Cleveland Clinic

Disease Management Project

May 2013

Physician's Guide to

Acute Coronary Syndrome

In collaboration with

BulletinHealthcare

Cleveland Clinic

Disease Management Project

Dear Healthcare Professional,

Welcome to the *Cleveland Clinic Physician's Guide to Acute Coronary Syndrome*, an information-packed tool brought to you by the Cleveland Clinic Disease Management Project (DMP) in collaboration with Bulletin Healthcare, the leading provider of medical news updates to healthcare professionals like yourself.

This guide covers a wide range of topics, from signs and symptoms of various angina conditions to diagnostic techniques to treatments involving everything from lifestyle modification to pharmacologic therapy and more. And it was researched and written by a leading expert in the field, Curtis M. Rimmerman, MD.

In addition to this guide, you will be receiving coronary artery disease news updates to provide you with the latest information related to various aspects of and new research on this topic.

We hope you find the *Cleveland Clinic Physician's Guide to Acute Coronary Syndrome* and the updates helpful, informative, and of value in your efforts to diagnose, treat, and provide positive patient outcomes. We look forward to hearing your thoughts about this content. Please send your comments to *diseasemanagement@ccf.org*.

To good health!

William Carey, MD
Editor-in-Chief
Disease Management Project
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Contents

Introduction

The term *acute coronary syndrome* (ACS) is in some cases used interchangeably with the term coronary artery disease (CAD). Strictly speaking, however, acute coronary syndrome is a subcategory of coronary artery disease. For example, CAD can be asymptomatic, but ACS almost always represents a symptom such as unstable angina or myocardial infarction.

Definition

Coronary artery disease (CAD) is characterized by atherosclerosis in the epicardial coronary arteries. Atherosclerotic plaques, the hallmark of atherosclerosis, progressively narrow the coronary artery lumen and impair antegrade myocardial blood flow. The reduction in coronary artery flow may be symptomatic or asymptomatic, occur with exertion or at rest, and culminate in a myocardial infarction, depending on obstruction severity and the rapidity of development.

Prevalence

According to the National Center for Health Statistics 2011 report, cardiovascular disease (CVD) remains the leading cause of mortality in the United States in men and women of every major ethnic group. It accounted for nearly 616,000 deaths in 2008 and was responsible for 1 in 4 deaths in the U.S. in the same year. CAD is the most common type of heart disease and, in 2008, 405,309 individuals died in the U.S. from this specific etiology. Every year, approximately 785,000 Americans suffer a first heart attack and another 470,000 will suffer an additional myocardial infarction (MI). In 2010, CAD alone was projected to cost the U.S. $108.9 billion, including the cost of healthcare services, medications, and lost productivity. CVD claims more lives each year than the next 4 leading causes of death combined—cancer, chronic lower respiratory diseases, accidents, and diabetes mellitus.

Pathophysiology

CAD is a chronic process that begins during adolescence and slowly progresses throughout life. Independent risk factors include a family history of premature CAD, cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, sedentary lifestyle, and obesity. These risk factors accelerate or modify a complex and chronic inflammatory vascular process that ultimately manifests as fibrous atherosclerotic plaque.

The most widely accepted theory of atherosclerosis states that the process represents the body's attempt to heal in response to an endothelial injury. The first step in the atherosclerotic process is the development of fatty streaks, which contain atherogenic lipoproteins and macrophage foam cells. These streaks form between the endothelium and internal elastic lamina. Over time, an intermediate lesion—composed of an extracellular lipid core and layers of smooth muscle and connective tissue matrix—eventually forms a fibrous cap. The edge of the fibrous cap (the *shoulder region*) plays a critical role in the development of acute coronary syndromes. The shoulder region is the site where most plaques lose their integrity or rupture. Plaque rupture exposes the underlying thrombogenic core of lipid and necrotic material to circulating blood and its thrombogenic particulates. This exposure results in platelet adherence, aggregation, and progressive luminal narrowing, which can rapidly progress and—often in the absence of coronary artery collateral development—are associated with acute coronary syndromes.

Vascular inflammation has emerged as a critical and established component of atherosclerosis genesis, activity, and potential plaque instability. Patients with established CAD who possess a confluence of risk factors known as the *metabolic syndrome* remain at particularly high risk for a future vascular event, such as an acute MI or cerebrovascular accident. Biochemical markers such as elevated levels of high sensitivity or ultrasensitive C-reactive protein in the absence of systemic inflammation are thought to signal an increased likelihood of vascular inflammation and to portend a higher risk of vascular events. This marker also may signal more rapidly advancing CAD and the need for aggressive preventive measures.

Signs & Symptoms

Patients with CAD can present with stable angina pectoris, unstable angina pectoris, or an MI. They may seek medical attention with their first symptomatic episode of chest discomfort. Many of these patients suffer from unrecognized CAD and may experience an acute plaque rupture or acute myocardial infarction as their first coronary artery diagnostic presentation. Electrical instability can ensue, including potentially lethal cardiac dysrhythmias.

Identifying high-risk persons before their first myocardial event is a multifaceted process that involves both patient- and physician-education efforts. Screening for coronary artery disease is not sufficient. Risk factor modification, from an early age, initiates primary prevention efforts, forestalling the development of symptomatic CAD. Severe CAD can be detected before a patient develops symptoms, especially in a high-risk patient subpopulation in which pre-test probability of flow-limiting coronary artery disease is higher than average.

Angina pectoris is a perceived symptom resulting from a mismatch of myocardial supply and demand. The compromised myocardial blood flow caused by obstructive CAD is not able to meet the metabolic and, specifically, the oxygen demands of the myocardial tissue. The anaerobic threshold is crossed and the patient develops symptomatic angina pectoris. Angina pectoris is typically categorized according to the Canadian Cardiovascular Society's functional classification system (Table 1). Unfortunately, not all patients present with typical angina pectoris symptoms. In approximately 30% to 40% of patients, myocardial ischemia will present in an atypical manner that may consist of subtle symptomatology—discomfort isolated to the arm, throat, or jaw not readily recognized by the patient as a cardiac symptom—or with exertional fatigue, "heartburn", or shortness of breath not equated with a cardiac cause. Many patients have no symptoms at all and those that do often find it difficult to recollect and describe the exact symptoms, provoking factors, and duration.

Stable Angina

Angina pectoris is said to be stable when its pattern of frequency, intensity, ease of provocation, or duration does not change over a period of several weeks. Identification of activities that provoke angina and the amount of sublingual nitroglycerin required to relieve symptoms are helpful indicators of stability versus progression. A decrease in exercise tolerance or an increase in the need for nitroglycerin suggests that the angina is progressing in severity or transitioning to an accelerating pattern.

Table 1. Canadian Cardiovascular Society Functional Classification of Angina Pectoris.

Class	Definition	Specific Activity Scale
I	Ordinary physical activity (e.g., walking and climbing stairs) does not cause angina; angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.	Ability to ski, play basketball, jog at 5 mph, or shovel snow without angina
II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening, when walking more than 2 blocks on level ground, or when climbing more than 1 flight of stairs at a normal pace and in normal conditions.	Ability to garden, rake, roller skate, walk at 4 mph on level ground, have sexual intercourse without stopping
III	Marked limitation of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on level ground or climbing 1 flight of stairs at a normal pace in normal conditions.	Ability to shower or dress without stopping, walk 2.5 mph, bowl, make a bed, play golf
IV	Inability to perform any physical activity without discomfort.	Anginal symptoms may be present at rest. Inability to perform activities requiring 2 or fewer metabolic equivalents without angina

Adapted from: Goldman L, Hashimoto B, Cook EF, Loscalzo A: Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. Circulation 1981;64:1227-1234.

Accelerating Angina

Angina pectoris is said to be accelerating when there is a change in the pattern of stable angina. This may include a greater ease of provocation, more prolonged episodes, and episodes of greater severity, requiring a longer recovery period or more frequent use of sublingual nitroglycerin. This suggests a transition and most likely reflects a change in coronary artery blood flow and perfusion of the myocardium. This frequently portends unstable angina or an acute coronary syndrome such as an acute MI. Should a patient transition from a stable to accelerating pattern of angina, acute medical attention is warranted.

Unstable Angina

Unstable angina pectoris occurs when the pattern of chest discomfort changes abruptly. Signs of unstable angina are: symptoms at rest, a marked increase in the frequency of attacks, discomfort that occurs with minimal activity, and new-onset angina of incapacitating severity. Unstable angina usually is related to the rupture of an atherosclerotic plaque and the abrupt narrowing or occlusion of a coronary artery, representing a medical emergency with an incipient acute coronary syndrome and an MI to follow. Immediate medical attention is mandatory.

Diagnosis

The initial diagnostic approach for CAD encompasses a detailed patient history that includes compiling a comprehensive list of CAD risk factors; a thorough physical examination to include an assessment of all peripheral pulses which, when abnormal, may signal the presence of underlying peripheral arterial disease; and an electrocardiogram. Once this initial evaluation is performed, laboratory blood tests, stress testing, and a cardiac catheterization may be necessary to obtain further diagnostic insight.

History

The history should include any current symptoms and a complete inventory of comorbid conditions. An inventory of cardiac risk factors and a complete family history are essential components. The history should also include information about the character and location of discomfort; radiation of discomfort; associated symptoms; and precipitating, exacerbating, or alleviating factors. The importance of the family history should not be underestimated. A detailed assessment, particularly of first-degree relatives, for the presence of CAD and age of diagnosis is imperative when evaluating a patient's risk-factor profile.

Physical Examination

The results of the physical examination of a patient with stable or unstable angina may be entirely normal. The presence of multiple risk factors or atherosclerosis in the carotid or peripheral arteries increases the likelihood that a chest-pain syndrome is related to myocardial ischemia. Evaluation should include measurements of blood pressure and the ankle–brachial index. Examination of the carotid arteries should include auscultation for bruits. Examination of the chest wall, neck, and shoulders for deformities and tenderness may be helpful in diagnosing musculoskeletal chest discomfort. Cardiac auscultation may detect murmurs caused by aortic stenosis or hypertrophic cardiomyopathy, either of which can cause angina in the absence of epicardial CAD. Assessment of the abdominal aorta for an aneurysm or bruits and palpation of lower extremity pulses is necessary to evaluate for peripheral vascular disease. Careful palpation of all peripheral pulses and assessment of symmetry versus diminution are also valuable noninvasive approaches for assessing the integrity of the arterial circulation. Finally, examination for xanthelasmas, tendon xanthomas, retinal arterial abnormalities, and peripheral neuropathy can be helpful.

Diagnostic and Imaging Studies

Electrocardiography

A resting 12-lead electrocardiogram should be obtained on all patients with suspected CAD. Electrocardiographic results are normal in approximately 50% of patients with chronic stable angina, and they can remain normal during an episode of chest discomfort. Importantly, a normal electrocardiogram does not exclude coronary artery disease (Figure 1). When abnormal, especially when Q waves are present, a regional myocardial territory of diagnostic duration can signify the presence of a past MI with high accuracy.

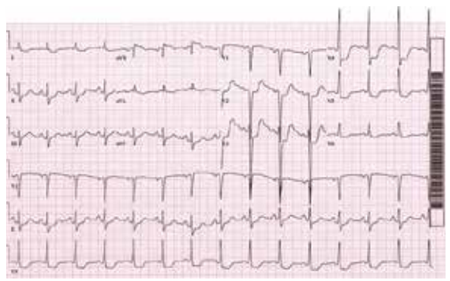


Figure 1. A 12-lead electrocardiograph of ischemic anterolateral ST-segment depression in a patient with known coronary artery disease.

Chest Radiography

The usefulness of a routine chest radiograph in a patient with chest discomfort has not been established. Calcification of the aortic knob is a common finding in older patients and is a nonspecific indicator of flow-limiting obstructive coronary disease. Coronary calcification also may be present. A widened mediastinum may signify an aortic aneurysm and represent the first clue of unstable aortic disease as the cause of chest discomfort.

Cardiac Computed Tomography Angiography

A noninvasive imaging assessment of coronary atherosclerosis is now possible in the form of cardiac computed tomography angiography. When negative, this test possesses a high negative predictive value. The positive predictive value also is high, but exact stenosis quantification can be complicated. Associated calcification can cause a blooming artifact, resulting in an overestimation of stenosis severity (Figure 2). Additionally, previous coronary artery intervention in the form of coronary artery stent placement can create a blooming shadowing artifact rendering stenosis severity assessment within the stent challenging.

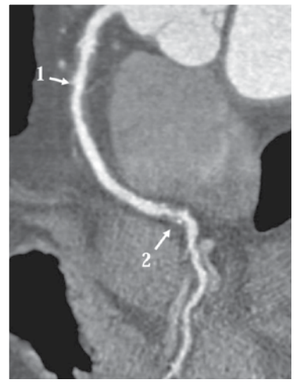


Figure 2. Computed tomography angiogram of the right coronary artery. (1, Mild proximal stenosis with expansive remodelling and predominantly nonexpansive plaque; 2, Partially calcified advanced mid to distal stenosis.)

Echocardiography

Echocardiography is recommended for patients with stable angina and physical findings suggesting concomitant valvular heart disease. It is invaluable for assessing the patient with suspected hypertrophic cardiomyopathy. It also is recommended for the assessment of global and regional left ventricular systolic function in patients who have been diagnosed with congestive heart failure, complex ventricular arrhythmias, or a history of MI. The echocardiogram is in many ways an ideal test when assessing a patient with known CAD. It is painless, carries no known risk, and the results are available within approximately 30 minutes. An experienced echocardiographer can identify 1 or more MIs; localize the infarct to a coronary artery distribution; and assess for associated ischemic structural complications such as a left ventricular aneurysm, left ventricular pseudoaneurysm, and ventricular thrombus.

Laboratory Studies

Routine laboratory measurements recommended as a part of the initial evaluation of patients with CAD should include determination of fasting glucose and fasting lipid levels (total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, and calculated low-density lipoprotein [LDL] levels). Other markers, such as lipoprotein(a) (Lp[a]) and high-sensitivity C-reactive protein, may be useful in assessing cardiac risk. High-sensitivity C-reactive protein is gaining greater prominence in assessing the inflammatory level of vascular disease and predicting future risk of vascular events, such as MIs and cerebrovascular accidents.

This was most recently highlighted in the Jupiter Trial in which patients with a LDL cholesterol level <130 mg/dL and a high-sensitivity C-reactive protein >2.0 mg/L were randomized to rosuvastatin 20 mg/d or placebo. Those with a high-sensitivity C-reactive protein >2.0 were shown to derive benefit from rosuvastatin based on a statistically significant reduction in myocardial event rates, cardiovascular mortality, and rates of death from any cause compared to those patients who were administered placebo.

Probability of Coronary Artery Disease

Once all these initial evaluations are complete, it is possible to estimate a patient's probability of existing CAD before proceeding with stress testing or coronary angiography (Table 2).

Stress Testing

Stress testing is another method for determining the presence of flow-limiting, functionally significant coronary artery disease. All stress-testing techniques include electrocardiography and blood-pressure monitoring. The absolute and relative contraindications to exercise stress testing are outlined in Figure 3.

Cardiovascular stress testing takes 2 forms—exercise and pharmacologic administration. The preferred method of cardiovascular stress testing is exercise, using a treadmill or bicycle. Through aerobic exercise, a higher rate pressure product (peak systolic blood pressure multiplied by peak pulse rate), and therefore greater cardiovascular stress, can be obtained. This permits an assessment of a patient's functional capacity, providing prognostic data using the sole parameter of attained metabolic equivalents or oxygen uptake. Heart-rate recovery—how fast the heart rate decreases after exercise cessation—is also a proven and prognostically important parameter.

The most common pharmacologic agents used for nonexercise stress testing are dobutamine, dipyridamole, and adenosine or one of its derivatives. Dobutamine echocardiography is useful for determining the presence of functionally significant obstructive CAD and assessing a patient following MI, especially for the presence or absence of myocardial viability. Using echocardiography, whether it is combined with exercise or dobutamine, the physician interpreter is focusing on the global and regional endocardial thickening responses to cardiovascular stress. This technique requires significant interpreter experience as the endocardial response to dobutamine can be both subtle and transient, requiring an experienced image acquisition and image interpretation sonographer physician team.

Nuclear stress testing is an equally important modality for assessing the coronary circulation. Unlike stress echocardiography, in which the endocardial thickening response to cardiovascular stress is the marker for inducible myocardial ischemia, nuclear stress testing relies on the concept of coronary flow reserve and differential myocardial blood flow. In the presence of exercise or the administration of a pharmacologic coronary vasodilator, the normal response is hyperemia, with a significant increase in myocardial blood flow. If there is no flow-limiting coronary obstructive disease, the pattern of hyperemia and blood flow is reflected as a symmetrical increase, with a homogeneous distribution of the blood flow tracer. In the presence of a severe flow-limiting coronary artery stenosis, dipyridamole or adenosine can induce coronary macrovascular and microvascular vasodilation, which results in differential myocardial blood flow that can be detected by radionuclide imaging with thallium 201- or technetium 99m (Tc 99m)-labeled radiopharmaceuticals (Tc 99m sestamibi or Tc 99m tetrofosmin). Functionally significant CAD can be suspected on nuclear perfusion imaging when an area of relative hypoperfusion is detected on peak stress images compared with resting images. Resting nuclear cardiac images may also be abnormal (Figure 4), signifying profound myocardial ischemia at rest or an irreversible myocardial scar consistent with past MI.

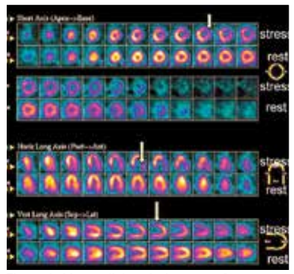


Figure 4. Myocardial perfusion scan. Stress images (arrows) demonstrate inferolateral and anterolateral (left circumflex) ischemia.

Table 2: Pretest Probability of Coronary Artery Disease By Age, Gender, and Symptom Status*

Age (years)†	Gender	Typical or Definite Angina Pectoris	Atypical or Probable Angina Pectoris	Nonanginal Chest Pain	No Symptoms
30-39	Male	Intermediate	Intermediate	Low	Very Low
	Female	Intermediate	Very Low	Very Low	Very Low
40-49	Male	High	Intermediate	Intermediate	Low
	Female	Intermediate	Very Low	Very Low	Very Low
50-59	Male	High	Intermediate	Intermediate	Low
	Female	Intermediate	Intermediate	Low	Very Low
60-69	Male	High	Intermediate	Intermediate	Low
	Female	High	Intermediate	Intermediate	Low

Adapted from Gibbons RJ, Balady GJ, Beasley JW, et al: ACC/AHA guidelines for exercise testing: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation 1997;96:345-354.

*High probability, >90%; intermediate, 10%-90%; low, <10%; very low, <5%.

†No data exist for patients aged <30 years or >69 years, but it can be assumed that the prevalence of CAD increases with age. In a few cases, patients at the extremes of each decade may have probabilities slightly outside the high or low range.

Figure 3. Absolute and Relative Contraindications to Exercise Stress Testing

Absolute Contraindications

- Acute MI within 2 days
- Symptomatic or severe aortic stenosis
- Decompensated heart failure
- Symptomatic or hemodynamically significant cardiac arrhythmias
- Unstable angina not previously stabilized by medical therapy
- Acute aortic dissection
- Acute myocarditis or pericarditis
- Acute pulmonary embolus or pulmonary infarction

Relative Contraindications

- Left main coronary artery stenosis
- Electrolyte imbalance
- Systolic blood pressure >200 mm Hg
- Diastolic blood pressure >110 mm Hg
- Tachyarrhythmias or bradyarrhythmias
- Hypertrophic cardiomyopathy, other forms of outflow-tract obstruction
- High-degree atrioventricular block
- Moderate stenotic valvular heart disease
- Mental or physical impairment leading to inability to exercise adequately

MI, myocardial infarction.

Adapted from Gibbons RJ, Balady GJ, Beasley JW, et al: ACC/AHA guidelines for exercise testing: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation 1997;96:345-354.

In the treatment of acute coronary syndrome (ACS)

BRILINTA provided superior reductions versus clopidogrel in thrombotic CV events, including CV death

The difference between treatments was driven by CV death and MI with no difference in stroke

BRILINTA plus aspirin significantly reduced the primary composite end point of CV death, myocardial infarction (MI),* or stroke by 16% RRR† (ARR‡ 1.9%) vs clopidogrel plus aspirin at 12 months§

At 12 months, for BRILINTA plus aspirin vs clopidogrel plus aspirin, there was no significant difference in Total Major Bleeding (11.6% vs 11.2%) and a somewhat greater risk of Non–CABG-related Major plus Minor Bleeding (8.7% vs 7.0%) and Non–CABG-related Major Bleeding (4.5% vs 3.8%), respectively

INDICATIONS

BRILINTA is indicated to reduce the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS) (unstable angina, non–ST-elevation myocardial infarction, or ST-elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined end point of CV death, myocardial infarction (MI), or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin >100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin >100 mg daily.

IMPORTANT SAFETY INFORMATION ABOUT BRILINTA

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg - 100 mg per day**

Please read additional Important Safety Information on next page and Brief Summary of Prescribing Information, including Boxed WARNINGS, on following pages.

CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage and active pathological bleeding such as peptic ulcer or intracranial hemorrhage. BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure; it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins. BRILINTA is also contraindicated in patients with hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product

WARNINGS AND PRECAUTIONS

- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor
- Premature discontinuation increases the risk of MI, stent thrombosis, and death
- Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes
- BRILINTA is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent CYP3A inducers. Avoid simvastatin and lovastatin doses >40 mg
- Monitor digoxin levels with initiation of, or any change in, BRILINTA therapy

ADVERSE REACTIONS

- The most commonly observed adverse reactions associated with the use of BRILINTA vs clopidogrel were Total Major Bleeding (11.6% vs 11.2%) and dyspnea (14% vs 8%)
- In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias. PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment

*Excluding silent MI.

†RRR=relative risk reduction.

‡ARR=absolute risk reduction.

§The PLATO (PLATelet Inhibition and Patient Outcomes) study was a randomized, double-blind, parallel-group trial comparing BRILINTA (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-mg to 600-mg loading dose, 75 mg daily thereafter) for the prevention of CV events in 18,624 patients admitted to the hospital within 24 hours of symptom onset of ACS (UA [unstable angina], NSTEMI [non–ST-elevation MI], or STEMI [ST-elevation MI]). Patients were treated for at least 6 months and up to 12 months. BRILINTA and clopidogrel were studied with aspirin and other standard therapies.

For more information, go to BRILINTAtouchpoints.com

Reference: BRILINTA Prescribing Information, AstraZeneca.

BRILINTA® ticagrelor tablets

AstraZeneca

BRILINTA® *(ticagrelor)* Tablets

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding [see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS].**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage [see CONTRAINDICATIONS].**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery [see WARNINGS AND PRECAUTIONS].**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA [see WARNINGS AND PRECAUTIONS].**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see WARNINGS AND PRECAUTIONS].**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day [see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES (14) in full Prescribing Information].**

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [*see Clinical Studies (14) in full Prescribing Information*]. BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [*see Warnings and Precautions* and *Clinical Studies (14) in full Prescribing Information*].

DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS

History of Intracranial Hemorrhage BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [*see Clinical Studies (14) in full Prescribing Information*].

Active Bleeding BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [*see Warnings and Precautions* and *Adverse Reactions*].

Severe Hepatic Impairment BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Hypersensitivity BRILINTA is contraindicated in patients with hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product [*see Adverse Reactions*].

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [*see Adverse Reactions*]. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [*see Warnings and Precautions* and *Adverse Reactions*].

Concomitant Aspirin Maintenance Dose In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [*see Dosage and Administration* and *Clinical Studies (14) in full Prescribing Information*].

Moderate Hepatic Impairment BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [*see Drug Interactions (7.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

ADVERSE REACTIONS

Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [*see Warnings and Precautions*]

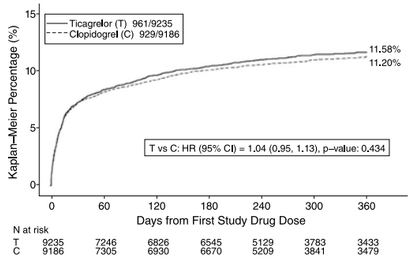
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel. No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Dyspnea[1]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[1] Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively. In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel. Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities Serum Uric Acid: Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group). Serum Creatinine: In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders – Hypersensitivity reactions including angioedema [*see Contraindications*].

DRUG INTERACTIONS

Effects of other drugs Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

CYP3A inhibitors [*see Warnings and Precautions* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

CYP3A inducers [*see Warnings and Precautions* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Aspirin Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [*see Warnings and Precautions* and *Clinical Studies (14) in full Prescribing Information*].

Effect of BRILINTA on other drugs Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

Simvastatin, lovastatin BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Digoxin *Digoxin:* Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Other Concomitant Therapy BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C: There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred. In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

Nursing Mothers It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

Pediatric Use The safety and effectiveness of BRILINTA in pediatric patients have not been established.

Geriatric Use In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [*see Contraindications, Warnings and Precautions,* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Renal Impairment No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken. Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

[*see section (13.1) in full Prescribing Information*]

PATIENT COUNSELING INFORMATION

[*see section (17) in full Prescribing Information*]

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Combining imaging with the electrocardiographic stress test adds approximately 15 percentage points to the sensitivity and specificity of the test. In certain cases, electrocardiographic stress testing is of borderline help, particularly in the presence of an abnormal resting electrocardiogram. The indications for cardiac stress imaging are outlined in Figure 5.

Figure 5. Indications for Cardiac Stress Imaging

- Resting ST-segment depression <1 mm
- Complete left bundle branch block
- Ventricular paced rhythm
- Ventricular pre-excitation syndrome
- Previous revascularization with PCI or CABG
- Inability to exercise

Adapted from Gibbons RJ, Balady GJ, Beasley JW, et al: ACC/AHA guidelines for exercise testing: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation 1997;96:345-354.

Cardiac stress imaging is useful for determining the extent, severity, and location of ischemia. The exercise portion of the test also provides prognostic information. Prognostic markers include the Duke treadmill score, heart rate recovery (HRR) score, and the chronotropic response index (CRI). The Duke treadmill scoring system is summarized in Table 3.

Table 3. Duke Treadmill Scoring System*

Risk Group	Annual Mortality Rate
Low (>4)	0.25%
Intermediate (-10-4)	1.25%
High (>-10)	5.0%

*The Duke treadmill score is calculated according to the following formula:

Exercise time (min)
- 5 (max ST-segment deviation [in mm, during or after exercise])
- angina score

where the score is 0 if there is no angina, 4 if angina occurs, and 8 if angina is the reason for stopping the test

Adapted from Mark DB, Shaw L, Harrell FE Jr, et al: Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849-853.

The HRR score is calculated according to the following formula:

HRR score = HR (at peak exercise) – HR (1 min. postexercise)

where HR is in beats per minute. A normal HRR score (>12 beats/min) is associated with a low risk of death, whereas a low HRR score (<8 beats/min) is associated with a high risk. HRR scores of 8 to 12 beats per minute indicate an intermediate risk.

The CRI is calculated according to the following formula:

(Peak HR – resting HR)/([220 – patient's age] – resting HR)

where HR is in beats per minute. A normal CRI (>0.8) is associated with a decreased probability of coronary artery disease and a lower risk of death. A low CRI (<0.8) in a patient who is not on beta-blocker therapy is associated with an increased likelihood of coronary artery disease and a higher risk of death.

Additional testing includes positron emission tomography (PET) imaging and cardiac magnetic resonance imaging (MRI). PET imaging is a form of pharmacologic nuclear cardiac stress testing that uses a coronary artery myocardial perfusion agent in the form of rubidium and 18F-deoxyglucose, which can assess myocardial metabolic activity. This test can be extremely helpful in assessing patients with ischemic heart disease, a past MI, and the extent of myocardial scar versus myocardial viability. Similarly, MRI with gadolinium also can be a useful modality to assess both the extent and location of ischemic myocardial dysfunction and myocardial viability, with MRI gaining in clinical use where offered, most typically in specialty centers.

Coronary Arteriography

Cardiac catheterization remains the gold standard for determining the presence of obstructive CAD. A cardiac catheterization yields a 2-dimensional rendering of the coronary artery circulation. To assist in circumventing the limitations of a 2-dimensional depiction of 3-dimensional anatomy, multiple views from varying angles are obtained with the extent of CAD severity typically ascribed to the angulation with the greatest stenosis severity within the particular coronary arterial segment.

Treatment

Once a cardiac catheterization has been performed, the 3 most common therapeutic options are medical therapy, including: lifestyle modification, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG).

Lifestyle Modification

Patients with documented CAD should actively pursue lifestyle modifications that reduce the risk of future cardiovascular events.

Smoking

Tobacco use is one of the most important reversible contributors to recurrent cardiovascular events. Tobacco use induces endothelial dysfunction, reduces coronary vasoreactivity, increases circulating carbon monoxide levels, impairs functional status, and raises blood pressure.

Exercise

Functional capacity is a strong predictor of major adverse cardiac events. Functional capacity can be improved by following an exercise program that includes at least 30 minutes of exercise 3 or 4 days a week (a daily regimen is considered optimal).

Weight Control

The best weight-management strategy is diet and exercise. Ideal benchmarks are a body mass index between 19 and 25 kg/m2 and a waist circumference ≤40 inches for men and ≤35 inches for women. Weight loss has a favorable effect on the metabolic syndrome and associated cardiac risk factors including hypertension, high LDL level, low HDL level, blood pressure, endothelial function, vascular inflammation, and glucose intolerance.

Pharmacologic Therapy

Antiplatelet Agents

Aspirin is the mainstay of antiplatelet therapy for patients who have known CAD or symptoms suggestive of CAD. Aspirin inhibits both cyclooxygenase and the synthesis of thromboxane A2. Clopidogrel, a thienopyridine derivative, blocks adenosine diphosphate–induced platelet activation. Clopidogrel is indicated as an alternative for patients who cannot take aspirin or in selected patients who have undergone percutaneous coronary intervention (PCI) with coronary artery stent placement.

Antianginal Agents

Beta blockers, calcium channel blockers, and nitrates are the mainstays of antianginal therapy. Unless contraindications exist, all patients who have a history of angina pectoris should carry sublingual nitroglycerin. Beta blockers are recommended as first-line therapy for the management of stable angina in all patients with established CAD.

Patients who have a history suggestive of vasospastic angina should be treated with a calcium channel blocker or a long-acting nitrate as an initial therapy. Either treatment option can also serve as a substitute for a beta blocker in the presence of traditional angina when intolerable beta-blocker effects ensue.

Nitrates improve exercise tolerance and prolong the time to onset of angina in patients with exertional angina. They are contraindicated in patients who have severe aortic stenosis or hypertrophic cardiomyopathy because they can adversely alter hemodynamics and exacerbate symptoms. Ranolazine may be useful for treating refractory angina pectoris. Unlike beta blockers, calcium channel blockers, nitrates, and ranolazine have not been demonstrated to reduce cardiac event rates or cardiac mortality.

Risk-Factor Management

Hypertension

Management of hypertension in patients with CAD is exceedingly important. Control of blood pressure reduces myocardial oxygen consumption and thereby reduces angina, and it also lowers the incidence of cardiovascular events.

Beta blockers devoid of intrinsic sympathomimetic activity represent first-line antihypertensive therapy for patients with a history of MI or coronary artery disease with angina. Angiotensin-converting enzyme (ACE) inhibitors are indicated for all patients with diabetes mellitus or a history of MI with impaired left ventricular systolic function. In the Heart Outcomes Prevention Evaluation (HOPE) study, high-risk patients for the presence of CAD without a history of MI, who were treated with the ACE inhibitor ramipril, experienced a significant reduction in major cardiac events.

Calcium channel blockers are useful for patients with hypertension and angina despite maximum tolerable administration of beta blockers. The long-acting dihydropyridines are preferred; short-acting preparations should be avoided because they are suspected of increasing the risk of cardiac events via precipitous blood pressure reduction and induction of the coronary steal phenomenon, diverting coronary arterial blood flow from flow-limited myocardial regions.

Hyperlipidemia

Guidelines of the National Cholesterol Education Program (NCEP) have recommended an LDL cholesterol level <70 mg/dL for all patients with coronary artery or other atherosclerotic disease. Patients whose LDL levels are >100 mg/dL should start pharmaceutical therapy. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the recommended first-line agents for patients who have CAD and elevated total and LDL cholesterol levels.

The NCEP also recommends a target HDL cholesterol level >45 mg/dL for men with CAD and >55 mg/dL for women. Patients with the metabolic syndrome (obesity, hypertension, and insulin resistance) often have HDL levels that are ≤35 mg/dL. These patients are at especially high risk for arterial vascular disease. Recommended lifestyle changes for these patients include regular exercise and weight loss, which are 2 of the most effective ways to raise HDL levels. If lifestyle changes fail to increase HDL levels to their target, drug treatment with a fibrate or niacin should be considered, particularly in patients whose triglyceride levels are >200 mg/dL.

Diabetes Mellitus

Diabetic patients with CAD have a particularly high risk for recurrent cardiovascular events, and they should be targeted for aggressive risk-factor modification. The American Diabetes Association recommends enhanced blood glucose control and monitoring with a hemoglobin A1c level lower than 7%.

Surgical Management: Revascularization

The primary revascularization options are PCI and CABG surgery. The most common PCI techniques are percutaneous transluminal coronary angioplasty and coronary stenting. A major limitation of PCI is restenosis at the intervention site. This represents the body's response to local injury with an exaggerated neointimal proliferative response. The use of drug-eluting stents, aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors lowers the rate of restenosis to <10% at 6 months in optimal circumstances.

The most common conduits for CABG are the saphenous vein and the internal thoracic (mammary) artery. The long-term patency rates of internal thoracic artery grafts are superior to those of venous grafts.

Outcomes

Percutaneous Coronary Intervention vs. Medical Therapy

Percutaneous coronary intervention is more effective than medical therapy in relieving angina, but it confers no greater survival benefit. Aggressive lipid-lowering therapy appears to be as effective as percutaneous coronary intervention plus usual medical care for preventing ischemic events.

Coronary Artery Bypass Grafting vs. Medical Therapy

CABG produces better survival rates than does medical therapy, in selected circumstances, and is recommended for symptomatic patients with left main coronary artery disease, 3-vessel CAD, or 2-vessel CAD marked by stenosis of the proximal left anterior descending artery. Coronary artery bypass graft surgery is more effective than medical therapy for the relief of angina, although this benefit narrows after a period of 5 to 10 years, most likely due to advancing native vessel CAD coupled with vein-graft attrition.

Percutaneous Coronary Intervention vs. Coronary Artery Bypass Grafting

Outcomes following percutaneous coronary intervention and CABG have been compared in high-risk patients. The 2 largest studies in the U.S. were the Emory Angioplasty versus Surgery Trial (EAST) and the Bypass Angioplasty Revascularization Investigation (BARI). In both trials, percutaneous coronary intervention was limited solely to angioplasty. Similarly, current CABG techniques, including the more frequent use of arterial conduits, were not included in either trial. EAST results have demonstrated that the long-term survival rates following percutaneous coronary intervention and CABG are comparable. BARI results have indicated that CABG produces better long-term survival rates than PCI (pre-stent). However, the benefit of CABG in BARI was not apparent until 7 years postoperatively, and it was largely attributable to the significantly higher survival rate in the subgroup of patients with diabetes mellitus. Both trials have shown that CABG is superior to PCI in relieving angina and obviating the need for repeat revascularization procedures. With the introduction of drug-eluting stents, coupled with improved catheterization techniques, CAD treatment is shifting away from bypass surgery toward a percutaneous approach. Restenosis rates have been lowered significantly and acute thrombotic complications are rare given the advances in antiplatelet therapy.

Summary

The diagnostic and treatment options for CAD are changing rapidly.

- New pharmaceuticals are being developed and introduced into the treatment armamentarium, particularly novel anti-platelet agents.
- Biologic markers are now used to track coronary artery disease activity at the vascular level, guiding medication selection and dose titration.
- Procedures are less invasive and offer percutaneous treatment options, such as drug-eluting stents, that were previously unavailable.
- Despite these advances, CAD and its deleterious manifestations represent the primary cause of mortality in the U.S. This is largely caused by poor dietary choices; sedentary lifestyles; suboptimal control of serum triglyceride, cholesterol, and glucose levels; inadequate prescription medication administration and delayed dose titration; and ongoing tobacco use.
- Efforts at primary and secondary prevention of obstructive CAD among the general public are still lacking.
- Public awareness campaigns are a partial success.
- It is imperative for the physician to allocate time to address the importance of lifestyle modification efforts.
- The genetic basis of CAD is being unraveled at an accelerated pace.
- The future genetic assessment of a person's lifetime risk for developing atherosclerotic vascular disease, formerly an idea, is now emerging as a reality.
- These findings can guide lifestyle modification, prescription, and the choice and dosage of specific pharmaceuticals.
- A preemptive approach is the best way to tackle the immensity of CAD.
- We must erase the myth that medications, stenting, and bypass surgery are curative approaches. Instead, the patient must meet the healthcare team at least halfway to achieve a successful health outcome.

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Notes

Notes

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Let us help you find the right system by visiting our website at softwareadvice.com/medical or calling our medical software analysts directly at (800) 234-5103.

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