The Pathophysiologic Basis of Managing Chronic Atherosclerotic Cardiovascular Disease

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KEYWORDS

• Coronary artery disease • Atherosclerosis • Atherothrombosis
• Myocardial infarction • Myocardial ischemia • Prevention of atherosclerosis

KEY POINTS

- Coronary heart disease is a complex disorder with many different manifestations and degrees of severity.
- The diagnostic and therapeutic strategy for managing coronary disease is based on assessing the particular patient's disease status and applying the understanding of the multiple contributing pathophysiologic processes.
- A cornerstone of chronic coronary heart disease management involves attenuating atherosclerosis progression and preventing its complications.
- Appropriate management of coronary artery disease also includes a responsibility to undertake primary prevention initiatives when appropriate.

INTRODUCTION/BACKGROUND

The primary care physician encounters and participates in managing the entire spectrum of chronic coronary disease from presymptomatic coronary atherosclerosis to advanced heart failure due to ischemic cardiomyopathy. Management responsibilities encompass many topics (as covered in this monograph) ranging from primary and secondary prevention, to symptom management and advanced therapy selection.

The chronic coronary disease knowledge base is vast—a multimodality discipline that integrates multiple disciplines and knowledge bases. The 2023 American Heart Association/ American College of Cardiology /American College of Clinical Pharmacy/American Society For Preventive Cardiology/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease is 83 printed pages long with hundreds of references.[1]

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How does the primary care physician master and apply this knowledge base to optimize care of the individual patient? The totality of available diagnostic and therapeutic options is large requiring informed choices among them.

This article describes a conceptual framework that applies a mechanistic understanding of coronary disease to navigate the totality of the coronary disease knowledge bases and management guidelines.

The principles of coronary disease evaluation and management are rooted in its pathogenesis and pathophysiology. Accordingly understanding the operative disease processes informs evaluation and management strategy. Individual patitent-specific management choices should be driven by the particular pathophysiologic processes involved.

The strategies that underpin this approach may be summarized as follows.

- Atherosclerosis prevention/attenuation
- Recognition of coronary disease and severity assessment ("Staging")
- Management of symptoms caused by coronary disease
- Prevention of atherothrombosis.
- Prevention and management of end-organ complications.

ATHEROSCLEROSIS PREVENTION/ATTENUATION

Arterial atherosclerosis, a generalized chronic progressive disorder, is the underlying cause of virtually all chronic coronary disease and, additionally, can affect virtually every organ system. Uncommon exceptions to this generality include spontaneous coronary artery dissection and arterial fibromuscular dysplasia. (See Eleonore Grant and Monika Sanghavi's article, "Ischemic Heart Disease in Women," in this issue). It is important to bear in mind that atherosclerosis occurs throughout the body. Consequently, a patient who has coronary artery atherosclerosis likely has significant atherosclerotic disease elsewhere and vice versa.

Most adverse cardiovascular events due to coronary heart disease are triggered by complications of atherosclerosis that are the consequence of ongoing disease progression. Thus, prevention and attenuation of the atherosclerotic process is foundational to coronary heart disease management. In particular, successful reduction of elevated low-density lipoprotein (LDL) cholesterol has major cardiovascular health benefits.[2]

Atherosclerosis is nearly universally prevalent in adults of all ages. Typically, it develops asymptomatically in early in life at which time early lesions are functionally unimportant. it progresses at variable rates, generally over many years, until it causes sufficient vascular obstruction to declare its presence. The patient's particular progression rate determines the age at first clinical presentation, and is modulated by a number of well-characterized genetic and behavioral characteristics.[3]

Prevention and/or attenuation of atherosclerosis progression is among the most important treatments that the primary care physician may institute. The aggressiveness and stage of an individual patient's atherosclerotic process determines the approach to this issue. (see article by Nelson and colleagues & Pagidipati and colleagues) The determinants of atherosclerotic risk are well characterized and include plasma LDL cholesterol, hypertension, diabetes mellitus, and cigarette smoking.[4] All patients who have clinically evident symptomatic atherosclerosis benefit from aggressive risk factor modification (secondary prevention). Completely asymptomatic patients may harbor advanced presymptomatic atherosclerotic disease and may benefit from preemptive preventative treatment (primary prevention) as may young

people who have no evident atherosclerosis but have characteristics associated with particularly extreme risk.

Consequently, the primary care physician is responsible to treat atherosclerotic risk factors in patients who have clinically evident atherosclerotic disease as well as to identify asymptomatic patients who have genetic and behavioral markers of increased atherosclerotic risk who will benefit from preemptive primary preventative treatment (see article by Nelson and colleagues & Pagidipati and colleagues). Recently, diabetes and obesity, long recognized as coronary risk factors, have assumed greater prominence not only as risk factors but also, with the emergence of Glucagon-like peptide receptor 1 agonists (GLP-1RA) and Sodium-Glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) have become independent therapeutic targets.

Thus, by careful attention to treatment of atherosclerotic risk factors, the primary care physician is in a position to have a strongly positive impact on coronary artery disease outcomes.

CORONARY DISEASE RECOGNITION,"STAGING" AND SEVERITY ASSESSMENT

Atherosclerosis by itself does not cause symptoms, but declares its presence by impairing arterial perfusion of the affected vascular bed causing either ischemia or infarction. Clinically evident coronary disease (symptomatic or asymptomatic) is a spectrum of conditions whose severity and prognosis ranges from a trivial nuisance to malignantly life-threatening.

As a generality, the prognosis associated with a given case of coronary disease is strongly related to the anatomic extent of the disease and the severity of cardiac ischemia that it causes. A therapeutic intervention's benefit potential is linked to the disease severity. Patients with the most severe coronary disease stand to benefit the most from therapeutic interventions whereas patients with less severe disease may have a favorable natural history without treatment.

There is a wealth of data relating coronary disease severity to prognosis and outcomes (see Michelle D. Kelsey and Anita M. Kelsey's article, "Diagnosing Coronary Artery Disease in the Patient Presenting with Stable Ischemic Heart Disease: the Role of Anatomic Versus Functional Testing," in this issue). Any clinical event that declares the definite or possible presence of coronary artery disease, such as the emergence of a chest pain syndrome or a myocardial infarction, demands an initial risk stratification evaluation to detect disease presence and assess its severity. The initial approach to coronary disease management involves assessing the anatomic (cofonary artery imaging) and functional (stress testing) disease severity. Anatomic and functional assessments provide complementary information and the best risk stratification combines both modalities.[5]

As the importance and value of therapies is linked to disease severity, diagnostic "staging" of coronary disease informs the understanding of a patient's prognosis enabling the physician to counsel the patient accurately with respect to the implications of his/her particular situation. It also informs therapeutic choices (see articles by Mehta and colleagues, Pagidipati and colleagues, Sherrie Khadanga and Tanesha Beebe-Peat's article, "Optimal Medical Therapy for Stable Ischemic Heart Disease in 2024: Focus on Exercise and Cardiac Rehabilitation"; Parth P. Patel and Alexander C. Fanaroff's article, "Optimal Medical Therapy for Chronic Coronary Disease in 2024: Focus on Antithrombotic Therapy"; Andrew M. Cheng and Jacob A. Doll's article, "When to Consider Coronary Revascularization for Stable Coronary Artery Disease," in this issue) such as the choice between medical and revascularization management.

MANAGEMENT OF SYMPTOMS CAUSED BY CORONARY ATHEROSCLEROSIS

As a generality, coronary disease causes symptoms in 1 of 2 ways.

- Symptom-producing myocardial ischemia
- Cardiac dysfunction secondary to either infarction, ischemia, or both.

Myocardial ischemia occurs when, because of epicardial coronary artery obstruction, there is a disparity between myocardial metabolic requirements and available coronary blood flow. The disparity may be ameliorated either by decreasing myocardial metabolic demand or by augmenting coronary blood supply. Most medical management strategies are based on attenuating myocardial metabolic requirements while coronary revascularization—by percutaneous intervention or coronary bypass surgery—is done to augment coronary blood supply.

Medical therapy for angina is a multidisciplinary process that utilizes different pharmacologic mechanisms to decrease myocardial metabolic requirements enabling satisfactory metabolism within a circumstance of constrained coronary supply (see article by Mehta and colleagues). Exercise training and conditioning can also alter this relationship favorably. (See Sherrie Khadanga and Tanesha Beebe-Peat's article, "Optimal Medical Therapy for Stable Ischemic Heart Disease in 2024: Focus on Exercise and Cardiac Rehabilitation," in this issue). The multiple pharmacologic approaches to attenuating metabolic demand include beta-blockers, calcium channel blockers and other vasodilators and myocardial metabolism modifiers.[6] As each of the agents works through a different mechanism, the choice of which agent(s) to employ, singly or in combination, is based on the assessment of the particular patient's characteristics.

It is noteworthy that successful medical therapy for symptomatic cardiac ischemia accomplishes more than just symptom attenuation. In particular, beta blockers exert their clinical effects by decreasing myocardial oxygen demand, improving ischemic threshold, and impeding maladaptive LV remodeling.[6]

Revascularization, either by percutaneous coronary intervention or by coronary bypass grafting, improves the myocardial supply-demand relationship by improving the coronary flow supply. In appropriately selected patients, successful revascularization can achieve gratifyingly greater symptomatic improvement, than can be achieved by medical therapy alone. Similarly, revascularization applied to properly selected patients with more severe coronary disease can lower the risk of cardiovascular death, myocardial infarction, and urgent revascularization.[7]

Selection of candidates for revascularization and of revascularization modalities is a complex process that involves weighing considerations of symptom and ischemia severity as well as anatomic suitability for successful revascularization. (See Andrew M. Cheng and Jacob A. Doll's article, "When to Consider Coronary Revascularization for Stable Coronary Artery Disease," in this issue).

Coronary artery disease also can cause cardiac dysfunction either because of loss of myocardium due to myocardial infarction or due to ischemic dysfunction or chronic myocardial fibrosis. Such patients fall at some point on the spectrum of chronic congestive heart failure. Consequently these patients, in addition to requiring therapy to ameliorate myocardial ischemia, also require failure for heart failure adjusted to the particular patient's heart failure stage (see Alex J. Chang and colleagues' article, "Medical Decision Making and Revascularization in Ischemic Cardiomyopathy," in this issue). There is some overlap between ischemia-specific and heart failure–specific therapy. For example, beta-blockers, blood pressure–lowering agents, and anti-diabetic agents have established roles in both conditions.

PREVENTION OF ATHEROTHROMBOSIS

Acute coronary syndromes constitute a spectrum ranging from unstable angina through non ST elevation myocardial infarction to ST elevation myocardial infarction. The vast majority of these scenarios are caused by intracoronary thrombi that generally form on a preexisting atherosclerotic plaque. A notable exception is spontaneous coronary artery dissection—a rare but clinically important event occurring predominantly in younger women with little or no accompanying coronary atherosclerosis. (See Eleonore Grant and Monika Sanghavi's article, "Ischemic Heart Disease in Women," in this issue). Consequently, preventing thrombus formation is a cornerstone of therapy of patients who harbor coronary atherosclerosis.

Because intracoronary thrombi are arterial rather than venous, the platelet is the therapeutic target. Consequently, therapeutic focus is on platelet inhibitors. Anticoagulants are of little, if any value. (See Khawaja Hassan Akhtar and Usman Baber's article, "Antiplatelet Therapy for Patients that Have Undergone Revascularization within the Past Year: Which Agents and for How Long," in this issue).

There are 2 categories of oral platelet-inhibiting drugs all of which act by inhibiting platelet actdivation. Aspirin acts on 1 of the 5 platelet activation mechanisms by permanently acetylating cyclooxygenase-1 (COX-1) in platelets, leading to the inhibition of thromboxane A_2 (TXA_2) synthesis. A second class of platelet inhibitors, including clopidogrel, prasugrel, and ticagrelor, act through a second platelet-activating mechanism by rendering the P2Y12 receptor unable to respond to adenosine diphosphate stimulation. Consequently, neither class of platelet inhibitors inactivates platelets completely and there is sufficient synergism between the 2 drug classes such that administering both classes concurrently produces greater platelet inhibition than either class by itself.

Low-dose (81 mg) aspirin has long been foundational therapy in patients with known coronary artery disease and is essential during acute coronary syndromes.[8] Numerous clinical trials have examined whether more aggressive platelet inhibition employing other platelet inhibiting drug clases–either in isolation or in combination with aspirin–can provide greater protection against future acute coronary events. In general, these trials show that increasingly aggressive platelet inhibition may modestly decrease acute coronary syndrome incidence, but at the price of increased bleeding.[9] Thus, the role of dual antiplatelet therapy in the management of chronic coronary disease is controversial whereas it is well accepted as temporary therapy for recently implanted coronary stents in most circumstances. It most likely should not be considered in patients who have any characteristic that increases bleeding risk including, in particular, patients who require oral anticoagulation for other reasons such as atrial fibrillation.

PREVENTION AND MANAGEMENT OF END-ORGAN COMPLICATIONS

Acute cardiac ischemic episodes and chronic myocardial ischemia can cause multiple detremental effects on the heart impairing its contractile function and, thus, exposing the patient to the risk of congestive heart failure. The pathogenesis is multifactorial including loss of functioning myocardium secondary to an ST elevation myocardial infarction event or progressive loss due to multiple small ischemic injury events which are not individually recognizable. Chronically ischemic myocardium can reprogram its metabolism to decrease its contractile function in order to preserve cellular viability in the setting of jeopardized coronary flow supply. This process, termed "hibernation," is potentially reversible if coronary flow is restored. In addition, in response to chronically inadequate coronary blood flow and adverse neurohumoral input, myocardium can

remodel both physically and metabolically. The end result of these processes leads to distortion of left ventricular size and geometry, development of myocardial fibrosis, and emergence of secondary functional mitral regurgitation.[10] (See Alex J. Chang and colleagues' article, "Medical Decision Making and Revascularization in Ischemic Cardiomyopathy," in this issue).

Once this process is established, it has the potential to become self-perpetuating leading to an ischemic cardiomyopathy with progressive chronic congestive heart failure. Naturally, should this clinical picture develop, a patient is on a very undesirable trajectory.

In addition to congestive heart failure, patients with severely decreased left ventricular contractile function are at risk of other problems including mitral regurgitation which can compound the effects of impaired ventricular contractility. It also creates the potential for ventricular thrombus formation with secondary risk of systemic embolization. In some patients a previous myocardial infarction can create an unstable electrophysiologic substrate that can cause ventriclar tachycardia. Finally, such patients can develop persistent atrial fibrillation with all of its adverse consequences.

Consequently, it is important to recognize the potential that ischemic cardiomyopathy may develop and to vigilantly monitor patients who have evident coronary artery disease for early harbingers of this adverse process.

SUMMARY AND CLINICS CARE POINTS

Coronary artery disease is a complex multifaceted disorder with a spectrum of severities and clinical manifestations. Its underlying pathogenetic mechanism is coronary artery atherosclerosis. Consequently, the primary care physician should always be focused on recognition of atherosclerotic risk and identification of its presence. Aggressive atherosclerosis preventative measures are important for any patient who has evident atherosclerosis and also for asymptomatic patients who have an adverse risk factor profile.

Once coronary disease is detected, its extent and severity should be assessed ("staged") by a combination of anatomic imaging and functional testing for cardiac ischemia. The therapeutic choices available for managing coronary artery disease are vast and include ischemia-modifying pharmacologic therapy and revascularization. Patients with known coronary disease should be systematically monitored for potential complicatations with a particular focus on preventing the development of ischemic cardiomyopathy.

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