## Web audio at CurrentPsychiatry.com

Dr. Gagliardi discusses why comorbid CAD and mental illness means poorer outcomes

# Your significant role in modifying risk factors for coronary artery disease and managing problems subsequently



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The problem is enormous: Heart disease is the leading cause of death in the United States, and coronary artery disease (CAD) is the most common form of heart disease—responsible for 385,000 deaths in the United States in 2009 (http://www.cdc.gov/heartdisease/facts. htm). Patients with psychiatric illness have higher rates of morbidity and mortality from CAD than the general population, and warrant consideration as a special population. You should be familiar with routine cardiac medications; your patients' medical problems; potential cardiac-related interactions among their psychotropic medications; and interactions among illnesses in their mental health and medical health domains (*Box*).

### CASE

## Type 2 diabetes mellitus plus a long history of heavy smoking

Ms. S, age 57, is an African American woman with chronic paranoid schizophrenia who has been seeing a psychiatrist for the past 10 years. Ms. S's psychiatric symptoms have been well controlled on risperidone, 3 mg/d.

Ms. S has a family history of diabetes, hypertension, and early CAD (a brother died of a myocardial infarction [MI] in his late 40s). She continues to smoke 2 packs of unfiltered cigarettes daily, as she has done for the past 40 years.

The psychiatrist has been following American Diabetes Association/American Psychiatric Association guidelines for

#### Disclosure

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monitoring; he has noticed that Ms. S's body mass index (BMI) has increased from 27 to 31 kg/m<sup>2</sup> over the past year. She has developed type 2 diabetes mellitus (T2DM).

At today's visit, Ms. S arrives a few minutes late and appears flustered and out of breath. She explains that she had to climb a flight of stairs to get to office because the elevator is broken.

During the visit, the psychiatrist notes that Ms. S occasionally winces and massages her left shoulder.

### Questions to ponder

- What else could the psychiatrist do to modify Ms. S's cardiac risk factors?
- What is Ms. S's 10-year risk of an acute coronary event?
- · What should her physician do now?

# Overview: Cardiac risk in patients with mental illness

Modifiable risks for CAD include hypertension, hypercholesterolemia, T2DM, obesity (all of which, taken together, constitute the metabolic syndrome), smoking, and a sedentary lifestyle. Some risk factors, including sex, age, and family history, are not modifiable. Whether or not this modification leads to better outcomes, psychiatric comorbidity is associated with higher morbidity and mortality from CAD.

Whether a common underlying pathological process manifesting in both CAD and mental illness exists, or whether the association is causal, are not well understood. Symptoms characteristic of depression (apathy, amotivation) and schizophrenia (disorganization, paranoia) could lead to poor self-care or impaired adherence to programs designed to lower CAD risk factors.<sup>1,2</sup>

People with mental illness smoke at a higher rate than those who do not have mental illness.<sup>3</sup> This finding is of particular relevance because smoking contributes to worse outcomes with respect to CAD, even when medications are prescribed to address metabolic risks.<sup>4</sup>

Lower socioeconomic status is associated with poorer prognosis from CAD<sup>5</sup> and is a risk factor for depression.<sup>6</sup>

### Box

# Key points: Managing coronary artery disease (CAD)

- Patients with CAD are at increased risk of clinical and subthreshold depression
- Depression and anxiety are associated with worse outcomes in CAD
- Patients with severe and persistent mental illness might not participate fully in primary care or might not engage in preventive health care
- Patients with severe and persistent mental illness could engage in behaviors that increase CAD risk, such as smoking or unhealthy eating
- Medications prescribed to treat psychiatric disorders, including antidepressants, antipsychotics, and stimulant medications, can pose direct and indirect risk to cardiovascular health
- Patients' CAD risk may be calculated using the Framingham Risk calculator or, more recently, the Pooled Cohort Equations, which can provide a quick estimate of overall risk in the next 10 years
- CAD risks may be reduced with primary or secondary prevention strategies

Depression is a strong independent predictor of worse survival in acute coronary syndromes.<sup>5</sup> Some experts consider depression to be a stronger risk factor for MI than traditional medical risk factors such as obesity, hypertension, and secondhand smoke.<sup>7</sup>

Interventions used to treat certain mental illnesses can exacerbate, or predispose to, metabolic syndrome (which, in turn, increases the risk of CAD). Although some studies have demonstrated metabolic derangements in medication-naïve patients who have a new diagnosis of schizophrenia,<sup>8</sup> there is a clearly established association between second-generation antipsychotic use and obesity, hypertension, hyperlipidemia, and T2DM. This association prompted development in 2004 of consensus recommendations for cardiovascular monitoring of patients who are taking an atypical antipsychotic.<sup>9</sup>

Some studies suggest that the stress of mental illness contributes to the pathogen-



## **Clinical Point**

Modifiable risks for CAD include hypertension, elevated cholesterol level, T2DM, obesity, smoking, and a sedentary lifestyle



continued on page 62



# **Clinical Point**

There is limited evidence that treatment of depression and anxiety can improve CAD outcomes continued from page 57

## Figure

# Framingham risk calculator for myocardial infarction

Attack	year rusk of Having a Hean
The risk assessment tool below uses information fr to predict a person's chance of having a heart attact designed for adults aged 20 and older who do not I 0 find your risk score, enter your information in the	om the Framingham Heart St ck in the next 10 years. This to have heart disease or diabete calculator below.
Age:	years
Gender:	○ Female ○ Male
Total Cholesterol:	mg/dL
HDL Cholesterol:	mg/dL
Smoker.	O No O Yes
Systolic Blood Pressure:	mm/Hg
Are you currently on any medication to treat high blood pressure.	○ No ○ Yes
Calculate Your 10-Year	Risk

esis of CAD.<sup>8</sup> Hypothesized mechanisms include:

- sympathetic activation
- vagal deactivation
- platelet activation
- hypothalamic-pituitary-adrenocortical pathways
- anticholinergic mechanisms
- inflammatory mediators, including cytokines.

Mental stress itself has the capacity to induce coronary ischemia.<sup>10</sup> The mental stress of psychiatric illness could have an important pathophysiologic role in CAD. It can be tempting to disregard chest pain in a patient who is known to have panic disorder, but that patient might in fact be experiencing stress-induced myocardial ischemia.<sup>11</sup>

As many as 30% to 40% of patients with CAD suffer from clinically significant symptoms of depression; as many as 20% of patients with CAD meet criteria for major depressive disorder, compared with 5% to 10% of people who do not have CAD.<sup>2</sup> Depression post-MI has been associated with a higher rate of sudden cardiac death and worse outcomes.<sup>12</sup>

Anxiety also can portend worse outcomes from CAD,<sup>13</sup> including higher all-cause mortality.<sup>14</sup> There is some hope, but limited evidence, that treating depression and anxiety, whether with antidepressant medication or behavioral therapy, can improve CAD outcomes.<sup>10,15</sup>

# Making a diagnosis of CAD

CAD can present in a variety of ways, ranging from unrecognized or so-called silent CAD (there is an association between T2DM and unrecognized CAD and between hypertension and unrecognized CAD) to stable angina, unstable angina, acute coronary syndrome, MI, and sudden cardiac death. A variety of abnormalities on resting and exercise electrocardiogram (ECG), including ST segment depression, ST elevation, Q

waves, and other morphological changes are indicative of CAD.

Other modalities, including coronary calcification score on computed tomography and coronary angiography can confirm the presence of CAD. Some clinicians recommend periodic ECG treadmill testing in patients who have:

- a total cholesterol level is >240 mg/dL
- systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or both
- a family history of MI or sudden cardiac death in young (age <60) firstdegree relatives
- a history of smoking
- diabetes.

# **Preventive guidelines**

**Risk stratification.** A low (<10%), moderate (10% to 20%), or high (>20%) 10-year risk of CAD can be ascertained using a risk calculator, such as one that is available through the Framingham Heart Study (*Figure*) and the National Heart, Lung, and Blood Institute (http://cvdrisk.nhlbi. nih.gov). Because patients with risk factors for CAD should be offered interventions including smoking cessation therapy, diet and exercise, aspirin, lipid-lowering thercontinued on page 67

#### continued from page 62

apy, and blood pressure modification strategies—whether or not they have evidence of CAD, the United States Preventive Services Task Force does not recommend for or against diagnostic screening in patients at moderate or elevated risk of CAD.<sup>16</sup>

There are guidelines in the literature recommending specific screening strategies for patients with mental illness, although the vetting and update process has been ill defined. Among patients with schizophrenia, though, regardless of antipsychotic prescription status, baseline and then regular monitoring of metabolic risk parameters is recommended.<sup>17</sup>

**Primary prevention.** Lifestyle modification and attention to modifiable coronary risk factors are important primary prevention strategies. Dietary modifications, exercise, not smoking, and maintenance of a normal BMI (<25 kg/m<sup>2</sup>) are associated with a lower risk of CAD.<sup>18,19</sup>

Lifestyle modifications can be challenging for patients with persistent mental illness, however: For example, patients with schizophrenia smoke more, eat less healthfully, and participate less in behavioral modification that targets risk factors than patients who do not have schizophrenia.<sup>20,21</sup>

According to 2012 evidence-based practice guidelines established by a collaboration that included the American College of Physicians and several cardiology and thoracic medicine societies, persons age >50 who do not have symptomatic CAD should take low-dose (75 to 100 mg/d) aspirin; the benefit of low-dose aspirin in persons at moderate or high risk of CAD is even greater. Other medications, including statins and fixed-dose combinations of antihypertensive medications in combination with a statin are not clearly beneficial as primary prevention strategies across the board, although selected high-risk populations might benefit.

Regrettably, the high-risk population of persons with mental illness and whose primary care is suboptimal has not been studied. It stands to reason that these patients would especially benefit from more attentive monitoring and intervention.



## A strategy for primary prevention of coronary artery disease

### Recommended

Diet rich in fruits, vegetables, legumes, nuts, whole grains, and omega-3 fatty acids and devoid of trans-unsaturated fatty acids

Exercise (30 to 60 minutes, at least 3 or 4 days a week)

Smoking cessation

### Not recommended

Routine stress testing and coronary calcium scoring in an effort to detect asymptomatic coronary artery disease

Supplemental vitamins  $B_{6}$ ,  $B_{12}$ , C, and E; folic acid; beta carotene

**Collaborative care?** Although many psychiatrists do not practice in such a model, a comprehensive approach to the care of their patients, using a collaborative care strategy that includes attention to the mental health diagnosis along with medical health, can result in improved health in both domains.<sup>22</sup> However, enlisting patients with paranoia or an inherent distrust of medications and health care providers to adhere to either a medication regimen or lifestyle modification can be challenging.

Common-sense strategies, such as creating a multidisciplinary team with the psychiatrist coordinating care and optimizing antipsychotic treatment, might provide benefit.<sup>1</sup> Data demonstrate that patients with severe mental illness who experience acute coronary events undergo revascularization at a lower rate than their mentally heathy counterparts, despite the fact that patients with severe mental illness die at a higher rate from their CAD than patients who do not have mental illness. An important role for the psychiatrist, even in the absence of a collaborative care program, is to be an advocate for appropriate guideline-based care.<sup>23</sup>

**Secondary prevention.** Once a patient develops CAD, ongoing risk factor modification is important. Adherence to a therapeutic regimen that variously combines



# **Clinical Point**

Exercise, dietary modification, not smoking, and maintenance of a BMI <25 kg/m<sup>2</sup> are associated with a lower risk of CAD



# **Clinical Point**

Enlisting patients who are paranoid or distrust health care providers to adhere to a drug regimen or lifestyle modification is challenging

# Table 2

# A strategy for secondary prevention of coronary artery disease

### Recommended

Aspirin (substitute clopidogrel if aspirin is not tolerated); oral anticoagulation is recommended instead if a left ventricular thrombus is present

Aspirin plus clopidogrel after stent placement: 4 weeks (bare metal stent) or 12 months (drugeluting stent)

Angiotensin-converting enzyme (ACE) inhibitor (substitute an angiotensin receptor-blocker if an ACE inhibitor cannot be tolerated)

Beta blocker

Blood pressure target of <130/80 mm Hg

Statin agent to lower lipid levels

Not recommended

Adding antiplatelet therapy to oral anticoagulation

Calcium-channel blocker, other than amlodipine and felodipine

Hormone replacement therapy (discontinue if primary prevention of coronary artery disease was the main indication for its use)

a platelet inhibitor, beta blocker, statin, and angiotensin-converting enzyme (ACE) inhibitor is associated with improved outcomes in patients with CAD.<sup>24</sup> Specific antiplatelet recommendations and a recommendation for single vs combination antiplatelet therapy depends on chronicity and type of revascularization in a setting of CAD.<sup>25</sup>

# Summary of guideline-based recommendations

Treatment guidelines published in the National Guidelines Clearinghouse address depression, CAD screening, and specific cardiac therapies, including ACE inhibitors, angiotensin-receptor blockers, oral anticoagulants, platelet inhibitors, beta blockers, and lifestyle modification.

**Primary prevention.** Recommendations for treatment to prevent CAD are listed in *Table 1 (page 67)*.

**Secondary prevention.** Recommendations for treatment after a diagnosis of CAD are listed in *Table 2*.

# Special considerations for psychiatric providers

You should be comfortable with patients' use of antihypertensive therapies and familiar with the potential these agents have to interact with psychotropics; in addition, you can take a more active role in prescribing, and monitoring patients' responses to, these medications. Provide appropriate monitoring of ACE inhibitors, statins, and beta blockers; also, provide appropriate monitoring of psychotropics in patients who take recommended cardioprotective medications.

In situations that prompt referral (such as recent MI, new symptoms of heart failure, any history of syncope or new identification of T2DM), ideally you should collaborate with the patient's primary care provider to help enhance adherence to recommended treatment strategies. You also should employ motivational interviewing techniques and offer strategies by which patients can engage in meaningful lifestyle modification.

There are official recommendations for depression screening strategies<sup>26</sup> and psychosocial risk screening for patients in whom CAD has been identified.<sup>27</sup> Official screening strategies for CAD in patients with psychiatric illness have not, however, been spelled out.

Primary CAD prevention with medication is not routinely recommended for the general population, but the increased risk of CAD associated with psychiatric diagnoses (particularly schizophrenia, as well as the medications used to treat it) might warrant consideration of aggressive primary prevention strategies.<sup>28</sup> For example, some experts recommend starting metformin to reduce the risk of T2DM in patients who have been started on olanzapine or clozapine, regardless of the baseline fasting blood glucose level.<sup>29</sup>

You should be fully informed and aware of patients' underlying medical conditions and the medications that are recom-



## **Clinical Point**

Second-generation antipsychotics are associated with significant weight gain and development of metabolic syndrome



# Baseline and ongoing monitoring of patients for whom a second-generation antipsychotic has been prescribed

	Parameter					
Timing	Body mass index (height and weight)	Abdominal circumference	Blood pressure	Fasting glucose	Fasting lipid profile	
Baseline	Х	Х	Х	Х	Х	
4 weeks	х					
8 weeks	х					
12 weeks	х		Х	Х	Х	
Quarterly	х					
Annually		Х	Х	Х		
Every 5 years					Х	

Before starting a second-generation antipsychotic, confirm any personal and family history of obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease. If the patient is overweight or obese, consider referral for nutrition and physical activity counseling. In addition, educate patients and family members regarding the signs and symptoms of type 2 diabetes mellitus

Source: Adapted from reference 9

mended to treat their conditions. Ideally, an integrated care strategy or, at the least, clear communication between you and the patient's primary care providers should be in place to avoid foreseeable problems.

**Stimulants.** Systematic reviews suggest an association between prescription stimulants and at least the 2 cardiovascular risk factors of elevated heart rate and blood pressure. Stimulants are *not* recommended, therefore, for routine use in patients who have known hypertension or CAD.<sup>30</sup>

**Second-generation antipsychotics** are associated with significant weight gain and development of metabolic syndrome.

**Selective serotonin reuptake inhibitors** are associated with an increased risk of gastrointestinal bleeding risk related to platelet inhibition and gastric effects. Risk increases with additional platelet inhibitors, such as aspirin or clopidogrel.<sup>31</sup>

Lithium is excreted solely by the kidney. Guidelines recommend ACE inhibitors and angiotensin receptor-blockers for patients with CAD or T2DM, and many patients with symptomatic congestive heart failure are prescribed a diuretic; all of these classes of medications impair excretion of lithium. In a nested casecontrol study, 3% of observed cases of lithium toxicity were attributable to a newly initiated ACE inhibitor or angiotensin receptor-blocker.<sup>32</sup> It is essential that you, and your patients taking lithium, be aware of the need to monitor the drug level frequently and be vigilant for symptoms of mild toxicity.

**Beta blockers.** No prospectively collected data support a association between beta blockers and depression.<sup>33</sup> Patients with CAD should be given a trial of a beta blocker to achieve optimal medical management; because they are at increased risk of depression in the first place, all patients with CAD should undergo monitoring for depressive symptoms.

**Clopidogrel** is activated through the cytochrome P450 2C19 isoenzyme; medications such as fluoxetine and fluvoxamine that inhibit the function of CYP2C19 can impair the effectiveness of clopidogrel.<sup>31</sup>

**Other considerations.** Patients taking a second-generation antipsychotic should

have baseline and periodic (monthly for the first quarter, then quarterly) assessments of BMI and, after monitoring at 3 months after baseline, annual monitoring of blood pressure, the fasting glucose level, and abdominal waist circumference. Lipid levels should be monitored every 5 years<sup>9</sup> (*Table 3*).

Baseline and periodic monitoring of hepatic enzymes is recommended for patients taking a statin. You, and the patient, should be alert to the possible development of muscle weakness or pain; establish a low threshold for screening for an elevated creatine kinase level, which signals rhabdomyolysis.

## **Case concluded**

Ms. S's psychiatrist measures her blood pressure and finds that it is 147/92 mm Hg. He uses the Pooled Cohort Equations to determine that her lifetime risk of cardiovascular event is 50% (compared with a 8% lifetime risk among a cohort in whom risk factors are optimized) and that her 10-year risk is 41% (compared with a 2.2% risk among optimized controls).

At this point, the psychiatrist starts metformin to prevent T2DM. He also starts Ms. S on a statin to prevent CAD in a setting of diagnosed T2DM.

Ms. S's exertional dyspnea and shoulder discomfort could be associated with angina, and the physician wisely refers her for urgent evaluation. Because he is aware of the literature demonstrating decreased revascularization among patients with mental illness, he urges her other health care providers to provide her with guideline-based strategies to treat her cardiovascular disease.

## **Related Resources**

- Elderon L, Whooley MA. Depression and cardiovascular disease. Prog Cardiovasc Dis. 2013;55(6):511-523.
- Interactive cardiovascular risk calculator developed from the Framingham Heart Study. https://www.framingham heartstudy.org/risk-functions/cardiovascular-disease/ 10-year-risk.php.
- Pooled Cohort Equations calculator. To determine estimated cardiovascular risk in comparison with peers with optimized risk factors. http://clincalc.com/cardiology/ascvd/ pooledcohort.aspx.
- To learn more about traditional cardiovascular risk factors from the Framingham Heart Study. http://www.framinghamheart study.org/risk-functions/.

### **Drug Brand Names**

Amlodipine • NorvascFluvoxamine • LuvoxClozapine • ClozarilLithium • Eskalith, LithobidClopidogrel • PlavixMetformin • GlucophageFelodipine • PlendilOlanzapine • ZyprexaFluoxetine • ProzacRisperidone • Risperdal

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## **Clinical Point**

Baseline and periodic monitoring of hepatic enzymes is recommended for patients who are taking a statin

# **Bottom Line**

Patients with psychiatric illness have higher rates of morbidity and mortality from coronary artery disease (CAD) than the general population. Symptoms characteristic of depression and schizophrenia could lead to poor self-care or impaired adherence to programs designed to lower CAD risk factors. Institute strategies for primary and secondary prevention of CAD among your patients, based on published guidelines, and be aware of, and alert for, adverse cardiac effects and an increase in risk factors for CAD from the use of psychotropics.



## **Clinical Point**

Stimulants are not recommended for routine use in patients who have hypertension or coronary artery disease College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60(24):e44-e164.

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# COMING SOON IN Med/Psych Update

# What can be done when chronic obstructive pulmonary disease (COPD) is comorbid with mental illness?

The prevalence of tobacco use and COPD appear especially high in people who have mental illness, contributing to high morbidity and mortality. Authors Abdulkader Alam, MD, and colleagues urge psychiatrists to play an integral role in

promoting tobacco cessation, referring patients for diagnosis, and encouraging adherence with treatment.

