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Cardiovascular Medicine: New Drug Developments for Complex Cardiovascular Diseases and Cardiovascular Imaging

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with complex pathophysiological mechanisms contributing to their progression. Traditional therapeutic approaches, while effective in many cases, are often insufficient for treating the more intricate and multifactorial forms of CVDs. In recent years, significant strides have been made in the development of novel drugs aimed at addressing these complex CV conditions. These new treatments are being designed to target specific molecular pathways, such as inflammation, oxidative stress, and endothelial dysfunction, which play key roles in diseases like atherosclerosis, heart failure, and arrhythmias. Additionally, emerging drug classes, including gene therapies and biologics, are offering promising new strategies for managing patients with advanced or refractory CVDs, paving the way for more personalized and effective interventions.

Keywords: Cardiovascular diseases, New drug developments, Complex cardiovascular conditions, Targeted therapies, Personalized medicine

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Introduction

CVDs

CVDs remain the leading cause of death globally, accounting for a significant portion of mortality across various regions (Figure 1). CVDs claimed an estimated 17.9 million lives in 2019, which accounted for 32% of all global deaths. Of these fatalities, a significant 85% were caused by heart attacks and strokes. These alarming statistics highlight the critical impact of CVDs on public health. A disproportionate number of CVD-related deaths occur in low- and middle-income countries, with over three-quarters of fatalities taking place in these regions. Additionally, among the 17 million premature deaths (under 70 years of age) from noncommunicable diseases in 2019, 38% were attributed to CV conditions, underscoring the urgent need for effective prevention and intervention strategies [2].

In high-income countries, CVDs mortality rates have declined by up to 60% over the last 60 years due to advances in prevention and treatment. Conversely, low- and middle-income countries have seen a 15% increase in CVD death rates over the past 20 years, highlighting a growing health challenge in these regions [3]. In Europe, CVD accounts for over 3 million deaths annually, with a higher proportion of deaths occurring in middle-income countries compared to high-income countries [4]. In Brazil, CVDs remain a significant health concern, with ongoing efforts to compile and analyze epidemiological data to inform public health strategies [5, 6]. The burden of CVD is notably higher in middle-income countries within the European Society of Cardiology member states, where disability-adjusted life years (DALYs) due to CVD are nearly four times higher than in high-income countries [7].

Many CVDs can be prevented by addressing modifiable risk factors such as tobacco use, unhealthy diets, obesity, physical inactivity, harmful alcohol consumption, and exposure to air pollution. Early detection of CVD is crucial to enable timely management through counselling and medication, helping to reduce the burden of these diseases and improve patient outcomes [2]. The statistics surrounding CVDs highlight disparities in healthcare access, economic burden, and mortality rates between high-income and low- to middle-income countries. These disparities are influenced by a range of factors, including socioeconomic status, healthcare infrastructure, and prevalent risk factors such as smoking, hypertension, and obesity.

Furthermore, the COVID-19 pandemic led to an increase in CVD mortality rates, reversing a decade of progress in reducing these rates. From 2020 - 2022, there were 228,524 excess CVD deaths in the United States alone [8]. Individuals with underlying CVD comorbidities who contracted COVID-19 faced worse outcomes, further highlighting the

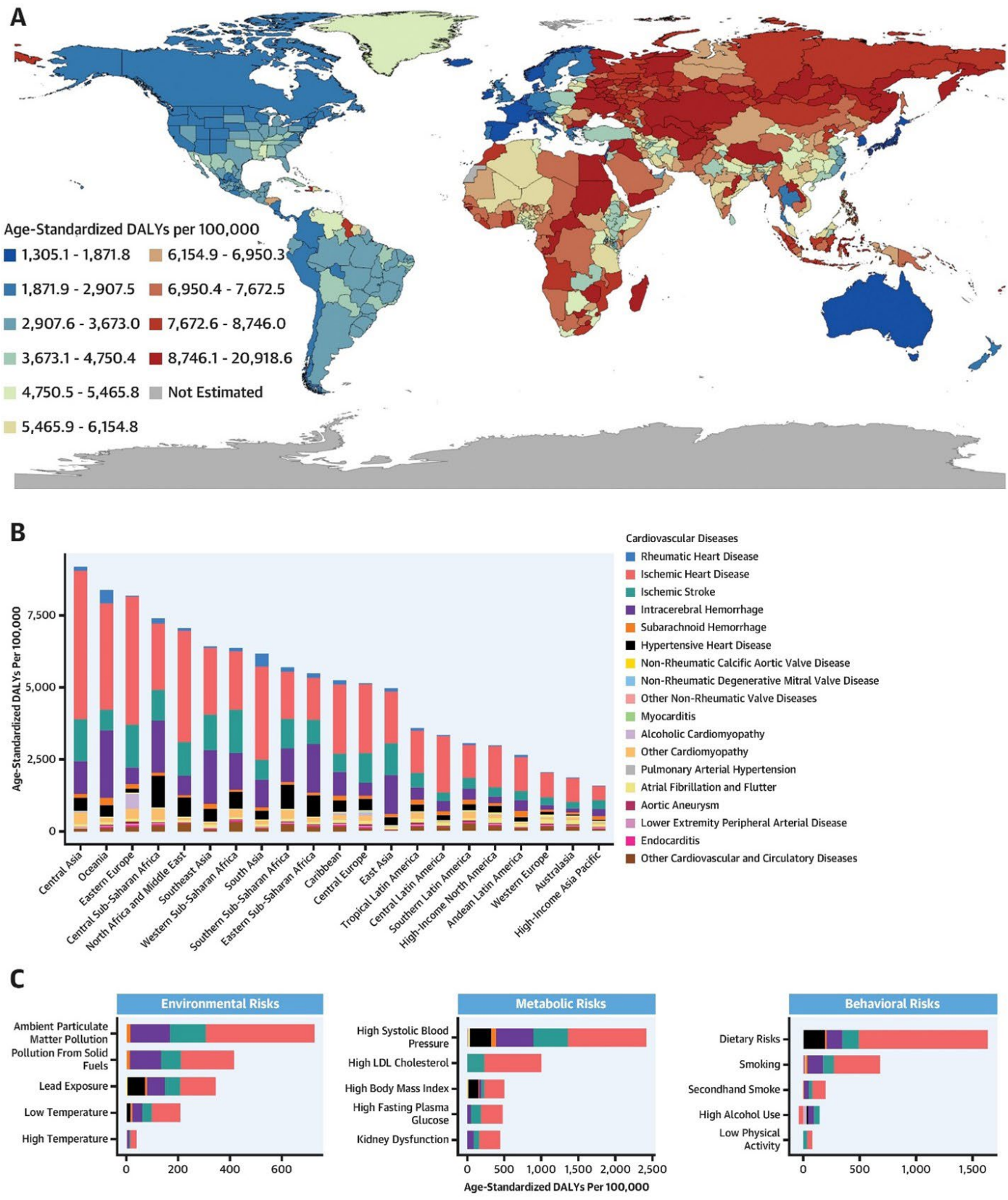

Figure 1: Age-standardized DALYs per 100,000 for **(A)** CVDs globally, **(B)** specific CVDs by region, and **(C)** global burden attributable to selected risk factors compared to the theoretical minimum risk level. Reproduced from [1].

need for effective management and prevention strategies [9]. While the global burden of CVDs remains substantial, there are ongoing efforts to address these challenges through public health interventions and healthcare improvements. However, the disparities between high-income and low- to middle-income countries underscore the need for targeted actions to reduce the CVD burden, particularly in regions where healthcare resources are limited.

Traditional Drugs Used in CVDs

Traditional drugs used in the treatment of CVDs have been integral in managing various heart-related conditions and preventing complications. These drugs primarily target the underlying risk factors of CVDs, such as high blood pressure, high cholesterol, and abnormal heart rhythms, and work to improve heart function [10, 11]. One of the key drug classes is antihypertensives, which includes medications like angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, and diuretics. ACE inhibitors, such as enalapril, lower blood pressure and reduce strain on the heart by blocking the enzyme that produces angiotensin II, a substance that narrows blood vessels. Beta-blockers, such as metoprolol, reduce heart rate and lower blood pressure, which helps prevent heart attacks and strokes [12, 13].

Another cornerstone in CVD treatment is antiplatelet and anticoagulant agents, which help prevent blood clot formation. Aspirin, one of the most commonly used antiplatelet drugs, inhibits the enzyme cyclooxygenase, reducing thromboxane production and preventing platelet aggregation [14, 15]. Similarly, warfarin is an anticoagulant that inhibits vitamin K-dependent clotting factors, helping prevent clot formation in conditions like atrial fibrillation or after a heart valve replacement [16]. These drugs are particularly important in preventing complications like heart attacks, strokes, and deep vein thrombosis, but they come with a risk of bleeding, making careful monitoring necessary.

Statins are another group of traditional drugs that have revolutionized the treatment of CVDs. Statins, such as atorvastatin and simvastatin, work by inhibiting HMG-CoA reductase, a key enzyme in cholesterol synthesis. This results in reduced levels of low-density lipoprotein (LDL) cholesterol, commonly known as "bad" cholesterol, which contributes to the buildup of plaque in the arteries. By lowering LDL cholesterol, statins help reduce the risk of atherosclerosis, heart attacks, and strokes. While statins are highly effective in reducing CV risk, they can cause side effects like muscle pain, liver enzyme abnormalities, and, rarely, rhabdomyolysis [17-19].

Lastly, nitrates, such as nitroglycerin, are used to manage angina and other symptoms of coronary artery disease (CAD). Nitrates work by relaxing and dilating blood vessels, improving blood flow to the heart and reducing chest pain. This class of drugs is particularly useful for patients with CAD, as it helps alleviate the strain on the heart by decreasing oxygen demand. However, nitrates can lead to side effects such as headaches, dizziness, and hypotension, especially when used in high doses or in combination with other medications that lower blood pressure [20, 21]. These traditional drug classes continue to play a vital role in CVD management, providing effective solutions for patients while enabling advancements in newer treatments.

The effectiveness of these traditional drugs lies in their ability to mitigate risk factors and prevent complications. For instance, beta-blockers reduce the workload on the heart by slowing the heart rate, while ACE inhibitors lower blood pressure and decrease strain on the heart [22]. Similarly, anticoagulants and antiplatelet agents like warfarin and aspirin help prevent blood clots that could lead to heart attacks or strokes [23]. Although newer therapies have emerged, traditional drugs remain a cornerstone in CVD management due to their proven efficacy, safety profiles, and cost-effectiveness. While traditional drugs used in the treatment of CVDs are effective in managing symptoms and reducing complications, they often come with potential side effects that vary depending on the drug class (Table 1). These side effects, though typically manageable, highlight the importance of individualized treatment plans and regular monitoring to ensure both efficacy and patient safety.

Table 1: Common drugs used in the treatment of CVDs, their modes of action, and potential side effects [24].

Drug class	Drug type	Mode of action	Side effects
Antihypertensives	ACE inhibitors	Inhibit ACE to lower blood pressure and reduce workload.	Dry cough, dizziness, hyperkalemia, and angioedema.
	Beta-blockers	Block beta-adrenergic receptors to reduce heart rate and blood pressure.	Fatigue, bradycardia, cold extremities, and dizziness.
	Calcium channel blockers	Inhibit calcium entry into smooth muscle cells to relax blood vessels.	Swelling (edema), dizziness, flushing, and constipation.
	Diuretics	Increase urine output to reduce blood volume and blood pressure.	Dehydration, electrolyte imbalance, and dizziness.
Antiplatelet agents (Prevent platelet aggregation to reduce clot formation)	Aspirin	Inhibits cyclooxygenase to prevent thromboxane formation.	GI irritation, bleeding, and tinnitus at high doses.
	Clopidogrel	Blocks ADP receptors on platelets to prevent clotting.	Bleeding, rash, and diarrhea
Anticoagulants (Inhibit clotting factors to prevent blood clot formation)	Warfarin	Inhibits vitamin K-dependent clotting factors.	Bleeding, bruising, and interactions with other drugs.
	Direct oral anticoagulants	Inhibit specific clotting factors (e.g., factor Xa and thrombin).	Bleeding, anemia, and GI upset.
Lipid-lowering drugs	Statins	Inhibit HMG-CoA reductase to reduce cholesterol synthesis.	Muscle pain, liver enzyme elevation, and headache.
	Ezetimibe	Inhibits cholesterol absorption in the small intestine.	GI upset and muscle pain (rare).
	Nitrates	Relax smooth muscle in blood vessels to improve oxygen delivery to the heart.	Headache, dizziness, and low blood pressure.
Antiarrhythmic drugs	Amiodarone	Modulates ion channels to regulate abnormal heart rhythms.	Lung toxicity, thyroid dysfunction, and skin discoloration.
	Digoxin	Increases cardiac contractility and slows heart rate by inhibiting Na^+/K^+ ATPase.	Nausea, dizziness, and arrhythmias at high doses.
Heart failure drugs	ARNI (Sacubitril/Valsartan)	Enhances natriuretic peptide effects while blocking angiotensin receptors.	Hypotension, dizziness, and hyperkalemia.
	Aldosterone antagonists	Block aldosterone to reduce fluid retention.	Hyperkalemia, gynecomastia (in men), and dizziness.

Development of New Drugs

New drug development (NDD) is a rigorous and multifaceted process aimed at bringing safe and effective therapies to patients. It begins with preclinical research, where scientists identify promising compounds and evaluate their potential through laboratory and animal studies. From there, drug candidates progress to clinical trials, which involve testing in humans across three phases to assess safety, efficacy, dosage, and potential side effects (Figure 2) [25]. This process, often spanning over a decade and costing billions of dollars, is essential for meeting stringent regulatory requirements before a drug can be approved by agencies like the Food Drug and Administration (FDA) or European Medical Agency (EMA) [25]. Despite its complexity, this pipeline is critical for addressing unmet medical needs and advancing healthcare innovations.

The NDDs significantly impacts market value, driven by the high costs and potential returns associated with pharmaceutical innovations. The market value of new drugs is influenced by various factors, including development costs, clinical trial phases, and the therapeutic areas they target. The average market value of successful pharmaceutical drugs is estimated at USD 1.62 billion, with discovery stage drugs valued at approximately USD 64.3 million. The costs associated with NDD are substantial, with the discovery stage costing around USD 58.5 million and clinical trial phases (I, II, and III) costing USD 0.6, 30, and 41 million, respectively [26].

In recent years, the FDA has approved a significant number of new drugs, with 37 new drugs approved in 2022 and 55 in 2023. These approvals include new chemical entities and new biological entities, with a focus on therapeutic areas such as oncology, central nervous system, and anti-infection. Many of these drugs have been approved through expedited review pathways, highlighting the industry's emphasis on accelerating the availability of innovative treatments. A notable proportion of these drugs are also targeted at rare diseases, reflecting a trend towards personalized medicine [27, 28].

Advancements in technology and research methodologies have revolutionized drug development. Areas such as precision medicine, artificial intelligence, and genetic engineering have accelerated the discovery and testing of novel treatments. For example, mRNA technology, initially explored for vaccines, has paved the way for groundbreaking therapies like the COVID-19 vaccines, which were developed in record time. While the path to NDD remains challenging, these innovations are transforming the landscape, enabling faster development timelines, improved success rates, and therapies tailored to individual patients' needs.

New Drugs in CVDs

The development of new drugs for CVDs has been a focal point of recent research, aiming to improve efficacy and safety over existing treatments (Table 2). Novel pharmacological agents have shown promise in reducing CV events and mortality, but they also present challenges, particularly concerning safety profiles. Between 1900 and 2020, the FDA approved a total of 302 new drugs for treating various CVDs. The period from 1980 to 2000 is often regarded as the golden era of CVDs drug discovery, with an average of about 9.1 new drug approvals annually significantly higher than the rate before 1980. However, this number has dropped substantially in the last two decades, with an average of just 3.55 new drugs per year, marking a decline of roughly 61% compared to 20 years ago. This trend contrasts

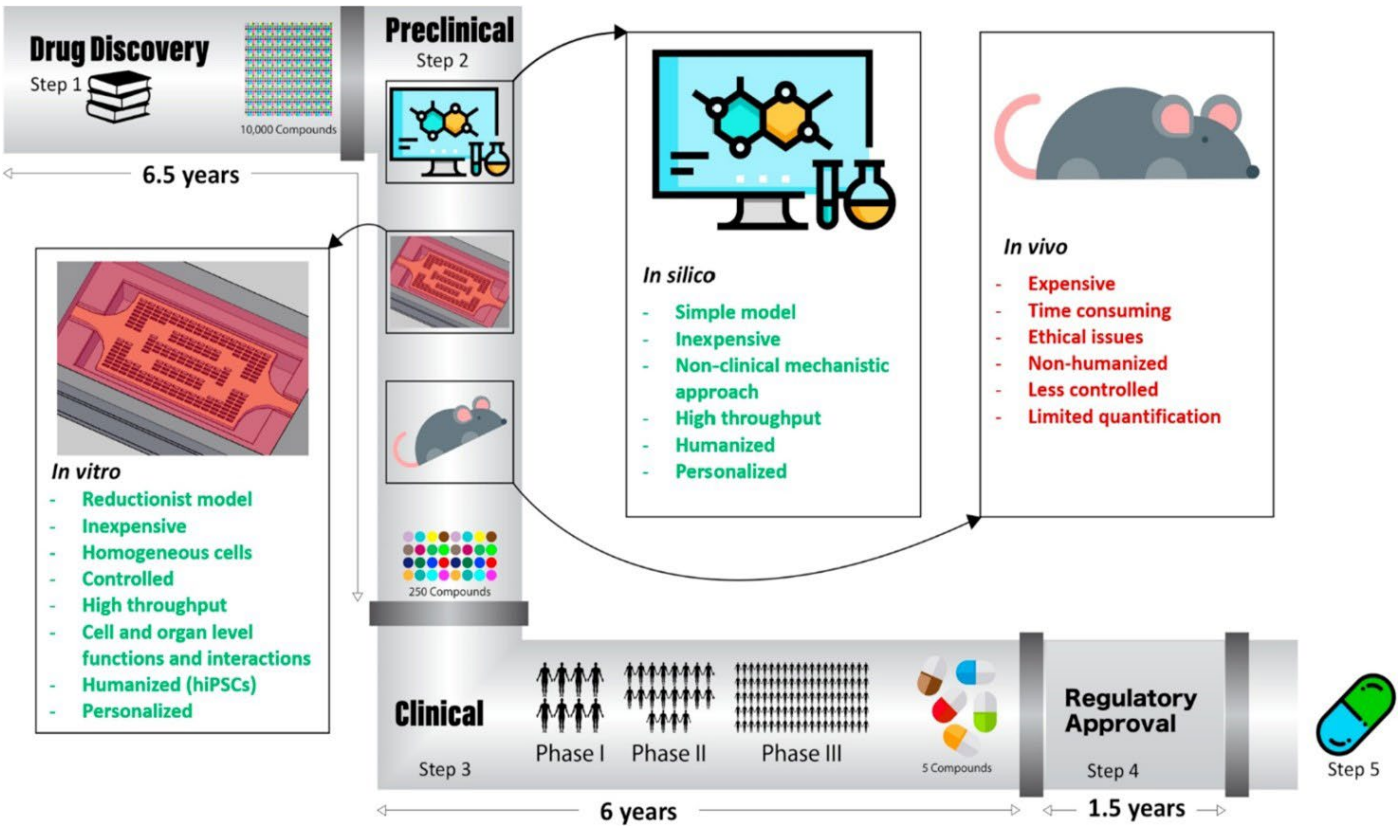

Figure 2: NDD pipeline. Reproduced from [25].

Table 2: Recent advancements in the development of new drugs for CVDs.

Drug/Drug class	Mechanism of action	Advantages over traditional treatments	Challenges
PCSK9 inhibitors (e.g., Evolocumab and Alirocumab)	Inhibit PCSK9 protein to enhance LDL receptor recycling, and leading to lower LDL cholesterol.	Significant LDL reduction beyond statins; effective in high-risk patients.	High-cost limits accessibility.
SGLT2 inhibitors (e.g., Empagliflozin and Dapagliflozin)	Reduce glucose reabsorption in the kidneys, and providing cardioprotective effects.	Proven to reduce heart failure hospitalizations and mortality in CVD patients.	Potential risk of urinary tract infections.
ARNI (Sacubitril/Valsartan)	Combines neprilysin inhibition with angiotensin receptor blockade for heart failure treatment.	Superior to ACE inhibitors in reducing heart failure progression and mortality.	Risk of hypotension and hyperkalemia.
Inclisiran	RNA-based therapy that inhibits PCSK9 production, and reducing LDL cholesterol levels.	Long-lasting effects with fewer injections required.	Limited long-term safety data available.
Omecamtiv mecarbil	Activates cardiac myosin to enhance cardiac contractility in heart failure patients.	Improves cardiac output without increasing oxygen demand.	Narrow therapeutic window; requires careful monitoring.
Bempedoic acid	Inhibits cholesterol synthesis upstream of HMG-CoA reductase, and lowering LDL cholesterol.	Suitable for statin-intolerant patients.	Risk of tendon rupture and hyperuricemia.
Novel anticoagulants (e.g., Factor XI Inhibitors)	Target factor XI in the clotting cascade to reduce thrombosis risk with less bleeding.	Reduced bleeding risk compared to warfarin and direct oral anticoagulants.	Still under investigation in clinical trials.
Gene therapy	Targets specific genes involved in lipid metabolism or cardiac repair.	Potential for long-term or permanent correction of CVD risk factors.	High cost and complex delivery systems.
mRNA-based therapies	Use mRNA to produce therapeutic proteins for CV protection.	Rapid development and potential customization for specific CVDs.	Limited clinical validation and scalability.

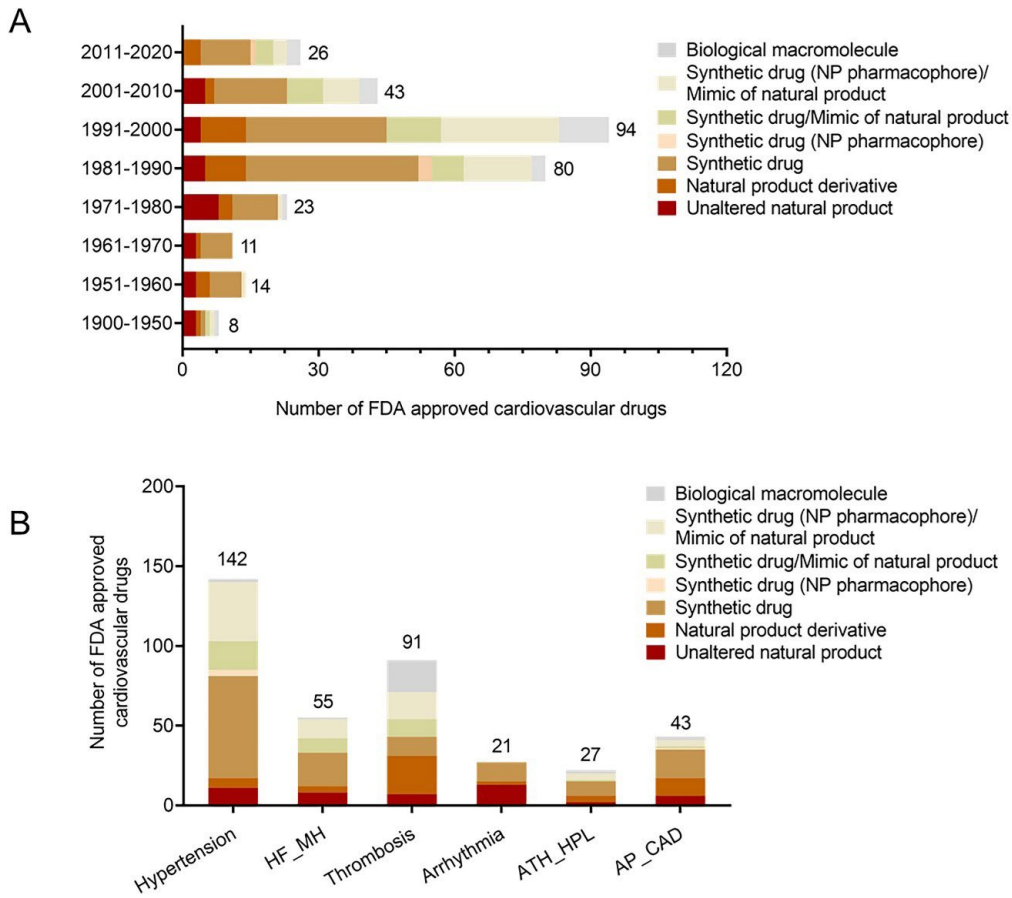

Figure 3: CVD drugs approved by FDA from 1900 to 2020. **(A)** Time to market distribution of FDA approved CV drugs. **(B)** Distribution of drugs for the treatment of 6 major CVDs including hypertension, heart failure and myocardial hypertrophy (HF_MH), thrombosis, arrhythmia, atherosclerosis and hyperlipidemia (ATH_HPL), and angina pectoris and CAD (AP_CAD). Reproduced from [29].

sharply with the rise in new drug approvals in oncology, which saw an increase from 2 - 11 new molecular entities in 2019 (Figure 3) [29]. However, recent advancements in drug development, including SGLT2 inhibitors and PCSK9 inhibitors, have shown promise in enhancing efficacy and safety, marking a new era in CVD management (Table 3).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as inclisiran, have emerged as a significant advancement in the treatment of hypercholesterolemia and atherosclerotic CVD. These agents work by enhancing the clearance of LDL cholesterol from the bloodstream, thereby reducing CV events and mortality. Inclisiran, a small interfering RNA, targets PCSK9 production, offering a novel approach with a favorable safety profile, especially in older patients [24, 37]. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, such as

Table 3: Selected clinical trials highlighting NDDs for CVDs.

Trial name	Drug	Objective	Patient details	Outcome	Confidence Interval (CI)
EMPA-REG OUTCOME [30]	Empagliflozin (SGLT2 inhibitor)	To evaluate the CV safety of empagliflozin in patients with type 2 diabetes and high CV risk.	Patients with type 2 diabetes and established CV (n = 7,020).	Reduced CV death by 38% and all-cause mortality by 32%.	CV death HR: 0.62 (95% CI: 0.49 - 0.77; p < 0.001); all-cause HR: 0.68 (95% CI: 0.57 - 0.82; p < 0.001).
FOURIER [31]	Evolocumab (PCSK9 inhibitor)	To assess the impact of LDL cholesterol reduction on CV outcomes in high-risk patients on statins.	Patients with atherosclerotic CVD and LDL cholesterol ≥70 mg/dl despite statin therapy (n = 27,564).	Reduced primary endpoint by 15% and key secondary endpoint by 20%.	Primary endpoint HR: 0.85 (95% CI: 0.79 - 0.92; p < 0.001); secondary HR: 0.80 (95% CI: 0.73 - 0.88; p < 0.001).
DECLARE-TIMI 58 [32]	Dapagliflozin (SGLT2 inhibitor)	To evaluate CV outcomes of dapagliflozin in type 2 diabetes with or at risk for CVD.	Patients with type 2 diabetes, with or without established CVD (n = 17,160).	Reduced CV death or HF hospitalization by 17%.	HR: 0.83 (95% CI: 0.73 - 0.95; p = 0.005).
DAPA-HF [33]	Dapagliflozin (SGLT2 inhibitor)	To investigate the efficacy of dapagliflozin in heart failure with reduced ejection fraction (HFrEF).	Patients with HFrEF (ejection fraction ≤40%), with or without type 2 diabetes (n = 4,744).	Reduced composite of worsening HF or CV death by 26%.	HR: 0.74 (95% CI: 0.65 - 0.85; p < 0.001).
REDUCE-IT [34]	Icosapent ethyl (EPA derivative)	To assess the effect of icosapent ethyl on CV risk in patients with elevated triglycerides on statins.	Patients with established CVD or diabetes with additional risk factors and elevated triglycerides (n = 8,179).	Reduced primary endpoint by 25% and key secondary endpoint by 26%.	Primary HR: 0.75 (95% CI: 0.68 - 0.83; p < 0.001); secondary HR: 0.74 (95% CI: 0.65 - 0.83; p < 0.001).
VERTIS CV [35]	Ertugliflozin (SGLT2 inhibitor)	To evaluate the CV safety of ertugliflozin in patients with type 2 diabetes and CVD.	Patients with type 2 diabetes and established CVD (n = 8,246).	Non-inferior to placebo for major adverse CV events; no superiority demonstrated.	HR: 0.97 (95% CI: 0.85 - 1.11; p < 0.001 for non-inferiority).
SOLOIST-WHF [36]	Sotagliflozin (SGLT1 and SGLT2 inhibitor)	To determine the efficacy of sotagliflozin in patients with diabetes and worsening HF.	Patients with type 2 diabetes and recent hospitalization for worsening HF (n = 1,222).	Reduced CV deaths and HF hospitalizations by 33%.	HR: 0.67 (95% CI: 0.52 - 0.85; p < 0.001).

dapagliflozin, have become integral in the management of heart failure, independent of left ventricular ejection fraction. Initially developed for type 2 diabetes, have shown substantial benefits in heart failure management, independent of diabetes status. They reduce CV mortality and hospitalization for heart failure, making them a cornerstone in heart failure treatment [24, 38, 39]. Mavacamten is a first-in-class drug approved for the treatment of obstructive hypertrophic cardiomyopathy. It works by modulating cardiac myosin, thereby improving cardiac function and symptoms in affected patients [38, 39]. Zilebesiran, an investigational agent, targets angiotensinogen to lower blood pressure, representing a potential new class of antihypertensive drugs [40]. Ivabradine is used as an adjunctive therapy in heart failure, has shown to improve heart rate control, which is crucial in managing heart failure symptoms and reducing hospital admissions [39].

Angiotensin-neprilysin inhibitors, like sacubitril/valsartan, have emerged as effective treatments for heart failure, providing superior outcomes compared to traditional ACE inhibitors [39]. Advances in understanding platelet activation have led to the development of new antiplatelet agents that aim to reduce thrombotic events with minimal bleeding risk. These agents are still in early clinical trials but hold promise for improving outcomes in patients with atherothrombotic diseases [41].

Emerging biological therapies, including gene therapy and RNA-based treatments, offer potential for repairing and regenerating damaged CV tissues. Although these therapies are in various stages of clinical validation, they represent a groundbreaking approach to CVD treatment [24]. siRNA therapies, such as olpasiran and patisiran, target specific genetic pathways involved in CVDs. Olpasiran reduces lipoprotein(a) levels, while patisiran improves outcomes in transthyretin amyloidosis-related heart failure [40].

The repurposing of existing drugs into fixed-dose combinations has shown promise in improving treatment adherence and outcomes. Examples include combinations for heart failure, atherosclerotic CVD, and Marfan syndrome [38]. Several investigational drugs are in development, targeting novel pathways such as advanced-glycation end products, arterial calcification, and the renin-angiotensin system. These drugs aim to address isolated systolic hypertension and other forms of vascular aging [42].

The development of new drugs for CVDs is witnessing significant advancements, driven by innovative therapeutic strategies and novel drug delivery systems. These advancements aim to address the limitations of traditional therapies and improve patient outcomes. The current trends in this field include the introduction of new pharmacological agents, the exploration of advanced biological therapies, and the development of novel drug delivery systems. These efforts are complemented by personalized medicine approaches and the integration of digital health technologies, which collectively promise to transform CVD management.

New Drugs in Valve Disease

Valve diseases, such as aortic stenosis and mitral regurgitation, have witnessed groundbreaking advancements through clinical trials focused on new drug and device developments. The PARTNER 3 trial assessed transcatheter aortic valve replacement (TAVR) in 1,000 low-surgical-risk patients with severe aortic stenosis. The trial demonstrated that TAVR was superior to surgical aortic valve replacement (SAVR) in reducing the composite endpoint of death, stroke, or rehospitalization at one year (HR: 0.54; 95% CI: 0.37 - 0.79) [43]. In the COAPT trial, transcatheter mitral valve repair (MitraClip) was evaluated in 614 patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation. MitraClip significantly reduced hospitalization for heart failure and all-cause mortality at 24 months (HR for hospitalization: 0.53; 95% CI: 0.40 - 0.70), providing a minimally invasive alternative for high-risk patients [44].

The EVEREST II trial investigated the safety and efficacy of the MitraClip device versus surgical repair in 279 patients with grade 3+ or 4+ mitral regurgitation. While surgery was more effective in reducing mitral regurgitation, the MitraClip had a better safety profile

and comparable clinical outcomes (success rate difference: -31% to -1%; 95% CI) [45]. The REPRISE III trial examined the Lotus valve system in 912 high-risk patients with severe aortic stenosis, showing non-inferiority to a bioprosthetic valve for effectiveness at one year (difference in rates: -0.4%; 95% CI: -6.0% to 5.2%) [46]. Lastly, the SURTAVI trial enrolled 1,746 intermediate-risk patients with severe aortic stenosis to compare TAVR and SAVR. The study found that TAVR was non-inferior to SAVR for the primary endpoint of death or disabling stroke at 24 months (HR: 0.89; 95% CI: 0.73 - 1.09) [47].

These trials highlight the evolution of transcatheter therapies in valve disease management, offering effective, less invasive options for diverse patient populations, including those at low, intermediate, or high surgical risk. The findings have not only expanded treatment possibilities but also improved outcomes and quality of life for patients previously deemed unsuitable for traditional surgical approaches.

New Drugs in CAD

Few clinical trials have explored novel pharmacological interventions for CAD, aiming to enhance patient outcomes through innovative therapeutic strategies. The BEAUTIFUL study evaluated ivabradine in over 10,917 patients with stable CAD and left ventricular dysfunction (ejection fraction < 40%). While ivabradine did not significantly reduce the primary composite endpoint of CV death, hospitalization for acute myocardial infarction, or worsening heart failure, a prespecified subgroup with baseline heart rates exceeding 70 bpm experienced notable reductions in coronary events by 22% ($p = 0.023$), fatal and nonfatal myocardial infarction by 36% ($p = 0.001$), and coronary revascularization by 30% ($p = 0.016$) [48].

The SIGNIFY trial involved 19,102 patients with stable CAD and elevated heart rates (>70 bpm), assessing ivabradine's efficacy. Although ivabradine effectively reduced heart rates, it did not significantly improve secondary outcomes across patient groups. However, comparisons with the SHIFT study indicated a reduction in CV death or hospitalization, suggesting potential benefits in specific contexts [49, 50].

The SHIFT study focused on patients with chronic heart failure, demonstrating that ivabradine significantly reduced the risk of the primary composite endpoint hospitalization for worsening heart failure or CV death by 18% ($p < 0.0001$) compared to placebo, alongside optimal therapy. These benefits were observed after three months of treatment, with consistent improvements across various subgroups [50]. The COURAGE trial compared percutaneous coronary intervention (PCI) with optimal medical therapy in patients with stable CAD. The study found no significant difference in the primary outcome of death or nonfatal myocardial infarction between the two groups, suggesting that PCI may not provide additional benefits over medical therapy alone in such patients [51]. The ALECARDIO trial assessed the dual PPAR agonist aleglitazar in 7,226 patients with type 2 diabetes mellitus and a recent acute coronary syndrome. The trial concluded that aleglitazar did not offer CV benefits, highlighting the challenges in developing effective therapies for this patient population [52].

These trials underscore the complexities of developing effective pharmacological treatments for CHD, emphasizing the need for targeted therapies tailored to specific patient subgroups to achieve optimal outcomes.

New Drugs in Imaging

Recent clinical trials have explored the integration of novel imaging techniques with pharmacological interventions to enhance the diagnosis and management of CVDs. The PROMISE trial evaluated 10,003 patients with stable chest pain, comparing anatomical testing using coronary computed tomography angiography to functional stress testing. The objective was to determine which strategy more effectively guides clinical decision-making. Results indicated no significant difference in the primary endpoint a composite of death, myocardial infarction, hospitalization for unstable angina, or major procedural complication between the two groups. This suggests that coronary computed tomography angiography is a viable alternative to traditional stress testing in this patient population [53].

The ULTIMATE trial assessed the impact of intravascular ultrasound (IVUS)-guided PCI compared to angiography-guided PCI in 1,448 patients with CAD. The study aimed to evaluate whether IVUS guidance could reduce target vessel failure rates. At three years, the IVUS-guided group exhibited a significantly lower incidence of target vessel failure (2.9%) compared to the angiography-guided group (5.4%), with a hazard ratio of 0.53 (95% CI: 0.31 - 0.92), indicating that IVUS guidance enhances long-term outcomes in PCI [54].

The SELECT trial investigated the CV outcomes of semaglutide, a glucagon-like peptide-1 receptor agonist, in patients with type 2 diabetes at high CV risk. The objective was to assess whether semaglutide could reduce major adverse CV events. Findings revealed that once-weekly subcutaneous semaglutide was associated with a decreased risk of major adverse CV events, comprising CV death, nonfatal myocardial infarction, and stroke, compared with placebo [55].

These trials underscore the evolving role of advanced imaging modalities in conjunction with pharmacotherapy, highlighting their potential to refine treatment strategies and improve patient outcomes in CV care.

Current Challenges and Future Directions

The development of new pharmacological entities for the prevention and treatment of CVDs faces several challenges (Table 4), yet it also presents promising future directions. Despite advancements in traditional therapies, the rising prevalence of CVDs necessitates innovative approaches to improve patient outcomes. Emerging pharmacological treatments, such as PCSK9 and SGLT2 inhibitors, have shown potential in reducing CV events, but the field continues to grapple with regulatory, economic, and ethical barriers. Future directions include the exploration of advanced biological therapies, personalized medicine, and novel drug delivery systems, which could revolutionize CVD management.

Current challenges

- Regulatory and economic barriers: The development of new CV drugs is hindered by stringent regulatory requirements and high costs, which can deter investment from the pharmaceutical industry. The time and expense involved in bringing a new drug from discovery to market are significant, reducing incentives for innovation despite the large potential market size for CVD treatments [56].

- Suboptimal pharmacotherapy: Current pharmacotherapy for CVDs remains inadequate, with many patients not achieving optimal outcomes. This highlights the need for more effective and safer pharmacological strategies, as existing treatments often fail to address the complex pathophysiology of CVDs [38, 57].

- Complexity of CVD pathophysiology: The multifaceted

nature of CVDs, involving genetic, lifestyle, and environmental factors, complicates the development of targeted therapies. This complexity necessitates a deeper understanding of disease mechanisms and the identification of novel therapeutic targets [58, 59].

Future directions

- Advanced biological therapies: Gene therapy, stem cell therapy, and RNA-based treatments offer groundbreaking potential for repairing and regenerating damaged CV tissues. These therapies are in various stages of clinical validation and could fundamentally change the CVD treatment landscape [24, 60].

- Personalized medicine: The integration of genetic profiling and biomarker identification into CVD management allows for tailored therapies that enhance treatment efficacy and minimize adverse effects. This approach is supported by advancements in precision medicine, which aim to align treatments with individual patient profiles [24].

- Innovative drug delivery systems: Emerging technologies, such as nanoparticle delivery mechanisms and novel genetic vectors, are being developed to improve the targeting and efficacy of CV drugs. These systems aim to address the shortcomings of existing pharmacological tools by enhancing drug delivery to specific subcellular compartments [59].

- Repurposing existing drugs: The repurposing of existing medications for new indications, such as treating obstructive hypertrophic cardiomyopathy and heart failure, is a promising strategy. This approach leverages the known safety profiles of existing drugs to expedite the development of new treatments [38, 57].

While the development of new pharmacological entities for CVDs faces significant challenges, the field is also ripe with opportunities for innovation. The integration of advanced biological therapies, personalized medicine, and novel drug delivery systems holds the potential to transform CVD management. However, addressing regulatory, economic, and ethical barriers remains crucial to realizing these advancements. By fostering interdisciplinary collaboration and prioritizing research, the future of CVD treatment could see a shift towards more personalized, effective, and accessible care.

Conclusions

The future holds significant promise for advancing therapeutic strategies. Innovations in precision medicine, advanced biological therapies, and novel drug delivery systems are reshaping the landscape of CVDs treatment. These approaches aim to address unmet medical needs, improve patient outcomes, and reduce mortality rates associated with these complex diseases. Emerging therapies, such as PCSK9 inhibitors, SGLT2 inhibitors, and RNA-based treatments, highlight the potential to transform clinical practices, providing more effective and safer alternatives to traditional medications. The integration of digital health technologies and genetic profiling further emphasizes the move towards personalized medicine, enabling tailored treatment strategies.

Despite these advancements, challenges remain in the development and implementation of novel therapies. Regulatory and economic barriers, the complexity of CVDs pathophysiology, and the high costs of drug development pose significant hurdles. Moreover, ensuring global accessibility and affordability of these therapies is critical to addressing health disparities, particularly in low- and middle-income countries where the burden of CVDs is disproportionately high. Overcoming these obstacles requires coordinated efforts among researchers, clinicians, policymakers, and industry stakeholders to streamline drug development processes and foster innovation.

Looking ahead, the convergence of cutting-edge technologies, interdisciplinary collaboration, and a patient-centric approach promises to revolutionize the management of CVDs. By addressing current challenges and leveraging opportunities for innovation, the future of CVD treatment lies in achieving more precise, effective, and equitable healthcare solutions. These advancements will not only improve survival rates but also enhance the quality of life for millions of individuals worldwide affected by CVDs.

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Conflict of Interest

None.

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