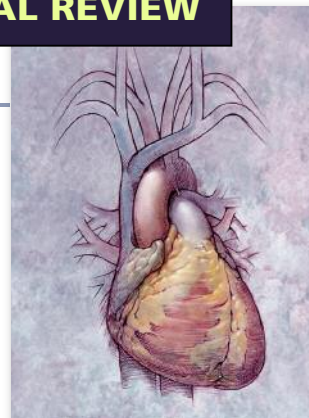


Stable Angina Pectoris: What Does the Current Clinical Evidence Tell Us?

Kenneth J. Tobin, DO



Coronary artery disease is the leading cause of death in the United States. The combination of noninvasive cardiovascular testing and invasive cardiac procedures accounts for a substantial portion of the yearly healthcare expenditure in the United States. Although the diagnosis of ischemically-driven chest pain may appear to be simple and straightforward, it often takes an astute clinician to confirm that clinically significant coronary artery blockage is the cause of a patient's chest pain. Cardiovascular research has provided convincing evidence that aggressive treatment of hypertension and hyperlipidemia—along with a management plan, based on the patient's combined risk factor profile, that includes blood glucose assessment, tobacco cessation, weight loss, healthy eating choices, and consistent aerobic exercise—must be provided to achieve optimal care for our patients. Over the ensuing decade, we will likely continue to see a shift away from routine percutaneous treatment of coronary lesions in favor of an aggressive assessment of a patient's cardiac risk profile followed by a treatment plan centered on active patient involvement including appropriate lifestyle changes and selective medications.

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Angina pectoris is defined as cardiac-induced pain arising from a lack of myocardial oxygen. Not only do 10.2 million Americans have this condition and approximately 500,000 new cases of angina occur each year, but ischemic heart disease is the leading cause of death in the United States.¹ Moreover, the lifetime risk of developing coronary artery disease (CAD) after 40 years of age is estimated at 49% for men and 32% for women.¹ Given the prevalence of this disease, it is important for clinicians to be familiar with the presenting symptoms, as well as current evidence-based treatment options.

Stable angina refers to predictable chest pain during exertional activity that resolves with rest or sublingual administration of nitroglycerin. Although not the topic of this review, unstable angina refers to an acute ischemic event and encompasses (1) new-onset cardiac chest pain, (2) angina at rest, (3) angina after a myocardial infarction, and (4) an accelerating pattern of previously stable angina. The terms unstable angina and non-Q wave myocardial infarction are often used synonymously, but a clinician should differentiate them on the basis of objective evidence of myocardial necrosis; a measurable rise in serum cardiac biomarker levels indicates non-Q wave myocardial infarction.

Among the causes of angina pectoris, the most common is CAD. At the cellular level, angina pectoris is a result of increased myocardial oxygen demand or decreased myocardial oxygen supply. In a patient with a stable hemoglobin level and oxygen saturation, the loss of compensatory dilatory autoregulation, vasoconstriction, or acute coronary artery thrombosis can reduce myocardial oxygen supply and thus induce angina. Conversely, a rapid heart rate, uncontrolled hypertension, or enhanced myocardial contractility may all lead to unmet myocardial cellular oxygen demands.²⁻⁴

The tenets and principles of osteopathic medicine can form a foundation for the evidence-based care of patients with chronic CAD, including those with stable angina. These tenets emphasize health maintenance, therapeutic lifestyle changes, the role of the musculoskeletal system, and patient-centered care.⁵

See related editorial on page 362.

From the Department of Internal Medicine, Division of Cardiovascular Disease at the University of Michigan Medical Center in Ann Arbor.

Address correspondence to Kenneth J. Tobin, DO, 1500 E Medical Center Dr, L3119 Women's Hospital, Box 0273, Ann Arbor, MI 48109-5000.

E-mail: kentobin@umich.edu

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To effectively incorporate osteopathic manipulative medicine in the care of a patient with angina pectoris, it is important to understand the interplay that occurs between the spinal column and the associated nerve pathways within this disease process. Chest pain associated with angina is due to stimulation of both chemosensitive and mechanoreceptive receptors of unmyelinated nerve cells found within cardiac muscle fibers and around the coronary vessels. This stimulation cascade is thought to occur when lactate, serotonin, bradykinin, histamine, reactive oxygen species, and adenosine are released into the coronary circulation during periods of lactic acidosis. Nerve stimulation via the sympathetic ganglia occurs most commonly between the seventh cervical vertebral and fourth thoracic vertebral portions of the spinal cord. This explains from an anatomic perspective why the most commonly recognized pain patterns associated with angina pectoris are discomfort in the chest, neck, jaw, and left arm.^{6,7} Following the theory that structure and function are interrelated, Rogers and Rogers proposed that osteopathic manipulative therapy can positively affect coronary perfusion.⁸

Diagnosis of Angina Pectoris

In patients with documented CAD who have predictable episodes of classic symptoms, the diagnosis of angina pectoris is straightforward. Most patients are familiar with the level of exertion that will induce angina, and they commonly describe their chest pain as a dull sensation or heaviness across the precordium that may radiate to the jaw or left arm. Some patients, more commonly women, have angina-equivalent symptoms such as exertional dyspnea, diaphoresis, or fatigue. Women also more commonly present with a nonexertional or atypical chest pain syndrome.

Defining the anginal pain in a patient with CAD is important and often helps guide appropriate testing and workup. The key to the diagnosis both in men and in women lies in a thorough history, which should always include information about the quality, location, and duration of the pain and the activities or factors that provoke or relieve the pain. By taking a detailed clinical history, the many diagnoses that may masquerade as angina may be eliminated (*Figure 1*). The classification system of the Canadian Cardiovascular Society⁹ is commonly used to define angina severity; according to this system, mild angina (class I) is defined as episodes that occur with maximal exertion, and severe angina (class IV) as episodes that occur with minimal or no exertion. The Canadian Cardiovascular Society system is useful for both stratifying risk and assessing efficacy of medical therapy.

Baseline electrocardiography, or ECG, is one of the initial tests performed in a patient with chest pain. A normal tracing does not exclude the diagnosis of ischemic heart disease, because more than 50% of patients with diagnosed angina have normal electrocardiograms at rest. The baseline electrocardiogram, however, may show evidence of pathologic Q

KEY POINTS

THE CLINICAL DIAGNOSIS OF ANGINA DEPENDS IN LARGE part on the detailed assessment of a patient's cardiovascular risk factor profile and of the typicality of his or her symptoms.

THE MOST COMMON SYMPTOM OF ANGINA PECTORIS is left-sided chest pain or pressure, possibly with associated radiation of pain or pressure in the jaw or left arm that occurs with exertion and is relieved with rest or sublingual administration of nitroglycerin.

WOMEN MORE COMMONLY PRESENT WITH ATYPICAL symptoms such as sharp, nonexertional chest pain, generalized fatigue, or right-sided chest pain.

RESULTS OF BASIC SCREENING TESTS (EG, 12-LEAD electrocardiography, laboratory tests [eg, cardiac bio markers], chest radiography) are normal in most cases.

FOR THE INITIAL DIAGNOSIS OF ISCHEMICALLY-DRIVEN chest pain, appropriate noninvasive testing, coronary angiography, or both are important because they enable the amount of ischemic myocardium to be defined and an overall treatment to plan be formulated.

EVEN WHEN INVASIVE PROCEDURES ARE CLINICALLY indicated, aggressive medical therapy with high doses of statins, attainment of appropriate blood pressure levels, smoking cessation, and use of antiplatelet therapy, as well as appropriate diet and exercise, are of paramount importance.

ROUTINE SCREENING FOR DEPRESSION SHOULD accompany the general evaluation of all patients with cardiovascular disease.

SINCE PERCUTANEOUS CORONARY INTERVENTION AND optimal medical treatment have equivalent outcomes in terms of death, myocardial infarction, and incidence of angina at 5 years, patient-centered care is a more appropriate choice than a "one-size-fits-all" algorithm.

waves or left ventricular hypertrophy, either of which increases the statistical probability that the patient has substantial CAD. Baseline laboratory tests should include a fasting lipid panel and determination of the serum glucose level to help define a patient's risk factor profile.

A detailed review of cardiac stress testing is beyond the scope of this article. Briefly, however, stress testing is an appropriate tool to screen for CAD in moderate-risk patient populations, as well as a useful test in defining risk among patients who have experienced acute ischemic syndrome and in assessing treatment efficacy in patients with chronic angina pectoris. Whenever possible, it is more useful to request an exercise stress test than a pharmacologically based study. The additional prognostic data obtained with an exercise stress test includes blood pressure, heart rate response, heart

Myocardial infarction/cardiac ischemia
 Vasospastic angina
 Pericarditis
 Aortic dissection
 Pulmonary embolism
 Esophageal spasm
 Gastroesophageal reflux disease
 Musculoskeletal pain
 Biliary colic
 Acute pneumonia

Figure 1. *Differential diagnosis of chest pain.*

rate recovery, metabolic equivalents attained, and electrocardiographic ST segment assessment. Myocardial imaging, whether it is with echocardiography or nuclear imaging, substantially increases the accuracy of stress testing (Figure 2).

Risk Factors for Coronary Artery Disease

To achieve effective primary and secondary prevention of CAD, risk factor modification must be addressed. Hypertension, hyperlipidemia, and diabetes are all treatable but not curable disease states. In contrast, obesity, sedentary lifestyle, and tobacco abuse are all major cardiac risk factors that potentially can be eliminated in an individual patient.

New Goals in Hypertension

Hypertension is a common, well-established, major cardiovascular risk factor. Current guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, or JNC 7 guidelines, define hypertension as blood pressure higher than 140/90 mm Hg¹⁰; however, a recent meta-analysis of 61 prospective, observational hypertension trials involving 1 million adults with no known vascular disease at baseline revealed that cardiovascular risk progressively increases when blood pressure is 115/75 mm Hg or higher.¹¹ Results of the CAMELOT (Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis) study demonstrated that patients with both hypertension and CAD have less plaque progression when their blood pressure is reduced beyond what is commonly considered adequate. Patients enrolled in this trial were, by current JNC 7 guidelines, normotensive. However, patients whose blood pressure was reduced to less than 120/80 mm Hg actually showed plaque regression in diseased coronary artery segments at intravascular ultrasound imaging.¹²

Clinical trials in patients with CAD have shown that blood pressure higher than 140/90 mm Hg is associated with a 20% to 60% increased risk of death, myocardial infarction, and stroke.^{13,14} Clinical wisdom suggests and published lit-

erature confirms that aggressive control of blood pressure is an important goal in CAD patients. In 2007, the American Heart Association updated their blood pressure goals for CAD patients to lower than 130/80 mm Hg.¹⁵

As treating clinicians, we have an abundance of antihypertensive agents at our disposal. There are often compelling reasons to choose specific medications, such as β -blockers for patients who have experienced a myocardial infarction or ACE (angiotensin-converting enzyme) inhibitors for patients with diabetes mellitus. However, it is more important to achieve consistent control of a patient's blood pressure than to belabor the perfect agent to prescribe. Stated differently, attaining appropriate control of blood pressure will have the most positive effect on cardiovascular risk reduction, regardless of which medication combination is chosen. The fact that more than 60% of hypertensive patients require two or three medications for adequate blood pressure control affirms this point.¹⁶

Setting the Bar for Lipids

The medical approach to patients with angina should always include aggressive lipid management. Recent guidelines recommend that in patients with known CAD, low-density lipoprotein cholesterol (LDL-C) levels should be lower than 70 mg/dL.¹⁷ In most patients, however, these levels cannot be attained without pharmacologic intervention. Regardless of how cholesterol levels are lowered, when they are lowered there is a parallel reduction in atherosclerotic cardiovascular disease. Among the available pharmacologic agents, statins remain the first choice for lowering LDL-C levels because statins have an excellent tolerability profile, positive nonlipid pleiotropic effects, and dramatic LDL-C-lowering properties.

In 2005, the Cholesterol Treatment Trialists' Collaborators published the findings of their meta-analysis on 90,056 individuals from 14 randomized trials of statins and showed that for every reduction in LDL-C of 38.6 mg/dL (1 mmol/L), there was a 12% reduction in mortality from all causes, a 19% reduction in mortality from CAD, a 24% reduction in

Cardiovascular risk progressively increases when blood pressure is 115/75 mm Hg or higher.

the incidence of first revascularization, a 17% reduction in incidence of first stroke (any type), and a 21% reduction in incidence of any major vascular event during a mean follow-up of 5 years. These benefits were observed in different age groups, across sexes, at different levels of baseline cholesterol levels, and equally among those with prior CAD and cardiovascular risk factors as in those without.¹⁸

The Heart Protection Study¹⁹ ushered in the era of "lower really is better." A group of 20,536 patients aged 40

Test	Advantages	Disadvantages
Exercise Stress Electrocardiography	□ Inexpensive □ Excellent positive predictive value in patients with three-vessel or left main CAD	□ Low sensitivity with single- or two-vessel CAD □ Higher rate of false-positive results
Stress Echocardiography*	□ Relatively inexpensive □ Added anatomic data attained† □ Increased specificity compared with that of stress nuclear imaging	□ Image quality reduced in patients with poor echocardiographic windows
Stress Nuclear Imaging‡	□ Assessment of left ventricular ejection fraction □ Increased sensitivity compared with that of stress echocardiography □ Relatively unaffected by patient body habitus compared with effect during stress echocardiography	□ Higher rate of false-positive results compared with that of stress echocardiography □ Requires expensive equipment, nuclear licensing, and large physical space □ More expensive than other stress tests

Figure 2. Advantages and disadvantages of stress tests. *With either exercise or dobutamine. †Left ventricular size and function, valvular anatomy and function. ‡With either exercise or pharmacologic agents. **Abbreviation:** CAD, coronary artery disease.

to 80 years with established CAD, other atherosclerotic vascular disease, or diabetes and with average LDL-C levels were randomly designated to receive either statin therapy or placebo. This trial showed a 24% reduction in major cardiovascular events, a 25% reduction in stroke, and a 13% reduction in overall mortality.¹⁹ Recalling that at the time of this trial, none of the 20,536 patients met guidelines of the National Cholesterol Education Program (NCEP) for statin therapy underscores the importance of these data on our current lipid treatment goals.

The Treating to New Targets (TNT) Study²⁰ is believed to be the first to compare the findings in a group of patients receiving moderate statin therapy with those of a group receiving a more intense dose of the same statin. Using atorvastatin at varying doses of either 10 mg or 80 mg in this 10,000-patient study eliminated concerns that outcome differences were induced from dissimilar statin preparations. The mean LDL-C level achieved was 101 mg/dL with 10 mg of atorvastatin and 77 mg/dL with 80 mg of atorvastatin. This LDL-C reduction was associated with a relative risk reduction of 22% for the primary end point of the first major cardiovascular event.²⁰

It is apparent that in both primary and secondary prevention lipid trials, achievement of a lower LDL-C level equates to reduced cardiovascular event rates. On the basis of evidence-based data, patients with established CAD benefit from reduction of their LDL-C levels to less than 70 mg/dL. It is unclear whether the statin dose or the resultant LDL-C level produces the best risk reduction.²¹ These same authors, however, concede that regardless of the answer, achievement of a low LDL-C level should be the primary goal of lipid therapy.

Metabolic Syndrome

The metabolic syndrome is defined as the presence of insulin resistance, hypertension, dyslipidemia, and abdominal obesity within an individual patient.²² Whether this is a true syndrome or merely a multitude of simultaneously occurring cardiovascular risk factors is debatable. The important aspect of this syndrome, however, is its recognition and the subsequent administration of aggressive, multilevel treatment, so that the undeniable cardiovascular risk is attenuated.

Therapeutic Lifestyle Changes Cessation of Tobacco Use

Cigarette smoking is probably the most important of the identified modifiable cardiovascular risk factors. The incidence of CAD is two to four times higher in smokers than it is in non-smokers.²³ The pathophysiologic process that leads to atherosclerosis caused by smoking likely stems from induced platelet inhibition, endothelial dysfunction, smooth muscle cell proliferation, and attenuated levels of HDL-C.²⁴ If a clinician does not aggressively address smoking cessation in every patient who smokes, it is my opinion that the clinician is not practicing appropriate cardiovascular disease prevention.

Exercise

Exercise should be encouraged in patients with stable angina once all testing (both invasive and noninvasive) has been completed and a solid medical regimen has been established.

An increased aerobic capacity allows the development of lower requirements of cellular oxygen, which then leads to increased exercise tolerance and often reduced angina symptoms. Consistent aerobic exercise has also been shown to improve endothelial function and, in patients with CAD,

positively affects baroreflex sensitivity and heart rate variability.²⁵

Alternative forms of exercise, such as tai chi and yoga, may be appealing to some patients and may enhance their physical as well as their psychological well-being. To my knowledge, there are no evidence-based data to prove that these types of exercise are equivalent to formal aerobic training in relation to cardiovascular risk reduction. However, conventional wisdom tells us that (1) doing any form of exercise is better than doing none at all, and (2) healthy life choices are more likely to be made by those who exercise.

Patient-Centered Care

A high-quality healthcare system, whether small in scale or global, must have patient-centered care as a core focus. As we look to the future and embrace medical advances in both the diagnosis and the management of diseases, we cannot lose sight of the importance of a patient's involvement in his or her medical care and the medical decision process. Patients should be informed about all levels of care, including treatment options, as well as benefits and risks of conservative vs aggressive medical plans.

A recently published article addressed this very issue and related how a detailed informed patient consent form may further patient-centered care.²⁶ The basis of this approach is appealing, because personal discussions of cost, alternative treatment options, and so on will serve only to enhance patient involvement in the choice of medical care. Among patients who are not involved in a healthcare field, however, there is a fine line between providing informed consent and understanding the details of medical care. The most challenging hurdle we as physicians face is how to find a way to explain basic, objective medical data in an emotionally sensitive environment. Meeting this challenge with each of our patients is what will make our healthcare system patient centered.

As osteopathic physicians, we must remember to not simply treat individual symptoms or illnesses, but to assess the patient from a global health perspective. For example, obesity begets diabetes and hypertension, which in turn lead to cardiovascular disease. From a global approach, one often-dismissed risk is depression. According to a World Health Organization survey, depression affects health more than does angina, diabetes, asthma, or arthritis. By the year 2020, depression will be second only to heart disease as a cause of disability in developed countries. It is estimated that 15% to 20% of patients with cardiovascular disease will also have clinical depression.²⁷⁻³⁰ The Heart and Soul Study³¹ included 1017 patients with stable CAD who were studied for 4.8 years. Patients in whom depression was identified were twice as likely to experience recurrent cardiovascular events. Physical inactivity was associated with a 44% greater rate of cardiovascular events. Patients with symptoms of depression were less likely to follow dietary, exercise, and medication recommendations.³¹

Depression and exercise should be viewed as an intertwined continuum, where lack of exercise begets depression, which reduces the initiative for exercise, and so on. Many people in this loop do not follow healthy diets, are more likely to use tobacco, and are much more likely to be overweight. Conversely, those who exercise regularly tend to experience less depression, avoid tobacco use, and consume a healthier diet. This philosophical approach could be compared with the proverbial chicken-and-egg debate. Do sedentary lifestyles lead to depression in some patients and subsequently a higher incidence of cardiovascular disease? Or, are those who experience depression less likely to maintain an active lifestyle, which in turn leads to an unhealthy cardiovascular profile? In either case, recognizing depression and encouraging exercise are two facets of an osteopathic approach to the treatment of cardiovascular disease that cannot be overstated.

Medical Therapy Versus Revascularization

One of the most energized debates within cardiovascular circles regarding the approach to the patient with chronic angina is the initial choice between medical therapy and an invasive approach. One of the early studies to address this debate was the Atorvastatin Versus Revascularization Treatment, or AVERT, trial, which compared the use of intensive lipid-lowering therapy with the use of percutaneous intervention (PCI) in a relatively low-risk patient population with angiographically proven one- or two-vessel disease.³² In this trial, 341 patients were randomly designated to either receive medical therapy with 80 mg of atorvastatin or to undergo PCI followed by usual medical care (which did include the option of statin therapy at the choice of the treating physician). Compared with the PCI group, the group that received medical treatment with atorvastatin experienced a 36% reduction in

It is estimated that 15% to 20% of patients with cardiovascular disease will also have clinical depression.

the composite endpoint of ischemic events. This difference was due primarily to more repeated PCIs, coronary artery bypass grafts, or hospitalizations for worsening angina.³² The important outcome was that high-dose statin therapy did not result in more cardiovascular events than would result from a PCI-based treatment plan.³²

The multitude of published studies comparing PCI to medical therapy must be interpreted carefully, because by the time that results of most trials are published the chosen percutaneous treatment modality may be outdated. Early trials used mainly plain balloon angioplasty, and subsequent trials

used early-generation bare metal stents rather than the current drug-eluting devices. Moreover, the medical treatment arms of most studies have been driven by guidelines that were current at the time the study was performed but often are outdated by the time the results of the trial are published. Specifically, in most if not all of these early trials, lipid therapy was not aggressive, hypertension management was not confirmed to be adequate, and dual antiplatelet therapy was in its infancy.

As physicians who are practicing evidence-based medicine and are striving to treat the patient, not merely the disease process, we should view the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial³³ as having produced the best data available up to this time. Considering this trial in population-specific borders, all participants underwent coronary angiography, and those with high-risk anatomic findings such as severe stenosis of the left main coronary artery were excluded. In fact, of the more than 35,000 patients screened, only 2287 met the study inclusion criteria.

The biggest difference between the COURAGE trial and essentially every other similar trial that preceded it was that in the COURAGE trial strict guideline-based medical therapy was followed in both groups. Among the entire cohort, 85% were taking a β -blocker, 93% were taking a statin, and 85% were taking an aspirin. There was essentially no difference between the treatment groups with respect to the primary endpoint of death or myocardial infarction: 19.0% in the PCI group versus 18.5% in the medical therapy group. There was a trend toward less angina in the PCI group during the first 3 years of the trial, but this was not apparent at 5 years. The final interpretation of the COURAGE trial results is not that medical therapy is superior to PCI, but rather that in select cohorts aggressive medical therapy is an appropriate first step in the treatment of ischemic heart disease.³³

From the perspective of a patient with coronary atherosclerosis, it requires faith to believe that taking daily medications such as statins, antiplatelet medications, or antihypertensive medications will actually do more good than would active intervention with PCI. This premise was clearly demonstrated in the Anglo-Scandinavian Cardiac Outcomes Trial, or ASCOT, a trial in which patients received medication for control of hypertension and statin therapy; this combination of medications reduced the combined endpoint of fatal and nonfatal myocardial infarctions by 46%.³⁴ This number, combined with the apparent lack of any published trial concluding that PCI reduces overall cardiovascular mortality in single-vessel CAD, underscores the ASCOT findings. The information in the National Health and Nutrition Examination Surveys, or NHANES, database suggests that only 35% of patients with CAD are at their appropriate LDL-C level goal, and of the 69% of patients who are aware that they have hypertension, only 31% achieve appropriate blood pressure control.³⁵ Personally speaking, I think the NHANES

Aggressive medical therapy is an appropriate first step in the treatment of ischemic heart disease.

data are more deserving of our attention than are the COURAGE trial data, especially in light of the mortality data from the American Heart Association, which indicate that the rate of death from cardiovascular disease has changed very little within the past 35 years. Imagine the dramatic reductions in cardiovascular mortality that we could achieve if we focused simply on improving patient compliance.

Comment

To treat chronic angina effectively, we must practice aggressive evidence-based, globally-centered cardiovascular medicine focused on multilevel risk reduction. The conservative use of PCIs to treat CAD is an important part of our treatment armamentarium. However, we must educate our patients so that they fully understand how effective positive lifestyle changes and strict medication compliance are to their cardiac profile. Despite what our patients are led to believe about the treatment of lipidemia through overly aggressive advertising campaigns that tout magical exercise machines, never-before-seen diet pills, or alternative medications that are not regulated by the Food and Drug Administration, our best tool in managing the disease is patient education and knowledge. The wise and seasoned cardiovascular physician takes an individual approach to each patient with chronic angina and combines both invasive and noninvasive treatment plans to effectively reduce symptoms, morbidity, and overall cardiovascular mortality.

Evidence-based treatment of chronic stable angina has shown that aggressive control of blood pressure and appropriate control of LDL-C levels are of paramount importance. Additionally, guided exercise programs and assessment for underlying depression cannot be overlooked. A patient-centered approach to care should be the focus for each patient with the diagnosis of chronic stable angina.

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