly affecting one’s functional capacity
      i. Disruptive mood dysregulation disorder
      ii. Major depressive disorder (MDD)
      iii. Persistent depressive disorder (dysthymia)
      iv. Premenstrual dysphoric disorder
      v. Substance/medication-induced depressive disorder
      vi. Depressive disorder due to another medical condition
      vii. Other specified or unspecified depressive disorder
   b. Differ in duration, timing, and presumed etiology
   c. MDD is the “classic” depressive condition
      i. Discrete episodes of at least two weeks duration
      ii. Clear change in affect, cognition, neurovegetative functions and inter-episode remissions

II. Epidemiology
   a. Sleep disturbance/fatigue often presenting complaint → MDD may be under-diagnosed
   b. Prevalence of MDD in the United States (US)
      i. Twelve-month prevalence among adults almost 7%\(^1\),\(^2\),\(^3\)
      ii. Lifetime prevalence \(-17%\(^1\),\(^2\)
      iii. Ages 18-29 years vs. 60 years and older – 3:1\(^1\)
      iv. Females vs. males – ranges 1.5-3:1
         1. Twelve-month prevalence of 8.2% vs. 4.8%\(^1\),\(^4\)
         2. Lifetime prevalence of 13.2% vs. 20.2%\(^1\),\(^4\)
   c. Global prevalence of MDD from 10 population-based studies (2003)\(^5\)
      i. Twelve-month prevalence ranged from 0.3% (Czech Republic) to 10% (US)
      ii. Lifetime prevalence ranged from 1.0% (Czech Republic) to 16.9% (US)

III. Risk factors\(^6\)
   a. Genetics/family history
   b. Biological
      i. Female > male
      ii. Medical illnesses such as cardiovascular (CV) disease (CVD), acquired immune deficiency syndrome (AIDS), respiratory disorders, cancer, neurologic conditions
   c. Environmental
      i. Marital status: divorced/separated/widowed > married/never-married
      ii. Low socioeconomic status
      iii. Low education
      iv. Stressful/traumatic life events
   d. Psychological
      i. Personality (e.g., neuroticism, low self-esteem)
      ii. Early-onset anxiety disorder
      iii. History of major depression or other mental health conditions
      iv. Substance misuse

IV. Personal and societal costs
   a. MDD ranked #2 of 30 leading diseases/injuries in the US for years lived with disability\(^7\)
b. MDD ranked among the top 15 diseases and risk factors in the US contributing to disability-adjusted life years (DALYs)\(^7\)

c. According to World Health Organization (WHO), depression will have the greatest burden among diseases in terms of DALYs by 2030\(^8\)

d. Economic burden of MDD in the US\(^3\)
   i. Increased from $173.2 billion in 2005 to $210.5 billion in 2010 (21.5% increase)
   ii. Total incremental costs, of which ~38% attributable to MDD itself vs. comorbid conditions
      1. Direct costs: 45-47%; $77.5 billion → $98.9 billion
      2. Suicide-related costs: 5%; $9.4 billion → $9.7 billion
      3. Workplace costs: 48-50%; $35.3 billion → $43 billion
   iii. In 2010, for every dollar spent on MDD direct costs, an additional $1.90 was spent on MDD-related indirect costs and another $4.70 on direct and workplace comorbidity costs incurred by individuals with MDD

V. Presentation
   a. Symptoms – SIG-E-CAPS
      i. S – sleep changes
      ii. I – interest (loss)
      iii. G – guilt
      iv. E – energy (lack)
      v. C – concentration/cognition (reduced and/or difficult)
      vi. A – appetite (weight changes)
      vii. P – psychomotor (agitation or retardation)
      viii. S – suicide/preoccupation with death
   b. Mood descriptors: depressed, sad, hopeless, discouraged, or “down in the dumps”

VI. Diagnosis\(^1\)
   a. Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) diagnostic criteria

<table>
<thead>
<tr>
<th>Table 1. DSM-5 diagnostic criteria for major depressive disorder (MDD)(^1)</th>
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<tbody>
<tr>
<td><strong>A.</strong> Five (or more) of the following symptoms present during the same two-week period, representing a change from previous functioning, and at least one of the symptoms is either depressed mood or anhedonia</td>
</tr>
<tr>
<td>Note: Do not include symptoms that are clearly attributable to another medical condition.</td>
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<tr>
<td>1. Persistent sad, anxious or “empty” mood</td>
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<td>2. Anhedonia: loss of interest or pleasure in daily activities</td>
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<td>3. Appetite and/or [undesired] weight changes</td>
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<tr>
<td>4. Insomnia or hypersomnia</td>
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<tr>
<td>5. Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>6. Decreased energy or fatigue</td>
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<td>7. Feelings of guilt or worthlessness</td>
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<tr>
<td>8. Difficulty concentrating, remembering, or making decisions</td>
</tr>
<tr>
<td>9. Thoughts of death or suicide, or suicide attempts</td>
</tr>
<tr>
<td><strong>B.</strong> Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning</td>
</tr>
<tr>
<td><strong>C.</strong> Not attributable to a substance or to another medical condition</td>
</tr>
<tr>
<td><strong>D.</strong> Not better explained by another psychiatric diagnosis</td>
</tr>
<tr>
<td><strong>E.</strong> There has never been a manic or hypomanic episode</td>
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</tbody>
</table>
b. Except weight changes and suicidal ideation, symptoms must be present nearly every day
c. Depression rating scales (Appendices 1 and 2)
   i. Screening in any setting: Two-item Patient Health Questionnaire (PHQ-2)\(^9\)
   ii. Nine-item Patient Health Questionnaire (PHQ-9)\(^{10}\)
   iii. Hamilton Depression Rating Scale (HAM-D, HDRS)\(^{11}\)
   iv. Montgomery-Åsberg Rating Scale (MÅDRS)\(^{12}\)
   v. Beck Depression Inventory-II (BDI-II)\(^{13}\)

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<th>Table 2. American Psychiatric Association (APA) 2010 Guidelines for the Treatment of MDD(^{14})</th>
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<td><strong>Level of Intervention</strong></td>
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</table>
| First-line | **Mild-to-moderate depression:** psychotherapy ± pharmacotherapy (SSRI, SNRI, mirtazapine, bupropion)  
**Moderate-to-severe depression:** pharmacotherapy ± psychotherapy  
**Severe depression:** may consider electroconvulsive therapy (ECT) |
| Second-Line | Switch to a different medication from list above as monotherapy  
Augment with antidepressant with a different mechanism  
Augment with an atypical antipsychotic  
Augment with psychotherapy |
| Third-Line | Switch to a different medication from list above as monotherapy  
Augment with an antidepressant with a different mechanism  
Consider tricyclic antidepressants (TCAs)  
Augment with lithium or triiodothyronine (T3) |
| Treatment Resistance | Monoamine oxidase inhibitor (MAOI)  
ECT |
| SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor |

I. Psychotherapy\(^2,5,14,15\)
   a. Cognitive behavioral therapy (CBT)
      i. Focuses on thoughts and beliefs as well as actions  
      ii. May be provided to individual, group, marital/couples, or family  
      iii. Recommended if thoughts or behaviors trigger/perpetuate depression
   b. Interpersonal therapy (IPT)
      i. Focuses on behaviors and interactions with family and friends  
      ii. Primary goal: improve communication skills and self-esteem  
      iii. Time-limited treatment for 12-16 weeks  
      iv. Works well for depression caused by loss (grief), relationship conflicts, major life events, and social isolation
   c. Compared to pharmacotherapy, no difference in outcomes for mild to moderate MDD

II. Pharmacotherapy
   a. Selective serotonin reuptake inhibitors (SSRIs, Table 3)\(^{16}\)
      i. Dose titration: generally increase in intervals of at least one week  
      ii. Side effects: agitation, insomnia, somnolence, gastrointestinal (GI) upset (diarrhea, nausea), headache, weight gain, sexual dysfunction, QT prolongation (citalopram)  
      iii. Contraindication: use of MAOI within 14 days (5 weeks for fluoxetine)
iv. Drug interactions
   1. Serotonergic agents (e.g., other antidepressants, tramadol, linezolid)
   2. Anticoagulants, antiplatelet agents, NSAIDS
      a. CYP2C19 inhibitors (e.g., fluoxetine and fluvoxamine) may decrease clopidogrel efficacy
      b. SSRIs have highest serotonin transporter affinity compared to other antidepressants
         i. Theory: increased risk of bleed (GI or elsewhere)
         ii. May wish to avoid SSRIs in patients at higher bleed risk
   b. See Appendix 3 for other classes of antidepressants

<table>
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<tr>
<th>Table 3. SSRIs with FDA approval for MDD16</th>
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<tr>
<td>Medication</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Escitalopram</td>
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<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Paroxetine</td>
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<tr>
<td>Sertraline</td>
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III. Electroconvulsive therapy (ECT)
   a. Effective in up to 80% of patients with either unipolar or bipolar depression⁴
   b. Generally safe but cardiac complications can occur

Cardiovascular Disease (CVD)

I. Epidemiology of CVD
   a. CVD: multiple individual, but often comorbid, complications of the heart and CV system
   b. Coronary heart disease (CHD)
      i. Leading cause of death for both men and women in the US and worldwide¹⁷,¹⁸
      ii. Atherosclerotic cardiovascular disease (ASCVD) contributes to CHD
   c. Heart failure (HF)
      i. Five-year mortality rate ~50%¹⁹
      ii. One-year mortality rate in New York Heart Association (NYHA) class III or IV: up to 50%¹⁹
   d. Myocardial infarction (MI)
   e. Stroke: fifth leading cause of death in the US²⁰,¹⁸
II. Risk factors

Table 4. Major risk factors for CVD

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Lack of routine physical activity</th>
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<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>Poor diet (diet high in saturated fat, trans fat, cholesterol and sodium)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Age – men after 45 years and women after 55 years</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Family history of premature heart disease – male first degree relative before age 55 years or female first degree relative before age 65 years</td>
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<tr>
<td>Overweight and obesity</td>
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<tr>
<td>Metabolic syndrome</td>
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<td>Sleep apnea</td>
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Comorbid Depression and CVD

I. Epidemiology

a. Diagnosing depression in patients with CVD can be difficult due to symptom overlap
b. Depression prevalence and severity interrelated with degree of cardiac dysfunction and the development of HF after index MI

c. Depressed patients more vulnerable to MI even after controlling CV risk factors

d. Depression and its proposed role in CVD

i. Increased activity of hypothalamic-pituitary-adrenal axis → increased secretion of corticotropin releasing hormone, adrenocorticotropic hormone and cortisol

   1. Cortisol may play important role in progression of HF
   2. Cortisol shown to be an independent predictor of cardiac events

   ii. Increased sympathoadrenomedullary activity → increased circulating catecholamines (e.g., norepinephrine predicts adverse HF prognosis)

iii. Increased platelet activation/aggregation through hyperactive 5HT2A signaling

Table 5. Prevalence of comorbid depression with various cardiovascular diseases

<table>
<thead>
<tr>
<th>Cardiac disease</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>CHD</td>
<td>20% of patients have major depression and 20% have minor depression at some point in the course of their illness</td>
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<tr>
<td>CAD/Post-MI</td>
<td>16%-20%</td>
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<tr>
<td>Cardiac catheterization</td>
<td>17%-23%</td>
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<tr>
<td>Unstable angina</td>
<td>15%</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>20%</td>
</tr>
<tr>
<td>Congestive HF</td>
<td>~22%, but as high as 70% in patients with ejection fraction &lt; 40% and/or greater degree of functional decline (i.e., NYHA Class III or IV)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CABG = coronary artery bypass graft

II. Personal and societal costs

a. Depression associated with psychological and social, plus cardiac, morbidity/mortality

   i. Depressed patients: twice the risk of adverse CV events within two years of MI/CABG

   ii. HF: greater severity of depression, worse prognosis, up to 8x the risk of death

   iii. Longitudinal multisite population-based study of elderly adults initially non-demented and with no symptomatic CHD or stroke

      1. Depressive symptoms (transient and cumulative) related to increased risk of CHD and stroke events over 10 years of follow-up

      2. Increased risk independent of many confounders (i.e., age, gender, CV status)
iv. Retrospective cohort study of depressed Veterans Affairs (VA) patients: 3x greater rate of all-cause mortality following acute MI in insufficiently treated vs. treated patients

b. Reduced quality of life
c. Increased rate of cardiac-related morbidity and premature mortality

d. Increased use of health care resources and costs of care (929% higher in one study)

e. Increased rate of hospitalizations and hospital readmissions (one incidence rate found to be 2.35 compared to those without depression; 95% CI 2.32-2.37)

f. American Heart Association statement: depression should be considered a risk factor for patients with CHD

III. Physiological effects of antidepressants in CVD

a. SSRIs

i. Antithrombotic effect: may normalize or even improve platelet function in CHD

ii. QT prolongation, usually only if underlying vulnerabilities or higher doses

iii. No change or possible increase in heart rate variability (HRV)

iv. Paroxetine reversed cardiac dysfunction and remodeling in post-MI HF in mice

v. In a veteran population, citalopram dose reductions (to ≤ 40 mg/d) were associated with increased risk of all-cause and depression-related deaths and hospitalizations

vi. Retrospective cohort in primary care patients with depression aged 20-64 years, on antidepressants: no increased risk of arrhythmia, MI or stroke with SSRIs; possible reduced risk of MI and arrhythmia with SSRIs, particularly fluoxetine

b. TCAs

i. Fast sodium channel inhibition: reduced sodium influx → widened QRS complex

ii. Anti-alpha-adrenergic effects: decreased myocardial contractility, hypotension

iii. Anticholinergic effects: increased heart rate → reduced cardiac output

iv. Reduce HRV

v. May have detrimental CV effects even in people with no CVD history

vi. Avoid in most patients with CHD

c. MAOIs

i. Hypotension and tachycardia

ii. Hypertensive crisis → must follow a tyramine-free diet

iii. Avoid in HF and hypertension

d. Serotonin norepinephrine reuptake inhibitors (SNRIs)

i. Not formally studied with many concomitant CVD

ii. Increased norepinephrine

1. Increased heart rate and blood pressure

2. May cause dangerous tachyarrhythmias

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Table 6. Risk factors for QT prolongation and possible Torsades de Pointes

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<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Female gender</td>
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<tr>
<td>Age &gt; 65 years</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Myocardial hypertrophy</td>
</tr>
<tr>
<td>Congenital long QT syndrome</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Hypokalemia</td>
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<tr>
<td>Hepatic or renal failure</td>
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Herbert | 7
iii. Venlafaxine may cause QT prolongation at toxic levels via sodium channel inhibition
iv. Generally not first-line with concomitant CVD

IV. Antidepressant treatment and CVD
a. Stroke (Appendix 4)
   i. Pre- and post-stroke SSRI use found to improve motor scores and cognitive functioning and also may reduce risk of new/recurrent CV events, especially following ischemic stroke30,35
   ii. Cochrane review: SSRIs reduce disability and neurological impairment scores in post-stroke patients36
      1. May support the use of SSRIs to treat depression post-stroke
      2. Insufficient evidence to make recommendations about the risk of bleed
   iii. Systematic review: SSRI use (compared to placebo or usual care) within 12 months of an index stroke improved disability, with greater benefit seen in patients who had depression at recruitment37
b. MI, HF, and CHD (Appendix 5)
   i. Post-MI SSRI use improved psychosocial outcomes but no survival difference38
   ii. In comorbid HF and MDD, sertraline use improved depression but no difference in CV outcomes19,39
   iii. Both exercise and sertraline improve CHD risk factors in patients with MDD40
   iv. Antidepressant use may increase the risk of HF, stroke and acute CVD death44

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<thead>
<tr>
<th>Literature Review</th>
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<tr>
<td><strong>Purpose</strong></td>
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<td><strong>Design</strong></td>
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</table>
| **Population** | Inclusion criteria:  
- Acute MI or hospitalized for unstable angina in the past 30 days, and  
- Experiencing a current episode of MDD  

Exclusion criteria (Appendix 6):  
- Cardiovascular reasons  
- Other medical reasons  
- Concomitant treatment exclusions  
- Psychiatric exclusions |
| **Outcome** | Change in left ventricular ejection fraction (LVEF) |
| **Methods** | Randomized to 24 weeks of either sertraline or placebo  
- Stratified by LVEF (<30% or ≥30%) and presence of two depression severity criteria (two or more prior depressive episodes and HAM-D score ≥18)  
- A priori determination: evaluate efficacy in those with higher depression severity  
- Evaluate efficacy in patients with at least one prior episode of MDD regardless of baseline HAM-D score  
- After 24 weeks of treatment, tapered off medication  
- At baseline and end of 16 weeks of treatment: multiple gated acquisition (MUGA) scans and 24-hour outpatient Holter ECG recordings  
- Other measurements:  
  - Secondary CV safety variables  
  - Laboratory markers  
  - Depression severity |
### Results

- 556 individuals met criteria for MDD and were not taking any antidepressant
  - Two-week placebo run-in period, 369 patients remained eligible and were randomized: sertraline: n=186, placebo: n=183
- Baseline characteristics similar between the two groups
  - Most patients were in their 50s or 60s
  - 40% of patients had a history of MI, ~50% with history of depression
  - 24% of patients had severe depression per HAM-D score ≥ 18 and multiple prior episodes of depression
- Mean duration of treatment ~150 days
- Mean (SD) final daily dose of sertraline was 68.8 (40.1) mg
- No significant difference in LVEF for patients on sertraline vs. placebo
- No significant between-group differences observed for secondary measures
- Nausea and diarrhea significantly more common in patients on sertraline
- CV events did not significantly differ between groups, but severe CV events numerically less frequent with sertraline (14.5% vs. 22.4%)
- Total population: sertraline significantly superior to placebo on CGI-I scale (measured over 24 weeks) but not the HAM-D scale (measured over the first 16 weeks)
- Recurrent depression groups: sertraline significantly superior to placebo on CGI and HAM-D measures
- Any prior history of MDD regardless of severity: significant improvements in depressive symptoms on both CGI-I and HAM-D for sertraline vs. placebo

### Author’s Conclusion

- Sertraline treatment was associated with no significant change in CV measures and did not differ from placebo
- Not statistically significant, but fewer severe cardiac events in sertraline group

### Critique

**Strengths:**
- Study design
- Multiple groups analyzed
- Achieved primary reason for study

**Limitations:**
- Sample size
- Delayed treatment initiation
- Exclusion criteria, generalizability
- Treatment duration and doses achieved
- High spontaneous recovery/placebo response rates

### Take Home

- Sertraline appears to be safe and, in patients with any recurrent major depression, an effective treatment in the setting of ACS
- Sertraline may contribute to fewer major adverse CV events post-MI, but a much larger sample of depressed patients with ACS would be needed to confirm this
- Depression that recurs or persists in ACS must be identified and treated

ACS = acute coronary syndrome

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**Purpose**

To document the short-term efficacy of citalopram and IPT in reducing depressive symptoms in patients with comorbid CAD and major depression

**Design**

Randomized, controlled, 12-week, parallel-group, 2 x 2 factorial design from May 2002 to March 2006

**Population**

Inclusion criteria:
- ≥ 18 years of age
- Current major depression per DSM-IV criteria, for ≥ 4 weeks and baseline HAM-D score ≥ 20

Exclusion criteria (Appendix 7):
- Psychiatric exclusions
- Medical exclusions
Population, cont. | Established CAD per hospital chart evidence of previous MI or cardiac revascularization or coronary angiography showing ≥ 50% blockage in at least one major coronary artery

Outcomes | Primary outcome: change in 24-item HAM-D score
Secondary outcome: BDI-II
Exploratory analyses: Inventory of Depressive Severity (IDS), Functional Performance Inventory (FPI) and Interpersonal Relationships Inventory (IPRI)

Methods | All patients randomized twice for 2 x 2 design
- Weekly IPT plus clinical management (CM) vs. weekly CM alone
  - CM = semi-structured 20-25 minute visits with information about depression and medication use, reassurance, and encouragement of adherence to medication and study protocol; also included monitoring for adverse effects and weekly MÅDRS
- Citalopram (10 mg daily for 1 week, then 20 mg daily) vs. matching placebo
  - If HAM-D score not ≤ 8 at 6 weeks, titrated to 40 mg daily
- At baseline and weeks 6 and 12: HAM-D, BDI-II, FPI, and IPRI; vitals; 12-lead ECG; and thyroid function test

Results | Randomized 284 patients, all of whom had at least one dose of study drug and at least one CM session
- 54 patients discontinued one or both treatments, most due to medication intolerance (n=22) or lack of efficacy (n=16); no difference between groups
- 86% of patients completed all 12 planned CM and/or IPT sessions, and only 17 patients completed < 10 sessions
- Baseline characteristics similar, though significantly fewer women randomized to IPT
  - Mean age 58 years, 25% women, > 50% with prior MI or at least one revascularization procedure, over two-thirds had most recent cardiac event > 6 months before randomization
  - Mean baseline HAM-D 29.7 (22.8 on 17-item scale) and BDI-II 30.2

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<thead>
<tr>
<th>Factorial groups</th>
<th>IPT vs. CM</th>
<th>C vs. P</th>
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<tbody>
<tr>
<td>HAM-D, mean (SD)</td>
<td></td>
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<tr>
<td>IPT + C</td>
<td>13.7 (9.98)</td>
<td></td>
</tr>
<tr>
<td>IPT + P</td>
<td>10.5 (9.96)</td>
<td></td>
</tr>
<tr>
<td>CM + C</td>
<td>16.1 (9.96)</td>
<td></td>
</tr>
<tr>
<td>CM + P</td>
<td>12.6 (9.97)</td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>12.1 (9.97)</td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>14.4 (9.97)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>14.9 (9.99)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>11.6 (9.99)</td>
<td></td>
</tr>
<tr>
<td>Between group diff (96.7% CI)</td>
<td>-2.26 (-4.78, 0.27)</td>
<td>3.33 (0.80, 5.85)</td>
</tr>
</tbody>
</table>

Table 7. Adjusted mean baseline to 12-week changes in 24-item HAM-D

- Citalopram superior to placebo in reducing depressive symptoms for all measures, apparent at 6 weeks (HAM-D score change 11.02 vs. 8.44, respectively; p=0.01)
  - Particularly better in those with recurrent depression vs. first episode
- No significant difference in improvements with IPT vs. CM alone
- No interaction between variables except for CM superior to IPT in those with low baseline perceived social support and low functioning in daily activities
- Serious adverse events, total: 12 CV and 23 non-CV, no difference between groups
- No difference between citalopram and placebo in any blood pressure or ECG changes
- Adverse events, citalopram > placebo: dizziness, diarrhea, somnolence, sweating, palpitations, and decreased libido or sexual difficulties

Author’s Conclusion | In patients with CAD experiencing a moderate to severe depressive episode, citalopram was superior to placebo, and IPT may not be better than CM alone

Critique | Strengths:
- Inclusion criteria
- Secondary, subgroup, exploratory
Limitations:
- Recruitment methods
- CM may be confused with IPT
| Critique, cont. | analyses | • Fourteen different IPT providers  
• No adjustment for additional analyses |
|---|---|---|
| **Take Home** | • It may just be the regular monitoring of mood and physical symptoms (with CM) that helps improve depression in CAD (rather than full IPT)  
• Citalopram (or sertraline as in SADHART) plus CM should be considered at least for acute-phase treatment in comorbid CAD and major depression |


**Purpose**  
To determine whether 24 months of treatment with escitalopram improves mortality, morbidity and mood in patients with chronic systolic HF and depression

**Design**  
Randomized, double-blind, placebo-controlled trial from March 2009 to September 2014

**Population**  
Inclusion criteria:  
• Established HF diagnosis (NYHA class II-IV) and LVEF < 45% within the last 3 months  
• DSM-IV diagnosis of current major depression  
Exclusion criteria:  
• MI within last 3 months  
• Recent or planned major cardiac surgery  
• Advanced renal failure or hepatic impairment  
• Thyrotoxicosis  
• Contraindication to SSRIs  
• Any current psychotherapy OR use of any antidepressants for mood disorder in adequate dose ≥ 8 weeks and positive clinical outcome  
• Absence of response to prior adequate escitalopram trial  
• QT prolongation or on QT-prolonging drugs

**Outcomes**  
• Primary (composite):  
  • Time to first event all-cause death or hospitalization  
• Secondary:  
  • MÅDRS sum score at 12 weeks, GAD-7, health-related quality of life  
  • Individual components of the primary outcome  
  • Escitalopram serum levels  
  • HF pharmacotherapy, HF severity, cardiac status and safety

**Methods**  
• One to one randomization to escitalopram (10-20 mg/d) or placebo for up to 24 months, plus optimal HF care  
  • Stratified based on gender, age (< 70 years vs. ≥ 70 years), severity of depression (PHQ-9 score ≤ 16 vs. > 16), and time elapsed since hospital discharge (≤ 4 weeks vs. > 4 weeks)  
  • After December 2011, limited max dose to 10 mg/d in patients ≥ 65 years  
  • Tolerance-guided up-titration of HF therapy  
  • Patient counseling and empowerment  
• After final visit, titrated off study medication + psychiatric closeout examination  
• In 2012, changed study duration to be event-driven  
• PHQ-9, QoL, GAD-7, MÅDRS and MMSE at baseline + months 3, 6, 12, 18, 24  
• Safety monitoring at each visit  
• Weekly during up-titration then bimonthly telephone monitoring of depressive symptoms and cardiac status  
• Hospitalization rate (60%) after recruiting 240 patients was higher than anticipated  
  • In 2014: terminated study early “based on futility” after a recommendation from the data and safety monitoring committee  
  • All enrolled patients completed at least 6 months of follow-up
### Results
- 372 patients (escitalopram n=185, placebo n=187) took ≥ one dose of study drug
- Median participation times: escitalopram 18.4 months, placebo 18.7 months
- Similar baseline characteristics
  - Mean age 62 years; ~1/3 of patients ≥ 70 years; 75% male
  - Escitalopram: 48% NYHA class III-IV; placebo: 58% NYHA class III-IV
  - Mean LVEF 35%; mean QT interval 440-450 msec
  - Concomitant HF therapy – ACEi or ARB 95%, beta-blocker 91-93%, MRA 58%, diuretic 81%, cardiac glycoside 22%, ICD 45%
  - History of depression ~12%; PHQ-9 scores 12-13 at randomization
- Primary endpoint: hazard ratio 0.99 (95% CI, 0.76-1.27)
  - Escitalopram: n=116 (63%)
  - Placebo: n=119 (64%)
- No significant differences for any time-to-event outcomes in unadjusted or adjusted analyses
- MÅDRS sum score changes from baseline: mean (SD)
  - Escitalopram: 20.2 (8.6) → 11.2 (8.1)
  - Placebo: 21.4 (8.8) → 12.5 (7.6)
- Anxiety and depression decreased comparably in both groups
- The only scale reaching statistical significance was between-group difference for the KCCQ symptoms score at 12 months: change from baseline (95% CI)
  - Escitalopram: 2.4 (-1.4, 6.2)
  - Placebo: 8.9 (5.6, 12.3)
  - Difference [escitalopram-placebo]: -5.8 (-10.4, -1.2); p = 0.01
- Detectable escitalopram levels during the first 12 months of follow-up in >70%
- No differences in HF medication titration, HF severity changes, or cardiac status
  - LVEF appeared to improve in both groups (from ~34% to ~40%)
- Higher baseline MÅDRS sum score (> 25) appeared to be associated with worse outcomes in the escitalopram group
- More patients in the escitalopram group discontinued therapy by 12 weeks compared to placebo (11% vs. 7%, respectively; p = 0.02)
- No differences in safety parameters or serious adverse events except for worsening depression occurring more often in the placebo group

### Author’s Conclusion
- Escitalopram is well-tolerated but does not change morbidity or mortality in patients with comorbid systolic HF and depression compared with placebo

### Critique
#### Strengths:
- Study design
- Escitalopram serum levels as a marker

#### Limitations:
- Terminated early
- Study population
- External validity
- Escitalopram serum levels as a marker
- Treatment confounders

### Take Home
- Eighteen months of treatment with escitalopram vs. placebo did not significantly reduce mortality or hospitalization, nor did it significantly improve depression
- Tolerance-guided up-titration of HF medications, patient counseling and empowerment are important components of HF management

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GAD-7 = Generalized Anxiety Disorder 7-Item scale; d = day; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; MRA = mineralocorticoid receptor antagonist; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire
Conclusion

I. Summary
   a. Depression and CVD are individually associated with significant morbidity and mortality, with even greater issues when occurring together
   b. Overwhelming evidence supports the safety of SSRIs in patients with CVD
   c. Larger randomized controlled trials may be needed to definitively support efficacy of SSRIs on a variety of CV measures in both depressed and non-depressed patients
   d. Choice of antidepressant in CVD requires individual patient assessment
      i. Risk-benefit ratio of treatment
      ii. Type and severity of depression and cardiovascular disease
      iii. Drug interactions (sertraline and citalopram have the fewest CYP interactions)
      iv. Patient preference/individual characteristics
      v. Previous and current drug and medical history

II. Recommendations
   a. Screen all patients with CVD and no documented depression
      i. At least with PHQ-2
      ii. If either or both answers are “yes”, screen with PHQ-9
   b. Consider SSRI initiation within 3 months post-stroke regardless of depression status
   c. CVD and comorbid depression
      i. Initiate or recommend psychotherapy early for patients with depressive symptoms
      ii. Consider SSRI initiation, preferably with sertraline, as early as possible in patients with CVD meeting criteria for depression
      iii. Routinely monitor symptoms of depression
      iv. If depressive symptoms do not improve within 4-6 weeks of treatment initiation/dose change, follow APA guidelines for therapy
   d. If significant risk factors for QT prolongation exist, ensure patient has had recent ECG and monitor patient more closely for adverse events regardless of antidepressant initiated

III. Future directions
   a. FOCUS, AFFINITY and EFFECTS trials\textsuperscript{41}
      i. Investigator-led, multicenter, parallel group, randomized placebo-controlled trials
      ii. Objective: determine whether routine administration of fluoxetine (20 mg daily) for 6 months after acute stroke improves patients’ functional outcome
      iii. Enrollment expected to end in 2018
      iv. FOCUS: Fluoxetine or Control Under Supervision (conducted in the United Kingdom)
      v. AFFINITY: Assessment of Fluoxetine In sTroke recovery (conducted in Australasia and Asia)
      vi. EFFECTS: Efficacy of Fluoxetine – a randomisEd Controlled Trial in Stroke (conducted in Sweden)
   b. Retrospective cohort studies continue to add to the clinical evidence of SSRIs in CVD, but these contain many potential confounders
   c. Need more large randomized, controlled trials to assess antidepressants in CVD
References


**Appendix 1. PHQ-2 Depression Rating Scale**

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rating Scale</td>
<td>Details</td>
<td>Scoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Nine-item Patient Health Questionnaire (PHQ-9)** | 1. Nine-item, self-administered scale  
2. Based on DSM-IV criteria for MDD and patient report of frequency of symptoms over the previous 2 weeks  
3. Used in clinical trials and clinical practice as both a diagnostic tool and as a rating scale to monitor symptom severity, determine need for treatment, and assess response to treatment | Items are scored from 0 (not at all) to 3 (nearly every day)  
20-27: severe  
15-19: moderately severe  
10-14: moderate  
5-9: mild  
1-4: minimal  
With treatment:  
Response: ≥ 5 point reduction in score  
Partial remission: score < 10  
Remission: score < 5 |
| **Hamilton Depression Rating Scale (HDRS or HAM-D)** | 1. Clinician-administered scale, typically 21 items but scored based on the first 17 items  
2. Ratings cover symptom severity experienced over the past week including evaluation of somatic symptoms  
3. Used in clinical trials and clinical practice to assess response  
4. Gold standard for clinical research | Eight items scored from 0 (absent) to 4 (severe) and 9 items scored from 0 (absent) to 2 (definite), depending on the item  
≥ 23: very severe  
19-22: severe  
14-18: moderate  
8-13: mild  
0-7: normal  
With treatment:  
Response: ≥ 50% reduction in score  
Remission: total score ≤ 7 |
| **Montgomery-Asberg Rating Scale (MÅDRS)**       | 1. Ten-item clinician-administered scale  
2. Places less emphasis on somatic complaints compared with HAM-D  
3. Symptoms at time of interview, with no time frame specified  
4. Used in clinical trials and clinical practice to assess response  
5. May be more sensitive to drug treatment response than HAM-D | Items are scored from 0 (absent) to 6 (severe)  
35-60: severe  
20-34: moderate  
7-19: mild  
0-6: normal/symptoms absent  
With treatment:  
Response: ≥ 50% reduction in score  
Remission: score ≤ 10 |
| **Beck Depression Inventory-II (BDI-II)**         | 1. 21-item, self-administered scale based on patient symptoms and attitudes over the previous 2 weeks  
2. Used in clinical trials and clinical practice to assess severity of depression in those with a formal diagnosis | Items are scored from 0 (absent) to 3 (severe)  
29-63: severe depression  
20-28: moderate depression  
14-19: mild depression  
0-13: no/minimal depression  
With treatment:  
Response: ≥ 50% reduction in score  
Remission: score < 10 |
<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial dose (mg/d)</th>
<th>Usual dose (mg/d)</th>
<th>Primary CYP enzyme/metabolism</th>
<th>Dose adjustment</th>
<th>Other pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50</td>
<td>50-100</td>
<td>Hepatic, not CYP</td>
<td>CrCl 30-50 ml/min: max 50 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCl &lt; 30 ml/min: 50 mg every other day</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30-60</td>
<td>60-120</td>
<td>1A2, 2D6</td>
<td>CrCl &lt; 30 ml/min: do not use</td>
<td></td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>20</td>
<td>40-120</td>
<td>3A4</td>
<td>CrCl 30-59 ml/min: max 80 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCl 15-29 ml/min: max 40 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCl &lt; 15 ml/min: do not use</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>37.5-75</td>
<td>75-375</td>
<td>2D6</td>
<td>Mild to moderate renal impairment: decrease usual dose by 25-50%</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>37.5-75</td>
<td>75-225</td>
<td>2D6</td>
<td>Hemodialysis: decrease usual dose by 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild to moderate hepatic impairment: decrease usual dose by ≥ 50%</td>
<td></td>
</tr>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amitriptyline</td>
<td>75, divided to 1-3</td>
<td>100-300</td>
<td>2D6</td>
<td>Hepatic: lower initial dose + gradual increase</td>
<td>Elderly: 10 mg TID and 20 mg at bedtime</td>
</tr>
<tr>
<td></td>
<td>doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>75, divided to 3</td>
<td>100-250</td>
<td>Hepatic, not CYP</td>
<td>None</td>
<td>Elderly: start at lower end of dosing range; use caution</td>
</tr>
<tr>
<td></td>
<td>doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>25-50, single or</td>
<td>100-300</td>
<td>2D6</td>
<td>Hepatic: lower initial dose + gradual increase</td>
<td>Elderly: 25-100 mg/d, max 150 mg/d</td>
</tr>
<tr>
<td></td>
<td>divided dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>25-50</td>
<td>100-300</td>
<td>2C19, 2D6</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>75</td>
<td>75-200</td>
<td>1A2, 2C19, 2D6, 3A4</td>
<td>Hepatic: lower initial dose + gradual increase</td>
<td>Elderly: 30-40 mg in divided doses or at bedtime, max 100 mg/d</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25 mg, 3-4x/day</td>
<td>75-150</td>
<td>2D6</td>
<td>None</td>
<td>Elderly: 30-50 mg/d in single or divided doses</td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Phenelzine</td>
<td>45, divided into 3</td>
<td>60-90</td>
<td>MAO – oxidation</td>
<td>Renal/hepatic impairment: avoid use</td>
<td>Irreversible, nonselective</td>
</tr>
<tr>
<td></td>
<td>doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>20, divided into 2</td>
<td>40-60</td>
<td>Hepatic</td>
<td>Renal/hepatic impairment: avoid use</td>
<td>Irreversible, nonselective</td>
</tr>
<tr>
<td></td>
<td>doses</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tranylcypromine</td>
<td>30, divided</td>
<td>30-60</td>
<td>Hepatic</td>
<td>Hepatic: avoid use</td>
<td>Irreversible, nonselective</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
<td>6</td>
<td>6-12</td>
<td>2B6, 2C9, 3A4/5</td>
<td>None</td>
<td>Irreversible, MAO-B selective</td>
</tr>
<tr>
<td>transdermal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion IR and</td>
<td>150</td>
<td>300-450</td>
<td>2D6</td>
<td>Renal: consider reducing dose and/or frequency for GFR &lt; 90 ml/min</td>
<td>NE and DA reuptake inhibition</td>
</tr>
<tr>
<td>XR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>150</td>
<td>300-400</td>
<td>2D6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Initial dose (mg/d)</td>
<td>Usual dose (mg/d)</td>
<td>Primary CYP enzyme/metabolism</td>
<td>Dose adjustment</td>
<td>Other pearls</td>
</tr>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15</td>
<td>15-45</td>
<td>2D6, 3A4</td>
<td>CrCl &lt; 40 ml/min and hepatic impairment: increase dose slowly as needed/as tolerated</td>
<td>Presynaptic alpha-2 antagonist and 5HT2/5HT3 antagonist</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>100</td>
<td>150-600</td>
<td>3A4</td>
<td>None, but not generally recommended with hepatic impairment (risk of hepatotoxicity)</td>
<td>Weak 5HT and NE reuptake inhibition, weak alpha-1 antagonist, 5HT2 antagonist, histamine antagonist (trazodone &gt; nefazodone)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>150</td>
<td>150-600</td>
<td>3A4</td>
<td>None</td>
<td>5HT reuptake inhibition, 5HT1A partial agonist</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>10</td>
<td>10-40</td>
<td>3A4</td>
<td>None</td>
<td>5HT reuptake inhibition + 5HT3/5HT7 antagonism, 5HT1a agonism</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>10</td>
<td>10-20</td>
<td>2D6</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; NE = norepinephrine; DA = dopamine; CrCl = creatinine clearance; d = day; 5HT = serotonin

---

**Appendix 4. Review of antidepressant use and risk of stroke in patients with or without depression**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention(s)</th>
<th>Outcome(s)</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Robinson et al., 2008</strong>&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Randomized, double-blind placebo-controlled plus a non-blind therapy group in 176 non-depressed patients within 3 months of an index stroke (ischemic or hemorrhagic)</td>
<td>Post-stroke escitalopram, placebo, or problem-solving therapy (PST) for 12 months</td>
<td>Post-stroke risk of depression ITT analysis: rate of depression</td>
<td>Placebo vs. escitalopram and PST: HR 4.5 (95% CI, 2.4-8.2); HR 2.2 (1.4-3.5) ITT, escitalopram vs. placebo: HR 2.2 (1.2-3.9) ITT, PST vs. placebo: HR 1.1 (0.8-1.5)</td>
</tr>
<tr>
<td><strong>Jorge et al., 2010</strong>&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Same as Robinson et al., but in 129 patients</td>
<td>Post-stroke escitalopram, placebo, or PST for 12 months</td>
<td>Change in scores from baseline to the end of treatment for RBANS and other tests</td>
<td>RBANS total score changes: escitalopram, 10.0; non-escitalopram, 3.1; p&lt;0.01 RBANS delayed memory score changes: 11.3 vs. 2.5; p&lt;0.01 (No significant differences for other tests)</td>
</tr>
<tr>
<td><strong>Chollet et al., 2011</strong>&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Randomized, double-blind, placebo-controlled in 113 non-depressed patients with ischemic stroke + unilateral motor weakness</td>
<td>Fluoxetine 20 mg/d or placebo for 3 months</td>
<td>Change in Fugl-Meyer motor scale (FMMS) score from day 0 to day 90 of treatment</td>
<td>FMMS change, fluoxetine vs. placebo: 34.0 vs. 24.3, p=0.003</td>
</tr>
<tr>
<td><strong>Mortensen et al., 2013</strong>&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Registry-based propensity score matched follow-up study post-hemorrhagic and ischemic stroke</td>
<td>Multiple morbidity and mortality outcomes in post-ischemic stroke SSRI users and non-users, including combined outcome of MI or recurrent ischemic stroke; median follow-up: 1159 days</td>
<td>Combined outcome: SSRI use vs. non-use, HR 0.77 (95% CI, 0.62-0.96) Risk of bleed, SSRI use vs. non-use: HR 1.33 (1.14-1.55)</td>
<td>Horse</td>
</tr>
</tbody>
</table>
Registry-based propensity score matched follow-up study in first-ever patients with hemorrhagic or ischemic stroke (HS or IS)

Risk of recurrent stroke and death in pre-stroke SSRI users and propensity score matched non-users

Prior HS, risk of severe stroke: SSRI use vs. non-use, OR 1.41 (95% CI, 1.08-1.84)
Prior HS, risk of death within 30 days, SSRI use vs. non-use: OR 1.60 (1.17-2.18)
Prior IS, no significant differences

Population-based nested case control; 3,957 cases and 7,779 matched controls

Risk of stroke recurrence based on post-stroke use of antidepressants by class (SSRI, TCA, or other)

TCAs: 1.41 (95% CI, 1.19-1.67)
SSRIs and other, no significant change in risk of stroke recurrence

Abrupt cessation of TCA (1-30 days): 1.87 (1.22-2.86)

HR = hazard ratio; ITT = intention-to-treat; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status

Appendix 5. Additional studies reviewing the effects of SSRIs in patients with MI, HF, or CHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient population</th>
<th>Intervention(s)</th>
<th>Outcome(s) and Result(s)</th>
</tr>
</thead>
</table>
| ENRICHD (2003)³⁸ | Randomized controlled trial for 6 months | 2,481 post-MI patients with depression and/or low perceived social support (LPSS) | Individual cognitive behavioral therapy (CBT), plus group when possible, or usual care; SSRIs added if severe depression or < 50% reduction in BDI score after 5 weeks | HDRS score change (for depression), intervention vs. usual care: -10.1 vs. -8.4 (p<0.001)    

ESSI score change (for LPSS), intervention vs. usual care: 5.1 vs. 3.4 (p<0.001)
No difference in survival between groups
Secondary analysis of antidepressant use vs. CBT alone or no treatment, risk of death or nonfatal MI: HR 0.63 (0.46-0.87)

| SADHART-CHF (2010)¹⁹,³⁹ | Randomized, double-blind, placebo-controlled | 469 patients ≥ 45 years old, with HF (with LVEF ≤ 45% and NYHA class ≥ II) and MDD | Sertraline or placebo; all received ‘nurse facilitated support’ from people with prior experience or training in clinical psychiatry | HDRS score change: -7.1 (sertraline) vs. -6.8 (placebo); p<0.001 from baseline, p=0.89 between groups
No difference in CV score changes |

| SMILE-II (2016)⁴⁰     | Randomized, parallel group, placebo-controlled | 202 patients with MDD | Group-based exercise, home-based exercise, sertraline, or placebo | All active treatment groups (exercise and placebo) improved CHD risk factors – composite CHD risk, p=0.001
- Intima-medial thickness: p=0.032
- Flow-mediated dilation: p=0.037
- Ten-year ASCVD risk score: p=0.049 |

| REGARDS (2016)⁴⁴     | Population-based, longitudinal cohort | 29,616 participants from the ‘Stroke Buckle’, ‘Stroke Belt’ and non-Belt states | 3.458 (11.7%) patients were using an eligible antidepressant
*Did not assess antidepressant exposure after baseline | Fully adjusted model:
Risk of all-cause mortality in antidepressant users: HR 1.12 (95% CI, 1.01-1.24)
Trends toward increased risk for individual outcomes of CHD, stroke and CVD death |

ENRICHD = Enhancing Recovery in Coronary Heart Disease Patients; SADHART-CHF = Sertraline Against Depression and Heart Disease in CHF; SMILE-II = Standard Medical Intervention versus Long-term Exercise-II; REGARDS = Reasons for Geographic and Racial Differences in Stroke
### Appendix 6. SADHART exclusion criteria

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Uncontrolled HTN (SBP &gt; 180 mmHg or DBP &gt; 100 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac surgery anticipated during the next 6 months</td>
</tr>
<tr>
<td></td>
<td>Index MI or unstable angina developed &lt; 3 months after CABG</td>
</tr>
<tr>
<td></td>
<td>Resting heart rate of &lt; 40/min (or &lt; 50/min if symptomatic or daytime sinus pauses of &gt; 3.5 seconds)</td>
</tr>
<tr>
<td></td>
<td>MI or unstable angina of non-atherosclerotic etiology (anemia, cocaine use, periprocedural)</td>
</tr>
<tr>
<td></td>
<td>Killip class III or IV status</td>
</tr>
<tr>
<td>Other medical</td>
<td>Persistent clinically significant laboratory abnormalities</td>
</tr>
<tr>
<td></td>
<td>Significant renal dysfunction, hepatic dysfunction, or other significant non-cardiac disease</td>
</tr>
<tr>
<td></td>
<td>Women of childbearing potential not using adequate contraception</td>
</tr>
<tr>
<td>Concomitant treatment</td>
<td>Current use of class I antiarrhythmic medications</td>
</tr>
<tr>
<td></td>
<td>Use of reserpine, guanethidine, clonidine, or methyldopa; anticonvulsants or neuroleptics; antidepressants; or regular benzodiazepine</td>
</tr>
<tr>
<td></td>
<td>Initiation of psychotherapy in the 3 months prior to study entry</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Alcohol or substance abuse or dependence in past 6 months</td>
</tr>
<tr>
<td></td>
<td>Psychotic symptoms, history of psychosis, bipolar disorder, organic brain syndrome, dementia (or a Mini Mental State Exam score &lt; 23)</td>
</tr>
<tr>
<td></td>
<td>Significant suicide risk</td>
</tr>
</tbody>
</table>

### Appendix 7. CREATE exclusion criteria

<table>
<thead>
<tr>
<th>Psychiatric</th>
<th>Depression due to a general medical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bipolar disorder or depression with psychotic features</td>
</tr>
<tr>
<td></td>
<td>Substance abuse or dependency in previous 12 months</td>
</tr>
<tr>
<td></td>
<td>Current antidepressant use</td>
</tr>
<tr>
<td></td>
<td>Serious suicide risk</td>
</tr>
<tr>
<td></td>
<td>Previous absence of response to citalopram or IPT</td>
</tr>
<tr>
<td></td>
<td>Two or more previous unsuccessful treatments for index depression episode</td>
</tr>
<tr>
<td></td>
<td>Lifetime history of early termination (&lt; 8 weeks) of citalopram or two other SSRIs because of adverse events</td>
</tr>
<tr>
<td></td>
<td>Mini Mental State Exam score &lt; 24</td>
</tr>
<tr>
<td>Medical</td>
<td>One week or less since hospital discharge from cardiac hospitalization</td>
</tr>
<tr>
<td></td>
<td>Unstable CAD based on clinical judgment (e.g., worsening angina or HF symptoms in the past week)</td>
</tr>
<tr>
<td></td>
<td>CABG planned within the next 4 months</td>
</tr>
<tr>
<td></td>
<td>Canadian Cardiovascular Society Angina Class of 4 (severe limitations)</td>
</tr>
</tbody>
</table>