Current Status and Research Advances in Pharmacological Treatment of Coronary Heart Disease

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Abstract

The core pathogenesis of coronary artery disease (CAD) involves multiple pathological processes—including lipid infiltration, chronic inflammation, and endothelial injury—collectively driving the formation and progression of atherosclerotic plaques. Current treatment strategies focus on comprehensive management, with pharmacological interventions encompassing lipid-lowering agents, antiplatelet drugs, therapies for myocardial ischemia, and measures to improve prognosis. Statins remain the cornerstone of lipid-lowering therapy, while novel agents such as PCSK9 inhibitors further enhance therapeutic efficacy; antiplatelet therapy has evolved from traditional dual-drug regimens to risk-based individualized approaches; β-blockers and RAAS inhibitors play pivotal roles in symptom control and prognosis improvement. However, clinical practice still faces challenges including the balance between efficacy and safety, poor patient adherence, and the lack of effective treatments for microvascular dysfunction. Recent research has systematically explored personalized step-down antithrombotic therapy, combination therapies and digital interventions to improve adherence, as well as functional assessments and non-invasive imaging for precise evaluation of microvascular dysfunction. Future CAD management will increasingly emphasize precision and personalization, leveraging novel targeted therapies, advanced imaging technologies, and multidimensional patient care strategies to achieve a fundamental reduction in disease burden.

Key words

Coronary atherosclerotic heart disease, Pharmacotherapy, Pathological mechanisms, Research progress

1. Introduction

Coronary heart disease (CHD) is a cardiac disorder caused by atherosclerosis of the coronary arteries, leading to narrowing or occlusion of the vascular lumen, which subsequently results in myocardial ischemia, hypoxia, and even necrosis. Clinically, it may manifest as angina pectoris, chest tightness, and in severe cases, myocardial infarction[1]. Its core pathogenesis involves the formation and rupture of atherosclerotic plaques driven by abnormal lipid metabolism, endothelial dysfunction, and chronic inflammation[2]. The "China Cardiovascular Health and Disease Report 2024 Summary" indicates that cardiovascular diseases remain the leading cause of death among urban and rural residents in China, accounting for approximately 48% of all deaths, with both the prevalence and mortality rates of CHD showing an upward trend, particularly prominent in rural areas[3]. In addressing this significant public health challenge, optimizing pharmacological treatment strategies is crucial.

Current treatment of coronary heart disease is based on evidence-based medicine and includes pharmacotherapy and revascularization. Pharmacotherapy relies primari

ly on statins for lipid reduction, antiplatelet agents, and antihypertensive drugs[4]. Although interventional therapy has advanced rapidly, there remain gaps between secondary prevention practices and clinical guidelines, disparities in regional healthcare levels, and challenges with drug efficacy-safety balance and poor patient adherence[5].

2. Pathological Mechanisms and Drug Targets of Coronary Heart Disease

The development of coronary heart disease fundamentally stems from atherosclerosis (AS). This pathological process is characterized by the progressive formation and accumulation of plaques in the coronary arteries, ultimately leading to luminal narrowing or even occlusion and subsequently triggering a series of clinical manifestations such as myocardial ischemia[6]. The pathogenesis of atherosclerosis is complex and multifactorial, involving the combined effects of various pathological processes. Several theoretical hypotheses have been proposed to explain its mechanisms, among which the lipid infiltration theory, inflammatory theory, and endothelial injury theory hold significant influence in both academic research and clinical practice[7].

The Fat Infiltration Theory is one of the earliest and most influential theories explaining the pathogenesis of atherosclerosis and coronary heart disease, proposed by Virchow in the 19th century. This theory posits that elevated levels of low-density lipoprotein (LDL-C) and very-low-density lipoprotein (VLDL) in plasma cross the damaged endothelium, deposit beneath the arterial intima, undergo oxidative modification, and are phagocytosed by macrophages to form foam cells, which subsequently stimulate smooth muscle proliferation and fibrosis, ultimately leading to the formation of atherosclerotic plaques[8]. This theory laid the theoretical foundation for lipid-lowering therapy.

The inflammatory theory posits that AS is an active process driven by chronic inflammation. Risk factors activate endothelial cells, recruit monocytes to differentiate into macrophages, which phagocytize lipids and form foam cells. NLRP3 inflammasomes activate pro-IL-1β, leading to IL-1β production that subsequently induces IL-6 and CRP secretion, thereby establishing a positive feedback inflammatory cycle[7]. Studies such as CANTOS and COLCOT have demonstrated that anti-inflammatory therapies like colchicine reduce cardiovascular events, indicating that the IL-1β/IL-6/CRP axis represents a critical therapeutic target[9-10].

The endothelial injury theory defines atherosclerosis (AS) as an excessive inflammatory-fibroproliferative response of the vascular wall to injury. Factors such as hypertension and oxidized low-density lipoprotein (ox-LDL) damage the endothelium, increase adhesion molecules and permeability, promote monocyte infiltration and foam cell formation, subsequently induce smooth muscle migration and proliferation, lead to fibrous plaque formation, and ultimately result in plaque rupture and thrombosis[11]. This theory integrates lipid metabolism, inflammation, and fibrosis mechanisms, providing a scientific basis for the development of antiplatelet, anticoagulant, and endothelium-protection therapies.

3. Research Progress on Core Therapeutic Drugs

3.1 Lipid-lowering drugs

Lipid-lowering therapy plays a pivotal role in reducing the risk of cardiovascular events, as it effectively reduces coronary plaque burden and optimizes its structural composition. Clinical practice has demonstrated that the use of statins combined with ezetimibe and preprotein convertase inhibitor 9 (PCSK9) inhibitors to lower low-density lipoprotein cholesterol levels consistently yields reductions in plaque burden and favorable morphological improvements[13].

In the pathogenesis of coronary artery disease, elevated cholesterol levels are widely recognized as a risk factor. The underlying pathophysiological mechanism involves the fact that endogenous cholesterol synthesis critically depends on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis. Consequently, statins—acting as potent selective inhibitors of HMG-CoA reductase and by inhibiting hepatic apolipoprotein B100 synthesis to reduce the assembly and secretion of triglyceride-rich lipoproteins, thereby suppressing secondary triglyceride accumulation—have become pivotal agents for preventing and treating cardiovascular diseases through LDL cholesterol reduction[14].

Acquired mutations in the PCSK9 gene lead to elevated LDL-C levels and early-onset coronary heart disease, as its encoded protein degrades LDL receptors. Monoclonal antibodies such as elotuzumab and the small interfering RNA drug Inclisiran can inhibit PCSK9 activity, significantly reducing LDL-C levels; administration of Inclisiran every six months markedly improves treatment adherence[15-16]. Clinical studies demonstrate that adding Inclisiran to a combination therapy of statins and ezetimibe can further reduce LDL-C levels by up to 85%[16-17]. However, its high cost limits its cost-effectiveness and restricts widespread use[18].

Although statins are widely recognized as the cornerstone of lipid-lowering therapy, their clinical application has yet to achieve a balance among efficacy, cost, and sa

fety. The primary limitation of statins lies in their safety profile, particularly muscle-related adverse reactions and potential elevations in liver enzymes, which directly contribute to the phenomenon of "statin intolerance"[19]. For patients diagnosed with statin intolerance or who fail to achieve target LDL-C levels despite receiving the maximum tolerated dose of statins, consideration should be given for adding or switching to other lipid-lowering agents[20-21]. Similarly, while PCSK9 exhibits strong lipid-lowering efficacy along with good safety and tolerability, its high cost poses the most significant cost-effectiveness challenge. Current treatment strategies are evolving from monotherapy to individualized, stepwise combination therapies. For high-risk or very high-risk patients who do not achieve targets or experience intolerance to statin monotherapy, combination therapy is recommended.

3.2 Antiplatelet and Anticoagulant Drugs

In the history of cardiovascular disease prevention and treatment, the development and application of antiplatelet and anticoagulant drugs have evolved from single-target therapies to multi-pathway inhibition, and from a "one-size-fits-all" approach to personalized precision medicine. From the century-old drug aspirin, to clopidogrel—which laid the foundation for dual antiplatelet therapy (DAPT)—to faster-acting and more potent P2Y12 inhibitors, and most recently to novel oral anticoagulants (NOACs) that have expanded their use in coronary heart disease, each advancement has profoundly transformed clinical practice[22].

Aspirin remains the cornerstone of treatment for atherosclerotic diseases to this day. As a cyclooxygenase inhibitor, it exerts both primary and secondary preventive effects by irreversibly inhibiting platelet aggregation[23]. The introduction of clopidogrel marked a milestone in antiplatelet therapy, with the pivotal CURE study demonstrating that the DAPT regimen combining aspirin with clopidogrel significantly reduced the risk of thrombotic events in patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI) compared to monotherapy with aspirin, thereby establishing DAPT as the standard approach post-ACS and PCI[22]. Subsequently, faster-acting and more potent P2Y12 inhibitors such as prasugrel and ticagrelor were developed; their enhanced efficacy, rapid action, and consistent platelet inhibition further reduced thrombotic events, reinforcing the DAPT strategy[22]. Notably, the use of novel oral anticoagulants (NOACs) in patients with coronary heart disease has become a prominent research focus in recent years. For stable ACS patients, adding ultra-low-dose oral anticoagulants to antiplatelet therapy—or even substituting aspirin with anticoagulants combined with P2Y12 inhibitors—has emerged as a current therapeutic direction[24].

3.3 Drugs for Counteracting Myocardial Ischemia and Improving Prognosis

For a considerable period, pharmacological treatment of coronary heart disease has primarily focused on alleviating myocardial ischemia symptoms caused by epicardial coronary artery stenosis. Nitrate agents, beta-blockers, and calcium channel blockers represent three classic classes of representative medications[25]. These drugs effectively control exertional angina by reducing myocardial oxygen demand or dilating the coronary arteries to enhance blood supply[26].

Early β-blockers such as propranolol were non-selective agents that simultaneously blocked both β1 and β2 adrenergic receptors[27]. By competitively antagonizing catecholamine action, they reduce heart rate, myocardial contractility, and cardiac output, thereby effectively lowering blood pressure[28]. However, since they also block β2 receptors on bronchial smooth muscle, non-selective β-blockers may induce or exacerbate bronchospasm, limiting their use in patients with respiratory comorbidities. To address the adverse effects of non-selective drugs on the respiratory system, pharmaceutical development has shifted toward highly selective β1-blockers. For example, metoprolol and bisoprolol exhibit high selectivity for cardiac β1 receptors while having minimal impact on β2 receptors in bronchial and vascular smooth muscle, enabling safer use in cardiovascular patients with mild respiratory conditions. Nevertheless, this selectivity is relative, and reduced bronchial function may still occur at excessive doses[29]. Therefore, careful evaluation and dosage control remain essential in clinical practice.

Renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and angiotensin receptor-mediated enkephalinase inhibitors, were initially recognized as cornerstone medications for heart failure treatment[30-31]. By targeting distinct pathways of the RAAS pathway, these inhibitors exert multiple cardioprotective effects—including blood pressure reduction, reversal of cardiac remodeling, stabilization of atherosclerotic plaques, and antiarrhythmic action—effectively lowering the overall risk of myocardial infarction, stroke, hospitalization for heart failure, and cardiovascular mortality in patients with coronary artery disease[30,33]. RAAS blockade constitutes a critical component of hypertension management, with ACEIs generally demonstrating superior protective efficacy compared to ARBs; thus, ACEIs should be employed in nearly all cases unless patient intolerance is present[32].

Nitroglycerin is the "gold-standard" medication for relieving acute angina attacks, with rapid and definitive efficacy[34]. It rapidly alleviates chest pain symptoms by dilating veins and coronary arteries, reducing cardiac preloa

d, and directly relieving coronary artery spasm[35-36]. For variant angina caused by coronary artery spasm, nitroglycerin serves as a crucial diagnostic and therapeutic tool. During coronary angiography, nitroglycerin injection promptly relieves spasms and restores blood flow, aiding in accurate diagnosis. Consequently, nitroglycerin plays an irreplaceable emergency role in the treatment of coronary heart disease[36-37].

4. Clinical Treatment Challenges and Research Strategies

4.1 Balancing the Prevention of Ischemic Events with Hemorrhage Risk in Antithrombotic Therapy

Antiplatelet and anticoagulant therapy forms the cornerstone of secondary prevention for coronary heart disease. While significantly reducing ischemic events such as myocardial infarction and intrastent thrombosis, it inevitably increases the risk of bleeding complications—a "double-edged sword" effect particularly pronounced in patients requiring long-term medication, creating complex clinical dilemmas. Even with novel dual-pathway inhibition strategies (e.g., combination with low-dose rivaroxaban), although ischemic events can be further reduced, this comes at the cost of elevated bleeding risk[38-39]. Achieving an optimal balance between adequate antithrombotic efficacy and minimal bleeding remains the central challenge in the management of coronary artery disease with antithrombotic therapy.

To address this challenge, current research strategies have shifted from the traditional dual antiplatelet therapy (DAPT) approach of "the longer, the stronger" to risk-stratified individualized downregulation therapy, including shortening the DAPT duration or discontinuing aspirin after short-term DAPT, while maintaining long-term monotherapy with P2Y12 inhibitors. Multiple randomized controlled trials have demonstrated that this strategy significantly reduces bleeding events without compromising anti-ischemic efficacy[38]. The clinical application of platelet function assays and rapid genotyping technologies has enabled the development of personalized treatment regimens tailored to patients' specific thrombotic risks and drug metabolism profiles, further optimizing the efficacy-safety balance[38-39]. Additionally, novel anticoagulants such as activated coagulation factor XI inhibitors, with their lower bleeding-related adverse effects, represent a key focus in next-generation antithrombotic drug development and are expected to expand therapeutic options for coronary artery disease thrombosis management in the future[39].

4.2 Insufficient patient compliance and treatment achievement rates

Poor medication adherence is one of the key reasons why patients with coronary heart disease fail to achieve target levels for blood pressure and lipid profiles as recommended by clinical guidelines. Studies indicate that among coronary heart disease patients diagnosed with hypertension, up to 83% have blood pressure levels exceeding 130/80 mmHg[40]. This poor adherence not only compromises short-term therapeutic outcomes but also significantly increases the risks of readmission and long-term mortality, particularly among elderly patients[41]. While targeted education programs have been proven effective in improving adherence, traditional intervention approaches yield limited results; moreover, neuropsychological factors such as patients' attitudes toward the disease and treatment, beliefs, and executive function directly influence medication adherence behaviors[46].

Therefore, the promotion of fixed-dose combination medications (Polypill) is a key strategy for improving medication adherence, with meta-analyses demonstrating their ability to reduce the risk of major adverse cardiovascular events[41]. Digital interventions based on mobile health technologies, such as SMS reminders and personalized health systems, have been systematically validated as effective in enhancing medication adherence, with behavioral improvements typically peaking at six months[41]. Furthermore, incorporating comprehensive psychological assessments and cognitive interventions in hospital settings, along with individualized guidance addressing patients' treatment beliefs and executive functions, is crucial for improving long-term adherence and prognosis[46].

4.3 Treatment gaps for coronary microvascular dysfunction

A significant proportion of angina patients, regardless of whether there are obstructive lesions in the epicardial coronary arteries, experience symptoms and ischemia stemming from coronary microvascular dysfunction (CMD); such cases account for approximately 40% of non-obstructive coronary angina patients[25]. However, currently available effective therapeutic agents targeting this pathological mechanism remain extremely limited, with no specific interventions specifically targeting microcirculation. Management of this condition remains a major clinical challenge, severely impacting patients' quality of life and prognosis, and posing substantial healthcare burdens[25].

To address this therapeutic gap, current research strategies focus on classifying patients into physiological phenotypes through invasive coronary artery function tests to guide individualized treatment. Meta-analyses indicate that management guided by functional testing does not si

gnificantly improve overall angina severity but demonstrates advantages in reducing angina limitation and enhancing patient satisfaction. Non-pharmacological approaches such as coronary sinus intervention (e.g., the A-Flux coronary sinus shunt device) and enhanced external counterpulsation are being explored to improve microcirculatory function[25]. Meanwhile, non-invasive imaging techniques like electrocardiography have been incorporated into relevant expert consensus guidelines, offering potential for early identification and precise diagnosis of coronary microvascular disease (CMD) and providing a basis for subsequent treatment planning.

4.4 Insufficient clinical promotion and application of novel drugs

Although novel cardiovascular drugs such as angiotensin receptor-enzymatase inhibitors (ARNIs), sodium-glucose cotransporter 2 inhibitors (SGLT2Is), and glucagon-like peptide-1 receptor agonists (GLP-1 RA) have demonstrated clear benefits in patients with coronary heart disease complicated by heart failure or diabetes through large-scale clinical trials, their utilization rate in real-world practice remains extremely low. Data indicate that over 70% of eligible patients do not initiate these medications within six months after discharge[42]. This inadequate adoption stems from multiple factors, including delayed awareness of these drugs among clinicians, issues related to drug accessibility and cost, and the absence of systematic standardized management protocols.

To accelerate the clinical translation and application of novel drugs, current strategies emphasize establishing guideline-based standardized discharge medication prescribing workflows and leveraging multidisciplinary collaboration models to enhance new drug adoption rates[42]. Targeted continuing education programs and clinical decision support systems enable healthcare professionals to promptly update their knowledge and optimize prescribing practices. Furthermore, ongoing monitoring of real-world studies and large-scale registry data helps evaluate the actual efficacy and safety of new drugs across diverse populations, thereby addressing clinical concerns and promoting evidence-based medicine[42].

5. Summary and Prospects

The pharmacological management of coronary artery disease has evolved from initially focusing solely on alleviating ischemic symptoms of epicardial large vessels to a comprehensive multi-target strategy centered on "lipid-lowering and anti-inflammatory effects," encompassing antithrombotic therapy, myocardial ischemia prevention, and neuroendocrine regulation. The combination of statins with novel lipid-lowering agents such as PCSK9 inhibitors significantly reduces low-density lipoprotein cholesterol levels and stabilizes plaques, while individualized antiplatelet therapy maintains anti-ischemic benefits while reducing bleeding risks. Renin-angiotensin-aldosterone system (RAAS) inhibitors and beta-blockers continue to play an irreplaceable role in improving prognosis[3,4,30]. However, this therapeutic approach still faces practical challenges including safety concerns in antithrombotic therapy, poor long-term patient adherence, lack of specific treatments for microvascular dysfunction, and delayed adoption of novel drugs[5,25,41-42].

Looking ahead, the treatment of coronary heart disease (CHD) will increasingly rely on the deep integration of precision medicine and multidimensional management strategies. By utilizing platelet function assays and genotyping to guide personalized antithrombotic regimens, employing non-invasive imaging technologies to accelerate novel drug development and plaque phenotype assessment, and leveraging digital health tools and psychological interventions to improve treatment adherence, a shift from "population-based guidelines" to "individualized treatment plans" is anticipated[38,43,46]. Concurrently, exploration of novel targets such as inflammatory pathways, reactive oxygen species clearance, and the lymphatic system will provide new breakthroughs in CHD managemen[43-45]. With the synergistic advancement of basic research, imaging technologies, and digital healthcare, pharmacological interventions for CHD are expected to achieve a fundamental reduction in disease burden in the future.

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