Review Article

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Pharmacotherapy in Chronic Coronary Syndromes: Current Evidence and Future Directions

Omid Moradi[1]; BCCP, Alireza Arzhangzadeh[2];MD, Sara Asadi[1];BCCP, Salma Nozhat[2];MD, Laleh Mahmoudi[1]*;BCCP

[1]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Cardiology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Chronic coronary syndromes (CCS) constitute a dynamic and heterogeneous spectrum of clinical manifestations that necessitate a comprehensive, patient-centered, and multidisciplinary management approach. Recent international guidelines for the management of patients with chronic coronary disease underscore a dual therapeutic paradigm that integrates rigorous, evidence-based lifestyle modifications with precisely targeted pharmacological interventions to optimize long-term cardiovascular outcomes. Non-pharmacological lifestyle strategies—such as structured exercise programs, dietary optimization, smoking cessation, and psychosocial support—form the cornerstone of cardiovascular risk reduction and have been shown to exert synergistic benefits when combined with pharmacotherapy. This narrative review aims to synthesize and critically appraise current evidence and consensus recommendations on the pharmacological management of CCS, with particular emphasis on mechanisms of action, comparative clinical effectiveness, safety profiles, and the evolving landscape of emerging therapies. The discussion encompasses established drug classes, including antianginal agents, lipid-lowering therapies, antithrombotic agents, and neurohormonal modulators, while also examining novel compounds such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, inclisiran, and bempedoic acid, which represent significant advances in lipid management. By integrating findings from recent landmark clinical trials with guideline-directed recommendations, this manuscript delivers a comprehensive and clinically relevant overview intended to inform and support the decision-making of cardiologists, clinical pharmacists, and researchers engaged in the field of cardiovascular therapeutics.

Keywords: Chronic coronary syndrome; Cardiology; Pharmacy; Lipid-lowering therapy; PCSK9 inhibitors; lifestyle modification.

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1. Introduction

Chronic coronary syndromes (CCS) represent a continuum of coronary atherosclerotic disease that, unlike acute coronary syndromes, manifests as stable and predictable episodes under stress or with exertion. The syndrome is a heterogeneous group of conditions that includes obstructive and nonobstructive CAD with or without previous myocardial infarction (MI) or revascularization, ischemic heart disease diagnosed only by noninvasive testing, and chronic angina with varying underlying causes (1). CCS is associated with significant morbidity and remains a primary contributor to cardiovascular mortality glob-

Corresponding Author: Laleh Mahmoudi, Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
Email: mahmoudi_l@sums.ac.ir

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ally (2).

CCS are no longer understood as simply the result of blocked arteries. Instead, they reflect a more intricate process—one where endothelial dysfunction, persistent low-grade inflammation, and often coronary microvascular dysfunction all play important roles. The inner lining of the arteries—the endothelium—normally helps regulate blood flow and keeps inflammation in check. But with ongoing exposure to risk factors like high blood pressure, diabetes, smoking, and elevated cholesterol, this protective barrier begins to break down. As nitric oxide levels fall and the vessel wall becomes more permeable, cholesterol particles and white blood cells start to enter the arterial wall, setting the stage for early plaque formation (3).

Over time, the process is fueled by chronic inflammation. Signals like interleukin-1β and high-sensitivity C-reactive protein (hsCRP) don't just mark inflammation—they help drive it, making plaques more unstable and increasing the risk of rupture, even in people whose cholesterol levels are well controlled (4, 5). At the same time, not all patients with angina have major blockages. In fact, many—particularly women and those with diabetes—have symptoms caused by dysfunction in the heart's small vessels. This microvascular dysfunction reduces blood flow where it's needed most, despite angiograms that may look completely normal. The combination of these mechanisms shows that CCS is much more than just a plumbing problem—it's a complex vascular disease that calls for therapies targeting the underlying biology, not just the symptoms (6).

Atherosclerotic plaque regression is a key therapeutic target for reducing cardiovascular risk by modifying plaque morphology and composition to halt progression and avert rupture. Recent meta-analyses indicate that a 1% plaque regression correlates with a 25% reduction in major adverse cardiovascular events (MACE) odds. Longitudinal data show plaque progression precedes MACE, with high-risk lesions (e.g., low-attenuation or spotty calcification) yielding 15-20% event rates at 12 months versus <1% for stable plaques (7).

The management of CCS has evolved over recent decades from a predominantly invasive or revascularization-focused approach to a comprehensive strategy that emphasizes risk factor modification, lifestyle interventions, and the tailored use of pharmacotherapy.

Recent updates in the 2024 European society of cardiology (ESC) Guidelines for the Management of Chronic Coronary Syndromes and the 2023 American heart association/American college of cardiology (AHA/ACC) Guideline for the Management of Patients with Chronic Coronary Disease have added knowledge to our understanding of CCS treatment (1, 8). Both guidelines underscore the importance of a multidisciplinary strategy that begins with lifestyle modifications and is complemented by the evidence-based selection of pharmacologic agents. The evolution in therapeutic targets has been highlighted by advances in our understanding of molecular pathways, thereby fostering the development of new medications and refined treatment algorithms.

This narrative review aims to provide an in-depth discussion of current pharmacotherapeutic approaches to patients with CCS with a focus on evidences behind the new therapeutic agents. We will review the various classes of medications recommended by the latest guidelines, discuss the mechanisms of action and comparative outcomes data, and examine emerging therapies that hold promise for future management. By consolidating recent trial data and current guideline recommendations, this review is intended to serve as an educational resource for clinicians and pharmacists who are involved in the management of patients with CCS.

2. Lifestyle Modification in Chronic Coronary Syndromes

Effective pharmacotherapy for CCS is underpinned by lifestyle modifications that address modifiable risk factors. This section outlines the recommended non-pharmacological and pharmacologic strategies for managing CCS.

Both ESC and North American guidelines strongly advocate for comprehensive

Table 1. Nutrition recommendation for patients diagnosed with CCS provided by AHA/ACC guideline

	Recommendation	COR	LOE
1	In patients with CCD, a diet emphasizing vegetables, fruits, legumes, nuts, whole grains, and lean protein is recommended to reduce the risk of CVD events.	1	B-R
2	In patients with CCD, reducing the percentage of calories from saturated fat (<6% of total calories) and replacing with dietary monounsaturated and polyunsaturated fat, complex carbohydrates, and dietary fiber can be beneficial to reduce the risk of CVD events.	2a	B-NR
3	In patients with CCD, minimization of sodium (<2,300 mg/d; optimally 1,500 mg/d) and minimization of processed meats (eg, cured bacon, hot dogs) can be beneficial to reduce the risk of CVD events.	2a	B-NR
4	In patients with CCD, limiting refined carbohydrates (eg, containing <25% whole grain by weight, including refined cold ready-to-eat breakfast cereal, white bread, white rice), and sugar-sweetened beverages (eg, soft drinks, energy drinks, fruit drinks with added sugars) can be beneficial to reduce the risk of CVD events	2a	B-NR
5	In patients with CCD, the intake of trans fat should be avoided because trans fat is associated with increased morbidity and mortality rates.	3	B-NR
6	n patients with CCD, the use of nonprescription or dietary supplements, including omega-3 fatty acid, vitamins C, D, E, beta-carotene, and calcium, is not beneficial to reduce the risk of acute CVD events.	3	B-NR

Chronic coronary syndrome (CCS), American heart association (AHA), American college of cardiology (ACC), Class of recommendation (COR), Level of evidence (LOE)

lifestyle modification as a cornerstone in the management of CCS (1, 8, 9). The following interventions are pivotal:

2.1. Smoking Cessation

Smoking is a well-known contributor to endothelial dysfunction and atherosclerotic progression. Smoking cessation programs are recommended as an initial intervention (COR=1) (1, 10). ESC guideline advises to stop smoking cigarette (8).

2.2. Dietary Modifications

Adoption of heart-healthy diets such as the Mediterranean (11) or Dietary Approaches to Stop Hypertension (DASH) (12) diet helps in improving lipid profiles and reducing inflammation (13). The recommendation by AHA/ACC guideline is provided in Table 1 (1). ESC guideline advises to follow Mediterranean diet in patients with CCS (8).

2.3. Physical Activity

Regular moderate-intensity physical activity, defined as at least 150 minutes per week, is shown to improve endothelial function, reduce blood pressure, and aid in weight management (COR=1) (1, 14-16). ESC guideline categorizes the physical activity into moderate and vigorous intensity and recommends 150 min/week of vigorous and 150-300 min/week of moderate intensity workout (COR=1, LOE=B) (8).

2.4. Weight Management

Maintaining an optimal body weight is crucial, as obesity is a recognized risk factor for CCS. It is recommended that patients with CCD and overweight or obesity should receive counseling on diet, lifestyle, and goals for weight loss. (COR=1) (1, 17). ESC guideline advises to maintain healthy BMI (define as 18.5-25 kg/m^2) (8).

Given that lifestyle interventions not only address the underlying pathophysiology of CCS but also potentiate the effectiveness of pharmacotherapy, they remain an integral part of both primary and secondary prevention

strategies.

3. Pharmacotherapy Overview

Pharmacologic management of CCS can be broadly categorized into agents that relieve symptoms (particularly those related to ischemia) and therapies that modify the risk of progression and adverse cardiovascular events. The main classes including antianginal agents, lipid-lowering therapies, antithrombotic agents, neurohormonal modulators. Each therapeutic class offers unique benefits, and their integration is often required to achieve optimal clinical outcomes.

3.1. Antianginal Therapies

Antianginal medications are primarily aimed at alleviating the symptoms of myocardial ischemia by reducing cardiac oxygen demand or by enhancing coronary blood flow (18). In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms (COR=1, LOE = B-R). In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms (COR=1, LOE = B-R) (1). Table 2 represent dosing, consideration and safety of antianginal therapies.

3.1.1. Beta-Blockers

3.1.1.1. Mechanism of Action

Beta-blockers reduce myocardial oxygen consumption by decreasing heart rate, contractility, and blood pressure. They also prolong diastolic time, which enhances coronary perfusion (19).

3.1.1.2. Clinical Use and Evidence

Long regarded as first-line therapy in the management of angina, beta-blockers have shown consistent efficacy in reducing ischemic symptoms. Their benefit is particularly pronounced in patients with coexisting conditions such as hypertension and heart failure (1, 8).

It is recommended that in patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death (COR=1, LOE = A). Furthermore, in patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy (COR=3, LOE=B-NR) (1).

Beta-blockers and/or CCBs are recommended by ESC to be used in controlling heart rate and symptoms in patients with CCS (COR=1, LOE = B). Furthermore, addition of the DHP-CCB to the pharmacotherapy alongside of a beta-blocker in patients with inadequate control of symptoms to each other is recommended by ESC (COR=2a, LOE = B) (8).

3.1.2. Calcium Channel Blockers

3.1.2.1. Mechanism of Action:

Calcium channel blockers exert their effects by inhibiting calcium influx in smooth and cardiac muscle cells, thus causing vasodilation and lowering myocardial contractility. This results in a reduction in both preload and afterload (20).

3.1.2.2. Comparative Outcomes

For patients who have contraindications to beta-blockers, or who have vasospastic variants of CCS, calcium channel blockers are effective alternatives. They can be used as monotherapy or in combination with beta-blockers for additive effects (8).

3.1.3. Nitrates

3.1.3.1. Mechanism of Action

Nitrates work by donating nitric oxide, thereby inducing vasodilation. This not

only reduces preload (via venodilation) but also dilates coronary vessels to improve myocardial oxygen supply (21).

3.1.3.2. Clinical Considerations

While nitrates are effective for rapid relief of anginal symptoms, issues such as tolerance may limit their long-term use. Intermittent dosing strategies are recommended to circumvent tolerance. In regard to sublingual nitroglycerine formulations, it is recommended that in patients with CCD they should be used for immediate short-term relief of angina or equivalent symptoms (COR=1, LOE = B-NR) (1). Furthermore, ESC guideline also recommends the use of short-acting nitrate formulation to be used in immediate relief of angina (COR=1, LOE = B). Long-acting formulation is recommended by this guideline as an add-on therapy (COR=2a, LOE = B) (8).

3.1.4. Ivabradine

3.1.4.1. Mechanism of Action

Ivabradine selectively inhibits the If ("funny") current in the sinoatrial node, leading to heart rate reduction without negatively affecting blood pressure or myocardial contractility (22). In patients with ischemia in the absence of obstructive coronary artery disease—often attributable, at least in part, to microvascular angina—Ivabradine may be beneficial (23). In this population, symptom improvement and angina relief occur without measurable changes in coronary microvascular function, suggesting that the therapeutic effect is primarily mediated through heart rate reduction (24). Ivabradine has shown similar benefits to atenolol and amlodipine in improving exercise tolerance and angina relief, and when added to atenolol, it further enhanced exercise capacity compared with placebo. However, in a large trial of patients with CCD, ivabradine did not reduce cardiovascular death or myocardial infarction and was associated with a higher risk of these outcomes, suggesting potential harm despite modest improvements in angina symptoms. The guideline recommends that in patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy (COR=3, LOE = B-R) (1).

ESC guideline recommends the medication in patients with left ventricular systolic dysfunction (LVEF<40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients (COR=2a, LOE = B) (8).

3.1.4.2. Indications

Ivabradine is beneficial in patients with angina and decreased LVED who cannot tolerate beta-blockers or in whom beta-blockers are contraindicated. Its unique mode of action complements other antianginal agents (25).

3.1.5. Ranolazine

3.1.5.1. Mechanism of Action

Ranolazine inhibits the late inward sodium current in myocardial cells, thereby reducing intracellular calcium overload. This leads to improved myocardial relaxation and decreased ischemia (26). In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment

with beta blockers, CCB, or long-acting nitrate therapies (COR=1, LOE = B-R) (1). ESC guideline also recommends this approach with different class of recommendation (COR= 2a, LOE = B) (8).

The TERISA trial was a multinational, randomized, double-blind, placebo-controlled study evaluating ranolazine in patients with type 2 diabetes mellitus and chronic stable angina who remained symptomatic despite 1–2 antianginal agents. Over 8 weeks, ranolazine significantly reduced the average weekly angina frequency and sublingual nitroglycerin use compared with placebo, with consistent benefit across most subgroups and greater effect in those with higher baseline HbA1c. The drug was well tolerated, with no excess in serious adverse events, suggesting that ranolazine offers an effective and safe option for angina

symptom reduction in this high-risk population (27).

Furthermore, in The ERICA trial, patients with chronic stable angina who continued to experience ≥3 anginal episodes per week despite receiving the maximum recommended dose of amlodipine (10 mg/day) were randomized to receive ranolazine 1,000 mg twice daily or placebo for 6 weeks in addition to amlodipine. Ranolazine significantly reduced mean weekly angina frequency and nitroglycerin consumption without affecting heart rate or blood pressure, with greater benefit observed in patients with higher baseline symptom burden (>4.5 episodes/week) (28).

3.1.5.2. Comparative Advantages

Ranolazine is particularly useful in patients with refractory angina where conventional therapies have failed. It has a favorable side effect profile and can be combined with other antianginal agents (8).

3.2. Lipid-Lowering Therapies

Aggressive management of dyslipidemia is essential for stabilizing atherosclerotic plaques and reducing the risk of cardiovascular events in CCS. Current guide-

Table 2. Antianginal therapies for patients with CCS.

Medication	Doses	Treatment considerations	Safety
Metoprolol	Initial 50 mg twice daily; usual dosing range = 50 – 200 mg twice daily; maximum = 200 mg/day	Increase in weekly intervals. Immediate release formulation could be used. For microvascular angina initiate with 50 mg/day	Consider concerns in diabetes, heart failure, myasthenia gravis, peripheral vascular diseases, psoriasis, thyroid disorders and vasospastic angina. Additional warning for carvedilol in patients with bronchospastic diseases.
Bisoprolol	Initial 2.5 mg once daily; maximum = 20 mg/day	Double the dose in ≥ 1-week intervals.	
Carvedilol	Initial 12.5 mg twice daily; usual dosing range = 25 – 50 mg twice daily	Increase the dose as tolerated to desired effect.	
Amlodipine	5-10 mg once daily	Beta blockers are preferred as initial therapy. Maybe added to the treatment regimen or used as an alternative	In patients with aortic stenosis, heart failure hepatic impairment and hypertrophic cardiomyopathy should be used with precautions
Diltiazem	Initial 30 mg 4 times daily; maximum 240 – 360 mg/day	Beta blockers are preferred as initial therapy. Maybe added to the treatment regimen or used as an alternative.Use immediate release formulations in divided doses. Do not use with beta blockers concomitantly. Increase in 1-2 days intervals.	Consider precautions in patients with accessory bypass tract electrophysiologic disorders. Also, in patients with hepatic impairment and LV dysfunction should be used with cautions.
Verapamil	Initial 80 – 120 mg 3 times daily; maximum 480 mg/day.	Beta blockers are preferred as initial therapy. Maybe added to the treatment regimen or used as an alternative.Use immediate release formulations in divided doses.Do not use with beta blockers concomitantly.Increase in ≥1-2 days intervals.	Consider precautions in patients with accessory bypass tract electrophysiologic disorders. Also, in patients with hepatic impairment, increased intracranial pressure, renal impairment, myasthenia gravis, arrythmias and LV dysfunction should be used with cautions.
Ivabradine	Initial 2.5-5 mg twice daily. Increase in 4 weeks intervals. Maximum 7.5 mg twice daily.	Consider using if symptoms not control by beta blockers or CCB, consider dihydropyridine CCB.Discontinue if no significant Improvement observed after 3 months.	Maybe associated with atrial fibrillation or bradycardia and conduction abnormalities.
Ranolazine	Initial 500 mg twice daily; maximum 1000 mg twice daily.	Maybe used in addition to beta blockers, long-acting nitrates or CCB.	The medication has do not benefit patients with acute coronary syndrome. Special caution should be considered in patients renal and hepatic inpairment

lines emphasize the importance of achieving and maintaining target low-density lipoprotein cholesterol (LDL-C) levels (1, 8). In patients with CCD, high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of MACE (COR=1, LOE =A). Furthermore, in patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE (COR = A, LOE =A) (1).

ESC guideline recommends that lipid-lowering therapy should be consider with the goal of LDL-C < 55 mg/dL and a ≥50% reduction in LDL-C vs. baseline (COR=1, LOE = A). high-intensity statin is recommended first (COR=1, LOE = A) (8).

3.2.1. Statins

3.2.1.1. Mechanism of Action

Statins inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. This inhibition leads to upregulation of LDL receptors in the liver and an enhanced clearance of LDL-C from circulation (29).

3.2.1.2. Evidence and Outcomes

Robust clinical trial data support statin therapy as the cornerstone of lipid-lowering management in CCS. Statins not only reduce LDL-C but also exhibit pleiotropic effects, such as improving endothelial function and exerting anti-inflammatory properties (30). In regard to atherosclerotic plaque regression, early intervention is crucial, as modifiable components diminish with advanced calcification, and recent studies highlight lipid clearance's role in near-complete regression in preclinical models (7). Statins, which lower LDL-C by 30-50%, have been extensively evaluated for their role in inducing coronary plaque regression, primarily through intravascular ultrasound (IVUS) and coronary computed tomography angiography (CCTA). Randomized trials and observational studies, such as REVERSAL, SATURN, and ASTEROID, demonstrate dose-dependent reductions in TAV (0-20% regression in high-intensity arms like atorvastatin 80 mg or rosuvastatin 40 mg, versus ~10% progression in controls), with greater efficacy in high-intensity regimens achieving LDL-C (31-33).

3.2.2. Ezetimibe

3.2.2.1. Mechanism of Action

Ezetimibe acts at the intestinal brush border to inhibit the absorption of cholesterol. When used in combination with statins, it confers additional LDL-C lowering effects (34).

3.2.2.2. Evidence, outcome and Clinical Implications

Ezetimibe is particularly useful in patients who are unable to achieve LDL-C targets with statin monotherapy or who experience statin-associated side effects (8).

The RACING trial, a multicenter randomized study of patients with atherosclerotic cardiovascular disease, demonstrated that moderate intensity statin plus ezetimibe combination therapy was non inferior to high intensity statin monotherapy for the 3 year composite endpoint of cardiovascular death, major cardiovascular events, or nonfatal stroke, with similar results in both elderly (≥75 years) and younger cohorts. Combination therapy achieved greater sustained LDL C reduction and, in patients ≥75 years, significantly lowered rates of intolerance related drug discontinuation or dose reduction and new onset diabetes compared with high intensity statin alone (35).

The guideline recommends ezetimibe in patients with CCD who are very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE (COR=2a, LOE=B-R) (1). ESC guideline recommends ezetimibe combination if a patient's goal is not achieved with the maximum toler-

ated dose of statin (COR=1, LOE = B) (8).

3.2.3. PCSK9 Inhibitors

3.2.3.1. Mechanism of Action

Monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) such as Evolocumab and Alirocumab work by preventing the degradation of LDL receptors. This leads to sustained reduction of circulating LDL-C (36).

3.2.3.2. Evidence, outcome and Clinical Implications

Clinical trials have demonstrated that PCSK9 inhibitors significantly reduce LDL-C levels and cardiovascular events in high-risk populations (37, 38). Results from clinical trials, including FOURIER and ODYSSEY, demonstrated that PCSK9 inhibitors are effective and safe in patients with ASCVD, especially those who don't reach their LDL-C goals with statins or cannot tolerate them. Their use is supported by current guidelines for patients with refractory hypercholesterolemia despite maximal statin therapy (1, 8).

In patients with CCD who are very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE (COR=2a, LOE = A) (1). In line with AHA/ACC guideline ESC guideline recommends combination with a PCSK9 inhibitor for patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe (COR=1, LOE=A) (8).

3.3. Antithrombotic Therapies

Antithrombotic agents form a critical component in the secondary prevention of atherothrombotic events in CCS. Current guidelines advocate for the use of antiplatelet therapy tailored to individual risk profiles. Table 3 represent dosing, consideration and safety of antithrombotic therapies.

3.3.1. Aspirin

3.3.1.1. Mechanism of Action

Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1), leading to decreased thromboxane A2 synthesis and a resultant reduction in platelet aggregation (39).

3.3.1.2. Evidence Base

Aspirin remains the cornerstone of antiplatelet therapy in CCS. Its efficacy in reducing cardiovascular events is well established in numerous clinical trials and is recommended for almost all patients with documented CCS (1, 8).

The guideline recommends low-dose aspirin 81 mg (75-100 mg) in patients with CCD and no indication for oral anticoagulant therapy, to reduce atherosclerotic events (COR=1, LOE=A) (1). ESC recommend aspirin 75–100 mg daily lifelong after an initial period of DAPT in CCS patients with a prior MI or remote PCI (COR=1, LOE=A) (8).

3.3.2. P2Y12 Inhibitors

3.3.2.1. Mechanism of Action

P2Y12 inhibitors, such as clopidogrel, prasugrel, and ticagrelor, block adenosine diphosphate (ADP) receptors on platelets, further reducing platelet aggregation (40).

3.3.2.2. Use in CCS

While dual antiplatelet therapy (DAPT) is frequently used in the acute setting or following percutaneous coronary interventions, long-term monotherapy with aspirin or in selected cases, P2Y12 inhibitors, is generally recommended in stable CCS unless additional risk factors warrant prolonged DAPT (1, 8).

In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and

bleeding events is recommended by the guideline (COR=1, LOE = A) (1).

Clopidogrel is recommended as an alternative to aspirin monotherapy in CCS patients with a prior MI or remote PCI by ESC guideline (COR=1, LOE = A) and adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at enhanced ischemic risks and without high bleeding risk (COR=2a, LOE=A) (8).

DAPT consisting of aspirin 75-100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting is recommended by ESC (8), and shorter duration of DAPT (1-3 months) could be considered in patients with high bleeding risk and not high ischemic risk (COR=1, LOE=A) (8).

3.3.3. Dual Pathway Inhibition

3.3.3.1. Emerging Strategies

Recent evidence has indicated that combining low-dose anticoagulation (e.g., rivaroxaban at a vascular-protective dose) with antiplatelet therapy may further reduce the risk of major adverse cardiovascular events in selected high-risk patients (41). This strategy, however, must be carefully balanced against the increased risk of bleeding.

The guideline recommends in patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for 1 to 4 weeks followed by clopidogrel alone for 6 months should be administered in addition to DOAC (COR=1, LOE=B-R). In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE (COR=2a, LOE=B-R) (1).

Furthermore, ESC guideline recommends that, in patients with an indication for

Table 3. Antithrombotic agents indicated in patients with CCS as primary prevention.

Medication	Doses	Treatment considerations	Safety
Aspirin	75 – 100 mg once daily	Higher doses may be considered (75 – 325 mg once daily) in patients undergone PCI.	Higher risk of bleeding is expected in older age. In patients with history gastrointestinal disorders should be used with caution. Avoid use in active gastrointestinal bleeding. Avoid use in hepatic impairment. Low dose aspirin is safe in renal impairment.
Clopidogrel	75 mg once daily	Could be used as an alternative agent to aspirin in single antithrombotic therapy.	Should be used with caution in patients with renal impairment and for CYP2C19.
Ticagrelor	60 mg twice daily	Should be used in combination with aspirin. Concurrent aspirin dose should not exceed 100 mg/day. Evaluate the patient for bleeding and ischemic risk. In patients undergone PCI higher doses should be used.	Use with caution in patients with increased risk of bradycardia. Use with caution in patients with moderate hepatic failure. Do not use in patients with severe hepatic dysfunction. Monitor the patients regarding renal function.
Rivaroxaban	2.5 mg twice daily	May consider in patients at high risk of cardiovascular events and low bleeding risk if therapeutic anticoagulation or DAPT is not initiated. Administer in combination with low dose aspirin.	Evaluate the patient for risk of bleeding. Avoid use or consider caution in hepatic impairment.

OAC who undergo PCI, initial low-dose aspirin once daily is recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel (COR=1, LOE=C). Limited aspirin administration (≤1 week) followed by OAC + clopidogrel is recommended in uncomplicated PCI. The duration of clopidogrel administration is based on ischemic risk of the patient (COR=1, LOE=A).

3.4. Neurohormonal Modulators

The renin-angiotensin-aldosterone system (RAAS) plays a critical role in the pathogenesis of cardiovascular disease and is a target for therapeutic intervention in CCS.

3.4.1. ACE Inhibitors and ARBs

3.4.1.1. Mechanism of Action

Angiotensin-converting enzyme (ACE) inhibitors prevent the conversion of angiotensin I to angiotensin II, resulting in vasodilation, reduced aldosterone secretion, and overall improvement in hemodynamics. Angiotensin receptor blockers (ARBs) offer similar benefits by directly antagonizing the effects of angiotensin II (42).

3.4.1.2. Guideline Recommendations

Both ACE inhibitors and ARBs are recommended in CCS, particularly in patients with hypertension, diabetes, or left ventricular dysfunction. Beyond blood pressure control, these agents have been shown to reduce adverse remodeling and improve clinical outcomes (1, 8). The guideline recommends In adults with CCD and hypertension ACE inhibitors and ARB, are recommended as first-line therapy for compelling indications (eg, recent MI or angina), with additional antihypertensive medications (eg, dihydropyridine CCB, long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control (COR=1, LOE=B-R) (1). ESC recommends ACEi or ARB as recommended by a specific indication (COR=1, LOE=A). also, this guideline recommends the classes of medication in high cardiovascular risk CCS patients (COR=2a, LOE=A) (8).

4. Emerging Therapies and New Medications

In recent years, the landscape of CCS pharmacotherapy has been enriched by the introduction of novel agents and innovative therapeutic modalities. This section highlights recent studies and new trial data that have influenced current practice and future directions.

4.1. Novel Lipid-Lowering Agents

4.1.1. Inclisiran

Inclisiran's siRNA-based mechanism offers a novel approach to LDL-C lowering with infrequent dosing (typically biannual), which may significantly enhance patient adherence and long-term outcomes (43). The ORION series of trials have demonstrated its efficacy and safety, positioning it as a promising adjunct or alternative to traditional PCSK9 inhibitors (44).

The guideline recommends in patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels (COR=2b, LOE=B-R) (1).

4.1.1.1. Mechanism of Action

Inclisiran is a novel small interfering RNA (siRNA) that targets hepatic PCSK9 mRNA. Its mechanism leads to a sustained reduction in PCSK9 protein levels and consequent LDL-C lowering with a markedly prolonged dosing interval (45).

4.1.1.2. Emerging Evidence

Recent phase III trials have shown that inclisiran can achieve significant LDL-C reductions in a safe and well-tolerated man-

ner, offering an alternative for patient adherence challenges associated with more frequent dosing regimens (1, 8).

4.1.2. Bempedoic Acid

The CLEAR Outcomes trial and related studies have shown that bempedoic acid provides significant LDL-C reduction with a favorable safety profile, particularly in patients with statin intolerance. Its liver-selective activation minimizes muscle-related side effects, a common limitation of statin therapy (46). The guideline recommends in patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels (COR=2b, LOE = B-R) (1).

Also, ESC guideline recommends bempedoic acid for patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended (COR=1, LOE=B) and for patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered (COR=2a, LOE=C) (8).

4.1.2.1. Mechanism of Action

Bempedoic acid inhibits ATP citrate lyase, an enzyme upstream of HMG-CoA reductase, leading to a reduction in LDL-C synthesis. Its activation primarily in the liver minimizes systemic side effects (46).

4.1.2.2. Clinical Data

Recent randomized controlled trials have demonstrated that bempedoic acid effectively reduces LDL-C levels, particularly in patients who are statin-intolerant or require combination therapy. This agent represents an important addition to our lipid-lowering armamentarium (47).

Furthermore, the agent has demonstrated significant anti-inflammatory effects, as evidenced by reductions in hs CRP across multiple clinical studies. In a cohort of patients with obesity, treatment with Bempedoic acid produced a placebo-adjusted decrease in hs CRP of 23.2% at six months (48). Similarly, among statin intolerant individuals, a median hs CRP reduction of 21.6% relative to placebo was observed over the same duration. These attenuations in inflammatory markers, in conjunction with concomitant reductions in low density lipoprotein cholesterol (LDL C), indicate that bempedoic acid may represent a valuable therapeutic option for patients with heightened cardiovascular and residual inflammatory risk (49).

5. Anti-Inflammatory Approaches

5.1. Low-Dose Colchicine

There is emerging evidence suggesting that low-dose colchicine, through its anti-inflammatory properties, may reduce cardiovascular events in patients with CCS. While currently more established in the context of acute coronary syndromes, ongoing studies are evaluating its role in chronic settings (50). This represents a shift toward targeting the inflammatory processes underpinning atherosclerosis.

Based on the recommendation provided by AHA/ACC guideline in patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events (COR=2b, LOE=B-R) (1). The recommendation by ESC is as followed. In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization (COR=2a. LOE=A) (8).

6. Future Directions in Pharmacotherapy

The future of CCS treatment is poised to benefit from several innovative strategies:

6.1. Gene Therapy and RNA-Based Therapeutics

Beyond inclisiran, ongoing research into gene-editing technologies holds promise for addressing the underlying genetic predispositions that drive dyslipidemia and atherosclerosis. Elevated lipoprotein(a) (Lp[a]) levels, which are genetically determined by the apo(a) isoform, are strongly linked to increased risks of coronary heart disease, stroke, and heart failure due to their pro-thrombotic, pro-inflammatory, and pro-atherogenic properties. Despite its clear role in cardiovascular disease, no approved pharmacological therapies currently exist to lower Lp(a). However, emerging RNA-based treatments targeting apo(a) expression—such as pelacarsen, olpasiran, SLN360, and lepodisiran—are showing promise in clinical trials (51).

6.2. Novel Anti-Inflammatory Agents

Targeting specific inflammatory cytokines or pathways (e.g., interleukin-1β antagonists) may further reduce the burden of atherosclerotic inflammation (52).

Anakinra, a recombinant interleukin-1 receptor inhibitor, is routinely used to treat various inflammatory conditions and is being explored as a potential means to lessen vascular inflammation in coronary artery disease (CAD) patients (53). Animal model studies have demonstrated that anakinra can enhance endothelial function (54). Although, two small randomized trials indicate that this treatment does not reduce the risk of cardiovascular events, more clinical studies are needed to evaluate this class of medications (55).

`The Ziltivekimab Cardiovascular Outcomes Study (ZEUS) is a global, randomized, placebo-controlled trial enrolling approximately 6,200 patients with stage 3–4 chronic kidney disease (CKD) and elevated high-sensitivity C-reactive protein (hs CRP) to determine whether long-term inhibition of interleukin 6 (IL 6) with ziltivekimab reduces major adverse cardiovascular events. Building on the RESCUE trial findings and advancing beyond prior IL 1β–targeted studies such as CANTOS, ZEUS aims to clarify whether directly targeting IL 6 can substantially lower residual inflammatory risk and improve both cardiovascular and renal outcomes in this high risk population (56, 57).

6.3. Personalized Medicine Approaches

RAdvances in genomics and biomarker profiling could enable tailored pharmacotherapy, wherein treatment is individualized based on genetic risk factors and the patient's unique disease phenotype.

Epigenetic modifications are instrumental in the onset and progression of coronary artery disease (CAD). Heritable changes not altering the DNA sequence but affecting gene activity through mechanisms like DNA methylation, histone modifications, and regulation by noncoding RNAs (miRNAs, lncRNAs, circRNAs)—influence key processes such as inflammation, oxidative stress, lipid metabolism, and vascular function. These changes, often established early in life through environmental and lifestyle factors, predispose individuals to CAD. By merging these epigenetic insights with personalized medicine, treatments based on an individual's genetic and environmental makeup, novel diagnostic and therapeutic strategies for CAD may soon emerge (58).

These future avenues underscore a broader trend toward precision medicine in cardiovascular care. While many of these approaches remain investigational, they represent exciting potential additions to our therapeutic arsenal.

7. Discussion

Lifestyle modification remains the foundational intervention across all patient populations. The synergistic effect of diet, exercise, and smoking cessation with pharmacotherapy has been well documented. Both guidelines reinforce that even the most potent

pharmacotherapies cannot compensate for ongoing lifestyle risk factors. Hence, a patient-centered approach that emphasizes behavior change and adherence to non-pharmacologic strategies is essential for achieving optimal outcomes (1, 8).

The management of chronic coronary syndromes has evolved into a refined interplay between lifestyle modification and pharmacotherapy. The 2024 ESC and 2023 North American guidelines emphasize that an optimal therapeutic strategy must be comprehensive—addressing both the modifiable risk factors and the underlying pathophysiological mechanisms driving myocardial ischemia.

Each class of medications offers distinct mechanisms of action and benefits. Antianginal agents such as beta-blockers, calcium channel blockers, nitrates, ivabradine, and ranolazine are primarily used to alleviate symptoms. Beta-blockers and calcium channel blockers, for instance, have robust data supporting their role in reducing myocardial oxygen demand (59, 60). Whereas nitrates are effective in acute symptom relief, the development of tolerance remains a challenge that is partly mitigated by dosing strategies (61).

Lipid-lowering therapies represent the cornerstone of prevention in CCS. Statins are the first-line agents not only for their LDL-C lowering properties but also for their pleiotropic effects, including plaque stabilization and anti-inflammatory benefits (62). Furthermore, the addition of ezetimibe can further reduce LDL-C when statin monotherapy is insufficient which is recommended in patients with CCS (8). Meanwhile, the advent of PCSK9 inhibitors and newer agents like inclisiran and Bempedoic acid offers the possibility of achieving lower LDL-C levels with novel mechanisms, thereby addressing residual cardiovascular risk (36, 44, 46).

Antithrombotic strategies are essential for reducing the risk of myocardial infarction and stroke in CCS. Aspirin remains the mainstay, while P2Y12 inhibitors and dual pathway inhibition (via the addition of low-dose rivaroxaban) provide incremental benefits, particularly in patients with high thrombotic risk (39-41). The therapeutic challenge lies in balancing the reduction in ischemic events with the potential risk for bleeding.

Despite these therapeutic advances, real-world application of therapeutic recommendations remains challenging. Issues such as medication adherence, polypharmacy in older populations, cost-effectiveness, and side effect profiles complicate the implementation of guideline recommendations (63). An integrated approach that combines patient education, careful monitoring, and regular follow-up is essential to mitigate these challenges and optimize patient outcomes.

Pharmacist-led interventions are emerging as a pivotal component in both primary and secondary prevention of cardiovascular diseases. Pharmacists contribute through patient education, meticulous medication management, drug safety oversight, and systematic monitoring of cardiovascular risk factors such as blood pressure, blood glucose, and serum lipid levels (64, 65). Systematic reviews and observational studies have consistently demonstrated that pharmacist involvement improves the management of hypertension, dyslipidemia, diabetes, and smoking cessation, and reduces hospitalizations in heart failure patients (66). Although evidence regarding improvements in patient satisfaction, adherence, and economic outcomes remains limited, the integration of pharmacists within a multidisciplinary healthcare framework has proven to be a highly efficient and accessible model for patient care.

Meta-analytical evidence further supports the critical role of pharmacists in cardiology. An umbrella review of randomized controlled trials, revealed that a majority of meta-analyses report significant benefits of pharmacist interventions. These benefits include notable reductions in blood pressure, enhanced control of lipid and glucose levels,

improved smoking cessation rates, and superior medication adherence. Additionally, pharmacist interventions have shown a significant impact on reducing all-cause mortality and enhancing quality of life among patients with chronic heart failure (67). Collectively, these findings underscore the substantial contribution of pharmacists to cardiovascular disease management and highlight the need for further research to delineate their impact within collaborative practice models.

8. Conclusion

The pharmacotherapy of chronic coronary syndromes has advanced significantly with the development of new medications and the refinement of existing treatment algorithms. Guidelines emphasize a dual approach combining lifestyle modifications with targeted pharmacotherapy. Antianginal agents, lipid-lowering therapies, antithrombotic strategies, and neurohormonal modulators each play a distinct role in the comprehensive management of CCS. Emerging therapies including RNA-based agents and novel anti-inflammatory drugs, promise to further enhance our therapeutic options and enable more personalized treatment paradigms. Ultimately, an integrated management strategy that resolves the interplay between symptomatic control and the modification of underlying risk factors is essential. Clinicians and pharmacists must remain vigilant in applying both established and emerging evidence in order to optimize therapy for patients with chronic coronary syndromes.

Authors contributions

MO contributed to the conceptualization of the manuscript, literature search, evidence synthesis, drafting of the original manuscript, and final revision of the article. AA contributed to the literature review, clinical interpretation of cardiology-related evidence, and drafting of relevant sections of the manuscript. AS contributed to the conceptualization, methodological supervision, critical revision of the manuscript, and interpretation of pharmacotherapeutic evidence. NS contributed to the literature search, data extraction from relevant guidelines and clinical trials, and drafting of selected sections. ML supervised the project, contributed to the conceptualization and critical intellectual revision of the manuscript, and approved the final version for submission. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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