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Treatise on Heart Disease in Indians

Enas A Enas
Basil Varkey

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CHAPTER 10

Angina Pectoris: Shift from Invasive Treatment to Medical Management

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INTRODUCTION

Angina, the classic symptom of coronary artery disease (CAD), is caused by restriction of oxygen-carrying blood to the heart muscle from plaque buildup in the coronary arteries. The pattern of chest discomfort can be crushing pain, pressure, tightness, or squeezing (Chapter 2). Stable angina, the most common type, features predictable episodes triggered by exertion or stress that typically resolve with rest or medication. The main focus of treatment for several decades was a mechanistic one, to open up the blocks with percutaneous coronary intervention (PCI) with stents or with coronary artery bypass graft (CABG) surgery. There has been a sharp and marked shift in the management of angina away from the mechanistic approach to guideline-directed medical therapy (GDMT) that tackles the underlying causes of CAD through lifestyle changes and medications. Invasive treatments are reserved now for select cases such as uncontrolled angina that significantly hinders the quality of life.[1-4] The magnitude of the shift in the management of angina since the 1990s in the US is illustrated in **Figure 1 and Table 1**.[5,6]

Cardiac catheterization and CABG surgery, once dominant,[7-11] have seen a marked decrease since 2000 **(Table 1)**. CABG surgery continues to have a role in select complex cases and PCI procedures have come down from its peak especially in those with stable CAD. Besides, the improved armamentarium of effective drugs, the increased recognition and control of major risk factors tobacco smoking, hypertension, diabetes, and cholesterol have resulted in a decline in CAD complications and in the use of invasive procedures.

In the sections that follow we explain the key studies that led to a rethinking of the management of angina and stable CAD from invasive procedures to GDMT that combines lifestyle changes and medications and go on to tabulate the key components of GDMT and the pharmacologic management of angina.

INSIGHTS FROM THE LANDMARK ISCHEMIA STUDY

This large National Institute of Health (NIH)-funded study (5,179 participants at a cost of $100 million) investigated the effectiveness of adding coronary artery revascularization procedures (CARP) to GDMT for stable CAD patients with moderate or severe ischemia. One half of the participants received GDMT only, the other half received GDMT plus CARP (PCI or CABG). The results confirmed and solidified conclusions of several smaller prior cardiovascular outcome trials (CVOTs).[13-16] The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) study excluded patients with left main CAD and acute coronary syndrome (ACS), where the

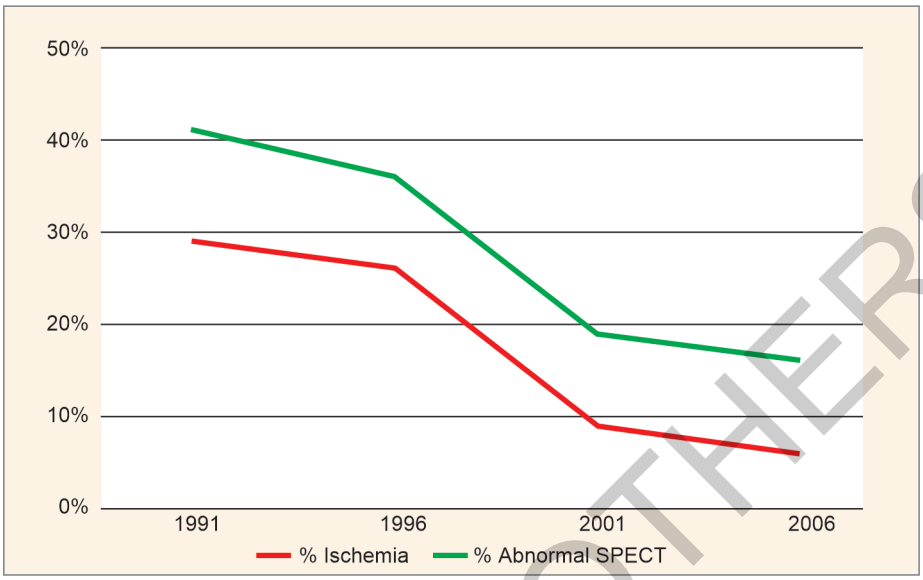

Fig. 1: Progressive decline frequency of abnormal and ischemic single photon computed tomography (SPECT) myocardial perfusion imaging (MPI) over the years.
Source: Adapted from Rozanski A, Gransar H, Hayes SW, Min J, Friedman JD, Thomson LE, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol. 2013;61(10):1054-65.[6]

TABLE 1: Trends of coronary interventions in the US from 1994 to 2014.[12]

Procedure/Intervention	*1994*	*2004*	*2014*
Coronary catheterization	1,160,000	1,500,000	1,000,000
Coronary artery bypass graft (CABG)	570,000	570,000	375,000
Percutaneous transluminal coronary angioplasty (PTCA)	400,000	800,000	475,000

Note: Decrease of coronary interventions in the United States from 2004 to 2014. By 2014 annual cardiac catheterizations decreased to one million, coronary artery bypass surgery to 375,000 and percutaneous transluminal coronary intervention to 475,000.[12]

benefits of CARP are well-established. Additionally, people with a high degree of left main stenosis identified through blinded computed tomography were not included. Death rates were similar in both groups. An important observation was that approximately 20% of patients initially randomized to the conservative approach eventually received CARP. This crossover did not demonstrate any harm associated with delaying intervention. The key findings of the ISCHEMIA trial and their implications are shown on **Table 2**.[15,17-20]

LIMITATIONS OF CORONARY ARTERY REVASCULARIZATION PROCEDURES

The commonly held notion that the risk of heart attack is determined solely by the severity of stenosis (blockage) of coronary

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TABLE 2: Rethinking coronary artery revascularization procedures (CARP) for stable coronary artery disease (CAD)—insights from ISCHEMIA trial.[15,17-20]

	Key findings	***Implications for treatment***
Manage angina with Guideline-directed Medical Therapy (GDMT)	Patients with minimal or no chest pain can be managed with GDMT even in the presence of moderate or severe ischemia	GDMT should be the mainstay of treatment for most patients, with CARP reserved for those with uncontrolled angina
No survival benefit	Extended follow-up for 7 years showed no significant difference in overall survival between the two strategies. This is particularly true in those with severe ischemia	Routine CARP does not improve survival in stable CAD patients
Relieving ischemia with CARP	No difference in outcome between patients with moderate and severe ischemia	ISCHEMIA trial questions the routine use of stress testing followed by CARP for silent ischemia
Delaying/ avoiding CARP	No harm was found among those switched from conservative to invasive arm because of intractable angina	Unnecessary CARPs can be avoided by a measured approach prioritizing GDMT and intervening in only those with intractable angina
Cost savings	Up to 80% of patients with occasional chest pain managed by medication can avoid CARP	A more conservative approach can lead to significant cost savings for healthcare systems
Repeat procedures	Atherosclerosis progression may necessitate repeating CARP every 7–10 years, even with LDL levels <70 mg/dL	Aggressive low-density lipoprotein cholesterol (LDL-C) lowering (to 40–50 mg/dL) may be necessary to maximize the long-term benefits of CARP
The CARP paradox	The US performs more CARPs per 100,000 persons than Canada, yet Canada has lower CAD mortality	A less intervention-heavy approach may yield better outcomes. Besides, a 50% reduction in CARP in the US was associated with continuing decline CAD in the US
Low rates of major adverse cardiovascular event (MACE)	Annual MACE rates were low at 2% in both groups possibly due to better control of risk factors	Reduce MACE rates to 2% per year with GDMT

arteries is open to question as severe stenosis may not always lead to a heart attack, and mild blockage may cause a heart attack as plaque rupture may happen in an area without severe stenosis.[21-24] Research studies and clinical trials have further informed us: (1) The severity of a single blockage does not necessarily correlate with total plaque burden and total plaque burden correlates well with ACS. Computed coronary angiography (CTCA), in post-hoc analysis of the previously discussed ISCHEMIA cohort data showed that the total plaque volume correlated with myocardial infarction and death.[25] Coronary artery calcium (CAC) score reliably assesses the total plaque burden; (2) *Paradox of remodeling:* Arteries widening (remodeling) to accommodate plaque buildup, while appearing helpful, might be linked to increased heart attack risk, potentially

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TABLE 3: Key components of guideline-directed medical treatment (GDMT).[13,14,17,26,28,29]

A heart-healthy diet	Rich in whole grains, nuts, fruits, legumes, and vegetables and markedly restricting saturated fat and instead use of monounsaturated and polyunsaturated fats (Chapter 16)
Aim for 150–300 minutes of physical activity per week	Aim for <4 hours of sitting daily and walk more as this simple change can improve your heart health, reduce chronic disease risk, and boost your overall well-being. Younger adults should strive for 10,000 steps a day and seniors >65 years should strive for 4,000 or more steps
Smoking cessation and nicotine exposure	This is crucial as it markedly reduces the risk of major adverse cardiovascular event (MACE) after an ACS by 70–80%
Maintaining healthy weight and waist circumference	For Indians a healthy BMI is <23; healthy waist circumference is 80 cm for women and 90 cm for men (Chapter 3)
Maintaining healthy blood pressure	Maintaining blood pressure <120/80 mm Hg (Chapter 5)
Maintaining fasting blood sugar <100 mg/dL	Hemoglobin A1C <7% if diabetes is present (Chapter 6)
Maintaining lower lipid goals	• *Individuals with ASCVD:* Goal of LDL-C <70 mg/dL and NHDL-C; <100 mg/dL • *Indians at very high-risk for primary prevention:* Goal of LDL-C <50 and NHDL-C <80 mg /dL (Chapter 15)
Adequate sleep	Getting 7–8 hours of sleep plus others in Life's essential 8 (Chapter 17)
Cardiac rehabilitation	Reduces recurrent heart attack, stroke, and death by 25–30% after ACS
Full adherence to anti-anginal and secondary prevention medications	Aspirin, or clopidogrel, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) statins and beta-blockers can reduce recurrent MACE by 75–80%

harboring more dangerous plaque; and (3) to pay attention to plaque characteristics not just severity of blockage as CTCA scans show that heart attack-causing lesions may only have mild narrowing.[22,23,26]

The ISCHEMIA study highlighted the benefits of GDMT as a first-line treatment for stable CAD. While CARP offers faster angina relief, it does not necessarily translate to improved survival rates. The study delineated the importance of careful patient selection and a measured approach that prioritizes GDMT and reserves CARP for those who continue to have angina on GDMT. Other than in ACS, an invasive approach with CARP is not to be considered as a life-saving modality.[18,27]

Coronary artery disease is a systemic disease (atherosclerosis) requiring systemic treatment rather than a focal disease requiring focal treatment. Thus, rather than favoring a mechanistic approach that focuses solely on blockages and how to open them, a more comprehensive approach to management of CAD, a manifestation is required. GDMT combines lifestyle changes and medications **(Table 3)**, targets inflammation and lipid buildup in the coronary arteries and throughout the systemic arteries and improves patient outcomes.[30-32]

STABLE ANGINA: MEDICATIONS

Medications used in the management of stable angina comprise ones that relieve

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symptoms and ones that aim to prevent heart attacks and strokes. Preventive medications are indicated in both primary prevention (before a heart attack) and in secondary [after a heart attack or other major adverse cardiovascular event (MACE)] prevention.

- *First line:*
  - Nitrates—sublingual; oral forms both short acting and long acting.
  - Calcium channel blockers—non-dihydropyridines (e.g., diltiazem, felodipine, and amlodipine).
  - Be aware that short acting nifedipine is not recommended as it may cause reflex tachycardia.
  - Beta-blockers, especially in those with previous heart attacks and poor heart function (left ventricular ejection fraction <40%).
- *Second and third line:*
  - Ranolazine
  - Ivabradine
- *Secondary prevention:*
  - Aspirin
  - *Clopidogrel:* Though aspirin and clopidogrel may be considered in select patients exercise caution because of the high risk of bleeding.
  - Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
  - Statins (Chapter 13) are important in secondary and primary prevention.
  - Beta-blockers for 1 year following ACS
- *New drugs:* Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium glucose co-transporter 2 (SGLT2) inhibitors are two classes of drugs that show great promise in reducing CAD progression and in reducing MACEs in patients (especially in those with type 2 diabetes). However, their role in the management of stable angina is not yet clear. A relatively small recent controlled trial (EMPT-ANGINA) of a SGLT2 drug showed beneficial antianginal effects in patients with diabetes.[33]

CURRENT AMERICAN CLINICAL PRACTICE GUIDELINES

The ISCHEMIA trial has significantly reshaped the 2021 American College of Cardiology and American Heart Association (ACC/AHA) guidelines (main points are given below) for coronary revascularization in stable CAD.[34]

- Guideline-directed medical therapy is the preferred initial approach, even for high-risk patients with extensive disease.
- The role of both PCI and CABG surgery is defined and the indications clarified.
  - For patients with significant left main disease, surgical revascularization is indicated to improve survival relative to that likely to be achieved with medical therapy.
  - Surgical revascularization may be reasonable to improve survival in triple-vessel CAD.
- In patients undergoing CARP adequate information about benefits, risks, therapeutic consequences, and potential alternatives in the performance of CARP should be given, with sufficient time for informed decision-making to improve clinical outcomes.
- Overall, the guidelines suggest that GDMT alone may be sufficient for as many as 80% of the patients with CARP reserved for those with uncontrolled angina.[34]

DIVERGENT MANAGEMENT OF CORONARY ARTERY DISEASE IN THE US AND INDIA

While CARP (both PCI and CABG) have declined in the US, there has been a rise in

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CARP in India. Between 2013 and 2018, PCI procedures in India more than doubled. Of note, 12% of PCIs were in young adults (<40 years of age) consistent with increased premature CAD in India.[35] However, premature onset alone would not be sufficient to explain the degree of divergence in usage of PCIs between the two countries. The overemphasis of PCI in India leads to two considerations: Overestimation of the advantages of PCI and/or the underestimation of what GDMT can do.

This imbalance between PCI and GDMT needs to be addressed as GDMT can improve patient outcomes, is cost effective and avoids procedure-related risks, reduce healthcare costs and financial strain for patients and bring cardiac care in alignment to proven practices. We suggest the following steps:

- Comprehensive educational initiatives targeting both physicians and patients on the long-term preventive power of GDMT and its efficacy in managing CAD.
- Evidence-based guidelines that prioritize GDMT as the first-line of treatment, and reserve invasive procedures to specific, high-risk scenarios (e.g., ACS) where invasive procedures such as PCI can offer the most benefit.
- Conducting robust studies in India comparing benefits, risks, and outcomes of and cost-effectiveness of PCI and GDMT within the Indian context.

TESTS WITH IMPROVED DIAGNOSTIC PRECISION TO GUIDE TREATMENT

The diagnosis of angina is gaining remarkable precision with advancements such as computed tomographic coronary angiography (CTCA) and fractional flow reserve computed tomography (FFRCT). Traditionally, diagnosing angina relied on subjective symptoms and stress tests, which have limitations. Symptoms can vary, and stress tests may not be definitive for all patients, especially those with atypical presentations. The 2021 ACC/AHA guidelines recommend CTCA as a Class I recommendation for suitable patients with stable chest pain.[4]

Computed tomographic coronary angiography offers a noninvasive way to visualize coronary arteries, providing a detailed anatomical picture of the extent of plaque buildup and narrowing. This allows for improved detection of CAD and identification of specific blockages contributing to angina. This procedure also helps differentiate critical blockages causing significant ischemia (oxygen deficiency) that contribute to angina from less critical blockages that may not require immediate intervention.

Fractional flow reserve computed tomography builds on CTCA by functionally assessing the impact of blockages on blood flow within the coronary arteries and can differentiate between patients who would best benefit from CARP from those who are unlikely to benefit. The Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) Registry found that a positive FFRCT result, indicating a significant blockage, led to treatment changes in two-thirds of patients compared to using CTCA alone, highlighting its use to avoid invasive coronary angiograms in patients with blockages that do not significantly impact blood flow. This combined approach with FFRCT offers a more precise approach to diagnosing angina, optimizing treatment decisions, and potentially reducing unnecessary interventions.[36]

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CHRONIC CORONARY DISEASE: A PATIENT-CENTERED APPROACH TO MANAGEMENT

Chronic coronary disease (CCD) encompasses a spectrum of heart conditions, including those with prior heart attack, weakened heart muscle (cardiomyopathy), chest pain (angina), blocked arteries, and high coronary plaque burden (high CAC score). The updated 2023 ACC/AHA guidelines prioritize both extending lifespan and improving quality of life for CCD patients. The main recommendations of the guidelines are:

- The use of GDMT in all patients with CCD.[37]
- Coronary artery calcium score to assess risk and for prompt therapeutic intervention (mostly GDMT) in patients with high CAC score to prevent a MACE. A CAC score >300 is associated with a 3–7-fold high risk of a MACE.[38]
- Coronary artery revascularization procedure is appropriate in two specific scenarios:[37,39]
  1. Relief of severe angina that limits daily activities despite optimal medical therapy,
  2. Improve survival in high-risk patients with severe left main artery disease or multivessel disease with severely weakened heart function [left ventricular ejection fraction (LVEF) ≤35%]. In these patients, coronary artery bypass (CABG) surgery combined with medication(s) is recommended.
- Caution against unnecessary cardiac tests: Routine periodic anatomic or ischemic testing in the absence of a change in clinical or functional status is not recommended for risk stratification or to guide therapeutic decision-making for patients with CCD.[37]

KEY TAKEAWAYS

- Guideline-directed medical treatment (GDMT) utilizes a powerful combination of heart-healthy lifestyle modifications (diet, exercise, and sleep smoking cessation) and effective medications that control cardiac risk factors, relieve angina, are cardioprotective and prevent MACE. Key elements of GDMT and antianginal and preventive medications are tabulated and detailed in the text.
- Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) procedures are no longer the primary treatment modalities for angina and stable CAD. This shift away from invasive procedures reflects a better understanding that CAD is a systemic disease and therefore addressing the underlying causes with GDMT is more apt and effective.
- Coronary revascularization procedures (CARP) that include CABG and PCI are limited to select patients in two scenarios: (1) Severe angina (that limits daily activities) despite optimal medication management; (2) Severe left main artery disease or multivessel disease with severely diminished left ventricular ejection fraction (LVEF).
- Guideline-directed medical treatment is the right choice for all patients with stable angina and many with chronic coronary disease (CCD).
- Several medications—first line and second line—are available for angina management. Secondary prevention to prevent major adverse cardiovascular events (MACE) is to be emphasized in all patients with angina.
- *Newer imaging tests:* Computed tomographic coronary arteriography (CCTA) and fractional flow reserve computed tomography (FFRCT) are more precise in diagnosing angina than currently used tests and are better guides to management.
- There is a remarkable divergence in the management of CAD between the US and India. While cardiovascular revascularization procedures (both CABG and PCI) have markedly decreased in the US, in India PCIs have very markedly increased. This is due to an overestimation of the benefits of PCI and an underestimation of the benefits of GDMT.

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- Research generated and evidence-based guidelines and educational efforts that target both doctors and the public are needed to increase the use of proven GDMT in India.

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This information-packed and well-referenced book is meant to be the one-source, state-of-the-art book on coronary heart disease (CAD) for cardiologists in particular, physicians in practice, and medical students, postgraduates, and researchers. But the book is not exclusively for this select group as the authors have striven to make it useful to all interested in CAD, the major risk factors for CAD, and all aspects of prevention. Thus, ample illustrations and tables are provided, scientific terms are explained, and each chapter ends with a table of "Key Takeaways". The initial chapter sets the stage, and the subsequent chapters explain how heart disease develops over time, how it presents, the major risk factors and how to control them, and present-day management of heart disease by medications and interventions and the book ends with chapters on prevention (including one on diet).



Enas A Enas MD FACC, a world-renowned Cardiologist, leads the CADI (Coronary Artery Disease in Asian Indians) Research Foundation, focusing on heart disease in people of Indian descent. He is Founder President and CEO, Coronary Artery Disease among Asian Indians (CADI) Research Foundation and Advanced Heart Lipid Clinic Downers Grove, Illinois, USA. His impactful CADI study revealed a higher heart disease rate in Indian Americans and linked it to elevated lipoprotein (a) [Lp(a)]. He has contributed over 100 scientific articles, more than 1,000 global lectures, and advocacy that led to the recognition of Lp(a) and South Asian ethnicity as risk-enhancing factors for heart disease.



Basil Varkey MD FRCP FCCP, after a distinguished and long academic career at the Medical College of Wisconsin, continues his passion for teaching, medical writing, and editing in retirement. He is Professor Emeritus of Medicine. A prolific writer in pulmonology, cardiology, clinical ethics, and others, his publications have been cited more than 4,000 times. Dr Varkey, a master Teacher, has won several awards and honors and was a two-term Governor of the American College of Chest Physicians.

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