Acquired ventricular septal defect (VSD) from septal wall rupture may complicate inferior or anterior STEMI, usually in patients with multivessel CAD. VSDs typically occur within 5 days of STEMI presentation. Patients present with worsening heart failure and shock, and a harsh holosystolic murmur may be heard at the left lower sternal border. The diagnosis is confirmed with echocardiography. Although initial management may include afterload reduction with medical therapy and IABP support, the mortality rate in patients with medically treated postinfarct VSDs approaches 100%. Surgical closure should be considered; however, the mortality rate in surgical series is still high (approximately 50%). Patch closure can be very difficult because of the necrotic tissue and inability to find viable myocardium to suture and patch. Percutaneous closure with a VSD occluder device is possible but often unsuccessful because of the nature of the defect, and residual shunting around the device is common.

When the posteromedial papillary muscle blood supply from the posterior descending artery is interrupted during MI, rupture may occur, resulting in severe acute mitral regurgitation several days after STEMI. Afterload reduction and IABP placement may be temporizing, although urgent surgical intervention usually is indicated. Acute severe mitral regurgitation also may result from LV dysfunction and is often related to an inferior MI with restriction of the posterior mitral leaflet, termed functional ischemic mitral regurgitation. Ischemic mitral regurgitation is treated with revascularization and medical therapy.

Non–ST-Elevation Acute Coronary Syndromes

NSTE-ACS, like STEMI, is on the spectrum of acute ischemic disorders attributable to plaque erosion or rupture and thrombotic occlusion, manifesting as acute chest pain at rest or with minimal exertion. Unlike the complete coronary obstruction resulting in STEMI, NSTE-ACS involves incomplete or transient obstruction without ST-segment elevation, although ST-segment depression is often present.

Risk Stratification

Initial assessment of suspected NSTE-ACS involves a careful history, physical examination, ECG, and serial biomarker measurement to determine the likelihood of a cardiac process. In patients with low likelihood of a coronary event, alternative causes should be investigated. In patients with an intermediate or a high likelihood of ACS, prognostic assessment with risk scores, such as TIMI and GRACE risk models, is indicated. The simpler of the two models, the TIMI risk score, predicts 14-day death, recurrent MI, and urgent revascularization rates (**Table 9**). The GRACE risk score (www.gracescore.org) incorporates examination findings, clinical features, ECG findings, and biomarker variables (creatinine levels, elevated cardiac enzymes) to predict in-house and postdischarge death and MI risk. Prognostic assessment along with serial troponin measurement and clinical status helps determine the most appropriate therapeutic strategy (**Figure 11**).

TABLE 9. TIMI Risk Score for Non–ST-Elevation Acute Coronary Syndromes

Prognostic Variables (1 Point Each)	
Age ≥65 y	
≥3 Traditional CAD risk factors[a]	
Documented CAD with ≥50% diameter stenosis	
ST-segment deviation	
≥2 Anginal episodes in the past 24 h	
Aspirin use in the past wk	
Elevated cardiac biomarkers (creatine kinase MB or troponin)	
TIMI Risk Score (Sum of Prognostic Variables)	
0-2	Low risk
3-4	Intermediate risk
5-7	High risk

CAD = coronary artery disease; TIMI = thrombolysis in myocardial infarction.

[a]Hypertension, hypercholesterolemia, diabetes mellitus, being a current smoker, family history of CAD.

Information from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284:835-42. [PMID: 10938172] doi:10.1001/jama.284.7.835

Invasive Versus Ischemia-Guided Treatment

Urgent invasive treatment (within 2 hours) is recommended for patients with NSTE-ACS who have hemodynamic instability, refractory chest pain, heart failure, or ventricular arrhythmias.

In high-risk and troponin-positive patients with NSTE-ACS who have been initially stabilized, an early invasive strategy improves the composite clinical end point of death, recurrent MI, and repeat hospitalization compared with an ischemia-guided approach. In patients with an elevated clinical risk score, significant ST-segment deviation, or elevated cardiac biomarkers, cardiac catheterization is usually performed within 24 hours of presentation. Other patients, including those with diabetes, stage 2 to 3 chronic kidney disease, LV dysfunction, and recent PCI without elevated risk scores, may be safely evaluated with coronary angiography within 72 hours of presentation (delayed invasive strategy). The choice of revascularization procedure (PCI or CABG) is based on the results of angiography.

With an ischemia-guided strategy, patients undergo noninvasive stress testing with LV function assessment before hospital discharge. Cardiac catheterization is reserved for patients with active or intermittent ischemia, including those with angina despite medical therapy or evidence of ischemia on stress testing, and patients at very high clinical risk based on risk score. The ischemia-guided approach is appropriate for low-risk patients (TIMI score <2 or GRACE score <109), particularly low-risk women, who may have worse outcomes with an early invasive approach. The recommendations for non–low-risk women are identical to those for men.

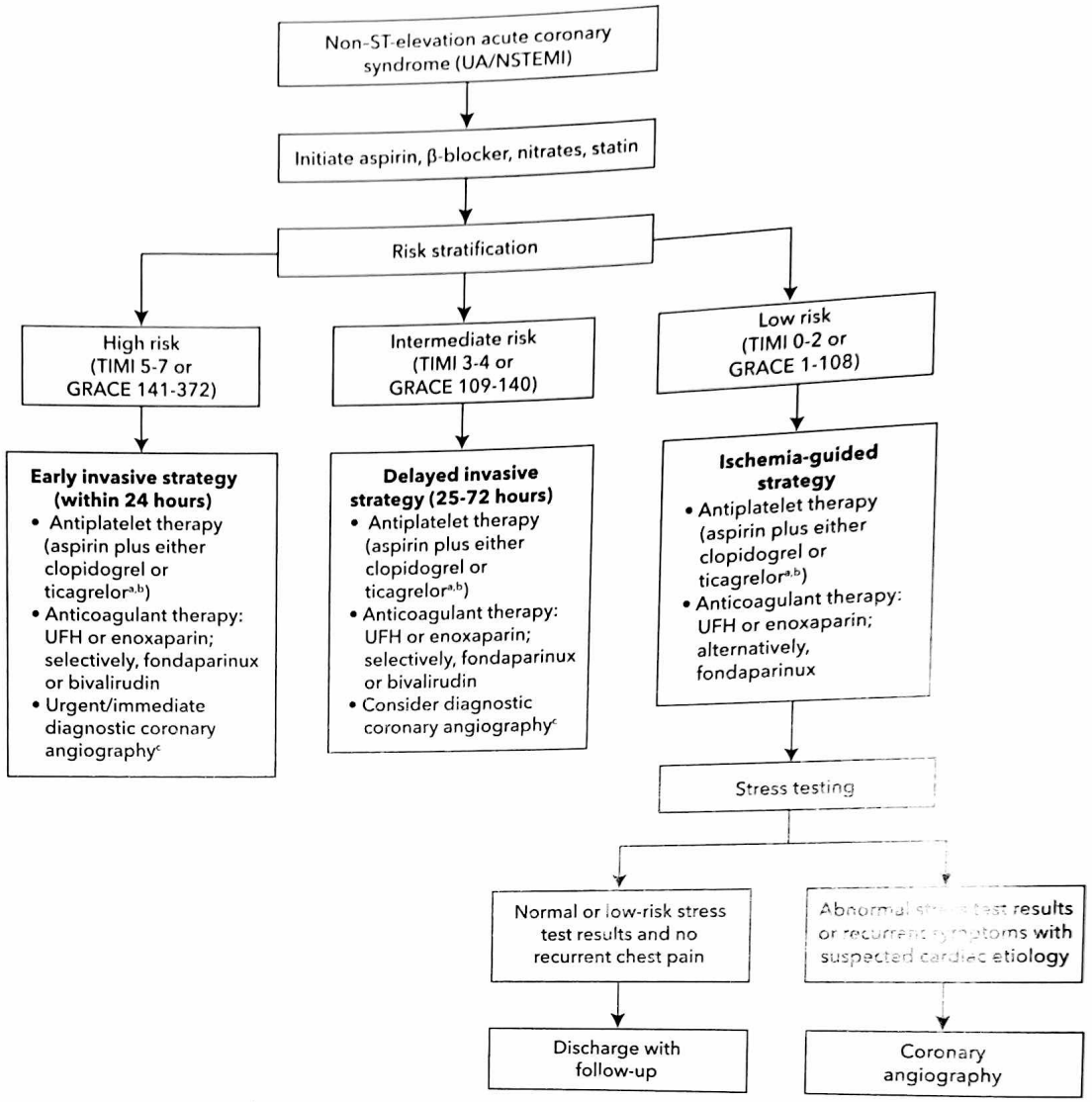

FIGURE 11. Initial management of non–ST-elevation acute coronary syndromes. NSTEMI = non–ST-elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

[a]Clopidogrel or ticagrelor may be administered at the time of hospital admission and diagnosis of acute coronary syndrome.

[b]If coronary artery bypass grafting is required, clopidogrel or ticagrelor should be stopped, and surgery should be delayed for at least 5 days.

[c]If the decision is made to withhold a $P2Y_{12}$ inhibitor until the time of angiography and a $P2Y_{12}$ inhibitor is desired, clopidogrel, ticagrelor, or prasugrel can be initiated.

Recommendations based on Amsterdam EA, Wenger NK, Brindis RG, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354-94. [PMID: 25249586] doi:10.1161/CIR.0000000000000133

KEY POINTS

- Patients with a non–ST-elevation acute coronary syndrome who have hemodynamic instability, refractory chest pain, heart failure, or ventricular arrhythmias require emergent coronary angiography and percutaneous coronary intervention.
- The decision to pursue an invasive versus ischemia-guided approach in patients with a non–ST-elevation acute coronary syndrome is guided by the patient's risk for clinical events, which in turn is determined by decision support tools, such as the TIMI or GRACE score.

Medical Therapy for Acute Coronary Syndromes

Medical therapies are consistent across the spectrum of atherothrombotic ACS (**Table 10**). However, importantly, thrombolytic therapy has no benefit in patients with NSTE-ACS and is not recommended.

All patients presenting with ACS should receive a loading dose of aspirin, supplemental oxygen for oxygen saturation less than 90% to 92%, therapy to relieve symptoms (nitrates), therapy to reduce infarct size (β-blockers, ACE inhibitors), high-intensity statin therapy, and antithrombotic therapy (antiplatelet agents and anticoagulants).

TABLE 10.1 Medical Therapy for Acute Coronary Syndromes

Medication	Drugs in Class	Dosage	Indications	Comments
Antiplatelet Medications				
Aspirin	N/A	81-162 mg/d	All patients with ACS, unless intolerant or allergic	Non-enteric formulation recommended for aspirin-naïve patients with ACS
			Aspirin desensitization may be considered for patients with allergy	
Clopidogrel	N/A	75 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS for at least 1 y	Clopidogrel is recommended as an alternative to aspirin for patients with stable CAD and intolerance or allergy to aspirin
Prasugrel	N/A	10 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS for at least 1 y; prasugrel is indicated only in patients with ACS in whom PCI is performed	Contraindicated with age >75 y or history of stroke/TIA
				Dosage adjustment to 5 mg/d should be considered for patients weighing <60 kg (132 lb)
Ticagrelor	N/A	90 mg twice daily	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS for at least 1 y	More rapid onset of action; does not require first-pass hepatic metabolism; no known genetic polymorphisms
				Increased risk for bleeding with aspirin doses ≥100 mg
Cardioprotective Medications				
β-Blockers	Atenolol, metoprolol, carvedilol, nebivolol, bisoprolol	Variable	All patients with prior MI or LV systolic dysfunction (only metoprolol succinate, carvedilol, or bisoprolol)	Avoid in patients with cardiogenic shock, hypotension, or conduction disturbances
ACE inhibitors	Benazepril, captopril, enalapril, fosinopril, perindopril, trandolapril, lisinopril, ramipril, quinapril	Variable	All patients with LV systolic dysfunction, hypertension, diabetes mellitus, or kidney disease	Particularly beneficial in patients with anterior MI
Angiotensin receptor blockers	Losartan, valsartan, olmesartan, candesartan, irbesartan, telmisartan	Variable	All patients with LV systolic dysfunction, hypertension, diabetes, or kidney disease who are intolerant of ACE inhibitors	Should not be used in patients already taking an ACE inhibitor
Aldosterone inhibitor	Eplerenone	25-50 mg/d	Patients with STEMI who have an LVEF ≤40% and either clinical heart failure or diabetes	Use with caution in patients with chronic kidney disease or hyperkalemia
High-intensity statin therapy	Atorvastatin	40-80 mg/d	All patients with evidence of CAD and age ≤75 y	
	Rosuvastatin	20-40 mg/d		
Moderate-intensity statin therapy	Atorvastatin	10-20 mg/d	All patients with evidence of CAD and age >75 y or otherwise intolerant of high-intensity statin therapy	Simvastatin dosage should be limited to 20 mg/d in patients taking amlodipine
	Rosuvastatin	5-10 mg/d		
	Simvastatin	20-40 mg/d		
	Pravastatin	40-80 mg/d		
	Lovastatin	40 mg/d		
	Fluvastatin	40 mg twice daily		

(Continued on the next page)

TABLE 10. Medical Therapy for Acute Coronary Syndromes (Continued)

Medication	Drugs in Class	Dosage	Indications	Comments
Antianginal Medications				
Nitroglycerin	Nitrostat (SL)	0.4 mg every 5 min for a total of three doses	As part of multimodality treatment of ongoing chest pain	Avoid nitrates with SBP <90 mm Hg or ≥30 mm Hg below baseline, bradycardia, tachycardia, RV infarction, PDE-5 inhibitor use within the last 24-48 h, HCM, or severe AS
	Nitronal (IV)	Initial IV infusion rate of 5-10 μg/min	Persistent chest pain following three SL doses and as part of multimodality treatment of heart failure, hypertension	
Nondihydropyridine calcium channel blockers	Diltiazem, verapamil	Variable	Patients with NSTE-ACS who are intolerant of β-blockers or with angina refractory to nitrates and β-blockers	No benefit in patients with STEMI May worsen clinical status with coincidental heart failure or LV dysfunction Avoid with evidence of heart failure, cardiogenic shock, or conduction abnormalities

ACS = acute coronary syndrome; AS = aortic stenosis; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy; IV = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N/A = not applicable; NSTE-ACS = non–ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PDE-5 = phosphodiesterase 5; RV = right ventricular; SBP = systolic blood pressure; SL = sublingual; STEMI = ST-elevation myocardial infarction; TIA = transient ischemic attack.

Antiplatelet Medications

Aspirin (162-325 mg) should be administered at presentation to all patients with ACS, followed by a daily dose of 81 to 162 mg. Early clopidogrel loading has been recommended in patients with ACS regardless of reperfusion or revascularization strategy, although the optimal timing for loading of other oral antiplatelet agents is less clear. Prasugrel loading before coronary angiography is not beneficial. Clopidogrel or ticagrelor therapy is recommended for 1 year after ACS presentation. Prasugrel is indicated only in patients treated with PCI because it is associated with comparable efficacy but increased bleeding when compared with clopidogrel in medically managed patients. Evidence supports continuing DAPT beyond 1 year in patients at high risk for recurrent vascular events, such as those with depressed LV function, saphenous vein graft stenting, or diabetes, in whom the benefit exceeds the bleeding risk.

Intravenous glycoprotein IIb/IIIa inhibitors are generally reserved for use during PCI in patients with evident thrombus at the time of coronary angiography and intervention. In patients tolerant of DAPT, upfront administration of glycoprotein IIb/IIIa inhibition in the emergency department is associated with lack of benefit and increased bleeding risk, and similarly, there is no proven role for initiation following successful PCI.

Anticoagulant Medications

The choice of anticoagulant during ACS depends on the reperfusion strategy available to the patient. In patients receiving thrombolytic therapy, anticoagulation with unfractionated heparin, enoxaparin, or fondaparinux is associated with reduced reocclusion of the infarct-related artery and improved outcomes.

In patients undergoing PCI for ACS, especially those with kidney dysfunction, unfractionated heparin is favored over enoxaparin because of the ability to monitor the degree of anticoagulation with activated clotting times. Fondaparinux is not indicated during PCI given the risk for procedural thrombosis.

For patients proceeding to the catheterization laboratory, anticoagulant therapy should be provided until revascularization with PCI or CABG. In medically treated patients, anticoagulation is recommended for at least 48 hours and is generally continued until discharge.

Antianginal Medications

Oxygen therapy, often considered an antianginal therapy, is no longer routinely indicated in ACS. Supplemental oxygen in the setting of normal oxygen saturation is associated with increased mortality in patients with ACS. Guidelines suggest initiating oxygen therapy in patients with oxygen saturation of less than 90% to 92% and maintaining saturation at 93% to 96%. The American Heart Association, however, recommends oxygen therapy for an oxygen saturation less than 90% or in the presence of heart failure or dyspnea without providing an upper oxygen saturation limit.

β-Blockers decrease myocardial oxygen demand, reduce the incidence of ventricular arrhythmias, and improve long-term survival in patients with ACS. These agents should be administered orally (not intravenously) within 24 hours of presentation, except in patients with evidence of hypotension, cardiogenic shock, pulmonary congestion, or atrioventricular block.

Nitrates are used primarily to manage angina symptoms in ACS. Sublingual nitrates should be administered at presentation

to relieve chest pain and thereby reduce counterproductive sympathetic drive. For patients with persistent chest pain despite β-blockade, intravenous nitroglycerin can alleviate symptoms, particularly in those with hypertension. Patients receiving nitroglycerin infusions for a prolonged time often require increased doses because of the development of nitrate tolerance. Nitrates should be avoided in patients who have had recent exposure (within 24–48 hours) to phosphodiesterase-5 inhibitors, such as sildenafil, and in those with shock or RV infarction.

Lipid-Lowering Medications

Statin therapy reduces mortality and adverse clinical event rates after ACS. High-intensity statin therapy is recommended because it improves outcomes compared with lower-intensity treatment. Initiating statins in the inpatient setting is associated with greater medication adherence. Furthermore, statin preloading before PCI has been associated with lower rates of periprocedural MI.

Angiotensin Receptor and Aldosterone Agents

ACE inhibitors are indicated in patients with ACS, particularly those with impaired LV function, heart failure, anterior wall infarction, or diabetes. ARBs may be used in patients intolerant of ACE inhibitors. These agents have shown significant early benefit following STEMI and should be administered within the first 24 hours of presentation in the absence of contraindications.

Eplerenone, an aldosterone antagonist, has proved beneficial in patients with STEMI who have an ejection fraction of 40% or less and either heart failure or diabetes, especially when initiated within 1 week of presentation. Potassium levels must be monitored carefully, especially in patients with preexisting kidney dysfunction and those receiving concomitant ACE inhibitors or ARBs.

KEY POINTS

HVC
- Thrombolytic therapy is not indicated in patients with non–ST-elevation acute coronary syndromes.
- All patients presenting with acute coronary syndrome should receive a loading dose of aspirin, supplemental oxygen for oxygen saturation less than 90%, nitrates, a β-blocker, an ACE inhibitor, a high-intensity statin, a $P2Y_{12}$ inhibitor, and an anticoagulant.
- Dual antiplatelet therapy is indicated for at least 1 year after acute coronary syndrome (ACS); clopidogrel and ticagrelor may be used in all patients with ACS, whereas prasugrel may be used only in patients treated with percutaneous coronary intervention.
- β-Blockers decrease myocardial oxygen demand, reduce the incidence of ventricular arrhythmias, and improve long-term survival in patients with acute coronary syndrome; however, these agents are contraindicated with cardiogenic shock or high-grade atrioventricular block.

Acute Coronary Syndromes Not Associated With Obstructive Coronary Artery Disease

Some patients with chest pain, elevated cardiac troponin levels, and characteristic ST-segment elevation on ECG have MI in the absence of obstructive CAD (MINOCA). Other related syndromes may mimic MINOCA but do not involve frank infarction. Regardless of whether there is irreversible myocardial injury, treatment of these conditions with thrombolytic agents and revascularization in the absence of occlusive coronary disease and plaque rupture is not beneficial or recommended.

Spontaneous coronary artery dissection (SCAD) is a common cause of chest pain among younger women who present with ACS and in the peripartum period. Although the pathophysiology is not clearly established, SCAD involves development of a nontraumatic and non-iatrogenic intramural hematoma with or without intimal dissection with luminal communication. The enlarging hematoma in the false lumen compresses the true lumen of the coronary artery and in potential combination with obstructing dissection leads to chest pain, ischemia, and/or infarction. Diagnosis requires a high index of suspicion and confirmation by invasive or noninvasive angiography, using care to minimize unnecessary radiation exposure. When associated with STEMI, SCAD may be managed invasively; CABG, however, is rarely indicated. PCI may be safely deferred when coronary flow is preserved and symptoms can be controlled and closely monitored, because acute vascular manipulation often results in dissection extension, and early vascular healing often occurs without further intervention.

Coronary vasospasm is sudden coronary artery constriction occurring spontaneously or following use of illicit substances (methamphetamines, cocaine) or prescription drugs (5-fluorouracil, bromocriptine). Spontaneous coronary vasospasm often occurs at night and may occur at rest or following exercise. ECG abnormalities may be nonspecific or mimic STEMI patterns. Coronary vasospasm is a diagnosis of exclusion and often involves coronary angiography to exclude fixed disease. Invasive provocative testing can be performed but usually is not indicated. Patients suspected of having vasospasm (or the related microvascular endothelial dysfunction) often are treated empirically with nitrates and/or calcium channel blockers.

Cardiac syndrome X is a poorly defined condition characterized by anginal chest pain in the presence of angiographically normal coronary arteries or insignificant CAD (<50% stenosis). Several hypotheses have been proposed to explain the pathogenesis of this syndrome, with one of the most accepted centering on microvascular dysfunction as the cause. Cardiac syndrome X is a frequent cause of chest pain syndromes in women and may be associated with adverse outcomes despite the frequent lack of traditional risk factors for CAD. Patients may be treated with β-blockers, calcium channel blockers, nitrates, and ranolazine.

Takotsubo cardiomyopathy presents as acute chest pain, ECG changes (often ST-segment elevation), and elevated

cardiac enzyme levels in the absence of coronary occlusion. Takotsubo cardiomyopathy more commonly occurs in women, and there is often an antecedent psychological or physical stressor. It is a diagnosis of exclusion based on lack of significant coronary stenosis with significant wall motion abnormality (often systolic apical ballooning and notable sparing of the base of the heart) on echocardiography or ventriculography.

Care After an Acute Coronary Syndrome

All patients with ACS should continue aspirin, preferably 81 mg/d, indefinitely. DAPT is recommended for at least 1 year (see Table 10). There is some evidence for extending DAPT beyond 1 year; however, the decision to prolong therapy should be individualized, with the risk for bleeding weighed against the risk for thrombosis.

Statin therapy should continue indefinitely. Patients with a history of multiple major atherosclerotic cardiovascular disease (ASCVD) events or one major ASCVD event and multiple high-risk conditions are judged to be at very high risk for recurrent ASCVD events. These patients may benefit from the addition of nonstatin drug therapy to maximally tolerated statin therapy (see MKSAP 19 General Internal Medicine 1).

β-Blockers should be continued indefinitely in all patients. ACE inhibitors should be continued indefinitely in patients with LV dysfunction and may be beneficial in patients with preserved LV function, especially in those with diabetes. Guidelines recommend avoiding NSAIDs if possible, because of the increased cardiovascular risk associated with these drugs.

In patients at risk for sudden cardiac death after MI, guidelines do not recommend placement of an implantable cardioverter-defibrillator for primary prevention within 40 days of infarction because of lack of benefit. Despite a theoretical primary prevention benefit in high-risk patients following MI, routine use of a temporary wearable cardioverter-defibrillator has not shown benefit in reducing arrhythmic death within 84 days of MI in the large, randomized VEST study. There are no clear indications for a wearable cardioverter-defibrillator; however, it is an option for select patients with a high risk for sudden death before implantation of a permanent defibrillator device.

Patients with ACS should be referred for cardiac rehabilitation, a medically observed exercise program that reduces mortality while improving functional capacity, medication adherence, and risk factor profiles. Patients at low risk (aged ≤75 years with symptoms less than New York Heart Association functional class III to IV, a normal ejection fraction, and no arrhythmia) who prefer home-based cardiac rehabilitation with remote coaching and indirect exercise supervision benefit as well.

Sexual activity can generally resume after 2 weeks in younger, previously fit patients with uncomplicated MI and after 6 weeks in patients with more extensive infarcts, assuming other aspects of cardiac rehabilitation are proceeding uneventfully. Patients should be counseled that erectile dysfunction and decreased satisfaction during sexual activity are not uncommon following MI. Drug therapy for erectile dysfunction is effective and safe for patients who are not taking nitrates (see MKSAP 19 General Internal Medicine 2).

Physicians should counsel patients that treatment goals after MI are focused on risk reduction and achieving baseline functional status, although that expectation must be tempered in those with post-MI heart failure or significant reduction in ejection fraction. Depression after MI is common, and screening is recommended; cognitive behavioral therapy and selective serotonin reuptake inhibitors are first-line therapies.

KEY POINT

- All patients with acute coronary syndrome should be referred for cardiac rehabilitation, which reduces mortality while improving functional capacity, medication adherence, and risk factor profiles.

Management of Coronary Artery Disease in Specific Populations

Patients With Asymptomatic Vascular Disease

Silent myocardial ischemia is a long-recognized syndrome with widely varying prevalence and risk estimates, and its recognition is increasing with the use of diagnostic chest imaging and dedicated coronary artery calcium scoring studies. Although it is clear that patients with silent myocardial ischemia, especially those with known underlying heart disease, have a worse prognosis, there are no guideline recommendations on which patients should be evaluated with stress testing, ambulatory monitoring, or cardiac catheterization nor on how establishing the diagnosis modifies secondary prevention opportunities.

Patients Older Than 75 Years

Patients older than 75 years are at heightened cardiovascular risk because of a higher prevalence and greater severity and extent of CAD. Comorbid conditions, loss of muscle mass, and gait abnormalities often limit or prohibit the use of exercise stress testing for prognostic and diagnostic purposes. When cardiovascular disease is identified, older adults often are not treated with recognized secondary prevention therapies (e.g., antiplatelet agents, β-blockers, ACE inhibitors, and statins). This is at least partly due a perceived heightened risk for adverse therapeutic response compounded by the lack of outcome data in these patients, who are often excluded from prospective trials. Furthermore, invasive angiography and revascularization are used less often in older adults, likely due to higher procedural morbidity and mortality. Exercise, diet, and healthy lifestyle choices remain essential elements of risk reduction in all age groups, with antiplatelet therapy, lipid-lowering therapy, blood pressure control, and glycemic control