Review

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A New Era of Disease-Modifying Pharmacotherapy in Cardiovascular Medicine

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Abstract

Background/Objectives: Cardiovascular disease (CVD) remains the leading cause of global morbidity and mortality. Although substantial therapeutic advances have been made over the past decades, the years 2024–2025 mark a turning point characterized by the emergence of mechanistically innovative, disease-modifying therapies that go beyond conventional risk-factor control. This narrative review aims to synthesize transformative pharmacological and regulatory milestones reshaping contemporary cardiovascular practice and establishing a roadmap for precision medicine implementation. **Methods:** We conducted a comprehensive narrative review of pivotal clinical trials, regulatory approvals and mechanistic frameworks for emerging cardiovascular therapeutics approved or under investigation during 2024–2025. The analysis encompasses novel agents across multiple disease domains including transthyretin amyloid cardiomyopathy (ATTR-CM), resistant hypertension, dyslipidemia, pulmonary arterial hypertension, hypertrophic cardiomyopathy, and cardiometabolic disease, with emphasis on their molecular targets, clinical efficacy, and practice-changing implications. **Results:** Key therapeutic advances include *acoramidis* and *vutrisiran* for ATTR-CM demonstrating significant reductions in cardiovascular mortality and hospitalization; *aprocitentan* for resistant hypertension alongside investigational angiotensinogen silencers and aldosterone synthase inhibitors; RNA-based dyslipidemia therapies (*inclisiran*, *lepodisiran*, *pelacarsen*, *olezarsen*) enabling durable lipid control; *sotatercept* introducing disease modification in pulmonary arterial hypertension; cardiac myosin inhibitors (*mavacamten*, *aficamten*) transforming hypertrophic cardiomyopathy management; and GLP-1 receptor agonist *semaglutide* receiving FDA approval for cardiovascular risk reduction in obesity. These agents collectively demonstrate mechanistic targeting, genetic precision, and disease modification beyond traditional risk-factor management. **Conclusions:** Cardiovascular medicine is transitioning from symptomatic palliation toward an era defined by molecular pathway targeting, individualized therapy, and durable disease control, establishing a new paradigm for precision cardiovascular care.

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1. Introduction

Cardiovascular disease (CVD) persists as the foremost contributor to global morbidity and mortality, despite decades of pharmacological advances [1]. The burden of heart failure, atherosclerosis, hypertension, cardiometabolic disorders, amyloid cardiomyopathies, and pulmonary vascular disease continues to grow, driven by population ageing, obesity, and risk factor accrual [2]. In this context, the period 2024-2025 has witnessed several first-in-class and mechanistically novel therapies, as well as expanded indications, that promise to alter the landscape of CVD prevention and treatment.

This narrative review is motivated by the need to synthesize these recent developments, beyond incremental improvements, in order to understand how they may shift clinical paradigms. Among these, some stand out. The approval of acoramidis (Attruby™), a near-complete (>90%) transthyretin (TTR) stabilizer for treatment of wild-type and hereditary transthyretin-mediated cardiomyopathy (ATTR-CM), marking a major advance in amyloidosis management [3]. In the pivotal ATTRibute-CM Phase 3 trial, acoramidis significantly reduced cardiovascular death and hospitalization in patients with ATTR-CM over 30 months [4]. Another innovation is aprocitentan (Tryvio™), a dual endothelin A/B receptor antagonist approved in 2024 for resistant hypertension; hypertension inadequately controlled despite multi-drug regimens [5]. Derived from the PRECISION trial, aprocitentan represents the first oral antihypertensive in decades acting via a novel pathway [6]. A third is the expanded indication for semaglutide: in early 2024, the U.S. Food and Drug Administration (FDA) granted a label expansion for adults with obesity or overweight and established CVD, to reduce risk of major adverse cardiovascular events (MACE), cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke [7]. These developments are not without precedent; however, their novelty lies in mechanistic diversity, broader disease targets, and shifting from risk factor modification to disease-modifying treatments. In amyloidosis, the priority has been advancing from stabilizers or silencers toward earlier detection and improved prognostication [8]. Concerning hypertension and metabolic risk, adding new classes (e.g. endothelin antagonism) or expanding existing ones (e.g. GLP-1 receptor agonists) suggest opportunities to target patients with unmet needs [9,10].

In this review, we aim to: (1) delineate the recent therapeutics and regulatory approvals in 2024-2025 that most substantially influence the prevention or management of CVD; (2) examine the mechanistic underpinnings of these innovations; (3) assess their clinical trial evidence, benefits, and limitations; and (4) project directions for implementation, diagnostic refinement, long-term safety, and health system adoption. Through this synthesis, we intend to inform clinicians, researchers, and policymakers about how cardiovascular practice may evolve in this new era.

2. Materials and Methods

We followed the Scale for the Assessment of Narrative Review Articles (SANRA) to enhance methodological rigor (aim; literature search; referencing; scientific reasoning; appropriate presentation; and interpretive balance) [11].

Literature Search

We searched PubMed/MEDLINE, Embase, and Cochrane Library (Jan 2020–Sep 2025) using combinations of controlled vocabulary and keywords: “cardiovascular pharmacology”, “transthyretin cardiomyopathy”, “vutrisiran”, “acoramidis”, “lipoprotein(a)”, “pelacarsen”, “lepodisiran”, “siRNA hypertension”, “zilebesiran”, “aldosterone synthase inhibitor”, “baxdrostat”, “GLP-1 cardiovascular outcomes”, “inclisiran label”, “apoC-III inhibitor”, “olezarsen”, “angiopoietin-like 3”, “sotatercept”, “pulmonary arterial hypertension”, “cardiac myosin inhibitor”, “mavacamten”, “aficamten”. We also reviewed recent guidelines/labels and regulatory

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communications, and high-impact conference outputs where peer-reviewed publications were pending. *Eligibility and selection*. Priority was given to randomized trials, meta-analyses, large prospective cohorts, pivotal open-label extensions, drug labels, and regulatory summaries. We included high-quality narrative reviews for context and mechanistic framing. Pediatric-only studies and non-cardiovascular indications were excluded. *Appraisal and synthesis*. We qualitatively appraised study design, endpoints (including "hard" outcomes), external validity, safety, and regulatory status. Given the narrative design, no pooled quantitative synthesis was attempted; instead, we triangulated across trial data, labels, and expert reviews to maintain interpretive balance and explicitly note uncertainty. *Referencing and transparency*. References are recent, traceable (with DOIs where available), and include regulatory documents for factual accuracy. We indicate where evidence remains preliminary or where outcome data are pending, consistent with SANRA's emphasis on scientific reasoning and appropriate presentation. All the found publications were grouped in 8 different categories (see the Results section, paragraphs 3.1 to 3.8.).

3. Results

3.1. Transthyretin Amyloid Cardiomyopathy (ATTR-CM): Stabilizers and Silencers

ATTR-CM is a progressive, life-threatening condition caused by the deposition of misfolded transthyretin protein in the myocardium [12]. Both wild-type and hereditary forms result in restrictive cardiomyopathy, heart failure, and premature mortality. Two complementary mechanistic approaches have emerged: transthyretin (TTR) stabilization prevents protein misfolding and amyloid formation, while TTR silencing reduces hepatic production of the precursor protein through RNA interference.

Acoramidis. Acoramidis is a near-complete (>90%) transthyretin stabilizer that binds to the TTR tetramer, preventing its dissociation into monomers and subsequent misfolding into amyloid fibrils [3], (Figure 1A). This mechanism directly addresses the pathophysiology of myocardial amyloid deposition. In late 2024, the U.S. FDA approved acoramidis (Attruby™) for the treatment of ATTR-CM, encompassing both wild-type and variant forms [7]. This approval was supported by pivotal Phase 3 trial data and long-term extension results, which collectively demonstrated significant reductions in cardiovascular death and cardiovascular-related hospitalizations, along with sustained improvements in functional capacity and quality of life over approximately 30 months of follow-up [13,14]. The therapeutic effect reflects its mechanism as a near-complete TTR stabilizer, which prevents misfolding and amyloid fibril deposition in the myocardium.

Vutrisiran. Vutrisiran is a subcutaneous small interfering RNA (siRNA) therapy that targets hepatic TTR mRNA, achieving sustained suppression (>80%) of circulating TTR protein production (Figure 1A). By reducing substrate availability, vutrisiran prevents new amyloid formation. In 2025, based on important studies, the FDA expanded the indication of vutrisiran (AMVUTTRA™) to include ATTR-CM. Evidence from the HELIOS-B trial demonstrated clinically meaningful reductions in all-cause and cardiovascular mortality, as well as fewer hospitalizations compared with placebo [15,16]. Together, TTR stabilization (acoramidis) and TTR silencing (vutrisiran, with *eplontersen* in development) represent complementary, disease-modifying strategies that are reshaping management across the amyloidosis spectrum. Stabilizers may be preferred in cardiac-predominant disease, while silencers offer advantages in mixed phenotypes with neurologic involvement. Head-to-head trials are needed to define optimal sequencing. Ongoing research focuses on earlier diagnosis through biomarker discovery, imaging refinement (bone scintigraphy, cardiac MRI with native T1 mapping), and genetic testing implementation. Combination therapies pairing stabilizers with silencers are under investigation.

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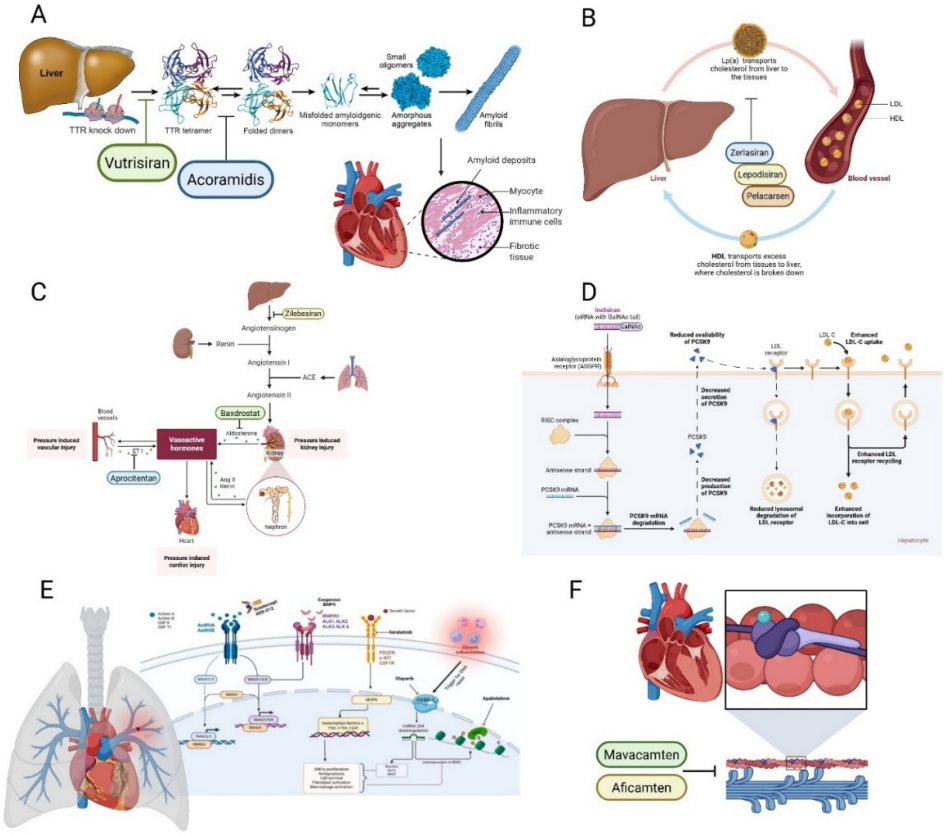

Figure 1. Emerging targeted therapies in cardiovascular and systemic cardiometabolic diseases. (A) Therapeutic strategies for transthyretin amyloid cardiomyopathy (ATTR-CM), including gene silencers (vutrisiran) and stabilizers (acoramidis), which prevent misfolding and deposition of amyloid fibrils in myocardial tissue. (B) Agents targeting lipoprotein(a) metabolism—such as pelacarsen, lepodisiran, and zerlasiran—reduce hepatic production and circulating Lp(a), thereby lowering residual cardiovascular risk. (C) Novel antihypertensive approaches including zilebesiran (an siRNA targeting angiotensinogen), aprocitentan (dual endothelin A/B receptor antagonist), and baxdrostat (aldosterone synthase inhibitor), aimed at upstream modulation of the renin–angiotensin–aldosterone system and vascular injury pathways. (D) Mechanism of PCSK9 inhibition via monoclonal antibodies or siRNA, leading to reduced PCSK9 expression, enhanced LDL receptor recycling, and lowered LDL-cholesterol levels. (E) Pathophysiological mechanisms and therapeutic targets in pulmonary arterial hypertension (PAH), including modulation of BMPR2/TGF-β signaling and restoration of endothelial balance with agents such as sotatercept. (F) Cardiac myosin inhibitors, such as mavacamten and aficamten, targeting sarcomeric hypercontractility in hypertrophic cardiomyopathy by reducing excessive actin–myosin cross-bridge formation.

3.2. Lipoprotein(a) [Lp(a)] Targeting: Antisense and siRNA

Elevated lipoprotein(a) [Lp(a)] is a genetically determined, independent risk factor for atherosclerotic cardiovascular disease (ASCVD), aortic stenosis, and thrombotic events [17]. Approximately 20-25% of the population has elevated Lp(a) levels (>50 mg/dL), which do not respond to statins or lifestyle modification. This important form of dyslipidemia has recently gained new and promising therapeutic perspectives [18,19]. Both antisense oligonucleotides (ASOs) and siRNAs target hepatic apolipoprotein(a) mRNA, reducing Lp(a) synthesis and circulating levels. These RNA-based therapies offer sustained effects with infrequent dosing.

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Lepodisiran, is a subcutaneous siRNA that induces degradation of apolipoprotein(a) mRNA in hepatocytes through RNA interference, leading to profound and durable Lp(a) reduction (Figure 1B). This drug demonstrated an approximately 94% sustained reduction in circulating Lp(a) levels at 6 months in Phase 2 trials, with an acceptable safety and tolerability profile [20]. In parallel, *pelacarsen*, a monthly subcutaneous antisense oligonucleotide that binds to apolipoprotein(a) mRNA, triggering its degradation and reducing Lp(a) production, is undergoing a large Phase 3 cardiovascular outcomes trial [Lp(a)HORIZON] designed to determine its impact on major adverse cardiovascular events (MACE) [21]. Moreover, additional siRNA and ASO agents, including *zerlasiran* (SLN360), are progressing through Phase 2 development, potentially offering greater flexibility in dosing schedules and enhanced durability of Lp(a) suppression [22].

These drugs will potentially transform cardiovascular prevention by addressing a major residual risk factor. Infrequent dosing (quarterly to biannually) may improve adherence compared with daily oral therapies. Key questions include: patient selection criteria (primary versus secondary prevention, Lp(a) thresholds), and long-term safety of profound Lp(a) suppression. Finally, integration with existing lipid-lowering strategies requires definition.

3.3. Hypertension: Upstream Modulation of the Renin-Angiotensin-Aldosterone System (RAAS) Axis

Resistant hypertension remains a major clinical challenge, contributing substantially to cardiovascular morbidity and mortality despite the availability of multiple therapeutic classes. Novel agents targeting upstream pathways of blood pressure regulation are generating considerable interest. Angiotensinogen siRNA reduces substrate availability for the entire RAAS cascade, while aldosterone synthase inhibition selectively blocks the final step of aldosterone production without affecting cortisol synthesis.

Zilebesiran, an investigational siRNA directed against hepatic angiotensinogen mRNA (Figure 1C), has demonstrated sustained reductions in both daytime and nighttime blood pressure with infrequent dosing in early-phase studies, although longer-term efficacy and safety remain under active investigation [23,24]. A Phase 3 program planned to initiate in 2025 and if confirmed in Phase 3, *zilebesiran* could revolutionize adherence by shifting from daily to quarterly or semi-annual dosing, potentially improving long-term cardiovascular outcomes in resistant hypertension. Similarly, *baxdrostat*, a highly selective aldosterone synthase inhibitor (Figure 1C), produced clinically meaningful improvements in systolic blood pressure in patients with uncontrolled or resistant hypertension in the Phase 3 BaxHTN trial, yielding placebo-adjusted reductions of approximately 9–10 mmHg and significantly higher attainment of target blood pressure goals [25,26]. Unlike non-selective inhibitors, baxdrostat does not affect cortisol production (CYP11B1), avoiding adrenal insufficiency risk. These upstream-acting agents promise simplified dosing schedules, improved adherence, and potentially more consistent long-term blood pressure control.

Aprocitentan, although not an upstream modulator of the RAAS, is a dual endothelin A/B receptor antagonist (Tryvio™), (Figure 1C), that received FDA approval in 2024 for the treatment of resistant hypertension [5]. This approval was based on the results of the PRECISION trial and provides a novel therapeutic option for this difficult-to-treat population [6]. *Zilebesiran* (infrequent dosing, comprehensive RAAS blockade) and *baxdrostat* (oral daily dosing, selective aldosterone inhibition) offer complementary approaches. Patient-specific factors (adherence potential, hyperkalemia risk, preference for oral vs. subcutaneous therapy) will guide selection. Long-term cardiovascular outcomes data, optimal patient phenotyping (plasma renin activity, aldosterone levels), and positioning within treatment algorithms remain to be established. Combination strategies with existing antihypertensives require investigation.

3.4. Heart Failure: Consolidation and Refinement

HF management has evolved from symptomatic palliation to evidence-based, guideline-directed medical therapy (GDMT) that modifies disease progression. Standards of care for HF, including angiotensin receptor–neprilysin inhibitors (ARNI), sodium–glucose cotransporter 2

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(SGLT2) inhibitors, β-blockers, and mineralocorticoid receptor antagonists (MRAs), continue to evolve, with recent syntheses emphasizing the importance of individualized sequencing and patient-tailored regimens to optimize outcomes [27]. In parallel, regenerative approaches such as mesenchymal stem cell (MSC) therapies remain under investigation. Preliminary results suggest potential improvements in ventricular function and symptoms, but inconsistent methodologies, small sample sizes, and short follow-up durations limit definitive conclusions, underscoring the need for larger, rigorously designed trials [28]. Furthermore, metabolic modulators, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are emerging as valuable adjuncts, intersecting with both HF and renal protection strategies, thereby broadening the therapeutic landscape [29,30]. The focus has shifted from choosing the right therapies to implementing them effectively in real-world practice, optimizing sequencing, accelerating titration, and overcoming clinical inertia to ensure timely and comprehensive treatment.

3.5. Lipid and Triglyceride Modulation Beyond Statins

Despite widespread statin use, substantial residual ASCVD risk persists. Patients with familial dyslipidemias, statin intolerance, or inadequate LDL-C reduction on maximum tolerated therapy require additional options. Hypertriglyceridemia, particularly severe forms, also necessitates targeted intervention [31]. A growing armamentarium of non-statin therapies now targets diverse mechanisms of lipid metabolism, offering options for patients with statin intolerance, familial dyslipidemias, or those unable to achieve optimal risk reduction on standard regimens. Non-statin lipid therapies target diverse mechanisms: PCSK9 inhibition (antibodies and siRNA), intestinal cholesterol absorption blockade (*ezetimibe*), hepatic cholesterol synthesis inhibition (bempedoic acid), apolipoprotein C-III reduction (*olezarsen*), and ANGPTL3 inhibition (*evinacumab*).

Inclisiran, a siRNA against PCSK9, has emerged as a transformative therapy [32,33]. By silencing PCSK9 production, *inclisiran* increases hepatic LDL receptor expression and enhances LDL-C clearance from circulation (Figure 1D). The ORION Phase 3 program demonstrated sustained LDL-C reductions of approximately 50% with twice-yearly maintenance dosing (after initial doses at baseline and 3 months). The convenience of biannual dosing addresses adherence challenges inherent to daily oral therapies [32,33]. In 2024, a U.S. label update positioned it as a potential first-line monotherapy for hypercholesterolemia, reflecting its robust low-density lipoprotein cholesterol (LDL-C) lowering efficacy and the convenience of twice-yearly maintenance dosing. Long-term cardiovascular outcomes trials are ongoing to establish definitive benefit [34].

Bempedoic acid, a largely accepted drug [35], particularly when combined with *ezetimibe*, has further reinforced therapeutic strategies for statin-intolerant or high-risk patients, providing significant incremental LDL-C reduction and improved attainment of lipid targets [36]. Bempedoic acid is an oral prodrug that inhibits ATP citrate lyase, a key enzyme in hepatic cholesterol synthesis upstream of HMG-CoA reductase (the statin target). It is activated only in the liver, avoiding muscle-related adverse effects. The CLEAR Outcomes trial (N=13,970) demonstrated that bempedoic acid reduced MACE (cardiovascular death, MI, stroke, coronary revascularization) by 13% (hazard ratio 0.87, p=0.004) in statin-intolerant patients over a median of 3.4 years. LDL-C reduction averaged 21% [35].

For severe hypertriglyceridemia, the approval of *olezarsen*, an antisense oligonucleotide (ASO) targeting apolipoprotein C-III (apoC-III), represents a significant therapeutic advancement [37]. ApoC-III inhibits lipoprotein lipase and hepatic uptake of triglyceride-rich lipoproteins; its reduction enhances triglyceride clearance. The Phase 3 BALANCE trial in familial chylomicronemia syndrome (FCS) demonstrated triglyceride reductions of approximately 50-80%, with significant reductions in pancreatitis events. Monthly dosing provided sustained triglyceride control [38]. Additionally, angiopoietin-like 3 (ANGPTL3) inhibition, exemplified by *evinacumab*, continues to show value in refractory hypercholesterolemia, while investigational siRNA-based approaches against triglyceride-rich lipoproteins are advancing rapidly [39,40]. *Evinacumab* is a monoclonal antibody that inhibits angiopoietin-like protein 3 (ANGPTL3), a regulator of lipid metabolism. ANGPTL3 inhibition increases lipolysis and hepatic lipid uptake, reducing LDL-C, triglycerides, and Lp(a). *Evinacumab*

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demonstrated LDL-C reductions of 47-56% in patients with homozygous familial hypercholesterolemia (HoFH), a population with limited therapeutic options [39]. FDA approved for HoFH in 2021, *evinacumab* provides a lifeline for HoFH patients who fail maximal therapy. Investigational siRNA approaches targeting ANGPTL3 may extend this mechanism to broader populations [40]. Collectively, these agents broaden the landscape of lipid management much beyond statins, moving toward precision therapy tailored to individual metabolic and genetic profiles.

3.6. Pulmonary Arterial Hypertension (PAH): A First-In-Class TGF-β Superfamily Modulator

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder characterized by pulmonary vascular remodeling, elevated pulmonary artery pressures, and right heart failure. Despite advances with vasodilator therapies (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogs), disease progression remains a major challenge, with 5-year survival rates of approximately 60% [41]. In PAH, suppression of the BMPR2 pathway leads to an imbalance between pro-proliferative and anti-proliferative signals, resulting in pulmonary vascular smooth muscle cell proliferation and endothelial dysfunction.

Sotatercept targets the underlying pathobiology of PAH by modulating the transforming growth factor-β (TGF-β) superfamily signaling pathway [42]. Sotatercept is an activin receptor type IIA-Fc fusion protein that acts as a ligand trap, sequestering activins and growth differentiation factors (GDFs) that promote vascular remodeling (Figure 1E). By rebalancing TGF-β superfamily signaling, *sotatercept* inhibits pulmonary vascular smooth muscle cell proliferation and promotes vascular normalization [43]. The pivotal Phase 3 STELLAR trial (N=323) evaluated *sotatercept* as add-on therapy to background PAH treatment. At 24 weeks, *sotatercept* improved 6-minute walk distance (6MWD) by a mean of 40.8 meters compared with placebo ($p<0.001$), reduced pulmonary vascular resistance by 28% ($p<0.001$), and significantly delayed time to clinical worsening (hazard ratio 0.16, $p<0.001$). Benefits were sustained through 24 months of follow-up in extension studies [44]. Additional analysis (SPECTRA) demonstrated improvements in right ventricular function and exercise tolerance, key determinants of prognosis in PAH [45]. Common adverse events included thrombocytopenia (generally mild and reversible), increased hemoglobin (requiring monitoring), telangiectasias, and bleeding events. Careful monitoring and dose adjustments mitigate risks.

3.7. Cardiometabolic Therapies with Cardiovascular Outcome Benefits

Cardiometabolic disorders such as obesity, diabetes, and HF are tightly interlinked, amplifying cardiovascular risk and adverse outcomes [3]. Recent therapeutic innovations now target these overlapping pathways, offering disease-modifying benefits that extend beyond traditional glucose or weight control.

Metabolic Modulators: GLP-1 Receptor Agonists

The intersection of cardiometabolic disease and cardiovascular prevention has been redefined by recent therapeutic breakthroughs. *Semaglutide*, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), became in 2024 the first weight-loss medication granted an FDA indication specifically to reduce cardiovascular risk in adults with established CVD [7]. Evidence from the SELECT trial demonstrated a 20% relative risk reduction in major adverse cardiovascular events (MACE; hazard ratio 0.80), underscoring the dual benefits of obesity treatment and cardiovascular protection, and thereby bridging two traditionally distinct areas of management [46,47]. Beyond glucose control and weight loss, GLP-1 RAs exert direct cardiovascular effects including improved endothelial function, reduced inflammation, and favorable hemodynamic effects. While not specifically HF trials, SELECT (semaglutide 2.4 mg) demonstrated MACE reduction in patients with obesity and established CVD, many of whom had HF risk factors [48]. Dedicated HF outcomes trials are ongoing [29,30]. GLP-1 RAs are increasingly integrated into HF management for patients with obesity, diabetes, and cardiometabolic risk, representing convergence of metabolic and cardiovascular therapeutics [49]. Meanwhile, sodium–glucose cotransporter 2 (SGLT2) inhibitors continue to provide robust benefits in HF and renal protection across the spectrum of ejection fractions and comorbid phenotypes,

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consolidating their role as foundational cardiometabolic agents [50]. SGLT2 inhibitors improve HF outcomes through multiple mechanisms: natriuresis, metabolic shift toward ketone utilization, reduced myocardial fibrosis, and improved mitochondrial function. Benefits extend beyond HF with reduced ejection fraction (HFrEF) to HF with preserved ejection fraction (HFpEF) [51,52] and chronic kidney disease [53], establishing SGLT2 inhibitors as foundational cardiorenal protective agents. SGLT2 inhibitors are now indicated across the HF spectrum and in chronic kidney disease (CKD) regardless of diabetes status, fundamentally reshaping preventive cardiology [54]. Beyond the established drugs dapagliflozin and empagliflozin, newer agents such as *bexagliflozin* are expanding therapeutic options in diabetes and demonstrating promising signals of benefit relevant to HF populations [55]. Together, these advances highlight a paradigm shift in which metabolic therapies are increasingly positioned as integral cardiovascular disease-modifying treatments, blurring traditional boundaries between endocrinology, nephrology, and cardiology.

3.8. Hypertrophic Cardiomyopathy (HCM): Cardiac Myosin Inhibition

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder and a leading cause of sudden cardiac death in young adults [56]. Traditional management has relied on symptomatic therapies such as β-blockers, calcium channel blockers, or septal reduction procedures, yet disease-modifying pharmacological options have been limited. Cardiac myosin inhibitors selectively reduce the number of myosin heads in the thick filament available for actin binding, thereby decreasing sarcomeric contractility and ameliorating hypercontractility-driven LVOT obstruction. This represents the first disease-specific, mechanism-based pharmacotherapy for HCM.

Mavacamten, the first-in-class cardiac myosin inhibitor (Figure 1F), established a novel therapeutic paradigm by directly targeting the hypercontractility that underlies left ventricular outflow tract obstruction [57]. Key Trials include EXPLORER-HCM (N=251), *Mavacamten* improved peak oxygen consumption (pVO_2) by 1.4 mL/kg/min *versus* placebo ($p<0.001$), reduced LVOT gradients by 47 mmHg ($p<0.001$), and improved symptoms (NYHA class improvement in 65% vs. 31%, $p<0.001$) over 30 weeks in symptomatic obstructive HCM patients [58]. VALOR-HCM (N=112): in patients eligible for septal reduction therapy, 67% of mavacamten-treated patients avoided the need for invasive intervention compared with 13% on placebo ($p<0.001$) [59]. Long-term extension studies confirmed sustained benefits and safety over 3+ years [59,60].

More recently, *aficamten*, a next-generation myosin inhibitor (Figure 1E), with similar mechanism to *mavacamten* but potentially improved pharmacokinetic properties, including shorter half-life (allowing faster dose adjustments) and fewer drug-drug interactions, has reported positive Phase 3 results in patients with symptomatic obstructive HCM and is currently under regulatory review [61,62].

Clinical trials demonstrated improvements in left ventricular outflow tract gradients, exercise capacity, and symptom burden, while ongoing long-term studies continue to evaluate safety with particular attention to effects on systolic function [60]. Key Trials include SEQUOIA-HCM (N=282): Aficamten demonstrated dose-dependent improvements in pVO_2, LVOT gradients, and symptoms at 24 weeks, with a safety profile comparable to mavacamten [63]. FOREST-HCM (N=159): 48-week results confirmed sustained benefits in LVOT gradient reduction (mean reduction >70 mmHg), symptom improvement (NYHA class improvement in 82% of patients), and exercise tolerance gains [60].

Mavacamten and aficamten share the same mechanism but differ in pharmacokinetics. *Mavacamten*'s longer half-life provides dosing stability but requires careful drug interaction management. *Aficamten*'s shorter half-life may facilitate faster titration and withdrawal if needed. Head-to-head comparison data are lacking; choice will likely depend on patient-specific factors (drug interactions, dose titration needs). Cardiac myosin inhibitors represent a transformative advance in HCM management, shifting from symptom palliation to targeted disease-specific therapy. However, they require specialized cardiology oversight, including genotype assessment, serial imaging, and careful patient selection (obstructive physiology, symptoms despite medical therapy). Together, these agents mark a significant advance toward precision, mechanism-based therapy for HCM, with the potential to alter its natural history.

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The key therapeutic agents, their mechanisms of action, and clinical outcomes are summarized in Table 1.

Table 1. Comprehensive overview of recent therapeutic advances in cardiovascular pharmacology.

Therapeutic Area	Drug/Agent	Mechanism of Action	Key Clinical Findings	FDA Status/Timeline
Transthyretin Amyloid Cardiomyopathy (ATTR-CM)	Acoramidis (Attruby™)	Near-complete TTR stabilizer preventing misfolding and amyloid fibril deposition	ATTRibute-CM: Significant reductions in CV death and CV hospitalizations; sustained improvements in functional capacity (6MWD) and quality of life	FDA approved late 2024 for wild-type and hereditary ATTR-CM
	Vutrisiran (Amvuttra™)	Subcutaneous siRNA suppressing hepatic TTR mRNA production (>80% reduction)	HELIOS-B: Clinically meaningful reductions in all-cause and CV mortality, fewer hospitalizations vs placebo; quarterly dosing	FDA indication expanded 2025 to include ATTR-CM
Lipoprotein(a) Targeting	Lepodisiran	Small interfering RNA (siRNA) targeting apolipoprotein(a) mRNA	ALPINE trial: ~94% sustained Lp(a) reduction at 6 months; well-tolerated with infrequent (quarterly to biannual) dosing	Phase 2 completed; Phase 3 ongoing
	Pelacarsen	Antisense oligonucleotide (ASO) targeting apolipoprotein(a)	Lp(a)HORIZON Phase 3 outcomes trial evaluating MACE reduction in patients with elevated Lp(a) and established CVD	Phase 3 ongoing (>7,000 patients enrolled)
RNA-Based Lipid Therapies	Inclisiran (Leqvio®)	siRNA targeting hepatic PCSK9 mRNA; induces sustained gene silencing via RNA interference pathway	ORION-10/11: 50-52% LDL-C reduction sustained with twice-yearly dosing; ORION-3: benefit maintained 4+ years; no immune-mediated reactions	FDA approved 2021; 2024 label update as potential first-line monotherapy
	Olezarsen (Tryngolza™)	ASO targeting apolipoprotein C-III (apoC-III) to enhance triglyceride clearance	BALANCE trial: 50-70% triglyceride reduction; prevents recurrent pancreatitis in familial chylomicronemia syndrome	FDA approved 2024 for FCS
	Evinacumab (Evkeeza™)	Monoclonal antibody inhibiting angiopoietin-like 3 (ANGPTL3)	Reductions in LDL-C, triglycerides, and Lp(a) in refractory homozygous familial hypercholesterolemia	FDA approved for homozygous FH
Gene Editing	VERVE-101	CRISPR base editor targeting hepatic PCSK9 gene; delivered via GalNAc-LNP for permanent gene modification	First-in-human trial (Phase 1b): Single-dose administration; preliminary evidence of PCSK9 reduction and LDL-C lowering in heterozygous FH	Phase 1b ongoing; first patient dosed 2022

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Resistant Hypertension	Zilebesiran	siRNA targeting hepatic angiotensinogen mRNA; upstream RAAS modulation	KARDIA-1: Sustained BP reductions (10-15 mmHg SBP) with quarterly or biannual dosing; benefits maintained 6+ months	Phase 2 completed; Phase 3 in development
	Baxdrostat	Highly selective aldosterone synthase (CYP11B2) inhibitor	BaxHTN Phase 3: 9-10 mmHg placebo-adjusted SBP reduction; 36% achieved target BP goal vs 18% placebo; favorable safety	Phase 3 completed 2024; regulatory submissions expected 2025
	Aprocitentan (Tryvio™)	Dual endothelin A/B receptor antagonist	PRECISION trial: 8 mmHg SBP reduction in resistant hypertension; well-tolerated	FDA approved 2024
Anti-Inflammatory Therapy	Canakinumab (Ilaris™)	Monoclonal antibody targeting interleukin-1β (IL-1β); selectively inhibits inflammatory pathway	CANTOS: 15% reduction in CV death/MI/stroke (150mg dose); 25% MACE reduction in hsCRP <2 mg/L responders; validates inflammatory hypothesis	Not approved for CV indication (cost/infection concerns)
	Colchicine (generic)	Microtubule polymerization inhibitor; disrupts neutrophil chemotaxis and NLRP3 inflammasome activation	COLCOT: 23% MACE reduction post-MI; LoDoCo2: 31% reduction in CV death/MI/stroke/revascularization in chronic CAD; inexpensive, oral	FDA approved for gout/pericarditis; used off-label for CV prevention
Heart Failure	Vericiguat (Verquvo™)	Oral soluble guanylate cyclase (sGC) stimulator; restores NO-cGMP signaling independent of nitric oxide	VICTORIA: 10% reduction in CV death/HF hospitalization in high-risk HFrEF with recent decompensation; greatest benefit with NT-proBNP >4,000	FDA approved 2021 as add-on therapy for chronic HFrEF
	Sacubitril-valsartan (Entresto™)	Angiotensin receptor-neprilysin inhibitor (ARNI); dual natriuretic peptide enhancement + angiotensin blockade	PARADIGM-HF: 20% reduction in CV death/HF hospitalization vs enalapril in HFrEF; evolution from omapatrilat avoiding angioedema	FDA approved; guideline-recommended first-line for HFrEF
	SGLT2 Inhibitors (dapagliflozin, empagliflozin)	Sodium-glucose cotransporter-2 inhibition; mechanisms include osmotic diuresis, metabolic shift, anti-fibrotic effects	Meta-analyses: 25-30% reduction in HF hospitalization across HFrEF and HFpEF; 12-14% CV death reduction; benefits within 30 days regardless of diabetes	FDA approved for HFrEF and HFpEF regardless of diabetes status
	Baroreflex Activation	Implantable device delivering electrical	BeAT-HF: Improved quality of life, 6-minute walk distance, and NT-proBNP in advanced HFrEF	Investigational device; ongoing trials

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	Therapy (BAT)	stimulation to carotid baroreceptors; restores autonomic balance	with persistent symptoms despite GDMT	
Pulmonary Arterial Hypertension	Sotatercept (Winrevair™)	Activin receptor type IIA-Fc fusion protein; modulates TGF-β superfamily to promote vascular remodeling reversal	STELLAR: 40.8m improved 6MWD at 24 weeks; 84% reduction in clinical worsening events; first disease-modifying therapy targeting vascular remodeling	FDA approved March 2024 as add-on therapy for WHO Group 1 PAH
Cardiometabolic/Obesity	Semaglutide (Wegovy™)	GLP-1 receptor agonist; pleiotropic CV effects beyond glucose/weight control	SELECT: 20% relative MACE reduction (HR 0.80) in overweight/obesity without diabetes; first weight-loss medication with CV risk reduction indication	FDA indication 2024 for CV risk reduction
	Tirzepatide (Zepbound™)	Dual GLP-1/GIP receptor agonist	Superior weight loss vs semaglutide (~22% at 72 weeks); CV outcomes trial (SURPASS-CVOT) ongoing	FDA approved for obesity; CV indication pending
Hypertrophic Cardiomyopathy	Mavacamten (Camzyos™)	First-in-class cardiac myosin inhibitor; reduces hypercontractility underlying LVOT obstruction	EXPLORER-HCM: Improved exercise capacity, NYHA class, LVOT gradient; first pharmacologic alternative to septal reduction therapy	FDA approved 2022 for symptomatic obstructive HCM
	Aficamten	Next-generation cardiac myosin inhibitor; shorter half-life allows faster dose titration	SEQUOIA-HCM Phase 3: Improved LVOT gradients, exercise capacity, symptom burden; potentially favorable PK profile vs mavacamten	Under FDA review; approval anticipated 2025

To facilitate the future integration of these emerging agents into clinical practice as they progress through regulatory approval, we have developed a comprehensive clinical flowchart that delineates both currently approved and investigational cardiovascular therapies according to disease presentation and mechanism of action (Figure 2).

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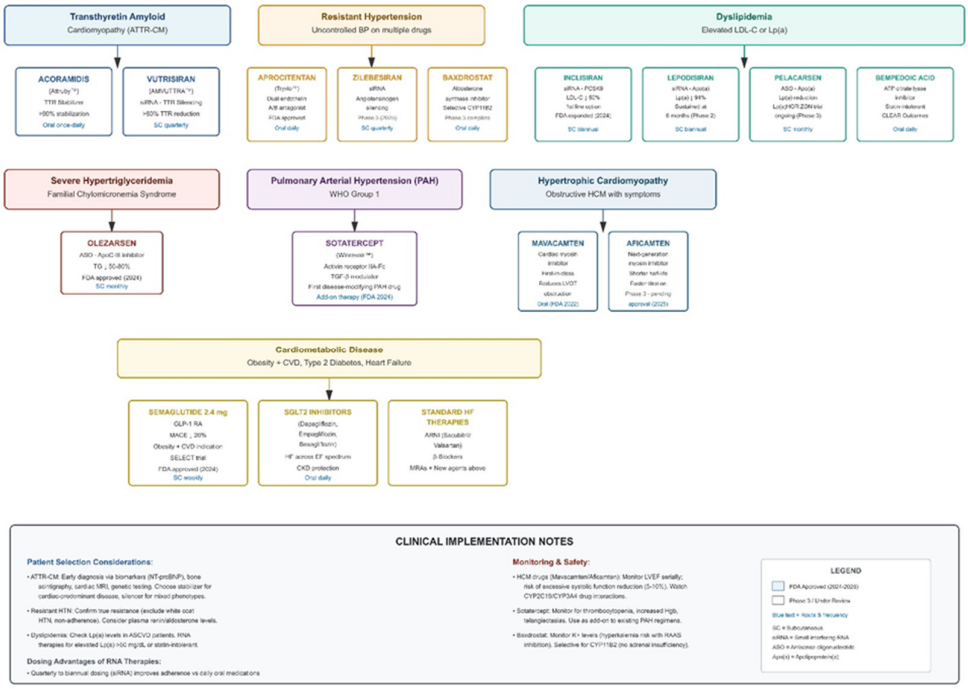

Figure 2. Clinical guide for current and emerging cardiovascular pharmacotherapies: a roadmap for future implementation.

4. Discussion

Cardiovascular pharmacology is entering an era where inherited and molecularly programmed risks are directly modifiable, a transition unimaginable in routine practice only a decade ago. Lp(a), once viewed as an untreatable residual risk factor, is now a prime target of ASO and siRNA therapies [20,21]. Agents such as *pelacarsen* and *lepodisiran* have demonstrated profound Lp(a) reductions in early trials, with Phase 3 outcome studies like Lp(a)HORIZON poised to determine whether these biomarker changes translate into reductions in myocardial infarction, stroke, and cardiovascular death [18,20,21]. Similarly, silencing of the RAAS through hepatic angiotensinogen suppression (e.g., *zilebesiran*) reflects a shift toward precision interventions designed to complement, or potentially supersede, traditional pathway blockade [23].

Therapeutic innovation has also reshaped the management of previously neglected rare cardiac conditions. In ATTR-CM, the availability of both stabilizers (e.g., acoramidis) and silencers (e.g., vutrisiran, with eplontersen in development) has yielded outcome signals suggesting meaningful reductions in mortality and hospitalizations [4,13–16]. These therapies are driving earlier diagnosis, genotype-informed care, and renewed emphasis on biomarker- and imaging-based surveillance.

Resistant hypertension, long a therapeutic challenge, may soon benefit from durable, upstream strategies. The siRNA agent *zilebesiran* achieves sustained angiotensinogen suppression, flattening day–night blood pressure variability with quarterly or semi-annual dosing [23,24]. While the aldosterone synthase inhibitor *baxdrostat* has delivered clinically relevant reductions in systolic pressure in Phase 3 studies [25,26]. If long-term safety and outcomes are confirmed, these agents could ease adherence burdens and redefine chronic hypertension care.

Therapeutics that bridge metabolic and cardiovascular domains are redefining prevention and treatment. GLP-1 RAs such as *semaglutide* now carry cardiovascular risk reduction indications in patients with obesity and established CVD (SELECT trial) [46,47], while SGLT2 inhibitors continue to demonstrate robust benefits across diabetes, HF, and CKD [50,55,64]. These advances embody the growing convergence of cardiology and endocrinology. The approval of *sotatercept*, an activin receptor type IIA-Fc fusion protein, introduced the first disease-modifying therapy for PAH [43,44].

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By targeting TGF-β superfamily signaling, *sotatercept* improved exercise capacity and delayed clinical worsening in pivotal trials, representing a paradigm shift when layered onto established vasodilator regimens [45]. Key areas of cardiovascular pharmacology are summarized in Figure 3.

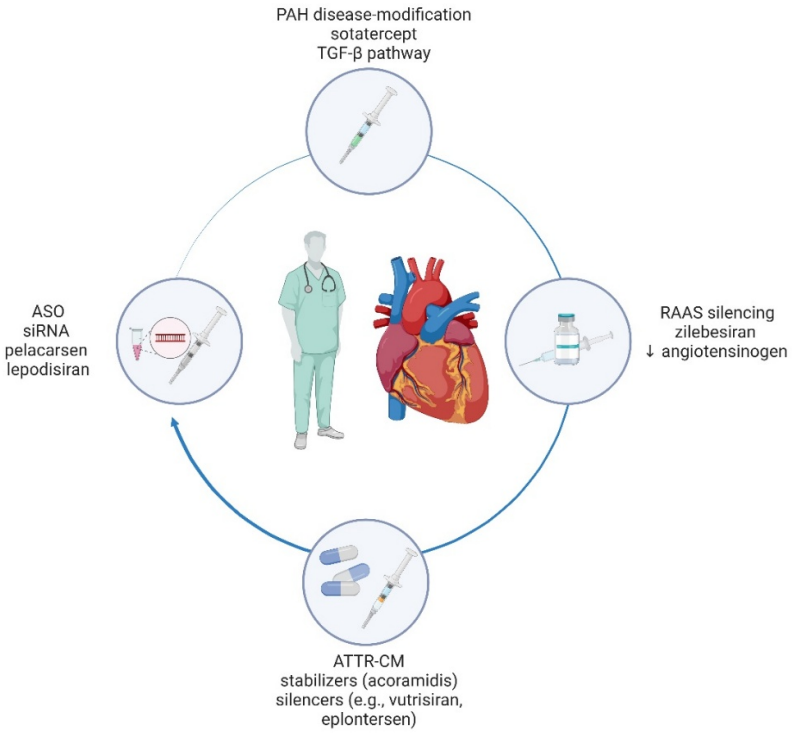

Figure 3. Emerging RNA-based and disease-modifying therapies in cardiovascular pharmacology. Illustration of major therapeutic innovations transforming cardiovascular care. Antisense oligonucleotide (ASO) and small interfering RNA (siRNA) therapies (e.g., pelacarsen, lepodisiran) target lipoprotein(a) [Lp(a)] to reduce residual atherosclerotic risk. Hepatic angiotensinogen silencing with zilebesiran provides sustained renin–angiotensin–aldosterone system (RAAS) blockade. In transthyretin amyloid cardiomyopathy (ATTR-CM), stabilizers (acoramidis) and silencers (vutrisiran, eplontersen) lower mortality and hospitalization rates. Sotatercept, an activin receptor type IIA-Fc fusion protein, modifies pulmonary arterial hypertension (PAH) by correcting dysregulated TGF-β signaling. Collectively, these approaches herald a shift toward precision, disease-modifying cardiovascular therapy.

Some considerations should be made regarding sex-differentiated responses and pharmacokinetics in cardiovascular drug therapy. In fact, profound sex differences influence the presentation, pharmacology, and outcomes of CVD, yet women remain underrepresented in clinical trials, perpetuating a male-default model of therapy [65]. Biological variations, including body composition, renal and hepatic function, and hormonal modulation, result in distinct pharmacokinetic and pharmacodynamic profiles in women, often leading to higher plasma drug levels and increased adverse effects [66]. These disparities affect all major drug classes: women experience stronger responses and more side effects to ACE inhibitors, ARBs, and calcium channel blockers; more frequent statin-associated myalgias despite similar efficacy; and greater bleeding risk with antiplatelets and anticoagulants [67]. Therefore, these innovative therapies, which have the potential to transform CV management, should also be thoroughly evaluated and integrated in female populations. This is essential to advance precision cardiovascular medicine and ensure equitable, biologically informed care for both women and men.

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4.1. Challenges, Open Questions, and Future Directions

CVD pharmacological treatment is substantially changing [68]. Despite dramatic reductions in Lp(a) or angiotensinogen, ultimate clinical validation requires proof of reduced death, myocardial infarction, stroke, and hospitalization. Phase 3 outcome trials such as Lp(a)HORIZON will be decisive [20,21]. The novel therapeutic platforms (siRNA, ASO, gene therapies, and long-acting enzyme inhibitors) necessitate multi-year safety surveillance to monitor for off-target effects, immunogenicity, and cumulative tolerability [69]. High acquisition costs and specialized delivery pathways risk widening global inequities. Equitable reimbursement models, enhanced diagnostic infrastructure, and patient adherence support will be essential [70]. Precision therapies demand reliable Lp(a) assays, amyloid imaging or biomarker confirmation, and genetic testing, yet these resources remain unevenly available across clinical settings. Head-to-head comparisons, subgroup analyses, and real-world effectiveness data are limited. Regulatory pathways for RNA- and genome-based therapies continue to evolve, particularly outside the U.S. and EU.

Looking Ahead. Gene editing and gene therapy are progressing from conceptual frameworks toward early clinical application in cardiomyopathies and inherited risk modulation [71,72]. In parallel, long-acting agents such as *zilebesiran* could normalize adherence by shifting treatment intervals to quarterly, semi-annual, or even annual dosing [23,24]. Finally, earlier detection of subclinical disease, ranging from amyloid cardiomyopathy to elevated Lp(a) or preclinical hypertension, may enable a transition toward truly preventive cardiovascular pharmacology, transforming outcomes for the next generation of patients.

Another area of growing relevance is the gut microbiome, which has emerged as a key modulator of cardiovascular health through its influence on metabolic and inflammatory pathways [73–75]. One of the most studied mediators is trimethylamine N-oxide (TMAO), a gut-derived metabolite produced via the gut–liver axis from dietary choline and L-carnitine. Elevated TMAO levels have been associated with increased atherosclerosis, endothelial dysfunction, thrombosis, and adverse cardiovascular outcomes [76]. To therapeutically target this pathway, early-phase clinical studies are investigating inhibitors of microbial TMA lyase, the enzyme responsible for generating trimethylamine (TMA), the precursor of TMAO [77–79]. This represents a novel, microbiome-focused approach to cardiovascular prevention and treatment. If proven effective in larger trials, this strategy could inaugurate a new era of cardiometabolic therapies that intervene at the level of gut microbial metabolism, offering truly personalized and upstream prevention of cardiovascular disease.

4.2. Limitations

This review has several limitations that warrant consideration. As a narrative synthesis, it does not include quantitative pooling of data and may be subject to selection bias in the identification and appraisal of studies. Although adherence to the SANRA guidelines strengthened methodological rigor, ensuring clarity of aim, structured literature search, balanced interpretation, and transparent referencing, some inherent constraints remain. Evidence from ongoing or recently completed trials was, in some cases, preliminary, and differences in study design, endpoints, and follow-up duration hinder direct comparison across therapies. Furthermore, long-term safety, real-world effectiveness, and cost-effectiveness data for many novel agents are still emerging, warranting cautious interpretation of their potential clinical impact.

5. Conclusions

Recent pharmacological advances are redefining the management of cardiovascular disease, shifting from conventional risk reduction toward mechanism-based, disease-modifying strategies. The emergence of transthyretin stabilizers and silencers, endothelin and RAAS modulators, RNA-based lipid therapies, GLP-1 receptor agonists, and TGF-β pathway inhibitors exemplifies this transition. Collectively, these developments promise earlier intervention, greater precision, and improved long-term outcomes across diverse cardiovascular phenotypes. While long-term data and

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real-world validation are still needed, the integration of these therapies into clinical practice heralds a new era of precision cardiovascular medicine, grounded in molecular understanding and translational innovation.

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Abbreviations

The following abbreviations are used in this manuscript:

6MWD	6-minute walk distance
ACE	Angiotensin-converting enzyme
ANGPTL3	Angiopoietin-like protein 3
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
ASO	Antisense oligonucleotide
ATP	Adenosine triphosphate
ATTR-CM	Transthyretin amyloid cardiomyopathy
Apo(a)	Apolipoprotein(a)
ApoC-III	Apolipoprotein C-III
BMPR2	Bone morphogenetic protein receptor type 2
BP	Blood pressure
CKD	Chronic kidney disease
CRISPR	Clustered regularly interspaced short palindromic repeats
CV	Cardiovascular
CVD	Cardiovascular disease
CYP11B1	Cytochrome P450 family 11 subfamily B member 1
CYP11B2	Cytochrome P450 family 11 subfamily B member 2 (aldosterone synthase)
CYP2C19	Cytochrome P450 2C19
CYP3A4	Cytochrome P450 3A4
EF	Ejection fraction
EMA	European Medicines Agency
FCS	Familial chylomicronemia syndrome
FDA	Food and Drug Administration (United States)
GDF	Growth differentiation factor
GDMT	Guideline-directed medical therapy
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GalNAc	N-acetylgalactosamine
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HMG-CoA	Hydroxymethylglutaryl-coenzyme A

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HTN	Hypertension
Hgb	Hemoglobin
HoFH	Homozygous familial hypercholesterolemia
K^+	Potassium
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LNP	Lipid nanoparticle
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
Lp(a)	Lipoprotein(a)
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cell
NO	Nitric oxide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDE5	Phosphodiesterase type 5
RAAS	Renin–angiotensin–aldosterone system
RNA	Ribonucleic acid
SANRA	Scale for the Assessment of Narrative Review Articles
SBP	Systolic blood pressure
SC	Subcutaneous
SGLT2	Sodium-glucose cotransporter 2
TG	Triglyceride
TGF-β	Transforming growth factor-beta
TTR	Transthyretin
WHO	World Health Organization
cGMP	Cyclic guanosine monophosphate
hsCRP	High-sensitivity C-reactive protein
mRNA	Messenger ribonucleic acid
pVO_2	Peak oxygen consumption
sGC	Soluble guanylate cyclase
siRNA	Small interfering RNA

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