

ANGINA PECTORIS: PATHOPHYSIOLOGY AND EVOLVING THERAPEUTIC STRATEGIES-A COMPREHENSIVE REVIEW

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Abstract

Angina pectoris, a medical disorder characterised by transient chest discomfort or pain due to myocardial ischaemia, remains a prevalent and debilitating condition worldwide. It is primarily caused by an imbalance between oxygen supply and demand in the myocardium resulting in oxygen deficit, often resulting from obstructive or non-obstructive coronary artery disease (CAD). Despite considerable advancement in diagnostic imaging, pharmacological interventions, and revascularization techniques, angina continues to pose an evident burden on patients' quality of life and healthcare systems globally. Traditional pharmacologic therapies, including β -blockers, calcium channel blockers, nitrates, and antiplatelet agents, have been the cornerstone of treatment. However, a considerable portion of patients persistently exhibit symptoms despite receiving guideline-directed medical therapy and undergoing revascularization procedures. The emergence of newer drugs such as ranolazine, ivabradine, and trimetazidine has provided additional therapeutic options, targeting distinct mechanisms of action to alleviate symptoms. In recent years, research into regenerative therapies has opened new frontiers in angina management. Gene therapy, stem cell interventions, and exosome-based treatments demonstrate potential in targeting the root causes of ischemia and promoting myocardial repair. Furthermore, advancements in drug delivery systems and the potential for personalized therapies are poised to improve clinical outcomes. This review delivers a comprehensive overview of the pathophysiology of angina pectoris, examines current treatment strategies, and explores the future potential of innovative therapeutic approaches. By highlighting the ongoing evolution in angina management, this review aims to contribute to the understanding and management of this chronic condition, thereby contributing to better clinical outcomes and improved quality of life.

Keywords: Angina Pectoris; Coronary Artery Disease; Ischemia; Pathophysiology; Pharmacotherapy

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Introduction

Cardiovascular disease is the main contributor of death worldwide, with coronary artery disorder accounting for nearly half of fatalities. Acute coronary syndromes are among its clinical manifestations and usually require urgent or emergency intervention. Chronic coronary syndromes may typically be treated on a non-hospitalized patient basis for both assessment and management, provided there are no identified high-risk factors. Since it was first used more than two centuries ago, the word “angina pectoris” has been widely used to refer to blocked coronary artery disease due to atherosclerosis. The idea that obstructive CAD is nearly the only cause of the connection between angina pectoris, myocardial ischemia, and coronary atherosclerosis has been reinforced by frequently documented evidence relating these conditions. Cardiac pain is the leading frequent diagnostic features of chronic coronary syndrome (CCS), the chronic type of coronary artery disease (CAD), which also defined from a probable CAD diagnosis based on symptoms, frequently confirmed via objective means (Knuuti *et al.*, 2020). Up to 50% to 70% on medical case having a diagnostic justification related to invasive coronary angiography have nonobstructive CAD or normal coronary arteries, based on studies examining the connection between the severity of CAD and angina. Arrhythmia, an abnormal heartbeat, can suddenly cause death in a person (Varney *et al.*, 2022). Treatment should be started within 3–4 min of the onset of severe arrhythmias since their impaired pumping ability can affect the cardiac capacity to deliver sufficient blood flow to meet the body’s metabolic demands. This is known as a “silent killer” since it can make the person feel dizzy, exhausted, or possibly suddenly die (Fu, 2015).

Atypical characteristics including severe exhaustion after exercise or dyspnea in the absence of pulmonary illness have recently been regarded as similar to chest pain counterparts. These uncommon symptoms without cardiac discomfort act as common during diabetics, females, and older adults. For a long time, it was believed that most patients who were presented with angina had severe coronary artery constriction, which prevented a rise in coronary blood circulation even while activity or stress increased the demand for oxygen in the heart. However, it has recently been discovered that many individuals with chronic and lethal angina, like ventricular fibrillation, and sustained ventricular tachycardia also exhibit extra non-obstructive coronary artery lesions that are at risk of rupturing

as well as frequently cause future negative clinical result (heart attack, acute chest pain, and sudden cardiac death). These lesions exist along with a significant reduction in the width of one or more heart coronary vessels (Varney *et al.*, 2022). The phrase “ischemic heart disease” appears inside the title and originated in America from the early education institution Heart Association and the American College of Cardiology. Current treatment recommendations instead of “coronary artery disease”, yet the majority of these therapy plans suggested by recommendations are also predicated on the idea that underlying obstructive CAD is the cause of myocardial ischemia (Fihn *et al.*, 2012). This notion is really false since a large number of patients who first appear with angina actually have either healthy cardiac arteries or blockage-free CAD, but they also show aberrant coronary blood flow capacity and/or small vessel disorder (Thadani, 2016). Angina pectoris was estimated to have cost between 8.9 and 75 billions US dollars in total in 2000. Because angina sufferers’ quality of life is impaired and it interferes with their capacity to carry out everyday tasks, angina has an impact on society as a whole. This places a significant strain on the healthcare system and necessitates ongoing investigation into the creation of treatments as well as preventative measures (Rousan *et al.*, 2017). A Person under treatment having chronic chest pain is susceptible to treatment having both invasive and non-invasive techniques. Invasive approaches (like coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting) decrease rates of refractory angina, rehospitalization, and myocardial infarction. Non-invasive alternatives for refractory angina consist of transcutaneous electrical nerve stimulation (TENS), opioids, medical management, and multidisciplinary programmes, which may enhance symptoms and quality of life (QoL) with minimal negative effects (Hoenig *et al.*, 2006).

The primary objectives of treatment are symptom relief, enhancing your living standards with antianginal medications, and making way of life changes, like those beside acute 3-channel that affect left heart chamber - related purpose or cases having left major disorder. The possible side-effect profile of antianginal medications should be considered while selecting them (Rousan *et al.*, 2017).

This review intends to outline the underlying mechanism of angina pectoris to understand the disease pathophysiology and its development and progression in the human body. The review also focuses on the current antianginal therapies that are

available and their mechanism of action. Lastly, the review aims to advance and emerging therapeutic approaches seek to address underlying vascular and cellular dysfunction, such as gene therapy, exosome-based therapy, and stem cell therapy. These advancements advocate for a transition towards tailored therapeutic modalities, which is also explained in brief. In conclusion, this review helps in the progressive understanding of the pathophysiological mechanisms of angina pectoris, coupled with the advent of biologically targeted and precision-orientated therapeutic inventions.

Methodology

This research is a narrative review aimed at summarising existing evidence regarding angina pectoris. A thorough investigation of pertinent literature was conducted through several esteemed databases to collect extensive and up-to-date information on the management of angina pectoris. The sources employed to gather relevant information included PubMed, Google Scholar, and Scopus. English articles concentrating on angina, its mechanisms, and recent innovative therapies for treating it were included. Titles and abstracts were examined for the relevance of the chosen articles, succeeded by a review of the full text. The reference list of chosen articles was examined to find extra sources. The outcome was presented as a brief overview on the specified title.

Pathophysiology of Angina Pectoris

Myocardial Oxygen Supply–Demand Mismatch

The heart's vascular network, including epicardial arteries, intramyocardial arteries, and arterioles, branches into capillaries to supply oxygen. Certain patients might experience clinical features and exhibit signs of ischemia, despite having no major coronary blocker visible on angiography, as a result of abnormalities in the blood flow of the coronary arteries, such as variant angina or dysfunction of the coronary microcirculation (Kunadian *et al.*, 2020).

Obstructive vs Non-Obstructive Coronary Disease

Obstructive coronary heart disease (CAD) is marked by the accumulation of atherosclerotic plaques that causes considerable constriction of arteries related to the coronary, subsequently resulting in diminished blood flow. Conversely,

non-obstructive CAD generally encompasses issues such as microvascular dysfunction, vasospasm, or inflammation. Even without significant blockages, this non-obstructive type of CAD can still cause ischemia or heart attack (Tudurachi *et al.*, 2024).

In healthy hearts, epicardial arteries provide minimal resistance to blood flow. Blockages hinder circulation, but autoregulation—a vessel dilation response to low oxygen—partially compensates. In conditions like atherosclerosis, blockages may be permanent (e.g., plaque buildup) or dynamic (e.g., vasospasms). This obstruction can cause myocardial ischemia, resulting in acidosis and impairment of the regular ATP sodium-potassium pump and membrane stability. Nitric oxide synthase converts L-arginine into NO, which relaxes arterial smooth muscle. Endothelial damage, caused by oxidised LDL or other factors, reduces NO production. Statins, exercise, and ACE inhibitors help improve endothelial function.

Acute coronary syndromes are commonly caused by a sudden decrease or blockage of blood flow, usually due to plaque rupture or erosion and subsequent coronary thrombosis (Arbab-Zadeh *et al.*, 2012).

Microvascular Angina

Unusual delayed reactions of the coronary microvessels, spasm of coronary microvasculature, and extravascular compressive forces have been recognized as harmful mechanisms in both chronic and acute types of ischemic heart disease. The state marked by anginal symptoms and signs of myocardial ischemia initiated by coronary microvascular impairment, in the absence of obstructive CAD, is referred to as microvascular angina (Kaski *et al.*, 2018).

Vasospastic Angina

Vasospastic angina (VSA) is a variant type of angina pectoris, characterized by angina episodes at rest, transient changes in the ECG, and maintained exercise capacity. VSA can be present in various clinical diseases, including stable angina and acute coronary syndrome (Picard *et al.*, 2019).

Mechanisms of Ischemic Chest Pain

Activation of afferent sympathetic fibres in the upper thoracic spinothalamic tract produces chest and arm pain, while activation of vagal afferent fibers that stimulate cervical spinothalamic tracts can cause neck and/or jaw pain symptoms (Jain *et al.*, 2017). The exact mechanisms that cause this pain are not fully understood, still this review elaborates its mechanism of occurrence in Figure 1.

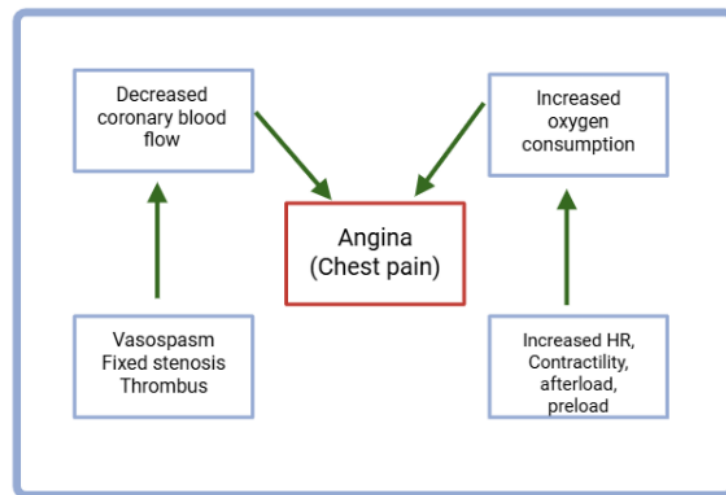


Figure 1. Mechanism of angina pectoris

Traditional / First-line Antianginal Pharmacotherapy

The intervention of stable angina pectoris (SAP) and other ischemic heart conditions relies on a combination of pharmacological strategies aimed at improving oxygen delivery to the myocardium, reducing cardiac workload, and preventing thrombotic events.

Present major guidelines, such as those from the European Society of Cardiology (ESC) and the National Institute for Health and Care Excellence (NICE), advocate a gradual method to antianginal therapy, differentiating between primary and supplementary (second-line) medications. β -blockers, calcium channel blockers (CCB), and short-acting nitrates are widely endorsed as primary agents for the symptomatic treatment of stable angina (Kunadian *et al.*, 2020).

Guidelines recommend beginning treatment with either a β -blocker or a CCB, and if monotherapy is inadequate, they should be combined, while short-acting nitrates are utilized for immediate symptom relief. Long-acting nitrates, ranolazine, ivabradine, nicorandil, and trimetazidine are considered second-line or supplementary medications (Nedoshivin *et al.*, 2022).

Renin-Angiotensin-Aldosterone System (RAAS) Blockers

Maintaining the balance between cardiovascular & renal systems, the RAAS acts as a robust and influential modulator. RAAS blocking by angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blockers has consistently been proven to repeatedly demonstrate to be a reliable

and productive approach. Blood pressure and renal urine output are elevated by angiotensin II, aldosterone, and norepinephrine (Maideen *et al.*, 2022). Bradykinin is yet another substance that leads to the dilation of blood vessels, and ACE inhibitors also enhance its formation.

ACE inhibitors can be classified according to their chemical structure into three groups: sulfhydryl-containing agents, such as captopril; dicarboxylate-containing agents, such as enalapril and lisinopril; and phosphonate-containing agents, such as fosinopril (Aggarwal *et al.*, 2016). Some medications are classified as prodrugs; however, captopril and lisinopril are not. A history of angioedema or acute renal dysfunction with anuria from prior ACE inhibitor exposure, pregnancy, and severe hypotension are among the conditions that exclude the use of ACE inhibitors. Additionally, ACE inhibitors may cause hypotension when used with other vasodilators like beta-blockers or nitrates, particularly if the ejection fraction is low.

Nitrates

A popular therapy for coronary artery disease is the use of organic nitrates. They are given to individuals who have heart failure, variant angina, and a sudden heart attack in addition to those who have stable angina pectoris (Parker and Parker, 1998). Nitrates are helpful for preventing acute incidents as well as responding to them. They lessen left ventricular preload and oxygen demand via vasodilation (Figure 2) (Kaski *et al.*, 2011). According to certain theories, nitrates are safe and useful for treating the symptoms of individuals suffering from acute and chronic ischemia syndromes brought on by coronary artery disease.

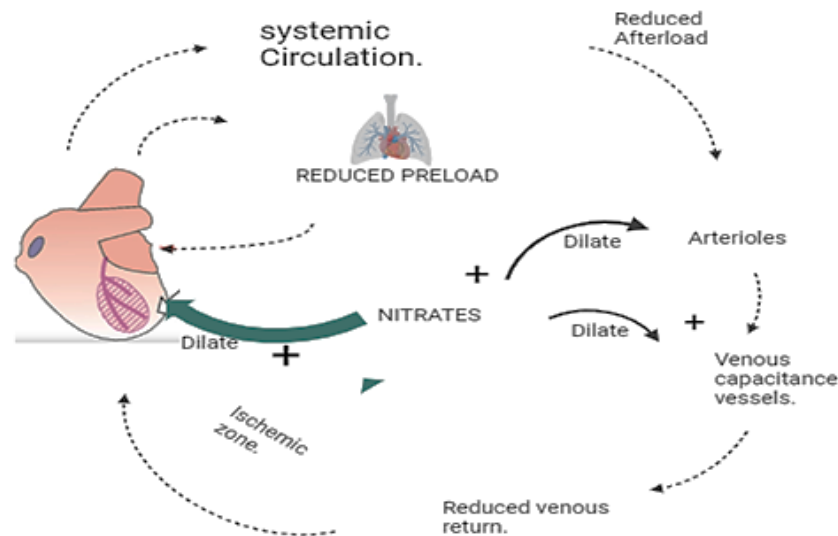


Figure 2. Mechanism of action of nitrates

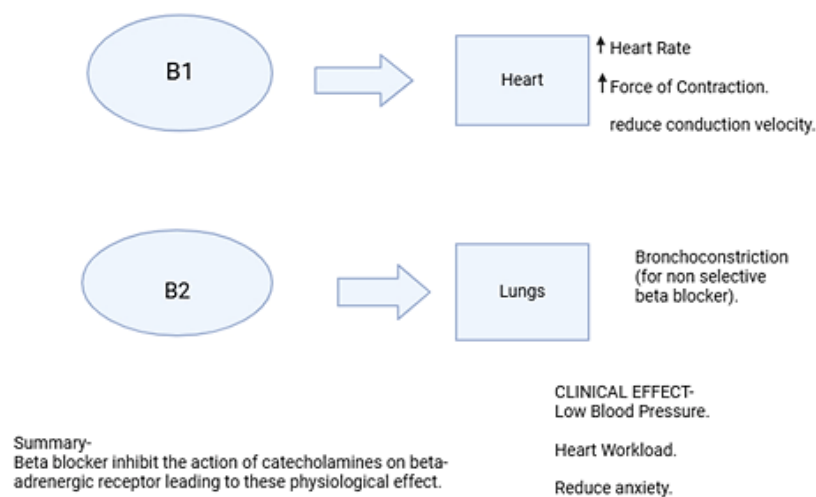


Figure 3. Mechanism of action of beta-blockers

Nitrates enhance exercise tolerance, the delay to angina onset, and ST-segment depression observed during a treadmill stress test in individuals with exertional stable angina. Organic nitrates act as prodrugs that require metabolism to generate nitric oxide, the key active agent in this drug category. Nitric oxide elevates intracellular cGMP levels; this facilitates the dephosphorylation of myosin light chains (Münzel *et al.*, 2014).

Beta-blockers

Beta blocker (BBs) reduce the prevalence of recurrent angina and myocardial infarction. They lower the need for oxygen by diminishing and

slowing the pace of the heartbeat and decreasing arterial pressure, decreasing the force of heart muscle contractions, and lowering the pressure on the heart's left ventricle. Lowering the heart rate causes the diastolic time to rise, which in turn improves coronary perfusion and the oxygen supply (Figure 3) (Hassan *et al.*, 2023).

β -blockers are recommended as the primary treatment for managing stable angina symptoms. Their effectiveness is comparable to that of other antianginal medications. Beta-blockers have negative effects on heart rate, conduction, and contractility (inotropic). They should be avoided in patients with bradycardia, conduction

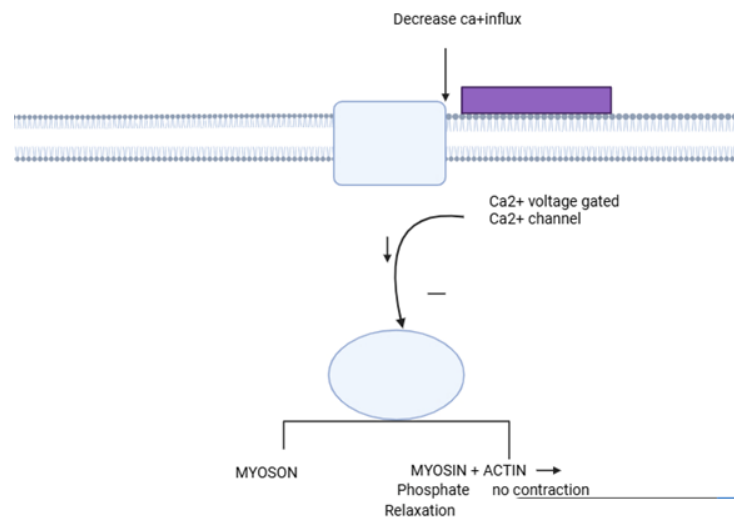


Figure 4. Mechanism of action of calcium channel blockers

abnormalities, or acute decompensated heart failure (Ferrari *et al.*, 2018). Furthermore, caution is advised when using beta-blockers during pregnancy, in individuals with low blood pressure, diabetes mellitus, or Raynaud's disease, and when they are used in combination with other drugs that also have negative effects on heart rate or conduction (Knuuti *et al.*, 2020).

Calcium Channel Blocker

Calcium channel blockers (CCB) are frequently utilized in individuals with vasospastic angina. Their major advantage is that they can prevent arterial vasoconstriction by causing vascular smooth muscle cells to relax (Radico *et al.*, 2014). When electrical depolarization takes place, these channels permit the entrance of extracellular calcium ions into cardiomyocytes, smooth muscle fibers, and the nodal cells of the atrioventricular and sinoatrial chambers (Shah *et al.*, 2022). By lowering blood pressure, contractility, and afterload, CCBs lessen the need for oxygen (Figure 4). Who are intolerant of beta-blockers (BBs) and who have peripheral vascular disease or variant angina are good candidates for CCBs. Patients suffering from heart failure should utilize CCBs with care (Kunadian *et al.*, 2020). Calcium channel blockers can have a positive impact on the coronary arteries' artery tone in that variant angina (Jansen *et al.*, 2022). It is advised to utilize non-dihydropyridine calcium channel antagonists instead of beta-blockers; however, dihydropyridine CCBs may be employed additionally to or instead of beta-blockers (Knuuti *et al.*, 2020).

Second – Line and Adjunctive Agents for Angina Pectoris

In addition to the first-line pharmacologic therapies, several second-line and adjunctive agents have been developed to target alternative pathways in angina pectoris management. These drugs, including trimetazidine, ivabradine, nicorandil, and ranolazine, offer distinct mechanisms of action addressing either metabolic, electrophysiological, or vascular contributors to ischemia and are especially useful in patients with persistent symptoms despite optimal therapy.

A comprehensive understanding of each agent's mechanism of action, appropriate dosing, potential contraindications, and key adverse effects is essential for optimizing treatment strategies in patients with angina pectoris. Table 1 summarizes these clinical considerations for Traditional/first-line antianginal pharmacotherapy (Kaski *et al.*, 2011).

Trimetazidine

Trimetazidine mainly blocks the final enzyme in the fatty acid beta-oxidation pathway, long chain 3-ketoacyl coenzyme, a thiol ester. This causes a partial shift in myocardial energy metabolism from fatty acid oxidation to glucose oxidation. Under ischemic conditions, this mechanism may be advantageous because glucose oxidation requires less oxygen to generate ATP. The precise mechanism through which trimetazidine exerts its antianginal effects is not fully understood (Thadani, 2016).

Table 1. Traditional/first-line antianginal pharmacotherapy

Class	Agents / Examples	Mechanism of Action	Indications	Cautions / Side Effects
Anticoagulants / Antiplatelets	Aspirin (75–162 mg/day), Clopidogrel	Inhibits platelet aggregation	First-line for Stable Angina Pectoris (SAP)	Avoid Dipyridamole in SAP; Clopidogrel if aspirin is unsuitable
RAAS Blockers	ACE Inhibitors (Enalapril, Lisinopril, Captopril), ARBs	Blocks Angiotensin II formation or receptor, reduces vasoconstriction and aldosterone effects	Hypertension, Diabetes, CKD, Cardiovascular Risk Reduction	Hypotension, hyperkalemia, angioedema, contraindicated in pregnancy
Nitrates	Nitroglycerin, Isosorbide Dinitrate	Converts to NO → ↑ cGMP → vasodilation, reduces preload and oxygen demand	Stable Angina, Variant Angina, Heart Failure, Acute MI	Headache, hypotension, tolerance with long-term use
Beta-Blockers	Metoprolol, Atenolol, Bisoprolol	↓ Heart rate, BP, myocardial contractility → ↓ oxygen demand	Stable Angina, Post-MI, Acute Coronary Syndromes	Bradycardia, hypotension, fatigue, avoid in conduction issues & acute decompensated heart failure
Calcium Channel Blockers (CCBs)	Amlodipine, Verapamil, Diltiazem	Blocks L-type calcium channels → vasodilation, ↓ afterload & contractility	Vasospastic Angina, Stable Angina (when BBs not tolerated)	Bradycardia (verapamil, diltiazem), edema, avoid in heart failure (non-DHPs)

Although trimetazidine is made accessible in Europe and some Asian nations, it is not authorized in the United States, where it is utilized as a supplemental therapy for angina. It is regarded as a metabolic modulation treatment that enhances the ischemic myocardium's consumption of glucose by primarily inhibiting free fatty acid oxidation. Trimetazidine is excreted in urine in 79–84% of cases, with 60% remaining as the parent component unaltered. Trimetazidine is 15% protein bound in plasma. Human serum albumin is capable of binding to trimetazidine (McCarthy *et al.*, 2016).

Ivabradine

Ivabradine lower pulse rate by, blocking the channels activated by cyclic nucleotides that are triggered by hyperpolarization and regulate the pacemaker current. Ivabradine lowers myocardial oxygen demand and heart rate by inhibiting this channel without affecting contractility (Oliphant *et al.*, 2016). Ivabradine should be taken with meals in order to minimize systemic exposure variability. When taken with meals, absorption is slowed by one hour, although systemic absorption is increased by 20–30%. The oral bioavailability of ivabradine is around 40%. Giving ivabradine to pregnant women may result in fetal harm. Ivabradine is also recommended for people with angina pectoris who are unable to take beta-blockers and for those whose symptoms are not sufficiently managed by beta-blocker medication at the recommended dosage. Ivabradine was not

observed to enhance for patient with stable heart artery disease who did not have clinical heart failure when added to usual therapy, according to the SIGNIFY study. Phosphenes, blurred vision, bradycardia, ventricular premature beats, first-degree AV block, nausea, dizziness, and atrial fibrillation are typical adverse effects (Chen *et al.*, 2021).

Ranolazine

The antianginal drug ranolazine targets a potassium current and a late sodium current. It could lessen sodium-dependent calcium overload, which causes problems including elevated diastolic tension, decreased ATP synthesis, and the risk of arrhythmias, by blocking the late sodium current (Rayner-Hartley and Sedlak, 2016). Ranolazine inhibits the late inward sodium influx under the conditions of reduced blood supply, treating inside the cell calcium excess, according to studies conducted in isolated myocytes and animals. Ranolazine substantially lower the incidence of chest pain episodes and prolongs the duration of activity and the time it takes for angina to strike.

The CYP3A4 enzyme is responsible for the fast, significant metabolism of ranolazine in the liver and gastrointestinal system, with CYP2D6 contributing just little (Saglietto *et al.*, 2021). Currently, the precise mechanism behind the antianginal effect of ranolazine remains unclear. Ranolazine's apparent terminal half-life is seven hours. Approximately three-quarters of the supplied

dosage is eliminated by the kidneys, and one-fourth is eliminated through the feces. About 5% of a dosage that is consumed is thought to be eliminated unaltered. While the evidence surrounding coronary microvascular dysfunction is somewhat conflicting, European consensus guidelines support the use of ranolazine for treating microvascular angina (Kunadian *et al.*, 2020).

Emerging and Novel Therapeutic Strategies

As cardiology advances, research is investigating novel strategies to treat angina pectoris. Future treatment approaches focus on regenerative medicine, personalized interventions, and technological advancements, aiming to restore myocardial function and improve patient outcomes. Table 2 summarizes the novel therapies for the treatment of angina pectoris.

Regenerative Therapies

Stem Cell Therapy: Therapy using stem cells offers a hopeful alternative for managing ischemic heart disease.

Mechanism - Stem cell treatment seeks to mend injured heart tissue, demonstrating potential in enhancing cardiac function and alleviating symptoms. Stem cells have shown significant promise in addressing a wide range of disorders. Even though the mechanism has not been established yet, it has been found through the accessible data that the stem cells are inclined to migrate to damaged areas such as cardiac tissues (Wei *et al.*, 2013).

Evidence summary - Preclinical research has shown that cell-based therapy is a hopeful new approach for enhancing vascularization and heart regeneration. Research on cell-based therapy has primarily concentrated on inhibiting cardiac

Table 2. Novel therapies for the treatment of angina pectoris

Novel therapies	Mechanism	Key evidence	Clinical limitation	Future direction
Stem cell therapy	Stem cells migrate toward the injured myocardium and support tissue repair	Enhanced vascularization, Improved symptoms, Increased survival; Showing stronger effects with CD34+ and G-CSF.	Inconsistency in efficacy; Variable mortality	Standardization of large clinical trials; gene editing; cost reductions; engineered scaffolds
Gene Therapy	Transmits angiogenic/function-repairing genes (e.g., VEGF-D) to ischemic heart tissue	Adenoviral/AAV vectors enhance blood flow and alleviate symptoms; over 300 participants treated in SERCA2a trials.	Limited gene absorption; immune system elimination; off-target/liver accumulation.	Minimally invasive administration; incorporation with revascularization/regeneration approaches
Exosome-Based Therapy	Exosomes transmit regenerative signals/miRNAs and enhance angiogenesis and ECM restoration.	MSC/MI-derived exosomes exhibit cardioprotective properties and angiogenic effects linked to miRNA	No uniform isolation; preliminary research phase.	Tailored cargo; hydrogel/patch/nanocarrier transport to ischemic heart tissues.
Emerging Biomarkers	Biomarkers assist in diagnosis, tracking, and predicting risk.	Troponins, hs-CRP, and Lp-PLA2 indicate diagnostic/risk potential.	Troponins are ineffective for unstable angina; new markers require validation.	Extensive multicentre validation; quick, cost-effective tests; combining conventional + innovative markers.
Personalized Antianginal Therapy	Customized medications according to patient-specific factors.	Coronary sinus reducer enhances symptoms and QoL in resistant angina.	Ongoing symptoms might obscure microvascular or vasospastic conditions.	Targeted antianginal treatment; personalized strategies in line with ESC guidelines
RNA-targeted Therapies	siRNA/ASO suppress disease gene; miRs/circRNAs regulate remodelling	Anti-miRs and miR delivery enhance remodelling/apoptosis; several agents are under investigation.	Delivery, toxicity, and stability concerns.	VEGF-mRNA treatments; enhanced delivery systems; novel RNA targets; integration of digital health

remodeling and dysfunction following myocardial infarction (MI). Earlier research indicated that stem cells might possess the ability to restore the myocardium (Li *et al.*, 2013). In a recent clinical study on microvascular angina, subjects experiencing ischemia and non-obstructive coronary artery disease who received intracoronary infusion of CD34+ cell therapy exhibited improved coronary flow reserve, reduced severity of angina, and enhanced QoL after 6 months. (Henry *et al.*, 2022). At present, there are no established clinical guideline recommendations for CD34+ stem cell therapy in cardiovascular conditions, and its application is confined to research in particular contexts like refractory angina and coronary microvascular dysfunction (CMD).

In a different study, 254 patients were administered granulocyte colony stimulating factor (G-CSF) therapy along with stem cell therapy, while 60 patients received stem cells without the G-CSF addition. In general, the major adverse cardiac event (MACE) and overall mortality decreased when cell therapy was administered alongside G-CSF (Jones *et al.*, 2019).

In summary, CD34+ cell therapy for patients with refractory angina leads to enhanced survival rates and fewer hospital visits as well as lower costs for cardiac interventions in the year after treatment.

Clinical limitation – Stem cell therapy has also demonstrated certain limitations due to the inconsistency in clinical effectiveness. Although meta-analysis of available data indicates enhancement in angina frequency, exercise ability, and certain cardiac outcomes, findings regarding mortality and significant adverse cardiac events are inconsistent (Lele *et al.*, 2025).

Future directions – Future and ongoing research must emphasize larger, randomized, multicentre trials employing standardized protocols to determine efficacy and safety more clearly. Studies are investigating gene editing, bioengineered frameworks, and exosome-derived treatments to improve cell viability and therapeutic outcomes. Advancement aimed at reducing expenses and streamlining delivery might expand clinical applications (Dabravolski *et al.*, 2025).

Gene Therapy: For patients whose antianginal medications do not yield adequate symptom relief, further procedures like angioplasty or bypass surgery might be necessary.

Mechanism - Ischemic muscle serves as a potential target for gene therapy utilizing naked plasmid DNA. Intramuscular transfection of genes that encode angiogenic cytokines, especially those

released by intact cells, could serve as an alternative treatment for patients with severe tissue ischemia when modern therapies (antianginal drugs, angioplasty, bypass surgery) have previously been ineffective and are not an option (Losordo *et al.*, 1999).

Evidence summary - The localized administration of therapeutic transgenes using first-generation human adenovirus serotype (HAd)-5 is considered safe in the short term and has demonstrated some effectiveness in treating drug-resistant angina pectoris and heart failure with reduced ejection fraction.

In a recent clinical phase I KAT301 trial, gene therapy using intramyocardial adenovirus-mediated vascular endothelial growth factor-D^{ANAC} (AdVEGF-D) led to a substantial enhancement in myocardial perfusion reserve and alleviated symptoms in patients with refractory angina during 1-year follow-up without significant safety issues (Leikas *et al.*, 2022).

The intracoronary application of gene therapy entails a straightforward cardiac catheterization, successfully administered to over 300 patients suffering from severe heart failure in the AAV1. SERCA2a studies. (Musolino *et al.*, 2025).

Clinical limitation - Even with HAd-5 achievements, the widespread use of therapeutic HAd-5 vectors aimed at cardiovascular tissues and internal organs is constrained by minimal gene transfer to target cells, immune system elimination, liver sequestration, unintended effects, and degradation of episomes (Schwartz *et al.*, 2022).

Future direction – Active research is focused on percutaneous invasive delivery techniques, like percutaneous or epicardial injection, to enhance targeting and lessen procedural risks. Integrating gene therapy with traditional revascularization or regenerative treatments might improve results, particularly in individuals with partial revascularization or microvascular issues (Nakamura *et al.*, 2024).

Exosome-Based Therapy: Exosome-based treatment utilizes tiny extracellular vesicles to transport therapeutic agents to heart cells. They might possess regenerative compounds that promote the proliferation and differentiation of cardiac progenitor cells, facilitating the repair of injured heart tissue following trauma or disease (Liu *et al.*, 2022).

Mechanism – Exosomes transport molecules that trigger regenerative signaling pathways in target cells as part of their content. Moreover, they influence the restructuring of the extracellular matrix (ECM), the foundation that underpins cells and therefore assists in tissue healing. Exosomes can support angiogenesis in the damaged heart and

supply endothelial cells with pro-angiogenic components such as vascular endothelial growth factor (VEGF), which promotes the formation of new blood vessels. Exosomes have garnered significant attention as a potential method for delivering therapeutic cargo because of their natural ability to transfer biomolecules between cells (Hassanzadeh *et al.*, 2024).

Evidence summary - In a mouse model of pressure-overload heart failure, Nakamura *et al.* investigated the cardioprotective impacts of intravenously administered adiponectin-induced MSCs-exosomes (Nakamura *et al.*, 2020). Research on exosomes obtained from the serum of individuals with MI showed that the generation and secretion of MI-exosomes were linked to cardiomyocytes. Additionally, microarray analysis showed that miRNA-143 was notably reduced in MI-exosomes. In the meantime, the increased expression and reduction of miRNA-143 could suppress and promote angiogenesis, respectively (Bei *et al.*, 2017).

Clinical limitation - Exosomes originating from cardiac stem cells possess therapeutic properties and can act as vehicles to transport therapeutic drugs to target cells, thereby providing a therapeutic benefit. Exosomes offer greater benefits than stem cell therapy, potentially aiding us via cell-free treatment. Despite certain progress being achieved, the study of exosomes remains in its infancy, and numerous issues persist, including the absence of standardized methods for isolation and purification (Li *et al.*, 2024).

Future direction - Tailored exosomes can carry specific miRNA (like miR-143) or proteins to promote tissue repair. Innovative delivery platforms like hydrogels, cardiac patches, and nanoparticle systems are being created to enhance exosome retention and targeted delivery to ischemic heart tissue, boosting therapeutic effectiveness and reducing off-target impacts (Hu *et al.*, 2022; McMullan *et al.*, 2025).

Emerging Biomarker: Improvements in our comprehension of the pathophysiology of acute coronary syndrome (ACS) have resulted in a significant rise in the creation of biomarkers for diagnosis.

Mechanism - Biomarkers assist in diagnosing, monitoring, and forecasting disease advancement. An ideal marker is one that shows a specific, easily measurable increase that directly corresponds with a diagnosis or a foreseeable outcome (Moe and Wong, 2010).

Evidence summary - Cardiac troponins vividly illustrate a scenario in clinical medicine where the evaluation of a marker and immediate

clinical decision-making are tightly connected. In individuals with stable angina (SA), circulating biomarkers are suggested to be possibly beneficial for risk stratification (Tsaknis *et al.*, 2014).

Increased levels of high-sensitivity C-reactive Protein (hs-CRP) have been previously associated with the size of the necrotic core in the affected lesion in SA patients. Recent data published concerning SA patients indicated that elevated neopterin levels exhibited an inverse relationship with LVEF values, and high neopterin levels were identified as an independent predictor for LV dysfunction (LVEF <45%).

Glycogen phosphorylase BB (GPBB) is a new cardiac biomarker that could assist in the early detection of myocardial ischemia. (Thupakula *et al.*, 2022).

Epidemiological research has indicated a notable link between conventional cardiovascular risk factors and Lipoprotein-associated phospholipase A2 (Lp-PLA2) levels in the overall population. (Lee, 2024).

Clinical limitation - Conventional biomarkers such as troponins are very sensitive for myocardial infarction but frequently do not differentiate unstable angina, resulting in diagnostic ambiguity. Numerous new biomarkers (e.g., mRNAs, inflammatory proteins) appear promising but need additional validation for specificity and consistency (Elgebaly *et al.*, 2021).

Future direction - Future research should involve larger, varied populations and multicentre approaches to confirm diagnostic and prognostic effectiveness. Creating a standardized, affordable, and swift testing procedure is crucial for clinical integration. Integrating both traditional and novel biomarkers could improve diagnostic precision and risk assessment.

Personalized Approaches to Antianginal Therapy

Choosing the most efficient antianginal treatment is essential for attaining symptom relief, reducing side effects, and enhancing adherence.

Mechanism - A personalized treatment approach that accounts for variables like blood pressure (BP), heart rate (HR), left ventricular (LV) performance, comorbidities such as heart failure and diabetes, concurrent medications, patient choices, and local medication availability might enhance results more efficiently than a uniform treatment protocol. No matter the initial treatment strategy, the effectiveness of antianginal therapy must be frequently evaluated, and modifications should occur if symptom relief is insufficient or if the initial plan is not well tolerated. Guaranteeing patients' compliance with the recommended treatment plan is

an essential element of effective management (Rinaldi *et al.*, 2025).

Evidence summary - In patients with refractory angina (lasting ≥ 3 months) who do not benefit from optimal medical treatment or are not candidates for revascularization, the coronary sinus reducer offers a novel treatment alternative, especially for those showing reversible ischemia. The coronary sinus reducer elevates venous pressure and reallocates blood flow to the, subendocardium, the myocardial area most impacted by ischemia, by creating a regulated constriction in the coronary sinus (Gallone *et al.*, 2020).

Recent findings from RCTs have shown marked symptom enhancement with coronary sinus reducers in contrast to placebo, while observational studies verify its safety and ongoing enhancements in quality of life (Foley *et al.*, 2024; Verheye *et al.*, 2024).

Clinical limitation - Furthermore, in individuals who persist with angina despite receiving optimal medical treatment and undergoing successful revascularization, it is essential to assess and investigate other underlying factors, such as coronary microvascular dysfunction or vasospastic angina, which might coexist with obstructive artery disease and considerably affect anginal symptoms and quality of life (Crea *et al.*, 2018).

Future direction - The principles of personalized cardiovascular therapy pertain to zero prevention, primary prevention, secondary prevention, and tertiary prevention. In recent years, significant efforts have focused on tailored antithrombotic approaches based on individual bleeding and ischemic risk factors, with the goal of optimizing the overall clinical benefit (Oliva *et al.*, 2023). The ESC's 2019 guidelines advocate for a personalized strategy, where antianginal drugs are customized based on each patient's comorbidities and haemodynamic characteristics.

RNA-targeted Therapies

Mechanism - RNA treatments offer a completely new approach to suppress or 'silence' the expression of nearly any gene responsible for disease. Both double-stranded small interfering RNAs (siRNAs) and single-stranded antisense oligonucleotide (ASO) approaches focus on degrading target mRNA transcripts to prevent protein synthesis (Arsenault, 2022).

Evidence summary - In clinical studies, anti-miRs targeting the liver-enriched miR-122 were administered at doses ranging from 3-7 mg/kg (5 injections per week). Adenovirus-mediated delivery of miR-214 or miR-21 leads to enhancements in LV remodeling and decreases in

myocardial apoptosis in rat models of myocardial infarction or ischemia-reperfusion injury (Batkai *et al.*, 2021). Thus, the blocking of miR-132 using anti-miR-132 has been shown to successfully reverse cardiac hypertrophy and heart failure and has advanced to clinical trials (Abdelmohsen *et al.*, 2017).

Circular RNA (circRNAs) function as miR sponges by attaching to and isolating miRs, which prevents their interaction with target mRNAs, resulting in an increase of target gene expression (Chia *et al.*, 2024).

Clinical limitation - Although there is excitement for innovative methods, creating RNA therapies for cardiovascular disease poses difficulties, with obstacles in the chemical nature, toxicity, and delivery of RNA therapeutics in pharmaceutical development. MicroRNAs, the most well-researched noncoding RNAs, have been found to regulate postinfarction angiogenesis and remodeling, cardiac fibrosis and hypertrophy, arrhythmias, atherosclerosis, and metabolic disorders (Lucas and Dimmeler, 2016).

Future directions - Clinical trials are examining mRNA therapies that encode VEGF to enhance angiogenesis and boost myocardial perfusion. Improvements in delivery methods, innovative RNA targets, and the incorporation of digital health tools are anticipated to propel future advancements, although successfully translating these into clinical practice will necessitate addressing considerable delivery and safety issues (He *et al.*, 2021).

Clinical Implications and Practical Approach

The management of stable angina focuses on controlling symptoms, minimizing risks, and tailoring therapy to the individual. First-line medications like beta-blockers, nitrates are typical, while second-line options like ranolazine, and nicorandil are included for ongoing symptoms or adverse effects. New findings challenge strict stepwise methods, advocating for customized strategies that consider heart rate (HR), blood pressure (BP), and ejection fraction (EF) (Balla *et al.*, 2018).

Initial treatment options as first-line medications are suggested at the start, particularly for patients with elevated heart rate, high BP, or angina alongside heart failure. Second-line agent should be introduced if symptoms continue or if first-line medications are not suitable or are poorly accepted. Evidence also backs the use of

combination therapy, such as pairing beta-blockers with CCBs or incorporating ranolazine for better symptom management (Palatini *et al.*, 2024).

Treatment can also be based on HR/BP/ejection fraction, as for patients exhibiting a rapid heart rate, standard BP, and regular ejection fraction, first-line therapy like beta-blockers is recommended. For individuals exhibiting a low HR along with normal BP and ejection fraction, it is advised to use nitrates, and CCBs, while beta-blockers are avoided.

Currently recognized as second-line treatment drugs are ranolazine, and ivabradine with increasing proof of their effectiveness. Rho-kinase inhibitors like fasudil, endopeptidase inhibitors like omapatrilat, angiogenic gene therapy, and stem cell therapy are experimental and not yet considered standard treatment.

Conclusion

Angina pectoris represents a multifaceted clinical syndrome rooted in myocardial ischemia, arising from oxygen deficit. Despite significant advances in both pharmacologic and interventional strategies, angina continues to impose a heavy strain on healthcare systems and patient quality of life worldwide. Traditional first-line therapies, including β -blockers, nitrates, calcium channel blockers, and antiplatelet agents, have played a pivotal role in symptom control and event prevention. However, a considerable proportion of patients continue to experience anginal symptoms even after optimal revascularization and guideline-directed medical therapy. The evolution of second-line and adjunctive agents such as ivabradine, ranolazine, nicorandil, and trimetazidine has expanded the therapeutic landscape by offering targeted and symptom-specific interventions. These agents address underlying metabolic, electrical, and vascular pathways, providing symptom relief in patients with refractory angina or contraindications to conventional therapy. Emerging regenerative strategies, including gene therapy, stem cell therapy, and exosome-based delivery systems, hold potential to restore myocardial perfusion and cardiac function, aiming not merely for symptom control but for structural cardiac repair. Parallel advances in diagnostic imaging and biomarker discovery promise to facilitate earlier diagnosis, more accurate risk stratification, and patient-specific management approaches. Despite all the recent breakthroughs in its diagnosis and management, angina continues to be a major clinical issue. The improvements in

the near future will rely heavily on figuring out ways that are more accurate and individualized to identify ischemia at its earliest stage, to be able to optimize the medical therapy and then customize the revascularization strategies accordingly.

Taken together, the management of angina pectoris is transitioning from symptomatic relief to disease-modifying therapies. Future research focusing on personalized medicine, innovative drug development, and regenerative cardiology is poised to redefine the therapeutic goals for this chronic and often debilitating condition, ultimately improving long-term outcomes and quality of life for affected patients.

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Ethics Statement

Ethical approval was not required for this study because it did not involve human participants, animals, identifiable personal data, or materials requiring institutional ethical review.

Declaration of Generative AI Use

The authors declare that no Generative AI tools were used in the preparation of this manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this work.

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