Psychosocial factors in acute coronary syndrome

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INTRODUCTION

Acute coronary syndrome includes suspected or confirmed cases of acute myocardial ischemia or infarction. The three types of acute coronary syndrome are ST-elevation myocardial infarction (MI), non-ST elevation MI, and unstable angina. (See "Acute coronary syndrome: Terminology and classification".)

Psychosocial factors such as stress and depression may be risk factors for acute coronary syndrome, although the mechanisms underlying the association remain uncertain. Emotional stress may also trigger takotsubo cardiomyopathy and spontaneous coronary artery dissection. (See "Clinical manifestations and diagnosis of stress (takotsubo) cardiomyopathy" and "Spontaneous coronary artery dissection".)

This topic discusses psychosocial factors that might precipitate acute coronary syndrome, mechanisms by which emotional stress may perhaps precipitate acute coronary syndrome, and depression following acute coronary syndrome.

CIRCADIAN VARIATION

The circadian variation in frequency of myocardial infarction (MI), sudden cardiac death, and myocardial ischemia is characterized by a morning peak. A meta-analysis of 66,635 patients with an acute MI and 19,390 patients with sudden death reported an excess of MIs (relative risk

1.38) and sudden deaths (relative risk 1.29) between the hours of 6:00 AM and noon compared with the rest of the day (figure 1A-B) [1].

The circadian variation in event frequency suggests that cardiac events may be triggered by external activities, particularly those activating the sympathetic nervous system [2]. Support for this comes from one study of 1225 patients that reported an absence of a circadian variation in diabetics, particularly those with evidence of cardiac autonomic neuropathy who have absent heart rate variability [3] and those taking beta blockers or aspirin at the time of admission for an MI [4]. (See "Diabetic autonomic neuropathy".)

Circadian variability in platelet aggregability and fibrinolytic capacity may be other factors contributing to the morning increase in MI. Among patients with stable coronary heart disease, plasminogen activator inhibitor-1 activity peaks in the early morning while tissue plasminogen activator activity is at its nadir; treatment with a beta blocker ameliorated this relatively prothrombotic state [5].

PRECIPITATING FACTORS

Psychosocial factors are associated with onset of acute coronary syndrome. One study found that among 849 patients with acute myocardial infarction (MI), 48 percent described one or more events that possibly triggered the MI, the most common of which was emotional upset (14 percent) [6]. Other studies have identified possible psychosocial triggers in up to 27 percent of patients [7-9]. The subsections below describe specific factors that may trigger acute coronary syndrome.

Life events and other crises — Multiple studies have established that adverse life events are associated with acute coronary syndrome [10]. As an example, a national registry study identified a group of patients with psychiatric disorders induced by an acute stressful life event (n >130,000) and a group of their full siblings without stress related disorders (n >170,000) [11]. The stress-related disorders included acute stress reaction, posttraumatic stress disorder, or adjustment disorder, and study subjects were followed for up to 27 years. After controlling for potential confounding factors (age, comorbid general medical disorders, and comorbid psychiatric disorders), the analyses found that among subjects followed for at least one year, the risk of MI was modestly greater in patients with stress-related disorders than the unaffected siblings (relative risk 1.3, 95% CI 1.2-1.4). In subjects followed for at least 10 years, the risk of MI was 60 percent greater in patients with stress-related disorders than the unaffected siblings.

In addition, a retrospective study of psychosocial cardiac risk factors compared patients with a first MI (n >11,000) with age- and sex-matched controls (n >13,000) from 52 countries on six continents [12]. One of the factors was stressful life events, such as marital separation or divorce, loss of job, violence, or death of a close family member. Stressful life events had occurred more frequently during the prior year in patients than controls (16 versus 13 percent; odds ratio 1.5, 95% CI 1.3-1.6). Additional information about the risk of acute MI soon after bereavement is discussed separately. (See "Bereavement and grief in adults: Clinical features", section on 'Morbidity'.)

Several retrospective studies indicate that disasters are associated with an increase in cardiovascular events [13]:

- Earthquakes – Multiple studies indicate that earthquakes are associated with an increased risk of MI [14-16]. As an example, the number of deaths related to coronary artery disease that occurred on the day of the 1994 Los Angeles earthquake was greater than the average number during the prior seven days (relative risk 3, 95% CI 2-4) [17].

- Hurricanes – A tertiary hospital in New Orleans examined all admissions that occurred for three years after a 2005 hurricane (n >21,000) and all admissions (n >21,000) for two years prior to the hurricane [18]. The percentage of admissions for MI was greater post-hurricane than pre-hurricane (2.0 versus 0.7 percent).

- Missile attacks – In the first week of missile attacks on Israel during the 1991 Iraq War, 20 civilians in the area served by one hospital suffered an acute MI, compared with only eight during a control period [19].

- Terror attacks – There was a statistically significant 49 percent increase in patients admitted with MI through 16 emergency departments within a 50-mile radius of the World Trade Center in the 60 days after September 11, 2001, compared with the 60 days beforehand (118 MIs after versus 79 before) [20].

Although it is tempting to attribute the increase in cardiovascular events following these traumas to mental stress, the role of other factors such as unaccustomed physical activity, altered sleep patterns, and diet needs to be considered [21].

Chronic stress — In addition to acute events, chronic stress is associated with acute coronary syndromes:

- In a prospective study of men and women with a mean age of 45 years (n >13,000), a questionnaire assessed levels of chronic psychosocial stress, which were high in 15

percent, moderate in 6 percent, and low in 80 percent [22]. At a mean follow-up of 21 years, 20 percent had suffered a first cardiovascular event (fatal or nonfatal MI or stroke, angina, or acute coronary syndrome). The risk of a first cardiovascular event was higher for those with moderate or high stress, though the magnitude of the increase was small (adjusted risk ratio 1.14).

- A prospective study enrolled 832 patients who returned to work after a first MI and followed them for at least two years [23]. Patients were assessed for high job strain, which was a combination of high psychological demands and little latitude to make decisions, and for recurrent coronary heart disease events (fatal coronary heart disease, nonfatal MI, or unstable angina). After adjusting for potential confounding factors (eg, sociodemographic factors, coronary heart disease risk factors, and social support), the analyses found that chronic high job strain was robustly associated with an increased rate of recurrent coronary heart disease events (hazard ratio 2.4, 95% CI 1.4-4.1).

- In the worldwide INTERHEART study, sources of chronic stress were divided into work stress, home stress, and financial stress [12]. Patients with a first MI reported more stress in each of these categories than controls. The proportion of MI patients experiencing moderate or severe work or home stress varied widely among regions, from 44 percent in North America to 16 percent in China and Hong Kong.

Anxiety — Anxiety as a cardiovascular risk factor has not been studied as extensively as other psychosocial factors. Nevertheless, multiple studies indicate that anxiety is a risk factor for cardiovascular disease and cardiac mortality:

- In a study of 735 men (mean age 60 years) without cardiovascular disease or diabetes who were followed for a mean of 12 years, the presence of anxiety independently and significantly predicted subsequent MIs [24].

- During a two-year follow-up of nearly 34,000 male health professionals in the United States who were aged 42 to 77 years and initially free of diagnosed disease, the age-adjusted relative risk of fatal cardiovascular disease was threefold greater for those having the highest levels of phobic anxiety compared with those with the lowest levels [25].

- A prospective study enrolled more than 5000 healthy women aged 46 to 54 years, assessed them at baseline for clinically significant anxiety, and followed them for up to 10 years [26]. After adjusting for potential confounding factors (eg, depression, diabetes, and smoking), the analyses showed that anxiety was associated with increased cardiac mortality (hazard ratio 2.8, 95% CI 1.2-6.6), as well as all-cause mortality (hazard ratio 1.8, 95% CI 1.1-2.7).

Depression — Depression is an independent risk factor for cardiovascular disease and cardiac mortality, both in otherwise healthy subjects and in those with known cardiovascular disease [12,27-29]:

- A prospective study included more than 400,000 individuals with no prior history of cardiovascular disease, who were assessed for depression at baseline with a self-report screening instrument, the two-item Patient Health Questionnaire (PHQ-2) (table 1) [30]. The median length of follow-up was eight years, during which time more than 4600 fatal and nonfatal coronary heart disease events occurred. After adjusting for potential confounding factors (eg, age, smoking, and history of diabetes), the analyses showed that each one-point increase in PHQ-2 scores was modestly associated with an increased risk of coronary heart disease, including symptom levels below the threshold that indicate potential depressive disorders (hazard ratio 1.11, 95% CI 1.08-1.14). The corresponding incidence of cardiac events per 10,000 person-years of follow-up was greater among individuals with a PHQ-2 score of 4 or more, compared with a score of 0 (21 versus 14).

  The same paper included a pooled analysis of participant-level data from 21 prospective studies of individuals with no prior history of cardiovascular disease (n >160,000); the results again showed a clinically small association between depressive symptoms at baseline and subsequent risk of coronary heart disease events (1.07, 95% CI 1.03-1.11) [30].

- A prospective study followed more than 93,000 postmenopausal women aged 50 to 79 years for an average of four years [31]. At baseline, 16 percent were currently depressed and 12 percent had a history of depression. After controlling for potential confounding factors (eg, age, diabetes, and hypertension), the analyses found that cardiovascular mortality was greater in patients with current or previous depression than patients without depression (0.8 versus 0.5 percent). In addition, all-cause mortality was greater in depressed patients (2.9 versus 2.2 percent).

- A systematic review of 28 studies in approximately 80,000 subjects examined whether cardiovascular disease and mortality was greater in depressed patients than nondepressed patients; the mean length of follow-up was 11 years [32]. Results from the meta-analyses showed that the probability of:

  - MI was greater in depressed patients than nondepressed patients (odds ratio 1.6, 95% CI 1.3-1.9).

  - Coronary artery disease was greater in depressed patients (odds ratio 1.5, 95% CI 1.3-1.7).

- Cardiac mortality was greater in depressed patients (odds ratio 1.6, 95% CI 1.4-1.8).

Multiple studies suggest that there is a dose-response relationship, such that more severe depression is associated with a greater risk of cardiovascular disease. In a prospective cohort of subjects ≥65 years of age (n >4400), who were initially free of cardiovascular disease at baseline and followed for up to six years, each five-unit increase in depression rating scale score was associated with an adjusted hazard ratio of 1.15 for developing coronary heart disease and 1.16 for all-cause mortality [33]. Those with the highest depression scores had a 40 and 60 percent increased risk of coronary disease and death compared with those with the lowest scores. A similar graded relationship was noted for the occurrence of MI in an epidemiologic study; the relationship was independent of coronary risk factors [34].

In addition, the risk of cardiovascular disease may be greater in patients diagnosed with depressive disorders than patients with depressive symptoms identified by rating scales. A systematic review of 28 studies in approximately 80,000 subjects found that the probability of cardiovascular disease was greater in patients with a clinical diagnosis of a depressive syndrome than those without a diagnosis (odds ratio 2.5, 95% CI 2.1-3.1) [32]. In addition, the probability of cardiovascular disease was greater in patients with depressive symptoms than those without depressive symptoms (odds ratio 1.4, 95% CI 1.3-1.5). Although depressive disorders and depressive symptoms were each associated with an increased risk of cardiovascular disease, the risk was greater in patients with depressive disorders.

Anger — Anger appears to be associated with deleterious effects on the cardiovascular system [35]. Patients with trait anger have a relatively stable personality, but manifest rage and fury more often, more intensely, and have longer-lasting episodes. The relationship between anger and coronary heart disease was evaluated in a prospective observational study of nearly 13,000 men and women [36]. Compared with normotensive subjects with low trait anger, normotensive subjects with high trait anger were at greater risk for all coronary heart disease events, including acute MI, cardiac mortality, silent MI, or coronary revascularization (hazard ratio 2.2), and for acute MI or cardiac mortality (hazard ratio 2.7). In hypertensive individuals, there was no relationship between trait anger and risk of coronary heart disease.

Episodes of anger may also trigger acute coronary syndrome:

- A prospective study interviewed nearly 300 patients during hospitalization for acute coronary syndrome and assessed whether they were angry in the two hours prior to symptom onset [8]. Onset of acute coronary syndrome was more likely in patients with anger than those with no anger (odds ratio 2.1, 95% CI 1.1-3.9).

- A meta-analysis of four observational studies (n >5000 cases of acute coronary syndrome) found that the risk of acute cardiovascular events was five times greater in the two hours following an outburst of anger, compared with other times [37]. However, heterogeneity across studies was substantial.

Anger in response to stress may be related to premature MI in young men. As an example, one longitudinal study of 1055 young medical students established anger reactions to stress through self-report questionnaires [38]. After a median follow-up of 36 years, those with the highest level of anger, compared with those with lower levels, had an increased risk of premature cardiovascular disease developing before the age of 55 (adjusted relative risk 3.1), coronary heart disease (adjusted relative risk 3.5), and MI (relative risk 6.4).

Seasonal pattern — Several studies have demonstrated a seasonal pattern of deaths from MI, with more fatal events (20 to 30 percent variation) occurring in the winter than the summer [39,40]. As an example, a registry study evaluated nearly 260,000 cases of acute MI during a 25-month period; approximately 53 percent more MIs occurred in the winter or spring compared with the summer (figure 2) [39]. The trends were independent of age, gender, geographic location, and the type of MI (ST elevation or non-ST elevation). In-hospital fatality rates for MI also followed a seasonal pattern, with a peak of 9 percent in winter and a nadir in the spring (8.4 percent).

A similar association between the season and death from MI was also noted in a study of 300,000 deaths from MI or stroke [41]. Deaths from MI were highest in January and lowest in September, with a relative risk difference of 18.6 percent.

Other social factors — Other psychosocial factors that have been identified as triggers of an acute MI include:

- **Substance abuse**

  - An acute coronary ischemic syndrome is the most common cardiac pathology associated with cocaine abuse and can occur with all routes of cocaine intake [42,43]. In a survey of 10,085 adults between the ages of 18 and 45, cocaine use accounted for 25 percent of nonfatal MIs [44]. (See "Clinical manifestations, diagnosis, and management of the cardiovascular complications of cocaine abuse".)

  - Smoking marijuana may rarely trigger acute coronary syndrome [45]. In one report of 3882 patients with an acute MI, 124 (3 percent) reported smoking marijuana in the prior year, 37 (1 percent) within 24 hours, and 9 (0.2 percent) within one hour [46]. The risk of MI was increased 4.8-fold over baseline in the 60 minutes after marijuana use

and then rapidly declined with time. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

- **Air pollution** – Exposure to particulate air pollution may also trigger acute coronary syndrome. (See "Overview of possible risk factors for cardiovascular disease", section on 'Air pollution'.)

- **Automotive traffic** – Exposure to vehicular traffic has been implicated as an MI trigger. In one analysis, 691 patients with an acute MI were interviewed about activities during the four days preceding the event [47]. Traffic exposure (defined as time spent in a vehicle) occurred during the hour before MI in 75 (12 percent) of 625 patients. Compared with the frequency of traffic exposure during the preceding three days, the likelihood of traffic exposure during the hour preceding MI was increased (adjusted odds ratio 2.7, 95% CI 2.1-3.6).

- **Heavy meals** – A study of more than 200 patients who were interviewed after an acute coronary syndrome event found that during the first hour after a heavy meal, there was a fourfold increase in relative risk of MI, compared with the same time period from the preceding day [48].

- **Day of the week and holidays** – A daily variation in MI has also been described with a peak incidence on Mondays [49]. Holidays such as Christmas and New Year's Day are also associated with increased cardiac mortality [50].

PATHOPHYSIOLOGY

There are several mechanisms by which emotional stress might trigger an acute myocardial infarction (MI) (algorithm 1). The physiologic changes that occur in the morning and raise cardiovascular risk, increases in blood pressure, heart rate, vascular tone, and platelet aggregability, also may result from mental stress [29]. These factors may all be related to abnormalities in autonomic tone and activation of sympathetic nervous system activity, which may enhance platelet aggregation and increase the susceptibility to serious ventricular arrhythmias.

Impaired autonomic function may also be involved in the association between depression and cardiovascular disease [51]. A study of 804 post-MI patients with and without depression who underwent 24-hour ambulatory monitoring found that those with minor or major depression had significantly decreased heart rate variability, indicating excessive sympathetic and/or reduced parasympathetic tone [52].

Myocardial ischemia and plaque rupture — Mental stress produces significant increases in heart rate and blood pressure that may lead to increased myocardial oxygen demand and plaque disruption [2]. In addition to a rise in the rate pressure product, there is also evidence that mental stress may lead to a primary reduction in myocardial oxygen supply. Whereas coronary arteries of normal patients dilate during mental stress, impaired dilation and even constriction has been demonstrated in atherosclerotic arteries [53].

The vasoconstriction induced by stress may not be immediate. In a dog model, profound coronary vasoconstriction could be demonstrated two to three minutes following elicitation of anger [54]. The vasoconstriction persisted well after heart rate and arterial blood pressure recovered.

Myocardial ischemia, as evidenced by ST depression and more sensitive means such as radionuclide ventriculography and positron emission tomography, has been shown to be precipitated by psychologically stressful circumstances (eg, public speaking). One study, for example, found that among 29 patients with coronary artery disease with exercise-induced wall motion abnormalities, 21 (72 percent) also exhibited wall motion abnormalities following mental stress [55]. The ischemia was usually silent, often without electrocardiogram abnormalities. (See "Silent myocardial ischemia: Epidemiology, diagnosis, treatment, and prognosis".)

Altered platelet activity — Although studies have not all shown consistent findings, mental stress enhances platelet aggregation secondary to sympathetic nervous system activation, and may promote mitogenic activity in plasma due to platelet-derived growth factors [56]. There is a compensatory increase in fibrinolytic activity following acute stress, but a diminished fibrinolytic response due to endothelial dysfunction may lead to a prothrombotic imbalance.

Altered cardiovascular risk factors — Although the effects of chronic stress on cardiovascular risk factors are less clear, depressed mood scores and increased sympathetic reactivity have been associated with elevated cholesterol levels [57]. The interaction of altered sympathetic and cortisol levels with oxidized low-density lipoprotein and macrophage activation is receiving increasing attention [58].

The new information on triggering can be incorporated into a hypothesis of the progression of coronary artery disease [58]. The onset of MI may occur when a vulnerable atherosclerotic plaque disrupts in response to mental stress or anger that produces transient pressure surges or vasoconstriction [2]. If the plaque disruption is major with extensive exposure of collagen and atheromatous core contents to the lumen, this may lead immediately to occlusive thrombosis, with MI or sudden cardiac death. If the disruption is minor, it may lead to

nonocclusive thrombosis. In this setting, the patient may be asymptomatic or develop unstable angina or non-ST elevation MI. The lesion may gradually heal with smooth muscle cell proliferation and a greater degree of stenosis. Alternatively, a further increase in coagulability or vasoconstriction may precipitate occlusive thrombosis, MI, and sudden cardiac death.

Central nervous system dysfunction — The association between psychosocial stress and acute coronary syndrome may involve dysfunction of neural circuits that include the amygdala, which participates in sympathetic responses to stress [59]. A retrospective study identified patients without known cardiovascular disease (n = 293) who underwent positron emission tomography/computerized tomography and were followed for a median of four years. After controlling for potential confounding factors (eg, diabetes, hypertension, and smoking), the analyses found that increased resting metabolic activity in the amygdala was associated with an increased risk of cardiovascular events such as MI, stroke, and unstable angina (hazard ratio 1.4, 95% CI 1.1-1.8) [59]. In addition, the study suggested that the link between amygdalar activity and cardiovascular disease may be mediated by arterial inflammation. A separate cross-sectional study of individuals with chronic stress (ie, posttraumatic stress disorder; n = 13) suggested that perceived stress was positively associated with amygdalar activity and arterial inflammation [59].

The relationship between stress and acute coronary syndrome may also involve the prefrontal cortex. A study of patients with stable coronary artery disease (n = 148) initially assessed activation of the prefrontal cortex with positron emission tomography during standardized mental stress testing; subsequently, patients were prospectively followed for a median of three years [60]. After adjusting for potential confounding factors (eg, age, smoking, and prior MI), the analyses found that a one standard deviation increase in prefrontal activation during mental stress at baseline was associated with a 21 percent increase in major adverse cardiovascular events (cardiovascular death, MI, unstable angina with revascularization, and heart failure hospitalization). Among those with higher prefrontal cortex stress reactivity, autonomic dysfunction and inflammation contributed to the increased risk of major adverse cardiovascular events.

MANAGING STRESS

For patients with coronary artery disease, interventions that can ameliorate stress include [27]:

- Reducing anger (see "Psychological factors affecting other medical conditions: Management", section on 'Anger')

- Relaxation exercises (see "Generalized anxiety disorder in adults: Cognitive-behavioral therapy and other psychotherapies", section on 'Relaxation training')
- Meditation (see "Complementary and alternative treatments for anxiety symptoms and disorders: Physical, cognitive, and spiritual interventions" and "Unipolar major depression: Treatment with mindfulness-based cognitive therapy")
- Exercise (see "Exercise prescription and guidance for adults")

DEPRESSION AFTER ACUTE CORONARY SYNDROME

The most common psychiatric disorder and symptom observed in patients with coronary artery disease is depression [27].

Overview — After acute coronary syndrome, depression appears to be a risk factor for adverse cardiovascular outcomes and mortality, and should not be viewed as a normal reaction to cardiac illness [27]. Psychotherapy and antidepressants, combined together or as monotherapy, can resolve depressive syndromes, and treatment may improve cardiovascular outcomes. (See 'Choosing a treatment regimen' below.)

Although many patients who are depressed after a myocardial infarction (MI) will spontaneously remit, it is not possible to predict which patients will do so. Thus, we suggest screening for depressive symptoms in patients with established coronary heart disease, which is consistent with practice guidelines. (See 'Screening' below.)

Many cardiologists diagnose and treat depression, as do primary care clinicians [28]. However, we suggest referral to mental health specialists for treatment-resistant depression and for severe major depression characterized by suicidal or homicidal ideation or behavior, psychosis, or catatonia. In addition, referral is indicated for patients who prefer psychotherapy and patients with comorbid psychopathology such as substance use disorders and anxiety disorders.

Prevalence — The risk of depression may be three times greater in patients with an MI, compared with the general population [28]. After an acute coronary syndrome event, the estimated prevalence of depression ranges from 20 to 30 percent [61].

The prevalence of unipolar depression after acute coronary syndrome varies across studies, such that structured interviews detect lower rates and rating scales yield higher rates. In a meta-analysis of eight studies that used structured interviews to assess patients hospitalized for an MI (n >10,000), the estimated prevalence of unipolar major depression was 20 percent (95%

CI 19-21 percent) [61]. By contrast, the same study found that in a meta-analysis of six studies, which used a rating scale to assess clinically significant depressive symptoms in hospitalized patients with MI (n >2200), the prevalence of depression was 31 percent (95% CI 29-33 percent).

Screening — Following an acute coronary syndrome, we suggest screening patients for depression within three months, if services are in place to ensure follow-up for diagnosis and treatment. This approach is consistent with multiple treatment guidelines [28]. Screening for depression in patients with recent acute coronary syndrome is supported by the American Heart Association scientific advisory that recommends screening for depressive symptoms in patients with established coronary heart disease [62], practice guidelines from the American Heart Association that recommend screening for depression to prevent cardiovascular disease in women [63], practice guidelines from the American Academy of Family Physicians that recommend screening for depression following an MI [64], and the United States Preventive Services Task Force practice guidelines that recommend screening for depression in all adults, including those with cardiovascular disease. (See "Screening for depression in adults", section on 'Routine for all patients'.)

Multiple self-report instruments are available to screen for depression, such as the Patient Health Questionnaire, including the two-item (table 1) and nine-item (table 2) versions, which are relatively short, free, and commonly used; the two-item version consists of the first two items from the nine-item version [28]. Other self-administered instruments include the Beck Depression Inventory and Hospital Anxiety and Depression Scale. A review of six prospective observational studies, which enrolled patients within three months of an acute coronary syndrome (n >1700) and screened them for unipolar major depression (table 3), found that the diagnostic accuracy of screening instruments in postacute coronary syndrome patients is satisfactory and comparable to what is observed in the general population [65]. Choosing an instrument and screening implementation are discussed separately. (See "Screening for depression in adults", section on 'Routine for all patients'.)

Indirect evidence that supports screening for depression in patients with recent acute coronary syndrome includes multiple randomized trials, which demonstrated that screening for depression in the general adult population improves depressive symptoms, if services are in place to ensure follow-up for diagnosis and treatment. (See "Screening for depression in adults", section on 'Improved depression outcomes'.)

However, screening for depression following an acute coronary syndrome is not universally endorsed, due to the lack of direct evidence that screening is beneficial [66,67]. Few high quality studies have evaluated screening for depression specifically in patients with recent acute coronary syndrome [68]. One randomized trial lasting 18 months compared screening plus

enhanced depression care with no screening and usual care in 999 patients who had no prior history of depression and were hospitalized for acute coronary syndrome in the past 2 to 12 months [69]. Quality-adjusted life years and depression-free days were each comparable in the two groups.

Assessment and diagnosis — The assessment and diagnosis of unipolar depressive syndromes, including unipolar major depression (table 3), is discussed in detail separately. (See "Unipolar depression in adults: Assessment and diagnosis".)

Evaluating patients with acute coronary syndrome for depression can be difficult because some symptoms of depression (eg, anorexia, insomnia, and fatigue) may be attributable to general medical disorders such as heart disease. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Diagnostic criteria'.)

The differential diagnosis of depression in patients with acute coronary syndrome includes adverse effects of cardiac medications [27]. As an example, clonidine, digoxin, and alpha-adrenergic blockers such as doxazosin may cause depression. In addition, amiodarone can lead to hypothyroidism that may manifest with depressive symptoms, including dysphoria, anergia, hypersomnia, impaired concentration and memory, and weight gain [70].

Adverse consequences — Among patients recovering from an MI, depression is associated with a poor prognosis, including increased mortality [27]:

- One review reported that among 20 studies of post-MI patients, 17 studies found that depression was associated with increased mortality [64].
- A review of 53 studies and four meta-analyses by the American Heart Association found that depression within a few weeks after acute coronary syndrome is a risk factor for adverse outcomes, including increased all-cause and cardiac mortality [71]. As an example, the most recent of the four meta-analyses examined the association between post-MI depression and mortality in 29 studies (n >16,000 patients with MI) [72]. Within two years of the MI:
  - All-cause mortality was two times more likely in depressed patients than nondepressed patients (odds ratio 2.3, 95% CI 1.7-2.9).
  - Cardiac mortality was three times more likely in depressed patients (odds ratio 2.7, 95% CI 1.7-4.4).
  - In addition, post-MI depression was associated with cardiac events such as cardiac arrest or recurrent MI (odds ratio 1.6, 96% CI 1.4-1.9).

Among patients with acute coronary syndrome who are depressed, more severe levels of depression and persistent depression are each associated with greater all-cause mortality. A prospective study enrolled 358 patients who were hospitalized for acute coronary syndrome and had unipolar major depression, and followed them for a median of seven years [73]. The mortality rate was greater in patients with a baseline score on the Hamilton Rating Scale for Depression (table 4) ≥18, compared with a score <18 (26 versus 12 percent). All-cause mortality was also greater in patients with little or no improvement in their depressive syndrome, compared with patients who improved very much (28 versus 12 percent). In addition, the association between baseline severity of depression and long-term mortality was independent of the association between failure to improve and mortality.

High levels of social support may perhaps reduce mortality among depressed post-MI patients. A study seven days after an MI in 887 patients found that mild to moderate depression, present in 32 percent, was associated with increased cardiac mortality during a one-year follow-up [74]. Although high levels of social support alone did not influence cardiac mortality, they were associated with improvements in depressive symptoms. In addition, high levels of social support appeared to buffer the impact of depression on mortality (figure 3).

Acute coronary syndrome may be associated with an increased risk of suicide [75]. A registry study identified nearly 20,000 people aged 40 to 89 years who died by suicide, and randomly selected nearly 200,000 controls matched by sex, date of birth, and calendar time (control was alive on the day that the case committed suicide) [75]. Patients who suffered an MI and had no prior history of psychiatric illness were three times more likely to commit suicide within one month of the MI, compared with individuals who had no history of MI or psychiatric illness (incidence rate ratio 3, 95% CI 2-7). The risk of suicide remained elevated for at least five years after an MI.

Additional information about risk factors for adverse outcomes after acute coronary syndromes is discussed separately. (See "Risk factors for adverse outcomes after ST-elevation myocardial infarction" and "Risk factors for adverse outcomes after non-ST elevation acute coronary syndromes".)

Several mechanisms may link depression to adverse cardiovascular outcomes. Depression is associated with autonomic dysfunction (eg, hypertension, resting tachycardia, and reduced heart rate variability), increased platelet activity, impaired vascular endothelial function, insulin resistance, and inflammation [27-29]. In addition, depression may be associated with functional impairment and negatively affect adherence with recommendations for post-MI therapy, such as cardiac pharmacotherapy, smoking cessation, exercise, and improved diet.

Course of illness — Depression that occurs soon after acute coronary syndrome often persists. A review of four prospective studies found that among patients who were hospitalized for an MI and developed depressive syndromes (major depression or minor depression) or clinically significant depressive symptoms, 40 to 70 percent remained depressed in the year after discharge [61]. This suggests that a substantial number of patients may benefit from treatment of depression following an MI. (See 'Choosing a treatment regimen' below.)

Choosing a treatment regimen — For patients with unipolar major depression after acute coronary syndrome (eg, within the past three months), we suggest psychotherapy plus an antidepressant. However, psychotherapy alone is a reasonable choice for patients who want to avoid adverse effects of antidepressants and drug-drug interactions, whereas medication alone is reasonable in patients who decline or do not have access to psychotherapy. No head-to-head randomized trials have compared these three standard treatment regimens in patients who have survived an acute coronary syndrome, and clinicians should attempt to accommodate patient preferences. In addition, it is reasonable to choose treatment based upon factors such as prior treatment history and cost.

Using patient preferences to guide treatment of depression is supported by a trial that enrolled patients with acute coronary syndrome and clinically significant depression (n = 157) and randomly assigned them to treatment based upon patient preferences or to usual care [76]. The active intervention arm initially offered patients psychotherapy and/or pharmacotherapy; patients who did not improve were allowed to intensify the initial treatment (eg, increase the frequency of therapy sessions or add a second medication), switch treatments (eg, from psychotherapy to pharmacotherapy), or combine psychotherapy with pharmacotherapy. Improvement of depression was greater among intervention patients and the clinical benefit was moderate to large. In addition, nonfatal MI and unstable angina occurred in fewer intervention patients than usual care patients (4 versus 13 percent).

Psychotherapy plus an antidepressant (preferred) — For patients who survive an acute coronary syndrome (eg, within the past three months) and have unipolar major depression, we suggest treating the depressive syndrome with psychotherapy plus an antidepressant. We typically use cognitive-behavioral therapy (CBT) plus a selective serotonin reuptake inhibitor (SSRIs) such as escitalopram or sertraline. However, there are several reasonable alternatives to CBT, including interpersonal psychotherapy and problem-solving therapy. In addition, there are several reasonable alternatives to escitalopram or sertraline, including serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, and the atypical antidepressants bupropion and mirtazapine. Additional information about choosing treatment

is discussed separately. (See 'Psychotherapy' below and 'Antidepressants' below and 'Collaborative care' below.)

Efficacy — Evidence supporting the use of psychotherapy plus pharmacotherapy includes multiple randomized trials in the general population of adults with unipolar major depression; these trials indicate that psychotherapy (eg, CBT or interpersonal psychotherapy) plus an antidepressant is more efficacious than either psychotherapy alone or an antidepressant alone. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants plus psychotherapy'.)

In addition, randomized trials in patients with acute coronary syndrome suggest that psychotherapy plus an antidepressant may be efficacious for unipolar major depression [65]:

- A six-month trial enrolled post-MI patients with a depressive syndrome and/or a low level of perceived social support (n >2400), and randomly assigned them to experimental treatment or usual care [77]. Experimental treatment consisted of CBT; in addition, 21 percent received an adjunctive antidepressant (eg, sertraline 50 to 200 mg/day) due to greater levels of baseline depression or nonresponse to CBT after five weeks. Among patients assigned to usual care, 13 percent received an antidepressant. Improvement of depression and perceived social support were each greater in patients who received experimental treatment than usual care, but the clinical effect was modest. Although recurrence of MI or death were each comparable for the two groups, antidepressant drugs were associated with a decreased risk of reinfarction or death.

- A meta-analysis of 35 randomized trials compared psychological interventions with usual care in patients with coronary heart disease (n >10,000), and found that depressive symptoms improved more in the group that received psychological interventions than usual care [78] (see 'Psychotherapy' below). In addition, improvement of depression was greater in studies that included adjunctive pharmacotherapy when clinically indicated, compared with studies that did not include pharmacotherapy.

The use of psychotherapy plus antidepressants for patients with comorbid coronary heart disease and depression has also been studied in the context of collaborative care. (See 'Collaborative care' below.)

Psychotherapy — Many patients with postacute coronary syndrome and unipolar major depression decline treatment with antidepressant drugs and prefer treatment with psychotherapy alone, due to concerns about adverse effects and drug-drug interactions with cardiac medications. For these patients, we suggest monotherapy with CBT or another psychotherapy, such as interpersonal psychotherapy and problem-solving therapy. Other

reasonable choices include psychodynamic psychotherapy and supportive psychotherapy. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Treatment options'.)

In a study of 73 patients who survived an acute coronary syndrome, had a depressive syndrome, and were offered treatment with psychotherapy, pharmacotherapy, both, or neither, most patients chose psychotherapy alone [79]:

- Psychotherapy alone – 56 percent
- Psychotherapy plus pharmacotherapy – 23 percent
- Pharmacotherapy alone – 12 percent
- No treatment – 8 percent

Efficacy — Evidence supporting the use of psychotherapy for postacute coronary syndrome depression includes numerous randomized trials in the general population of adults with unipolar major depression; these trials indicate that psychotherapy (eg, CBT) is more efficacious than a control condition (eg, waiting list or usual care). (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of psychotherapy' and "Unipolar major depression in adults: Choosing initial treatment".)

In addition, randomized trials suggest that psychotherapy can be efficacious for treating unipolar major depression in patients who survive an acute coronary syndrome. Although the benefit of psychotherapy for depression is clinically small, psychotherapy may also reduce cardiac mortality:

- A meta-analysis of 35 randomized trials compared psychological interventions with usual care in patients with coronary heart disease (n >10,000) [78]. The psychological interventions included CBT, relaxation techniques, and emotional support. Some studies included or permitted other interventions, such as cardiac rehabilitation or antidepressants, for both the psychotherapy and usual care groups. Most patients were post-MI (66 percent) or had undergone a revascularization procedure such coronary artery bypass graft (27 percent). Depressive symptoms improved more in the group that received psychological interventions than usual care, but the clinical effect was small. In addition, psychological interventions provided a small to moderate improvement of anxiety and stress that did not occur with usual care. Psychotherapy also resulted in a 21 percent reduction of cardiac mortality (relative risk 0.79, 95% CI 0.63-0.98).

- A meta-analysis of 11 randomized trials compared psychological interventions (eg, CBT or relaxation) with control conditions (eg, usual care) in patients with coronary heart disease and depression (n >2000); most patients were enrolled after an acute coronary syndrome

[80]. Some studies included other interventions for both the psychotherapy and control groups. Improvement of depression was greater in patients who received active treatment, compared with controls, but the clinical effect was small.

- A meta-analysis of 12 randomized trials compared CBT with control conditions in patients (n >2200) with cardiovascular disease (primarily acute coronary syndrome) and depression [81]. CBT was administered over 4 to 12 sessions; controls typically received usual care, and some trials permitted adjunctive antidepressants. Improvement of depression was greater in patients who received CBT than controls, and the clinical benefit was small to moderate. In addition, CBT provided a small to moderate benefit for anxiety. However, heterogeneity across studies was moderate to large, both for improvement of depression and anxiety. Only two studies with a total of 260 patients assessed posttreatment cardiovascular events as an outcome, and the rate was comparable for patients treated with CBT and the controls.

Antidepressants — Antidepressants are often used to treat unipolar major depression in patients with recent acute coronary syndrome (eg, within the past three months) because psychotherapy may not be available, or patients may decline psychotherapy or not respond to it. Patients with a history of major depressive episodes before an MI may be more likely to respond to antidepressant therapy than patients with no prior episodes [82].

Choice of drug — For patients with acute coronary syndrome who prefer pharmacotherapy rather than psychotherapy for treating unipolar depressive syndromes, we suggest an antidepressant and generally select an SSRI because SSRIs have demonstrated efficacy, are well tolerated, and have been more widely studied and may be more cost effective than other antidepressants [27,28,83]. Although there is no evidence that one SSRI is more efficacious than another, we typically choose escitalopram or sertraline because they have demonstrated efficacy for postacute coronary syndrome depression [84]. In addition, escitalopram and sertraline are not likely to cause drug-drug interactions with cardiac medications; these interactions can lead to adverse side effects.

Citalopram is generally avoided in patients with heart disease, including patients with recent MI. The US Food and Drug Administration issued a warning that citalopram causes dose-dependent QT interval prolongation that can lead to arrhythmias and thus recommends not using citalopram in patients with recent acute MI. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Citalopram'.)

Reasonable alternatives to SSRIs for the initial treatment of major depression include other second-generation antidepressants, such as SNRIs (eg, venlafaxine) and atypical

antidepressants (eg, bupropion or mirtazapine) (table 5) [76]. These other, non-SSRI antidepressants are suitable for patients who have not responded to SSRIs for past episodes of unipolar depression, as well as patients who do not respond to initial treatment of the current depressive episode with one or two trials of an SSRI.

Tricyclic antidepressants are potentially cardiotoxic and are generally avoided in patients with heart disease [28,85,86]. In addition, tricyclics are often poorly tolerated (table 6) and are potentially lethal in overdose. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Cardiac'.)

Monoamine oxidase inhibitors are also avoided in patients with heart disease because these medications can cause episodes of hypotension [28]. In addition, monoamine oxidase inhibitors can cause lethal drug-drug and drug-food interactions, and overdoses with these drugs are dangerous. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

Administration — Antidepressants can be started once the diagnosis of unipolar major depression has been made, provided the acute coronary syndrome has been stabilized. Following administration of starting doses, clinicians should titrate the dose up to therapeutic doses of antidepressants, rather than using subtherapeutic doses to avoid adverse effects [27].

In addition, patients receiving antidepressants for depression postacute coronary syndrome may require relatively prolonged treatment trials to determine whether the drug is effective [28]. A small randomized trial compared fluoxetine (mean dose 47 mg/day) with placebo in 54 patients with unipolar major depression after their first MI [87]. Study drugs were initiated three months following the MI and administered for up to 25 weeks. Response (reduction of baseline symptoms ≥50 percent) after nine weeks of treatment was comparable in the two groups; however, at week 25, response occurred in more patients with fluoxetine than placebo (48 versus 26 percent).

Additional information about the administration of antidepressants, including the starting and usual daily doses (table 5), are described elsewhere. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Prescribing SSRIs' and "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects" and "Atypical antidepressants: Pharmacology, administration, and side effects" and "Serotonin modulators: Pharmacology, administration, and side effects".)

Efficacy — Evidence supporting the use of antidepressants for treating major depression following acute coronary syndrome includes numerous randomized trials in the general population of adults with unipolar major depression; these trials indicate that antidepressants

such as SSRIs are more efficacious than placebo. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

Multiple randomized trials in patients who survive an acute coronary syndrome also support using antidepressants for treating major depression [88]:

- A meta-analysis of four randomized trials compared SSRIs (citalopram, fluoxetine, or sertraline) with placebo for treating unipolar major depression in patients with coronary heart disease (n = 734); the trials lasted 9 to 26 weeks [89]. Improvement of depression was greater with SSRIs than placebo, and the clinical benefit was small to moderate.

- A meta-analysis of five trials, lasting 4 to 24 weeks, compared antidepressants with placebo in patients with coronary artery disease plus depressive syndromes (n = 891) [90]. Active treatment included the SSRIs citalopram, escitalopram, fluoxetine, or sertraline. Response (reduction of baseline depressive symptoms ≥50 percent) was more likely with antidepressants than placebo (odds ratio 2.7, 95% CI 1.7-4.5).

  Although noncardiac adverse effects such as headache were more likely with antidepressants than placebo (odds ratio 1.4, 95% CI 1.1-1.9), cardiac safety did not differ between the two groups. As an example, the most recent of the five trials found that cardiovascular outcomes, such as results from echocardiograms, electrocardiograms, and laboratory tests for troponin I and CK-MB, were comparable for escitalopram and placebo [91]. Additional information about SSRIs and cardiac safety following acute coronary syndrome is discussed below. (See 'Safety and adverse cardiac events' below.)

Among patients with acute coronary syndrome who are depressed, clinicians can expect that response will occur in approximately 60 percent [83]. In addition, antidepressants may be more likely to improve the depressive syndrome in patients with a prior history of depression and those whose current depressive episode is more severe [92].

Multiple randomized trials indicate that using antidepressants in patients with recent acute coronary syndrome and depression may improve cardiac outcomes as well as depressive symptoms. (See 'Overview' below.)

Safety and adverse cardiac events

Overview — Multiple randomized trials have found that SSRIs are safe for patients with unipolar major depression after acute coronary syndrome (eg, within the past three months). In addition, these trials suggest that SSRIs may protect patients against subsequent adverse cardiac events. Although clinicians may be reluctant to prescribe antidepressants to patients

who have suffered a recent MI, due to concerns about mortality and major adverse cardiac events such as recurrent MI, unstable angina, or revascularization procedures, the trials indicate that these concerns appear to be unfounded. As an example, a systematic review identified six randomized trials that compared an SSRI with a control condition in patients with coronary artery disease and depression (n = 1091) [93]. Study treatments were administered for 8 to 26 weeks, and patients were followed posttreatment for up to eight years. The SSRIs included citalopram, escitalopram, fluoxetine, paroxetine, or sertraline; the controls received placebo or no intervention. A series of meta-analyses showed that:

- All-cause mortality, angina, congestive heart failure, hospitalizations, and stroke were each comparable for patients treated with SSRIs and controls. In addition, cardiovascular mortality and percutaneous intervention were each comparable for the two groups in the one study that assessed these outcomes.

- MI occurred less often in patients treated with SSRIs than controls (relative risk 0.54, 95% CI 0.34-0.86). When the analysis was restricted to the four trials that included only postacute coronary syndrome patients (n = 753), the result was nearly the same: SSRIs reduced the risk of MI by 44 percent.

However, citalopram is generally avoided in patients with heart disease, including patients with recent MI, due to concerns that citalopram causes dose-dependent QT interval prolongation that can lead to arrhythmias [94]. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Citalopram'.)

Short-term — Randomized trials lasting 9 to 26 weeks indicate that short-term use of SSRIs is safe [83]:

- A review of three studies found that antidepressants had a neutral or beneficial effect upon mortality [95]. The studies included a randomized trial that compared sertraline with placebo [82]; a trial that randomly assigned patients to CBT or usual care, but permitted use of antidepressants such as sertraline in both treatment groups [77] (see 'Psychotherapy plus an antidepressant (preferred)' above); and a trial that randomly assigned patients to mirtazapine or placebo and then permitted use of citalopram if there was no response to mirtazapine or placebo [96].

- A meta-analysis of three randomized trials compared SSRIs (citalopram, fluoxetine, or sertraline) with placebo for treating unipolar major depression in patients with coronary heart disease (n = 707) [89]. All-cause mortality was comparable for SSRIs and placebo (relative risk 0.4, 95% CI 0.1-2.0). In addition, readmission to the hospital for a cardiac

event such as MI, unstable angina, or stroke was comparable for SSRIs and placebo (relative risk 0.7, 95% CI 0.4-1.2).

Among SSRIs, sertraline is the most widely studied in patients with recent acute coronary syndrome and appears to cause little or no cardiac effects. As an example, a 24-week randomized trial compared sertraline (50 to 200 mg/day) with placebo in 369 patients with unipolar major depression who had been hospitalized for MI or unstable angina; the mean time from the cardiac event to the start of study drugs was 34 days [82]. All patients were prescribed cardiovascular medications and the mean number of concomitant drugs in the sample was 11. Sertraline and placebo were comparable with regard to cardiac side effects, including left ventricular ejection fraction, premature ventricular complexes, QTc intervals >450 milliseconds, MI, angina, blood pressure, and pulse. The incidence of severe cardiovascular events with sertraline and placebo was 15 and 22 percent.

Longer-term — Although questions have been raised about the longer-term safety of SSRIs in patients with acute coronary syndrome [97], SSRIs appear to be safe beyond six months, and may perhaps reduce the incidence of major adverse cardiac events after MI or unstable angina:

- A one-year randomized trial compared escitalopram (10 to 20 mg/day) with placebo for preventing depression in nondepressed patients with an acute coronary syndrome (n = 239) [98,99]. Fewer episodes of depression occurred with escitalopram, and all of the cardiovascular safety outcomes were comparable for escitalopram and placebo, including the incidence of ventricular arrhythmia and ST-segment depression, length of the QTc interval, echocardiographic results, and the incidence of major adverse cardiac events (death, recurrent acute coronary syndrome, or revascularization).

- A 24-week randomized trial compared escitalopram (mean dose 8 mg/day) with placebo in patients with depressive syndromes following recent MI or unstable angina (n = 300); during the treatment period, results from echocardiograms, electrocardiograms, and laboratory tests such as troponin I and CK-MB were comparable for the two groups [91].

  In addition, during subsequent prospective follow-up lasting for a median of eight years, there were fewer adverse cardiac events in patients treated with escitalopram during the trial [100]. Specifically:

  - The composite outcome of all-cause mortality, MI, and percutaneous coronary intervention occurred in fewer patients who received escitalopram than placebo (41 versus 54 percent). Most of the benefit with escitalopram was observed in the first four years of follow-up and the advantage of active drug persisted in analyses that

controlled for potential confounding factors such as diabetes, hypertension, and smoking.

- The individual outcome of MI occurred in fewer patients who received escitalopram than placebo (9 versus 15 percent).
- The incidence of other individual adverse cardiac events, including all-cause mortality, cardiac death, and percutaneous coronary intervention, was comparable with escitalopram and placebo.

- Another 24-week trial compared sertraline (mean dose 69 mg/day) with placebo in patients who were hospitalized for acute coronary syndrome and had unipolar major depression [73]. Among 359 patients who were followed posttreatment for a median of seven years, all-cause mortality was 21 percent in both groups.

Additional information about the potential adverse effects of SSRIs, including QTc interval prolongation and increased risk of bleeding, are discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects'.)

Drug-drug interactions — The SSRIs fluoxetine, fluvoxamine, and paroxetine are moderate to potent inhibitors of hepatic cytochrome P450 drug metabolism and can cause drug-drug interactions by altering blood levels of other medicines, such as anticoagulants, antiplatelet agents, beta-blockers, and statins, which depend upon hepatic enzymes for clearance or activation [101,102]. Additional information about drug-drug interactions that involve SSRIs is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions'.)

Specific interactions of an antidepressant with another medication, such as a cardiac drug, may be determined by using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Exercise — Aerobic exercise may be beneficial for depression in patients with acute coronary syndrome that is stable:

- A four-month trial randomly assigned 101 patients with coronary heart disease (eg, prior MI) and depression to aerobic exercise, sertraline (50 to 200 mg/day), or placebo [103]. Exercise consisted of three supervised sessions per week, during which patients walked or jogged on a treadmill for 30 minutes at 70 to 85 percent maximal heart rate reserve. Improvement of depression was greater with exercise or sertraline than placebo, and improvement was comparable for the two active treatments. There was also a trend for

greater improvement of heart rate variability (a biomarker of cardiovascular risk) with exercise or sertraline than placebo, and a trend for greater improvement with exercise than sertraline.

- A prospective, four-year observational study of nearly 2100 patients who were hospitalized for an MI found that the rate of all-cause mortality among those who regularly exercised was half the rate of those who did not (6 versus 12 percent), which was statistically significant after controlling for potential confounding factors (eg, smoking, body mass index, and general medical comorbidities) [104]. In addition, nonfatal MI occurred in fewer exercisers than nonexercisers (hazard ratio 0.6, 95% CI 0.4–0.8).

Information about the cardiac benefits and risks of aerobic exercise in the general population are discussed separately, as are suggestions for prescribing exercise. (See "The benefits and risks of aerobic exercise" and "Exercise prescription and guidance for adults".)

In addition, the benefits of exercise for the general population of patients with depression are discussed separately, as are suggestions for prescribing exercise to depressed patients. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Exercise'.)

Collaborative care — Collaborative care is a health care model that integrates psychiatric treatment into primary care practices. Patients are treated by a team that usually includes a primary care clinician, a case manager such as a nurse or social worker who provides support and outreach to patients, and a mental health specialist (eg, psychiatrist) who provides consultation and case supervision. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (eg, patient education, CBT, or problem-solving therapy), scheduled follow-up visits, communication among members of the treatment team, and measurement-based care. The specific interventions are administered according to patient preferences.

Collaborative care programs can be useful for patients with comorbid coronary heart disease and depression [27,28]. Evidence supporting the use of collaborative care in this population includes numerous randomized trials in the general population of primary care patients with depression, as well as the general population of patients with comorbid depression and general medical illness. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments".)

In addition, randomized trials suggest that collaborative care can be efficacious for treating comorbid coronary heart disease and depression. As an example, a meta-analysis of six randomized trials, lasting 3 to 12 months, compared collaborative care with usual care in 1284 patients [105]. Patient preferences determined whether psychotherapy (eg, CBT or problem-

solving therapy), pharmacotherapy (eg, SSRIs, SNRIs, bupropion, or mirtazapine), both, or neither were administered. The primary findings were as follows:

- Depressive symptoms, anxiety symptoms, and quality of life each improved more with collaborative care than usual care, and the clinical benefit was small to moderate.
- Remission of depression was 80 percent more likely with collaborative care (relative risk 1.8, 95% CI 1.3-2.4).
- Major adverse cardiac events (eg, subsequent MI, revascularization procedure, or stroke) were comparable for collaborative care and usual care (relative risk 0.9, 95% CI 0.5-1.4), as was mortality (relative risk 1.4, 95% CI 0.5-3.6).

Monitoring — For treating depression after acute coronary syndrome, we suggest measurement-based care, in which clinicians systematically monitor depressive symptoms with a standardized scale to improve treatment outcomes. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

Maintenance treatment — Maintenance treatment for patients who respond to acute treatment of depression that is comorbid with an acute coronary syndrome is discussed separately. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

PREVENTION

Although multiple studies support a role for mental stress as a trigger of myocardial infarction (MI) and for cardiac events after an MI, the clinical utility of this finding remains unclear.

A framework for preventing cardiovascular events at times of increased risk due to known triggers has been designated as Triggered Acute Risk Prevention [106]:

- Determining the absolute cardiovascular risk of a particular individual. Individuals at low risk of having atherosclerotic disease or vulnerable plaques might not require intervention for major emotional stress because their absolute risk of an event attributable to the trigger is low.
- Modifying or avoiding the specific triggering activity in individuals considered to be at increased absolute risk. Psychosocial treatment or behavior therapy may prove useful in reducing the adverse consequences of mental stress in triggering cardiovascular events. Strategies include incorporating relaxation techniques at the time of a severe emotional

stress and providing sensitive social support at the time of bereavement. (See "Bereavement and grief in adults: Management", section on 'Management'.)

- Long-term preventive approaches directed against the specific trigger. As an example, stress reduction training may limit the frequency and intensity of anger and anxiety.

- Long-term behavioral and pharmacologic measures directed at traditional risk factors, such as hypertension and hyperlipidemia. This should reduce the likelihood that a trigger would produce an acute cardiovascular event by reducing the atherosclerotic burden, the number of vulnerable plaques, and the vulnerability of individual plaques.

- It is often not possible to avoid stressors that provoke acute emotional stress; thus, benefit may be gained through efforts to interrupt the link between the stressor and the cardiovascular event by pharmacologic means. Although data are limited, one study found that aspirin modified the relative risk of anger producing MI [8]. Beta blockers may also be protective, although they do not reduce mental stress-induced blood pressure surges.

The use of psychotropic drugs and agents such as aspirin and beta blockers may be warranted in selected patient populations, particularly at times of increased stress, such as following bereavement, although further study is required.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Heart attack recovery (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The circadian variation in frequency of myocardial infarction (MI), sudden cardiac death, and myocardial ischemia is characterized by a morning peak. This suggests that cardiac events may be triggered by external activities, particularly those activating the sympathetic nervous system. (See 'Circadian variation' above.)

- Acute coronary syndromes may be triggered by acute and chronic stress, anxiety, depression, and anger. (See 'Precipitating factors' above.)

- Hypothesized mechanisms by which emotional stress might trigger an acute MI include increases in blood pressure, heart rate, vascular tone, and platelet aggregability, which in turn may disrupt a vulnerable atherosclerotic plaque. (See 'Pathophysiology' above.)

- Interventions that can ameliorate stress in patients with coronary artery disease include reducing anger, relaxation exercises, meditation, and exercise. (See 'Managing stress' above.)

- After an MI, major depression develops in approximately 20 percent of patients. (See 'Prevalence' above.)

- Following an acute coronary syndrome, we suggest screening patients for depression, provided that adequate services are in place to ensure follow-up for diagnosis and treatment (**Grade 2C**). We typically screen patients within three months of the acute coronary syndrome event. However, screening is not universally endorsed. (See 'Screening' above.)

- Depression in patients with acute coronary syndrome is associated with an increased risk of all-cause mortality, cardiac mortality, and cardiac morbidity. In addition, patients with an MI are at increased risk of committing suicide within one month of the MI, compared with individuals with no history of MI. (See 'Adverse consequences' above.)

- For patients with unipolar major depression after acute coronary syndrome (eg, within the past three months), we suggest psychotherapy plus an antidepressant (**Grade 2C**). Psychotherapy alone is a reasonable choice for patients who want to avoid adverse effects of antidepressants and drug-drug interactions; medication alone is reasonable in patients who decline or do not have access to psychotherapy. (See 'Choosing a treatment regimen' above and 'Psychotherapy plus an antidepressant (preferred)' above.)

- When psychotherapy is chosen (alone or in combination with an antidepressant), we suggest cognitive-behavioral therapy (CBT) in most patients (**Grade 2C**). Reasonable alternatives to CBT include problem-solving therapy and interpersonal psychotherapy. (See 'Psychotherapy' above.)

- When antidepressant therapy is chosen (alone or in combination with psychotherapy), we suggest the selective serotonin reuptake inhibitors (SSRIs) escitalopram or sertraline, rather than other options (**Grade 2C**). Citalopram is generally avoided in patients with heart disease due to dose-dependent risk of QT-interval prolongation. Reasonable alternatives to SSRIs include serotonin-norepinephrine reuptake inhibitors such as venlafaxine, and the atypical antidepressants bupropion and mirtazapine. (See 'Antidepressants' above.)

- Exercise may be beneficial as adjunctive treatment for patients with unipolar major depression after acute coronary syndrome. (See 'Exercise' above.)

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