

# Depression, Anxiety and Cardiovascular disease

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## Objectives

At the end of this activity participants will have a better knowledge of :

- Prevalence and evaluation of depression and anxiety in cardiac patients.
- Screening tools for diagnosis and further management.
- Treatment options, implications of using certain medications




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## Prevalence of Depression & Anxiety in Cardiovascular Disease

- Depressive symptoms in 17.5% and anxiety symptoms in 32.5% subjects in a study, using standard scales of assessment<sup>1</sup>.
- Almost 15-20% patients with coronary artery disease and heart failure meet the criteria for major depressive disorder<sup>2</sup>. This is approximately 3 times than the risk in general population (6-7%)

1. Carvalho RG, Bertelli ED, Paiva L, Rossi LA, Dantas RA, Pompeu DA. Anxiety, depression, resilience and self-esteem in individuals with cardiovascular diseases. Rev Lat Am Enfermagem. 2016 Nov; 28:242-2636.  
2. Huffman JC et al. Depression and cardiac disease: epidemiology, mechanisms and diagnosis. Cardiovasc Psychiatr Neurolog. 2013




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## Panic disorder and coronary artery disease

- Almost 25% cases with chest pain of cardiac nature visiting EDs were found to have panic disorder
- There is a group of patients that have panic disorder and coronary artery disease simultaneously: hard to perform study on this population they both can present with chest pain
- Younger age, female gender, atypical quality and location of chest pain and high level of self reported anxiety: clues that predict a higher association of panic disorder in population presenting with chest pain

Wyszynski et al. The patient with cardiovascular disease. Manual of Psychiatric Care for Medically Ill. American Psychiatric Publishing, Inc. 2005, Arlington, VA




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## Post traumatic stress disorder and cardiovascular disease

A large meta-analysis<sup>1</sup>: >40,000 subjects found:

- PTSD was associated with 53% increased risk of incident cardiac events after adjusting for demographical, clinical and psychological factors

Another meta-analysis of 24 studies:

- A 12% prevalence of PTSD secondary to acute coronary syndrome<sup>2</sup> (as a result of ACS)

1. Bernstein et al. PTSD risk of incident cardiovascular disease in aging veterans. Am J Geriatr psychiatry 2016; 24: 192-200  
2. Endersson et al. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome: a meta-analytic review. Heart 2012; 7: e38915




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## PTSD: A causal risk factor for coronary heart disease?

A twin study found PTSD to be *independently linked to* increase the risk of incident coronary events outside of the influence of genetic factors and behavioral factors<sup>1</sup>

Vaccarino et al. Posttraumatic stress disorder and incidence of coronary heart disease: a twin study. J Am Coll Cardiol 2013; 62: 970-78




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## Cardiac implants and anxiety mimics

- **Pacemaker syndrome:** dysfunctional atrial contraction against a closed tricuspid valve → AV dysfunction and RV-LV dyssynchrony → low cardiac output → lightheadedness, apprehension, diaphoresis, palpitations
- **Implantable Cardioverter-Defibrillator:** “phantom shocks”: known to cause depression (18-41%), anxiety (13-38%), PTSD (20%) and severe sleep problems: irrespective of being shocked or not!



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## PTSD/ anxiety and ICD

Risk factors:

- Young age
- Female gender
- Low socioeconomic support
- Pre-existing psychiatric disease

A 2013 study showed significant association between ICD placement and development of anxiety on a 12 month follow up, irrespective of the frequency of pacing (after adjusting for confounders like age, sex, depression, cardiac health)

Schulz SM, Massa C, Grzbiela A, Dengler W, Wiedemann G, Paul P. Implantable cardioverter defibrillator shocks are prospective predictors of anxiety. Heart Lung. 2013; 42(2):105-11.



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## Depression and anxiety predict development of CHD



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### Predictive influence of depressive symptoms in coronary heart disease

A meta-analysis looked into 11 cohort studies

- Subjects had *clinically diagnosed unipolar depression*
- Primary outcome: *myocardial infarction, coronary death, and cardiac death*
- Bipolar depression was excluded
- Angina pectoris was not a measured outcome (depression is commonly seen in subjects complaining of chest pain without any evidence of CAD)

Rogalski R. Depression as a predictor for coronary heart disease: a review and meta-analysis. Am J Prev Med 2002; 23(1): 51-61




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### Predictive influence of depressive symptoms in Coronary heart

Clinical depression was a strong predictor of development of coronary heart disease in initially healthy population

•RR 2.69, 95% CI=1.63-4.43,  $p < 0.001$

Rogalski R. Depression as a predictor for coronary heart disease: a review and meta-analysis. Am J Prev Med 2002; 23(1): 51-61




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### Depression and anxiety predict response to treatment in CHD




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## Depression-anxiety as a predictor of treatment response in CHD

Severe depression at baseline  
 Stressful life events in last 8 weeks  
 - Predicted poor response to treatment of CHD<sup>1</sup>  
 Depression → decrease in physical functioning and increase in mortality after cardiac surgery<sup>2,3</sup>

1. Carney RM et al. Clinical predictors of depression treatment outcomes in patients with coronary heart disease. *Journal of Psychosomatic Research* 2016; 88: 36-41  
 2. Blumenthal JA et al. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet* 2003; 362:604-609  
 3. Kendler F et al. Predictive relationship between depression and physical functioning after coronary surgery. *Arch Intern Med* 2010; 170(19):1717-21




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## Depression and anxiety influence long term outcome after CHD




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## Influence on long term outcome after CHD

Pre-myocardial anxiety in the preceding 2 hours  
 - ↑ 10-year mortality rate in >65 year old<sup>1</sup>  
 Moderate/high stress (per Perceived Stress Scale-4) at the time of myocardial infarction<sup>2</sup>  
 - ↑ 2 year mortality  
 - ↑ risk of angina in following 1 year

1. Smeijers L, Mostofsky E, Tofler GH, Muller JE, Kop WJ, Mittleman MA. Anxiety and anger immediately prior to myocardial infarction and long-term mortality: Characteristics of high-risk patients. *J Psychosom Res*. 2017; 93:19-27  
 2. Arnold SV, Smolderen KG, Buchanan DM, Li Y, Spertus JA. Perceived Stress in Myocardial Infarction. *Journal of the American College of Cardiology* 2012; 6 (18): 1756-1763




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## Depression and all-cause mortality after acute coronary syndrome

Enhancing Recovery in Coronary Heart Disease (ENRICHD) study<sup>1</sup>:

- Increased risk of all cause mortality after 30 months and 5 years of ACS
- Significance persisted after adjusting confounders

Lichman et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations. A scientific statement from the American Heart Association. Circulation 2014; 129: 00-00




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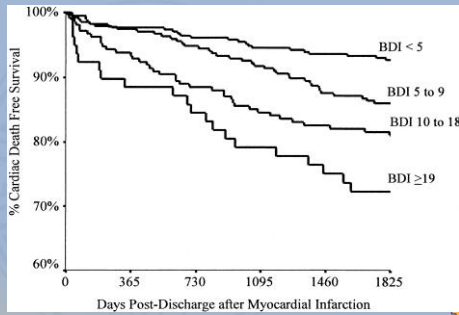
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Long-term survival after MI in relation to Beck Depression Inventory Score during hospitalization: gradient relationship between severity of depression and 5 year survival rate



François Lespérance et al. Circulation. 2002;105:1049-1053



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## American Heart Association's scientific statement

After an extensive review of 53 studies and 4 meta-analysis, AHA made a statement, published in 2014:

Depression is an *individual risk factor* for adverse medical outcomes in patients with acute coronary syndrome<sup>1</sup>

Lichman et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations. A scientific statement from the American Heart Association. Circulation 2014; 129: 00-00




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## Depression and CHD: Relations: molecular, physiological and behavioral basis



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## Depression and CHD: Behavioral aspects

- Poor health behavior (↓ physical activities, poor diet, lack of exercise, smoking, poor medicine adherence → Obesity)
- Diabetes
- Hypertension (through hypothalamic –pituitary axis dysfunction in response to stress)
- Poor sleep (mediator or confounder in explaining the association between depressive sx and cardiovascular mortality)



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## Depression, sleep and cardiovascular disease

Prospective cohort study of 667 subjects with stable coronary heart disease:

- Greater severity of depressive symptoms at baseline predicted poorer sleep quality at 5 year follow up

Subjects with sleep problem had a 2 fold increased risk of all-cause hospitalization in heart failure population<sup>2</sup>.

1. Sun NL, et al. Direction of Association Between Depressive Symptoms and Lifestyle Behaviors in Patients with Coronary Heart Disease: the Heart and Soul Study. *Ann Behav Med.* 2016; 50(4):252-62.

2. Johnson et al. The Course of Sleep Problems in Patients With Heart Failure and Associations to Rehospitalizations. *J Cardiovasc Nurs.* 2015; 30(4):27-36.



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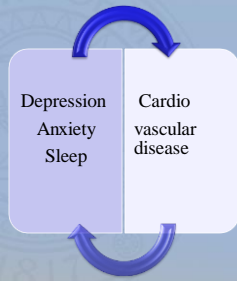
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### Reverse Causality




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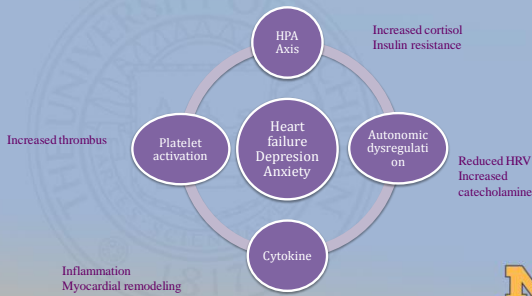
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### Depression-anxiety and CHD: Multilayer relation




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### Depression and CHD: Relations

- Inflammatory biomarkers: CRP, interleukin-6, soluble intercellular adhesion molecule-1, and fibrinogen  
Immunologic/inflammatory reactions →
  - Endothelial dysfunction
  - Increased thrombus formation
- Abnormalities in autonomic nervous system

All of the above are established in pathophysiology of cardiovascular diseases




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## Immune mechanism of depression-anxiety-CHD

- Increased level of CRP in acute coronary syndrome patients that have depression<sup>1</sup>
- Cytokines → affect synthesis, release, re-uptake of serotonin, dopamine, noradrenaline, glutamate and brain derived natriuretic factor (BDNF)
- Increased interleukin 1  $\beta$ , interleukin 6 and tumor necrosis factor  $\alpha$  were found in depression, PTSD consistently and they are key contributors of atherosclerosis

1. Smith JG et al. Acute coronary syndrome and depression: A review of shared pathophysiological pathways. Australian & New Zealand Journal of Psychiatry 2015, Vol. 49(11) 994-1005




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## Platelet-endothelial injury theory

Platelet activation is one of the triggering factors for acute coronary syndrome

- Platelets are activated to aggregate in presence of high circulating serotonin (treatment implications with SSRI)
- S allele of a serotonin transporter gene (5-HTTLPR) increases the risk of subsequent cardiac events and depression<sup>1</sup>
- BDNF is low in both depressed population and population with ACS

1. Smith JG et al. Acute coronary syndrome and depression: A review of shared pathophysiological pathways. Australian & New Zealand Journal of Psychiatry 2015, Vol. 49(11) 994-1005




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## Autonomic dysfunction theory

- Heart Rate Variability (HRV) negatively correlated with severity of depression in CHD and after ACS<sup>1</sup>
- Reduced HRV persisted after cardiac surgery<sup>2</sup>
- Low HRV and increased CRP and IL-6 were associated with post ACS subjects that had depression<sup>3</sup>

1. Stein PK et al. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. Journal of Psychosomatic Research 2000; 48: 493-500

2. Patton E et al. Association between depression and heart rate variability in patients after cardiac surgery: A pilot study. Journal of psychosomatic Research 2012; 73: 42-46

3. Fisure-Smith et al. The relationships among heart rate variability, inflammatory markers and depression in coronary heart disease patients. Brain, Behavior and Immunity 2009; 23: 1140-1147




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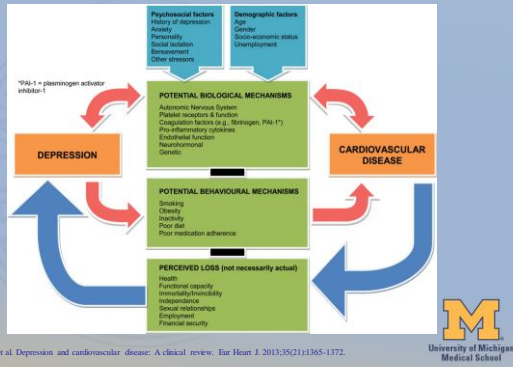
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## Biopsychosocial model




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## Diagnosis of depression and anxiety in cardiac patients

Several self report screening tools

- Beck's depression inventory (BDI)
- Patient health questionnaire-2 and 9 (PHQ-2 and PHQ-9)
- Hospital anxiety depression scale (HADS)
- Cardiac depression scale (CDS)

All of them have variable sensitivity and specificity in diagnosing major depressive disorder: does not substitute clinical diagnosis




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## Who should be screened and when?

All patients should be screened after an acute cardiac event/chronic cardiac problem (for example: CHF)

- Screening within *1 month* of acute cardiac event
- Screening *annually* for maintenance
- Screening of *high risk population* (refusing treatment, weight loss, suicidal, crying spells, changes in mood, preexisting psychiatric disorder) immediately after a cardiac event
- Re-screen in *2 months* of acute event when negative in first screening




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## Screening cardiac patients for depression and anxiety

American Heart Association recommends:

### Patient Health Questionnaire-2

- depressed mood in past 2 weeks
- anhedonia in past 2 weeks



### Patient Health Questionnaire-9

-Nine Diagnostic and Statistical Manual IV criteria

-Used for *screening* of depressive sx and measure *severity* of sx




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## Patient health Questionnaire 2: scale

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.

Two item on Likert type scale of 0-3

\*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.




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## Patient Health Questionnaire 2: psychometric properties

PHQ-2 Score	Sensitivity	Specificity	Positive Predictive Value
1	97.2	59.2	15.4
2	92.7	73.7	21.1
3	82.9	90.0	38.4
4	73.2	93.3	45.5
5	53.7	96.8	56.4

Kroenke et al. The Patient Health Questionnaire-2: validity of a two item depression screener. Medical Care 2003; (41): 1284-1294




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## PHQ-9

### PHQ - 9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

PHQ-9 total score




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## PHQ-9

- Major depression:  $\geq 5$  items positive for “more than half the days” and 1 of the symptoms is depressed mood /anhedonia
- Other depression:  $< 5$  items positive for “more than half the days”
- Score  $\geq 10$ : higher probability of clinical depression  $\rightarrow$  refer for structured clinical evaluation
- Sensitivity 88%, specificity 88%




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## Patient Health Questionnaire-9

PHQ-9 Score	Depression severity	Proposed Action
1-4	No depression	No need of further testing
5-9	Mild	Watchful waiting, repeat PHQ-9 in a month
10-14	Moderate	Refer for clinical evaluation: possible pharmacotherapy and psychotherapy
15-19	Moderate to severe	Immediate treatment: medication and psychotherapy
20-27	Severe	Expedited referral to psychiatrist, medication and psychotherapy




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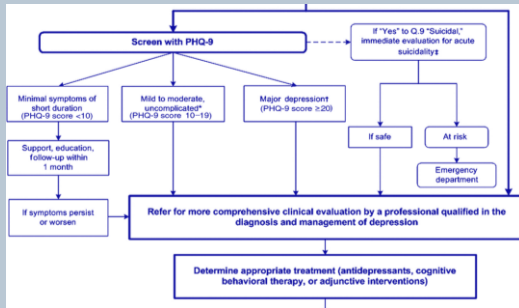
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## American Heart Association recommendations



Lichman JH et al. Circulation. 2008;118:1768-1775

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## Guidelines for screening anxiety disorder in CHD

No specific guidelines from AHA

Might be due to the high prevalence of anxiety symptoms in angina and myocardial infarction.

- A study showed high false positive scores on anxiety rating scales: higher scores need further psychiatric evaluation → reduces cost effectiveness of routine screening<sup>1</sup>

<sup>1</sup> Banevicius et al. Screening for anxiety disorders in patients with coronary artery disease. Health Quality Life Outcomes 2013; 11:37




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## Diagnostic dilemmas in medically ill

- Overlap between psychological reactions to life-threatening illness (e.g. panic attack symptoms resembling angina/ pulmonary embolism)
- Assumption that depressive state is “normal” in medically ill
- Vegetative symptoms of depression-anxiety (low appetite, poor sleep, fatigue, weight loss, racing heart etc.) are **less reliable** in diagnosing depression and anxiety in medically ill




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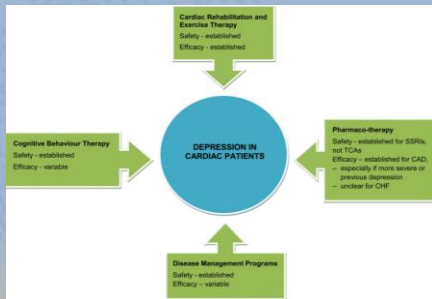
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## Depression and anxiety in cardiovascular disease: Treatment



Hane et al. Depression in cardiovascular disease: A clinical review. Eur Heart J. 2013;35(21):1365-1372




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## Therapeutic alliance

- Pivotal in establishing a plan for wholesome treatment including secondary prevention
- *Limit interference of personal experience*, as that might push away the patient or normalize poor behaviors leading to poor prognosis
- *Empathy*, not indulgence, not overstatement
- Important during cardiac rehabilitation phase: known to reduce mortality, improve functional capacity, reduction of angina symptoms : Behavioral treatment model




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## Depression-anxiety in CHD: Medications

- Selective serotonin receptor inhibitors (SSRI): most studied
- Serotonin norepinephrine reuptake inhibitors (SNRI)
- Others

### Things to check:

- Drug interactions
- Effects of medications on heart rate and conduction
- Monitoring protocol




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## Assessment of patient's interpretation of medications

- Patient might have specific interpretation of medication effect
- Health literacy might vary
- Patient might be less receptive due to stressful medical conditions
- Assess their need of control
- Assure: "this pill will make you feel better" might not be good enough
- Repetitive explanation



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## SSRI/SNRI

- First line medication: low side effect profile, less drug interactions, well tolerated
- Recommended to have a full psychiatric evaluation before starting antidepressant meds in CHD
- Sertraline, citalopram and fluoxetine are widely studied
- Sertraline is most researched (SADHART study, published in 2002)



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## SSRI/SNRI: Things to monitor

- Most SSRI/SNRIs interact with antiplatelet medications and Coumadin (blood thinners): may increase risk of bleeding (gastrointestinal, post surgery): proton pump inhibitors, close eye on bleeding symptoms are recommended
- QTc : few cases reported bradycardia and syncope: regular QTc monitoring, caution in atrial fibrillation, syncope are needed
- In SDAHART study: no significant effect on QTc prolongation beyond 450 msec, no adverse cardiac side effects with sertraline



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## Risk factors and implications: long QT

Risk factors for long QT	Implications of long QT
<ul style="list-style-type: none"> <li>• Female, age</li> <li>• Congenital LQTS</li> <li>• Electrolyte imbalance (low sodium, potassium, magnesium)</li> <li>• Heart disease (MI, LVH, MVP, bradycardia)</li> <li>• Malnutrition</li> <li>• Anorexia nervosa</li> <li>• Other medical conditions resulting in electrolyte imbalance: renal, hepatic dysfunction, diabetes)</li> </ul>	<ul style="list-style-type: none"> <li>• Can cause TdP, but long QT is not the only cause of TdP</li> <li>• Height of pathologic U wave is a better predictor of drug induced TdP than only QTc</li> </ul>

Beach et al., QTc Prolongation, Torsades de Pointes, and Psychotropic Medications. Psychosomatics 2013; 54:1-13




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## Citalopram and QTc

- In 2011: FDA recommended a maximum daily dose of 40 mg daily (20 mg daily in hepatic impairment and > 60 year old patients) and contraindicated its use in long QT
- In 2012: FDA revised the “contraindication” statement in long QT and said it is “not recommended”

### Other SSRI and QTc

- Despite structural similar the FDA recommendation dose not extend to escitalopram
- Active metabolite didesmethyl citalopram is associated with ↑QTc
- No specific recommendation/ warning for other SSRI




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## Recommendations for QTc monitoring

- EKG monitoring for 24 hours after citalopram overdose, longer with >600 mg total dose
- Substitute other antidepressants:
  - Venlafaxine: >440 ms in 18%<sup>1</sup>, > 500ms in 1%
  - Mirtazapine: in overdose: >440 in 16%<sup>1</sup>, >500 in none
  - Duloxetine : no association
  - Bupropion: no association
- Limit use of antipsychotic meds (Thioridazine> ziprasidone> Haloperidol intravenous> haloperidol oral> olanzapine/risperidone/quetiapine)
- FDA recommends cardiac monitoring of ALL patients on haloperidol intravenous.

Waring et al. Evaluation of a QTc monitoring for risk management after antidepressant overdose. Br J Clin Pharmacol 2010; 70: 881-885




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## QTc prolongation risk stratification

	Association with QTc Prolongation	Association with Torsades de Pointes
<b>High risk</b>		
Thioridazine	+++	+++
Haloperidol (IV)	+++	+++
Ziprasidone	+++	+
<b>Moderate risk</b>		
Fluphenazine	++	-
Haloperidol (PO/IM)	++	++
Iloperidone	++	-
Paliperidone	++	-
Risperidone	+	+
<b>Low risk</b>		
Asenapine	+	-
Lurasidone	+	-
Quetiapine	+	+
Minimal risk		
Aripiprazole	-	-

Beach et al. QTc Prolongation, Torsades de Pointes, and Psychotropic Medication. Psychosomatics 2013; 54:1-13




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## Other antidepressants

Venlafaxine	↑ blood pressure with >300 mg dose, tachycardia, caution in CHF, caution during discontinuing
Mirtazapine	potential for increased appetite and serum cholesterol
Bupropion	Monitor blood pressure in hypertensive patients
Stimulants (methylphenidate)*	Not recommended for post myocardial infarction, congestive heart failure, uncontrolled hypertension and tachycardia
Tricyclic antidepressants	Usually avoided, <b>prolongs QTc</b> , increased risk of arrhythmia, orthostatic hypotension
Trazodone	Increased risk of cardiac arrhythmia and orthostatic hypotension in higher doses




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## Drug interactions

Fluoxetine (potent 2D6 inhibitor)	Carvedilol, metoprolol, digoxin, nifedipine
Paroxetine	Flecainide
Desipramine	Enalapril, captopril, ramipril
Stimulants	Clonidine, doxazosin, prazosin, coumadin
Bupirone	Diltiazem




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## Stimulants in cardiac disease

### Indications:

- Acute need to improve energy (not eating, not participating in physical therapy/refusing treatment)
- Cognitive impairment interfering with capacity to participate in medical decisions
- Significant weight loss due to depression

### Cautions:

- History of substance abuse
- Recent myocardial infarction
- Uncontrolled hypertension, CHF, arrhythmia
- Delirium, psychosis




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## Anti-anxiety medications

Benzodiazepines are generally safe unless :

- Delirium
- History of substance use (consider a short course when absolutely needed, with a plan to taper judiciously)
- Older patients (risk of fall and cognitive impairment)
- Comorbid respiratory failure
- Dementia (risk of disinhibition)




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## Psychotherapy in CHD

Cognitive behavioral therapy (CBT): most studied

- Effective in reducing depressive symptoms
- Not shown to influence mortality and hospitalization
- Limited evidence in management of anxiety in CHD




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## Other forms of psychotherapy studied in CHD population

- Mindfulness meditation
- Guided heart rate variability-biofeedback
- The above two methods are shown to reduce stress, anxiety and depressive symptoms (similar to exercise programs)




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## Motivational interview: nurse led protocol to improve self-care in heart failure

- Single home visit after discharge from hospital
- 3-4 telephone calls by nurse
- 90 day follow up period
- Improved self-care maintenance
- MI alone is most likely not enough to improve quality of life

Matteson et al. Motivational interviewing to improve self-care for patients with chronic heart failure: MIF-RF randomized controlled trial. Patient Educ Couns. 2016; 99(2):256-64.




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## Cardiac rehabilitation and disease management programs

### Cardiac rehabilitation program:

- Reassurance, education, exercise
- Significantly reduce cardiovascular events and depression and anxiety<sup>1</sup>
- Effect could also be due to the exercise and or psychological support and milieu environment

Lewis et al. Effects of self-help post-myocardial-infarction rehabilitation on psychological adjustment and use of health services. Lancet 1992; 339: 1036-1040




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Thank you




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Post session test

1. A 67 year old white male is admitted to ICU after a myocardial infarction with symptoms of severe depression and the psychiatry started him on sertraline. He is also on heparin as a bridge to warfarin for a past history of DVT. What is the lab test to monitor his safety?

- a) Bleeding time and clotting time
- b) Sodium and potassium level
- c) Upper GI endoscopy
- d) No additional test needed




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Post session test

2. A 60 year old male with aortic artery dissection is currently in cardiac rehabilitation program after a long ICU and medical floor stay. He is reluctant in participating in physical exercise and refuses his blood pressure medication occasionally. He is unwilling to stay further in hospital and wants to go home to take care of his tax consultancy business. No past psychiatric history. How will you proceed to screen him for a possible depression?

- a) Chat with him
- b) Chat with the physical therapist
- c) PHQ-9
- d) PHQ-2




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### Post session test

3. A 65 year old female with history of sick sinus syndrome is currently admitted to ICU after an acute coronary syndrome event. She is depressed per psychiatric evaluation. As the psychiatry residents are discussing medication safety, they include you in that discussion. Which medication is relatively safer in this patient?

- a) Nortriptyline
- b) Sertraline
- c) Citalopram
- d) Desipramine



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### Post session test

4. A 55 year old male with previous history of depression and anxiety is currently following up with cardiology clinic after an acute coronary syndrome. He has been on venlafaxine 375 mg daily for 6 months but his blood pressure is uncontrolled even with adjustment of his medications. Consulting psychiatrist has agreed on changing venlafaxine to sertraline. Which symptom would you watch for during the switch period?

- a) Blood pressure and heart rate
- b) Agitation
- c) Stomach pain
- d) Pedal edema



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