CONT.

anterior STEMI generally leads to an apical VSD. VSDs typically occur within 3 to 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 owing to 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.

Acute severe mitral regurgitation may occur as a result of papillary muscle rupture. Most often, the posteromedial papillary muscle ruptures with right coronary artery occlusion. This complication tends to occur several days after STEMI. Afterload reduction and IABP placement may be tried, but urgent surgical intervention is usually necessary. Acute severe mitral regurgitation may also result from left ventricular 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.

KEY POINTS

- Primary percutaneous coronary intervention is preferred to thrombolytic therapy for the treatment of ST-elevation myocardial infarction.
- If primary percutaneous coronary intervention (PPCI) is not available within 120 minutes of first medical contact, patients with ST-elevation myocardial infarction should receive thrombolytic therapy and be urgently transferred to a PPCI-capable center.
- β-Blockers reduce the incidence of ventricular arrhythmias and improve long-term survival in patients with ST-elevation myocardial infarction; however, these agents are contraindicated when signs or symptoms of cardiogenic shock are present.
- All patients presenting with an ST-elevation myocardial infarction should be treated with aspirin, anticoagulation therapy, and a $P2Y_{12}$ inhibitor.

Non-ST-Elevation Acute Coronary Syndromes

NSTE-ACS is a common presentation of CAD. The chest pain associated with an NSTE-ACS is generally acute, is new in onset, and often occurs with rest or minimal exertion. The pathogenesis is plaque rupture within a coronary artery and transient or incomplete occlusion of the vessel. NSTEMI is differentiated from unstable angina by the presence of elevated serum cardiac biomarkers at the time of evaluation.

Risk Stratification

Many treatment options are available for patients with NSTE-ACS, and risk stratification tools can be used to aid in diagnostic and therapeutic decision making. The two most commonly used risk scores are the TIMI and GRACE risk models. The simpler of the two models, the TIMI risk score, predicts 14-day death, recurrent MI, and urgent revascularization rates (**Table 11**). The GRACE risk score (available at www.gracescore.org) is more complex, requiring a nomogram to calculate. It incorporates physical examination findings (heart rate, blood pressure, Killip class), clinical features (age, cardiac arrest at admission), electrocardiographic findings (ST-segment deviation), and biomarker variables (creatinine levels, elevated cardiac enzymes) to predict in-house and postdischarge death and MI risk. These scoring systems are useful in determining which patients may benefit most from more aggressive strategies, such as anticoagulation or an early invasive approach (**Figure 9**). An elevated troponin level is itself a powerful predictor of outcomes and identifies patients who will benefit from aggressive medical and invasive strategies (coronary angiography).

Medical Therapy

Medical therapies for patients with NSTE-ACS are similar to those for other ACS presentations; however, some unique features in this patient population are highly relevant to the

TABLE 11. 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, McCabe CH, Horacek T, Papuchis G, 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]

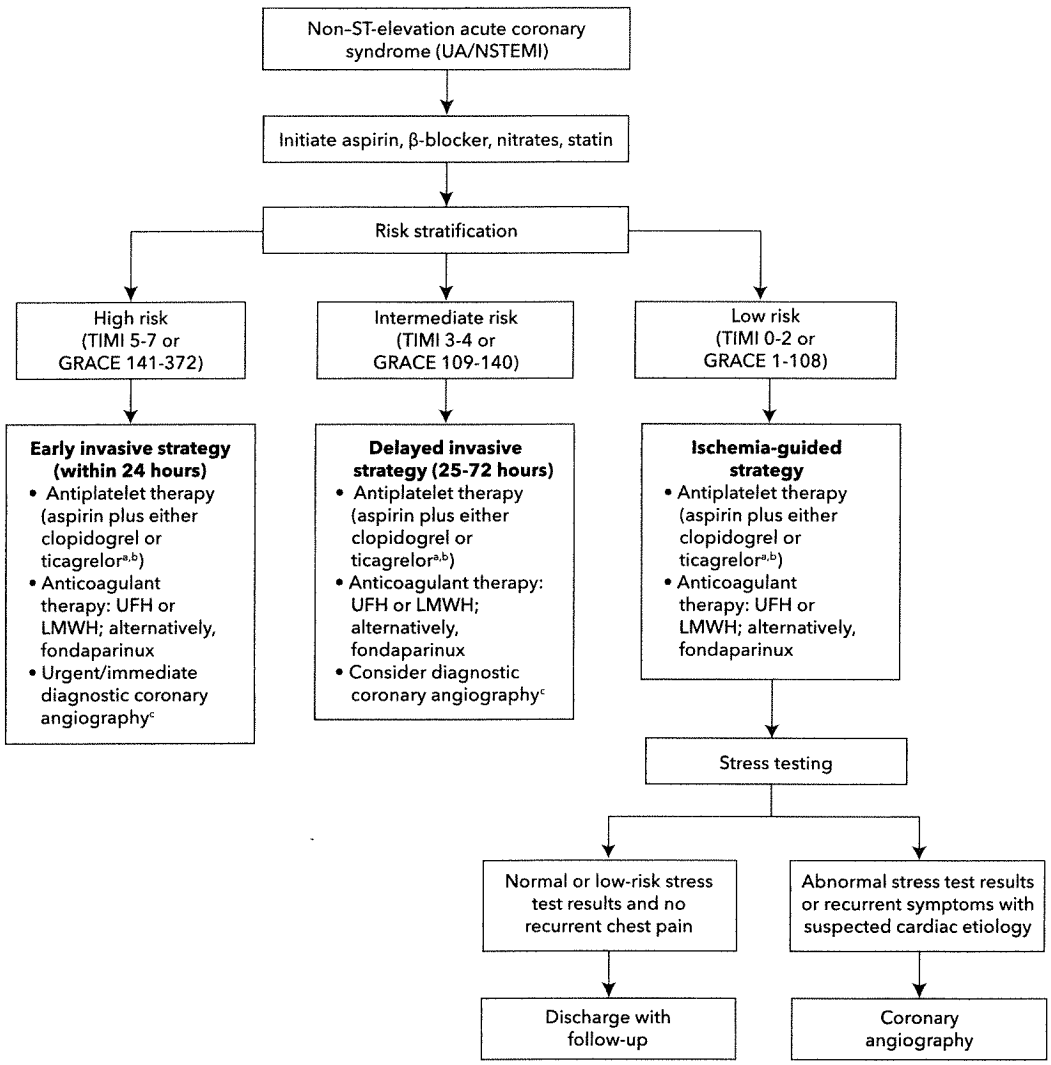

FIGURE 9. Initial management of non-ST-elevation acute coronary syndromes. LMWH = low-molecular-weight heparin; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

[a]Clopidogrel or ticagrelor may be dosed 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, Casey DE Jr, Ganiats TG, Holmes DR Jr, 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

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treatment of this condition. Notably, thrombolytic therapy is not beneficial in patients with NSTE-ACS and is not recommended. Medical therapies for the treatment of NSTE-ACS are summarized in Table 10.

Antiplatelet Medications

Aspirin (162-325 mg) should be administered at presentation to all patients with definite or likely NSTE-ACS, followed by a daily dose of 81 to 162 mg. Early clopidogrel loading has been recommended in patients with NSTEMI; however, the optimal timing for loading of other oral antiplatelet agents is unclear. Prasugrel loading before coronary angiography is not beneficial. Clopidogrel or ticagrelor therapy is recommended for 1 year after NSTE-ACS presentation, regardless of the treatment strategy. Prasugrel is indicated only in patients treated with PCI. Evidence supports continuing DAPT beyond 1 year in patients at high risk for recurrent vascular events (such as those with depressed left ventricular function, saphenous vein graft stenting, or diabetes) in whom the benefit exceeds the bleeding risk.

The use of intravenous glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban) has decreased over the past decade. Although these drugs had been shown to improve outcomes in patients with NSTE-ACS (particularly higher-risk and troponin-positive patients), subsequent study demonstrated

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no benefit of upstream glycoprotein IIb/IIIa blockade and an increased risk for bleeding. These agents are generally reserved for use during PCI; however, given the advent of quicker-acting and more potent oral antiplatelet agents, administration of glycoprotein IIb/IIIa inhibitors in the setting of PCI has also significantly declined.

Anticoagulant Medications

Patients with definite NSTE-ACS should undergo anticoagulation. Intravenous unfractionated heparin and subcutaneous enoxaparin are most commonly used. Intravenous heparin is preferred in patients with kidney dysfunction because enoxaparin and similar agents are partially cleared by the kidneys. 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

β-Blockers should be administered within 24 hours of NSTE-ACS because these agents reduce ventricular arrhythmias and long-term mortality. β-Blockers are not appropriate for patients with evidence of heart failure or shock at presentation. Likewise, these agents should not be given to patients with bradycardia, heart block, or a PR interval greater than 240 ms on ECG.

Calcium channel blockers are recommended for patients with NSTE-ACS intolerant of β-blocker therapy or in patients with angina symptoms despite therapy with nitrates and β-blockers. The nondihydropyridine calcium channel blockers reduce heart rate, blood pressure, and cardiac contractility, thereby reducing myocardial oxygen demand. However, because of these hemodynamic effects, use of these agents is also contraindicated in the setting of shock, pulmonary edema, or significant conduction disease. Importantly, short-acting dihydropyridine calcium channel blockers are contraindicated, owing to their ability to acutely lower the blood pressure and raise the heart rate.

Nitrates are primarily used to manage angina symptoms in patients with NSTE-ACS. Sublingual nitrates should be administered at presentation to relieve chest pain. 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 will often require increased doses due to the development of nitrate tolerance. Nitrates should be avoided in patients who have had recent exposure (within 24-48 hours) to phosphodiesterase type 5 inhibitors such as sildenafil.

Patients with chest pain refractory to antianginal medications should be evaluated for noncardiac causes of chest pain and biomarker elevation, as well as for the possibility of severe underlying CAD or electrocardiographically silent coronary thrombosis.

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.

Invasive Versus Ischemia-Guided Treatment

Immediate 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 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. The type of revascularization procedure (PCI or CABG) depends on the results of angiography.

An invasive strategy improves the composite clinical endpoint of death, recurrent MI, and repeat hospitalization compared with an ischemia-guided approach in high-risk and troponin-positive patients with NSTE-ACS. An invasive strategy is the favored approach, with the exception of patients with extensive noncardiac comorbid conditions (such as cancer), in whom the clinical benefits of revascularization may be lower, and patients with acute chest pain unlikely to be related to CAD.

With an ischemia-guided treatment strategy, patients undergo noninvasive stress testing 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). H

KEY POINTS

- In patients with a non-ST-elevation acute coronary syndrome, initial risk stratification with the TIMI or GRACE risk scores aids in diagnostic and therapeutic decision making.
- Thrombolytic therapy is not indicated in patients with non-ST-elevation acute coronary syndromes. HVC
- The decision to pursue an invasive approach versus an ischemia-guided approach in patients with a non-ST-elevation acute coronary syndrome depends on the patient's risk for clinical events.
- Dual antiplatelet therapy is indicated for at least 1 year after a non-ST-elevation acute coronary syndrome (NSTE-ACS); clopidogrel and ticagrelor may be used in all patients with NSTE-ACS, whereas prasugrel may be used only in patients treated with percutaneous coronary intervention.

Acute Coronary Syndromes Not Associated with Obstructive Coronary Disease

Elevations in cardiac enzymes, particularly cardiac troponins, coupled with ECG changes provide excellent diagnostic discrimination for ACS. However, conditions not caused by acute coronary plaque rupture can present with similar findings, and treatment of these conditions with antithrombotic agents and revascularization is not beneficial or recommended.

Patients with accelerated hypertension, significant left ventricular hypertrophy, and cardiomyopathies may present with chest pain and elevated cardiac troponin levels caused by elevated left ventricular filling pressures or wall tension rather than plaque rupture. The ECG findings are often abnormal in these patients. Patients with supraventricular tachycardias, which may also dramatically increase the rate-pressure product, often present with chest pain, ST-segment depressions, and elevated cardiac enzyme levels, even if no CAD is present.

Coronary vasospasm is sudden constriction of a coronary artery. It may occur spontaneously or follow use of illicit substances (methamphetamines, cocaine) or prescription drugs (5-fluorouracil, bromocriptine). ECG abnormalities may be nonspecific or mimic STEMI patterns. Coronary vasospasm is a diagnosis of exclusion. Unless the patient has a history of vasospasm, patients often undergo coronary angiography, which may reveal normal findings or slowed coronary flow resulting from microvascular dysfunction. Provocative testing can be performed but is not usually indicated. Patients suspected of having vasospasm (or the related microvascular dysfunction) are usually treated empirically with nitrates and/or calcium channel blockers.

Takotsubo cardiomyopathy, alternatively termed stress cardiomyopathy or apical ballooning syndrome, is a relatively uncommon form of ACS (see Heart Failure). Patients present with acute chest pain, ECG changes (often ST-segment elevations), and elevated cardiac enzyme levels. Takotsubo cardiomyopathy most commonly occurs in women, and there is often, but not always, an antecedent psychological or physical stressor. Patients may initially be diagnosed with STEMI but found to have no significant coronary stenosis at the time of cardiac catheterization. Systolic apical ballooning and notable sparing of the base of the heart on echocardiography or ventriculography are characteristic of this syndrome.

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). Cardiac syndrome X is a frequent cause of chest pain syndromes in women, and patients often present without traditional risk factors for CAD. Several hypotheses have been proposed to explain the pathogenesis of this syndrome. One of the most accepted centers on microvascular dysfunction as the cause. Patients may be treated with β-blockers, calcium channel blockers, and nitrates.

Patients with chronic inflammatory muscle diseases or neuromuscular diseases may have elevated levels of cardiac troponin T due to expression of this enzyme in skeletal muscle. The cardiac troponin I level is normal in these cases, which can be helpful in differentiating ACS from these other entities.

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 in stented and medically treated patients; 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. β-Blockade and ACE inhibitor therapy should also be continued indefinitely in patients with left ventricular dysfunction; continuation of these medications is reasonable in patients with normal left ventricular function. Guidelines recommend avoiding NSAIDs if possible, owing to the increased cardiovascular risk associated with these drugs. Patients should be referred for cardiac rehabilitation, a medically observed exercise program, to improve functional capacity and risk factor profiles.

Management of Coronary Artery Disease in Special Populations

Women

Clinical Presentation

Women usually develop ischemic heart disease at an older age than men and more commonly present with stable CAD than an ACS. In women with typical angina symptoms, nonobstructive coronary stenoses are present on coronary angiography in more than 50% of cases, and microvascular dysfunction (endothelium-dependent or endothelium-independent) is thought to be a predominant cause of symptoms in these patients. In women with acute MI, the predominant symptom is chest pain or pressure; however, women can often have atypical symptoms, such as fatigue, dyspnea, nausea, or abdominal symptoms.

Several unique manifestations of cardiovascular disease, including spontaneous coronary artery dissection, takotsubo cardiomyopathy, and coronary vasospasm, occur primarily in women. Spontaneous coronary artery dissection is a common cause of chest pain among younger women who present with ACS. In many cases, spontaneous coronary artery dissection occurs in the peripartum period and is thought to be caused by hormonal changes, although the true cause is unknown. Given the preponderance of young women with this condition, minimizing radiation exposure and avoiding invasive angiography are recommended. This can typically be achieved with the use of supportive care with or without CT angiography. In severe cases, vessel occlusion causes STEMI and necessitates emergent revascularization.

Evaluation and Treatment

Noninvasive stress testing for the evaluation of CAD symptoms has a lower sensitivity and specificity in women than in men,

and ST-segment deviation has a lower reported accuracy in women. Therefore, stress testing with imaging provides better accuracy in women (see Diagnostic Testing in Cardiology). Despite these differences, the same guideline recommendations apply to both women and men.

Reports from observational studies and substudies of randomized controlled trials suggest that women have worse outcomes after STEMI presentation. The cause of these worse outcomes is thought to be delays in recognition of CAD and longer overall ischemic time. Complication rates are also reported to be higher in women who undergo reperfusion therapy for STEMI. The COURAGE trial demonstrated that among patients with stable angina treated with revascularization, women had lower rates of overall mortality and nonfatal MI but a higher rate of complications compared with men. Overall, treatment guidelines do not differ for men and women.

Diabetes Mellitus

Risk and Evaluation

Diabetes has been proposed as a CAD equivalent because age-adjusted risk for CAD events is two- to threefold higher in patients with diabetes. Cardiovascular morbidity and mortality are also significantly higher in this population, especially in patients with type 2 diabetes. Much of the risk has been attributed to the higher incidence of known cardiovascular risk factors; however, evidence suggests that underlying vascular dysfunction may play an important role.

Patients with diabetes may present with atypical cardiac symptoms, such as dyspnea or nausea, requiring a high index of suspicion for CAD during their evaluation. The diagnostic accuracy of noninvasive stress testing in symptomatic patients with diabetes is similar to that in patients without diabetes. Although traditional risk factors for CAD should be aggressively managed in patients with diabetes, screening for CAD in asymptomatic persons is controversial, and routine stress testing is not recommended.

Medical Therapy and Secondary Prevention

Medical therapy for patients with diabetes and CAD includes aggressive risk factor reduction, glucose control, and antianginal therapy. The American College of Cardiology/American Heart Association recommend antihypertensive treatment with a target blood pressure below 130/80 mm Hg in patients with diabetes. In contrast, the American Diabetes Association recommends a systolic blood pressure goal of less than 140 mm Hg and a diastolic blood pressure goal of less than 90 mm Hg for most patients. Lower systolic and diastolic blood pressure targets may be appropriate for individuals at high risk for cardiovascular disease, if they can be achieved without undue treatment burden. ACE inhibitors and ARBs are preferred in the setting of hypertension because of their kidney-protective effects. High-intensity statin therapy is indicated in most patients with diabetes and CAD.

Aspirin is recommended for secondary prevention in all patients with diabetes and CAD. Primary prevention is recommended for patients with diabetes with a 10-year cardiovascular risk greater than 10% or one additional risk factor.

Tight glycemic control reduces microvascular complications; however, it does not reduce the risk for MI. In a recent study, liraglutide, a glucagon-like peptide-1 analogue, was associated with reduced risk for cardiovascular death in patients with type 2 diabetes and high cardiovascular risk. Initial studies suggested thiazolidinediones, specifically rosiglitazone, were associated with an elevated risk for cardiovascular events, although a subsequent clinical trial demonstrated no elevated risk for MI or death. Consequently, the FDA has removed the restriction on rosiglitazone use in patients with type 2 diabetes and CAD. Metformin does not have any cardiovascular effects, but caution should be exercised in patients undergoing coronary angiography, patients who have had an MI, and patients with heart failure because of concern for potentially fatal lactic acidosis.

Invasive Treatment

The choice of revascularization strategy (PCI or CABG) in patients with diabetes is based on many factors, including the severity and extent of CAD, comorbid conditions, and degree of atherosclerotic narrowing of small, distal vessels. Mortality rates are similar between the two procedures; however, CABG is generally preferred because it is associated with lower rates of repeat revascularization. In patients who undergo PCI, drug-eluting stent placement is recommended to reduce the occurrence of target vessel revascularization because of higher rates of restenosis in patients with diabetes.

KEY POINTS

- Stress testing is not routinely recommended in asymptomatic patients with diabetes mellitus to detect subclinical coronary artery disease. **HVC**
- Coronary artery bypass grafting is the preferred mode of revascularization in patients with diabetes mellitus.

Heart Failure

Pathophysiology of Heart Failure

Heart failure is a clinical syndrome characterized by signs and symptoms of fluid overload and decreased cardiac output. Heart failure can result from systolic or diastolic dysfunction. In cases of systolic dysfunction, multiple causes result in reduced stroke volume and ejection fraction, termed heart failure with reduced ejection fraction (HFrEF). Common causes of HFrEF include coronary artery disease (CAD), myocarditis, valvular heart disease, infiltrative processes, and hypertension. Diastolic dysfunction is usually characterized by a stiffened left ventricle with abnormal relaxation during diastole, resulting in an increase in left