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The Pharmacist's Role in Managing Cardiovascular Disease: Updates on Pharmacologic Therapies

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ABSTRACT

Cardiovascular disease (CVD) remains a leading cause of mortality, with

pharmacologic treatment being the primary therapeutic approach. This article provides an update on pharmacologic therapies for hypertrophic cardiomyopathy (HCM), familial hypercholesterolemia (FH), and heart failure (HF). Mavacamten, a first-in-class cardiac myosin inhibitor, has been approved for treating symptomatic obstructive HCM, improving functional capacity and symptoms by reducing cardiac contractility and left ventricular outflow tract (LVOT) obstruction. Inclisiran, a novel synthetic small interfering ribonucleic acid (siRNA) therapy, offers a new approach for treating heterozygous FH by targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) mRNA, leading to enhanced low-density lipoprotein (LDL) clearance. For heart failure with reduced ejection fraction (HFrEF), guideline-directed medical therapy (GDMT) aims to mitigate compensatory mechanisms and improve survival outcomes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, initially developed as glucose-lowering agents for type 2 diabetes, have demonstrated cardiovascular benefits and are now incorporated into GDMT for HFrEF. Empagliflozin has also received an expanded indication for heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF). These advancements in pharmacologic therapies for CVD have significant implications for patient outcomes and nursing practice.

Keywords: pharmacologic treatment, CVD, Cardiovascular Disease

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality in both the United States (US) and globally. Nearly half of adults over 20 years of age in the US have one or more forms of CVD, and the prevalence increases with age (Tsao et al., 2023). While lifestyle modifications and surgical interventions play critical roles in managing CVD, pharmacologic treatment remains the primary therapeutic approach for most patients. This article provides an update on pharmacologic therapies for three types of CVD hypertrophic cardiomyopathy (HCM), familial hypercholesterolemia (FH), and heart failure (HF). The discussion focuses on clinical indications, pharmacological mechanisms, practical considerations for the safe and appropriate use of medications, and implications for nursing practice.

Recent advancements in pharmacologic therapies have revolutionized the treatment landscape for cardiovascular disease, offering more precise, effective, and patient-centered options. Novel agents like mavacamten for hypertrophic cardiomyopathy and inclisiran for familial hypercholesterolemia exemplify this trend, directly addressing disease mechanisms with improved outcomes. Similarly, the expanded use of SGLT2 inhibitors for heart failure has broadened therapeutic possibilities, particularly for patients with preserved ejection fraction. These innovations not only enhance survival rates but also improve quality of life, underscoring the importance of integrating cutting-edge therapies into clinical practice. Such progress reflects a pivotal shift toward personalized medicine in cardiology.

The continuous evolution of pharmacologic treatments in cardiovascular disease underscores the critical need for healthcare providers to remain informed about emerging therapies. These advancements have not only transformed clinical outcomes

but have also introduced complexities in patient management, including the necessity for specialized monitoring and tailored therapeutic strategies. By addressing underlying pathophysiological mechanisms, novel treatments like mavacamten and inclisiran exemplify a shift toward precision medicine. Additionally, the integration of multidisciplinary approaches, particularly the role of pharmacists and nurses, ensures that these innovations translate into optimal patient care and outcomes. This review aims to provide a comprehensive overview of these groundbreaking therapies, their mechanisms, and their implications for practice.

Hypertrophic Cardiomyopathy

HCM is one of the most common inherited forms of CVD, with an estimated prevalence of at least 1 in 500 individuals (Semsarian et al., 2015). The disease typically manifests after the third decade of life but can present at any age. HCM is characterized by nondilated left ventricular (LV) hypertrophy (LVH) without other cardiac or systemic causes of LVH. In adults, HCM is diagnosed when LV wall thickness exceeds 15 mm as determined by echocardiography or cardiac MRI. In children, it is defined as an increase in LV wall thickness by at least two standard deviations above the mean for age or body mass index (Ommen et al., 2020).

HCM is an autosomal dominant genetic disorder caused by pathogenic variants in genes encoding cardiac sarcomere proteins. To date, over 1,500 pathogenic variants have been identified, making the condition genetically and clinically heterogeneous. The precise mechanisms by which specific variants produce distinct clinical phenotypes are not fully elucidated, but it is hypothesized that HCM mutations lead to cardiac hypercontractility and activation of signalling pathways, resulting in hypertrophy and fibrosis (Maron et al., 2012). These changes lead to a small, stiff ventricle with impaired systolic and diastolic function despite preserved LV ejection fraction (LVEF). In approximately two-thirds of cases, hypertrophy results in left ventricular outflow tract (LVOT) narrowing, causing obstruction of blood flow from the LV into the ascending aorta. This obstruction creates a systolic pressure gradient that limits LV ejection and is quantified in millimeters of mercury, serving as a key prognostic indicator.

For most patients, HCM follows a benign course with normal life expectancy. However, patients with severe obstructive disease or diastolic dysfunction may experience limiting symptoms, including fatigue, dyspnea, angina, palpitations, and syncope. A minority of patients may develop life-threatening complications, such as progressive HF, atrial fibrillation with thromboembolism, or sudden cardiac death (Maron, 2018).

Conventional Treatment of Hypertrophic Cardiomyopathy

Historically, pharmacologic management of HCM has aimed at symptom relief. Non-vasodilating beta-blockers, such as metoprolol and propranolol, have been the cornerstone of therapy and were among the first agents studied for treating LVOT obstruction, albeit in small or non-randomized trials. These beta-blockers are also effective in alleviating ischemic chest discomfort and dyspnea caused by LVOT obstruction. Non-dihydropyridine calcium channel blockers, such as diltiazem and verapamil, are alternative options for patients who cannot tolerate beta-blockers.

Disopyramide, a negative inotropic agent, may further alleviate symptoms associated with LVOT obstruction when used alongside a beta-blocker or non-dihydropyridine calcium channel blocker. Diuretics are occasionally used for patients with nonobstructive HCM who have pulmonary edema or overt HF, but care must be taken to avoid hypovolemia, hypotension, and worsening LVOT obstruction. Despite their symptomatic benefits, these therapies do not address the underlying pathophysiology of HCM or alter its progression, highlighting the need for novel treatments targeting disease mechanisms.

Novel Pharmacologic Therapy: Mavacamten

Mavacamten (Camzyos) is a first-in-class cardiac myosin inhibitor approved for treating symptomatic (New York Heart Association [NYHA] class II or III) obstructive HCM to improve functional capacity and symptoms. Mavacamten is a reversible inhibitor that selectively reduces cardiac myosin-actin cross-bridge formation in the sarcomere during systole and diastole. This mechanism decreases cardiac contractility, reduces LVOT obstruction, promotes a relaxed energy-efficient state, and improves cardiac filling pressures.

Early studies demonstrated that mavacamten improved LV filling and reduced LVOT gradients (Green et al., 2016). Subsequent phase II trials confirmed these findings, paving the way for the phase III EXPLORER-HCM study. This study enrolled 251 adults aged 18 years or older with obstructive HCM and an LVEF of at least 55%, randomly assigning participants to mavacamten or placebo. The primary endpoint was defined as either a ≥1.5 mL/kg/min improvement in peak oxygen consumption (VO2) and NYHA class reduction by at least one category, or a ≥3.0 mL/kg/min increase in peak VO2 without NYHA class worsening. After 30 weeks, 37% of patients receiving mavacamten met the primary endpoint compared to 17% in the placebo group ($P = 0.0005$). Mavacamten also showed significant improvements in resting and postexercise LVOT gradients. In an extension study with a median follow-up of 62 weeks, mavacamten demonstrated sustained benefits in functional capacity, LVOT gradients, and NYHA classification, with no significant long-term adverse effects reported (Spertus et al., 2021).

In April 2022, the US Food and Drug Administration (FDA) approved mavacamten. The drug is available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program due to its potential to lower LVEF and induce systolic HF. Prescribers must enroll in the REMS program, complete a knowledge assessment, and adhere to strict monitoring protocols. Nurses can serve as “physician designees,” assisting with patient counselling on HF risks, drug interactions, and the importance of compliance with monitoring requirements. Patients must also enroll in the REMS program and undergo regular echocardiographic assessments.

Mavacamten is initiated at a recommended dose of 5 mg once daily for patients with an LVEF ≥55%. Dosing is adjusted based on echocardiographic evaluations at 4, 8, and 12 weeks and then every three months, with careful monitoring of LVEF and LVOT gradients. Therapy is discontinued if LVEF falls below 50% or if

patients experience worsening HF symptoms or clinical status. Mavacamten is extensively metabolized in the liver, primarily by cytochrome P450 (CYP) 2C19, with minor contributions from CYP3A4 and CYP2C9, making drug–drug interactions a common consideration. The concomitant use of moderate to strong CYP2C19 and CYP3A4 inhibitors or inducers is contraindicated. However, no dosage adjustments are required for patients with renal or hepatic impairment.

Mavacamten is generally well-tolerated, with dizziness (27%) and syncope (6%) being the only adverse effects reported more frequently than with placebo. Decreased left ventricular ejection fraction (LVEF), occurring in approximately 6% of patients, is dose-dependent and typically manifests around four weeks after initiation. Risk factors for decreased LVEF include concomitant use of cytochrome P450 (CYP450) inhibitors, concurrent illness, uncontrolled tachyarrhythmias, and the combined use of disopyramide with verapamil or diltiazem (Ho et al., 2020; Olivotto et al., 2020).

As the first treatment directly addressing the underlying pathophysiology of hypertrophic cardiomyopathy (HCM), mavacamten represents a significant milestone in the management of this condition. The drug is also being evaluated for patients with nonobstructive HCM and a high symptom burden. Preliminary evidence from the MAVERICK-HCM study has set the stage for larger clinical trials that are currently ongoing. Additionally, the U.S. Food and Drug Administration (FDA) has accepted a supplemental drug application to expand mavacamten's indication for reducing the need for septal reduction therapies in patients with obstructive HCM and New York Heart Association (NYHA) class IV symptoms, based on findings from the VALOR-HCM studies.

Despite its advancements, mavacamten's limitations, such as its long half-life and potential for drug-drug interactions, have spurred the development of aficamten, a second-generation cardiac myosin inhibitor. Phase II studies, including the REDWOOD-HCM trial, have demonstrated that aficamten effectively reduces left ventricular outflow tract (LVOT) gradients and alleviates heart failure (HF) symptoms in obstructive HCM.18 Approval from the FDA will likely depend on the outcomes of the ongoing Phase III SEQUOIA-HCM trial.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a prevalent inherited disorder of lipid metabolism, affecting one in 250 individuals in the United States19 and one in 200 worldwide. The disorder is characterized by markedly elevated levels of low-density lipoprotein (LDL) cholesterol and an increased risk of premature coronary heart disease. FH is an autosomal dominant condition caused by pathogenic mutations in the LDL receptor (LDL-R), apolipoprotein B (ApoB), or proprotein convertase subtilisin/kexin type 9 (PCSK9) genes, which regulate LDL clearance from circulation. Homozygous inheritance of pathogenic variants results in more severe disease but is significantly less common, with a prevalence of approximately one in 200,000 to 300,000.

Numerous diagnostic criteria exist for FH with varying approaches and no established consensus on their superiority. In 2015, the American Heart Association

(AHA) introduced simplified criteria for diagnosing heterozygous FH without genetic testing. This framework defines heterozygous FH as an LDL cholesterol level exceeding 190 mg/dL in adults or 160 mg/dL in children, alongside a first-degree relative with either premature coronary artery disease or a confirmed FH-causing mutation (Gidding et al., 2015).

FH is frequently asymptomatic, though physical signs such as xanthelasmas, tendon xanthomas, and corneal arcus may be present and aid in diagnosis. Left untreated, affected individuals face a 50% risk of fatal or nonfatal cardiac events by age 50 in men and by age 60 in women, highlighting the importance of early diagnosis and treatment.

Conventional Approach to Familial Hypercholesterolemia Treatment

Since cardiovascular outcomes in FH are primarily determined by the duration and severity of LDL elevation, treatment focuses on early and sustained LDL reduction. Guidelines recommend LDL targets below 100 mg/dL (2.6 mmol/L) for adults with FH, or a reduction of at least 50%. More stringent goals, such as LDL levels below 70 mg/dL (1.8 mmol/L), are advised for those with atherosclerotic cardiovascular disease or diabetes. For children over 10 years old, an LDL target below 135 mg/dL (3.5 mmol/L) is recommended (Grundy et al., 2019).

While lifestyle modifications, including dietary changes and smoking cessation, are critical in FH management, most patients require multidrug therapy to meet LDL targets. High-intensity statins such as rosuvastatin and atorvastatin are first-line therapies, capable of lowering LDL levels by 50% to 60%. Patients intolerant to high-dose statins should be prescribed moderate-intensity alternatives. When statin monotherapy is insufficient, ezetimibe, which inhibits intestinal cholesterol absorption, is a well-tolerated second-line agent. Previously, niacin and bile acid sequestrants were considered third-line options, but these have largely been supplanted by PCSK9 inhibitors, such as evolocumab and alirocumab, which provide superior LDL reduction but are often cost-prohibitive.

A New Option for Familial Hypercholesterolemia Treatment

Inclisiran (Leqvio), an innovative synthetic small interfering ribonucleic acid (siRNA) therapy, offers a novel approach for treating heterozygous FH in adults. Inclisiran specifically targets PCSK9 mRNA for degradation, leading to reduced PCSK9 levels, increased LDL receptor recycling and expression, and enhanced LDL clearance from circulation.

Initial studies demonstrated sustained reductions in LDL cholesterol following a single dose of inclisiran (Fitzgerald et al., 2017). These findings were corroborated by phase II trials, which revealed dose-dependent reductions in both LDL and PCSK9 levels, with the greatest effects observed after multiple doses. Large phase III trials (ORION10 and ORION11), which included 1561 and 1617 patients, respectively, assessed inclisiran's safety and efficacy in patients with inadequately controlled LDL levels despite maximal statin therapy, with or without additional

therapies (Ray et al., 2020). Participants were randomly assigned to receive inclisiran (administered on day 1, day 90, and every 6 months) or placebo. After 18 months, LDL cholesterol levels were reduced by 52.3% in ORION10 and 49.9% in ORION11 ($P < 0.001$). Additionally, inclisiran improved other lipid parameters, such as triglycerides and lipoprotein A, while increasing high-density lipoprotein (HDL), with no significant adverse events observed.

Inclisiran received FDA approval in December 2021. Administered via subcutaneous injection, inclisiran is dosed at 284 mg initially, followed by a second dose at 3 months and subsequent doses every 6 months. It does not require dose adjustments for renal or hepatic impairment. Monitoring includes a baseline lipid profile, followed by fasting lipid profiles 4–12 weeks post-initiation and every 3–12 months thereafter. Adverse reactions are generally injection site-related (erythema, pain, rash in 8% of patients), with arthralgia (5%) and bronchitis (4%) also reported.

Like PCSK9 inhibitors, inclisiran represents a major advancement in lipid management, addressing a gap for high-risk patients unable to achieve LDL targets with conventional oral therapies. Its infrequent dosing and favorable side effect profile have significant implications for patient adherence and outcomes, particularly given the high discontinuation rates associated with statins. Enhanced adherence may also be facilitated if health care providers, including nurses, administer the injections.

HEART FAILURE

Heart failure (HF) is projected to affect nearly 8 million individuals in the United States by 2030. It is characterized as a structural abnormality in the heart that disrupts its ability to fill with or eject blood effectively. The classification of HF primarily depends on left ventricular ejection fraction (LVEF), which quantifies the percentage of oxygenated blood expelled from the heart during each contraction (Heidenreich et al., 2022). Guidelines from the American College of Cardiology Foundation, the American Heart Association (AHA), and the Heart Failure Society of America define HF with reduced ejection fraction (HFrEF) as an LVEF of ≤40%, while HF with preserved ejection fraction (HFpEF) is identified with an LVEF >50%. More recently, HF with an LVEF between 41% and 49% has been termed HF with mildly reduced EF (HFmrEF). LVEF serves as a critical prognostic marker and guides the pharmacological management strategies aimed at improving survival outcomes. Although landmark trials in HF predominantly focus on HFrEF, emerging research has identified specific pharmacological interventions for HFpEF.

Conventional Approach to Treatment of Heart Failure with Reduced Ejection Fraction

The primary goal of guideline-directed medical therapy (GDMT) for HFrEF is to mitigate the compensatory mechanisms triggered by reduced cardiac output. Neurohumoral activation, such as heightened activity in the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), alongside changes in Vaso modulating peptide hormones, temporarily stabilizes the circulatory system to maintain homeostasis but eventually leads to cardiac remodelling and disease progression (Vaduganathan et al., 2020).

The pharmacologic foundation of GDMT aims to enhance survival and minimize HF-related hospitalizations and mortality. Evidence-based treatments for HFrEF include RAAS inhibitors with or without a neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and, more recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors. Quadruple therapy has demonstrated a reduction in cardiovascular death or HF-related hospitalizations by up to 62%, potentially extending life expectancy by 1.4 to 6.3 years.

RAAS inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), prevent RAAS-mediated vasoconstriction, reducing cardiac workload and aldosterone-induced cardiac fibrosis and remodelling. The angiotensin receptor-neprilysin inhibitor (ARNI), valsartan/sacubitril (Entresto), combines RAAS inhibition with the prevention of neprilysin-mediated inactivation of vasodilatory peptides. In the PARADIGM-HF trial, valsartan/sacubitril showed a 20% reduction in cardiovascular death, HF hospitalizations, and sudden cardiac death compared with enalapril, an ACEI. Current guidelines recommend initiating ARNIs or transitioning patients from ACEIs or ARBs to ARNIs in symptomatic HFrEF.

Beta-blockers, specifically metoprolol succinate, bisoprolol, and carvedilol, are endorsed in guidelines to reduce morbidity and mortality in HFrEF.39 The cardio selective beta-blockers, metoprolol succinate and bisoprolol, selectively inhibit beta-1 adrenergic receptors on the heart, which are stimulated by the sympathetic nervous system in response to reduced cardiac output. This suppression prevents further loss of myocardial contractility, slowing ventricular remodelling and disease progression. Carvedilol, with its beta-1, beta-2, and alpha-1 blocking effects, offers additional benefits through vasodilation and blood pressure reduction.

MRAs such as spironolactone and eplerenone provide mortality and morbidity benefits in HFrEF by targeting aldosterone, a hormone upregulated during RAAS activation that promotes cardiac fibrosis and remodeling. By counteracting aldosterone, MRAs are thought to reverse structural cardiac damage and reduce the likelihood of complications such as atrial fibrillation.

A Repurposed Treatment Option for Heart Failure with Reduced Ejection Fraction and Heart Failure with Preserved Ejection Fraction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, including dapagliflozin (Farxiga) and empagliflozin (Jardiance), have recently been incorporated into GDMT for HFrEF. Initially developed as glucose-lowering agents for type 2 diabetes, subsequent studies demonstrated cardiovascular benefits, including reductions in HF hospitalizations in patients with diabetes and established cardiovascular disease (CVD) or those at high CVD risk (Wiviott et al., 2019).

Two significant phase III trials, DAPA-HF and EMPEROR-Reduced, investigated dapagliflozin and empagliflozin, respectively, in patients with LVEF ≤40% and New York Heart Association (NYHA) class II–IV HF receiving GDMT.

Both trials reported a 25% reduction in the composite endpoint of cardiovascular death or HF-related hospitalizations compared with placebo over a median follow-up of 16–18 months. A meta-analysis of these trials demonstrated a significant reduction in all-cause mortality with SGLT2 inhibitor therapy (Zannad et al., 2020). These findings supported the FDA approval of dapagliflozin in May 2020 and empagliflozin in August 2021 for reducing cardiovascular death and HF hospitalizations in adults with HFrEF.

In 2022, empagliflozin received an expanded FDA indication for HFpEF and HFmrEF. This decision was based on findings from the phase III EMPEROR-Preserved trial, which evaluated patients with LVEF >40% and NYHA class II–IV HF receiving GDMT. Over a median follow-up of approximately 26 months, empagliflozin demonstrated a 29% reduction in HF hospitalizations, though it did not significantly affect all-cause mortality. This expansion represents a major advancement for patients with HFpEF, who have limited treatment options.

The mechanisms underlying the benefits of SGLT2 inhibitors in HF remain incompletely understood but are believed to involve a combination of metabolic (e.g., natriuresis, increased insulin sensitivity), hemodynamic (e.g., osmotic diuresis, volume reduction), and organ-specific effects (e.g., reduced left ventricular mass).

SGLT2 inhibitors are administered orally, with a starting dose of 10 mg once daily for HF patients, regardless of diabetes status. Both dapagliflozin and empagliflozin require caution in patients with estimated glomerular filtration rates (eGFR) below 25 mL/min/1.73 m^2 and 20 mL/min/1.73 m^2, respectively, and are contraindicated in dialysis-dependent individuals. Monitoring parameters include blood glucose, kidney function, and volume status. Notable side effects include acute kidney injury, recurrent urinary tract infections (8%–9%), and genitourinary fungal infections (2%–6%), which may necessitate discontinuation. Other SGLT2 inhibitors, such as canagliflozin and ertugliflozin, are not yet FDA-approved for HF treatment.

Conclusion

Cardiovascular disease remains a significant global health challenge, necessitating continuous advancements in pharmacologic treatment strategies. This paper has highlighted major developments in the treatment of hypertrophic cardiomyopathy, familial hypercholesterolemia, and heart failure, showcasing innovative therapies like mavacamten, inclisiran, and SGLT2 inhibitors. These breakthroughs not only enhance patient outcomes but also signify a shift towards more targeted and personalized interventions.

Pharmacists, as integral members of the healthcare team, play a crucial role in ensuring the safe and effective use of these therapies. Their involvement in patient education, adherence monitoring, and mitigation of adverse effects is essential in optimizing treatment outcomes. Continued research and collaboration among healthcare professionals will further refine the management of cardiovascular conditions, improving both longevity and quality of life for affected individuals.

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