Advancements in cardiovascular pharmacology

Giustino Varrassi,[1,2] Joseph V. Pergolizzi,[3] Giacomo Farì,[4] Ameen A. Al-Alwany,[2] Matteo L.G. Leoni[5]

[1]Fondazione Paolo Procacci, Rome, Italy; [2]College of Medicine, University of Baghdad, Iraq; [3]NEMA Research Group, Naples, FL, USA; [4]Department of Experimental Medicine (Di.Me.S.), University of Salento, Lecce, Italy; [5]Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome, Italy

ABSTRACT

Cardiovascular pharmacology is entering a period of profound transformation, driven by novel therapies that extend far beyond traditional approaches. Recent advances include RNA-based drugs targeting lipoprotein(a) and angiotensinogen, new stabilizers for transthyretin amyloidosis, and selective aldosterone synthase inhibitors for resistant hypertension. These developments illustrate a decisive shift from symptomatic management toward disease modification and precision targeting. Yet, significant challenges remain. Translating biomarker reductions into hard outcomes such as reduced mortality, myocardial infarction, or stroke requires large, long-term clinical trials now underway. Equally critical is the need for rigorous monitoring of long-term safety, particularly for new platforms such as siRNA and gene therapies, where off-target effects and tolerability over decades remain uncertain. High cost and limited accessibility further threaten to widen global health inequities, while gaps in diagnostic infrastructure hinder appropriate patient selection. Regulatory frameworks, especially outside high-income regions, must also evolve to keep pace with these scientific advances. Despite these obstacles, the future is rich with promise. Gene editing and novel gene therapies hold the potential to correct underlying disease mechanisms, while long-acting drugs offer solutions to adherence challenges. Personalized, multimodal strategies, combining metabolic, anti-inflammatory, and genetic risk-modifying agents, may soon become standard, tailored to each patient's biomarker and genetic profile. Importantly, early detection of subclinical disease could shift cardiovascular pharmacology from treating advanced illness toward prevention and preservation of health. The coming decade will determine whether these breakthroughs translate into equitable, lasting improvements in outcomes, heralding a new era in cardiovascular care.

Correspondence: Prof. Giustino Varrassi, Fondazione Paolo Procacci, Via Tacito 7, 00193 Roma, Italy.
E-mail: giuvarr@gmail.com

Key words: cardiovascular diseases; cardiovascular pharmacology; RNA-based drugs; gene therapies; personalised therapy.

Contributions: all the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no competing interests, and all authors confirm accuracy.

Acknowledgments: the authors are very grateful to Fondazione Paolo Procacci for the support provided during all the publication process.

Received: 24 September 2025.
Accepted: 11 November 2025.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Advancements in Health Research 2025; 2:122
doi: 10.4081/ahr.2025.122

Introduction

Cardiovascular disease (CVD) continues to be a leading cause of morbidity and mortality globally. Recent years have seen more modest numbers of "first-in-class" cardiovascular drug approvals compared to past decades, but 2024-2025 have nonetheless delivered a number of promising innovations, both therapeutic and mechanistic, that could reshape prevention, management, and treatment of heart disease, hypertension, lipid disorders, and related conditions. Below are several of the most exciting developments, followed by a discussion of what they may mean, and what obstacles lie ahead.

Key developments

Transthyretin amyloid cardiomyopathy (ATTR-CM) – Acoramidis (Attruby/Beyonttra)

In late 2024, the U.S. FDA approved acoramidis for treatment of transthyretin-mediated amyloid cardiomyopathy (wild type or variant).[1] Acoramidis is a near-complete (>90%) stabilizer of transthyretin, designed to mimic the naturally protective T119M mutation.[2] Clinical trials (ATTRibute-CM) showed that over 30 months, treatment with acoramidis significantly reduced cardiovascular death and hospitalizations and improved functional outcomes in those patients.[3]

Its approval fills a critical therapeutic gap: ATTR-CM is often underdiagnosed, and until recently, there were few treatments that could slow or reverse the disease. The drug provides an oral option with a favorable safety profile (most common side effects being gastrointestinal).[4]

Lipoprotein(a) as a target: lepodisiran and pelacarsen

Lipoprotein(a) (Lp(a)) has long been recognized as a genetically determined risk factor for atherosclerotic cardiovascular disease, but until recently effective and specific interventions to reduce Lp(a) were lacking.[5] Two agents in development are promising: i) Lepodisiran, an siRNA agent developed, recently, in a phase 2 trial achieved around 94% reduction in Lp(a) *versus* placebo at the highest dose over six months, with no serious adverse events linked to the therapy;[6] ii) Pelacarsen (an antisense oligonucleotide targeting LPA mRNA) is in phase 3 trials (not yet approved) to test whether lowering Lp(a) with this agent will reduce major cardiovascular events.[7]

RNA interference (siRNA) and upstream targets in hypertension

Hypertension remains a major global challenge, especially in cases resistant to standard therapies.[8] Novel approaches are moving upstream in established pathways: i) Zilebesiran (ALN-AGT01) is a siRNA agent targeting angiotensinogen synthesis in the liver; single or infrequent subcutaneous doses produce sustained reductions in blood pressure, both daytime and nighttime, for up to 24 weeks in phase 1/2 trials;[9] ii) Relatedly, baxdrostat, a more recent development, directly and selectively inhibits aldosterone production.[10] In the BaxHTN phase 3 trial (in patients with resistant hypertension), it significantly lowered systolic blood pressure (9-10 mmHg more than placebo) and helped around 40% of participants achieve target blood pressures.[11]

Heart failure with reduced ejection fraction (HFrEF) advancements

Drug therapy in HFrEF continues to evolve. Recent reviews highlight how the standard of care is being augmented/improved, both by refining existing classes (ARNI, SGLT2 inhibitors, MR antagonists, etc.) and by novel agents targeting unmet aspects of heart failure pathophysiology.[12,13]

Novel mechanisms and label expansions

Some existing therapeutics have received important *label expansions* to broader patient populations or risk-factor settings, e.g. semaglutide (GLP-1 agonist) and bempedoic acid in lipid management.[14,15] Imatinib (traditionally a cancer drug) has been explored in pulmonary arterial hypertension (PAH) as adjunct therapy, with meta-analysis suggesting improvements in outcomes when added to background therapy.[16]

Implications for clinical practice

From risk factor modification to genetic/molecular precision

Therapies like lepodisiran and pelacarsen illustrate the shift from treating modifiable risk factors (e.g. LDL cholesterol, hypertension) to addressing *genetically programmed* risk (Lp(a)). Likewise, targeting upstream elements like angiotensinogen or aldosterone production may allow less frequent dosing, more consistent control, and potentially better adherence/compliance.

Better options for rare or previously untreatable diseases

ATTR-CM, once a disease with very poor prognosis and limited treatment, now has a stabilizer (acoramidis) to change its natural history. This is emblematic of the advance of precision medicine in cardiology.

Treatment paradigm shifts in hypertension

With agents like zilebesiran and baxdrostat, the potential is there for treatments that are less burdensome in dosing (infrequent injections, *etc*.), and more effective in patients with resistant hypertension. If long-term safety and outcome data are favorable, they may become part of earlier lines of therapy.

Integration of metabolic drugs with cardiovascular benefit

GLP-1 agonists, SGLT2 inhibitors, e*t*c., continue to show benefits beyond glycemic control, improving cardiovascular outcomes, heart failure risk, renal protection. Expanding labels and evidence bring them more into the mainstream even for non-diabetic cardiovascular patients.

Challenges, open questions and future directions

Despite the enthusiasm surrounding these innovations, several challenges remain before they can be fully integrated into clinical practice. Perhaps the most pressing is the translation of biomarker improvements into clinical outcomes that improve on the current standards of care.[17] While agents that lower Lp(a) or suppress angiotensinogen production demonstrate striking biological effects, the real test lies in whether these changes reduce mortality, myocardial infarction, stroke, or hospitalizations. Large phase 3 trials, such as the Lp(a)HORIZON study, are underway,[18] but results will take years to mature. Until then, the risk persists that promising mechanistic effects may not translate into tangible patient benefit. Equally important is the question of long-term safety. Novel platforms such as long-acting inhibitors and protein stabilizers introduce mechanisms for which there is limited long-term clinical experience.[19] Monitoring for unforeseen toxicities, immune responses, or off-target and as understanding how well patients tolerate these therapies over decades rather than months will be critical.

The issue of cost and equitable access also looms large. Many of these drugs, particularly RNA-based therapies, come with high price tags, creating barriers for widespread use. Ensuring that patients in low- and middle-income regions can access these advances is a global health imperative, requiring parallel innovation in reimbursement systems, healthcare infrastructure, and strategies to support adherence.[20]

Another challenge lies in diagnostics and patient selection. These therapies are highly specific, often requiring advanced biomarker testing or genetic confirmation. Yet, many patients remain undiagnosed or underdiagnosed due to limited awareness or access to specialized testing. Without investment in diagnostic infrastructure, the therapeutic revolution risks being restricted to a small, privileged segment of the population.

Finally, evidence and regulatory gaps remain. Even as approvals are granted, important questions remain: how effective

are these therapies across different subgroups? How durable are their benefits? How do they compare head-to-head with each other and to currently available therapies? For genome- and RNA-based therapies, regulatory pathways are still evolving, particularly outside the U.S. and Europe, raising issues of harmonization and oversight.

Looking ahead, however, the opportunities are as compelling as the challenges. Gene editing and gene therapy are beginning to move from concept to reality, offering the tantalizing prospect of correcting underlying genetic causes of disease rather than merely managing their consequences.[21,22] Personalized, multimodal strategies may become the standard, with treatment tailored to each patient's biomarker profile, genetic variants, and comorbidities. At the same time, long-acting drugs, administered monthly or even annually, promise to improve adherence and long-term disease control, as exemplified by early results with agents like Zizebesiran.[9,23]

Equally transformative is the potential shift toward prevention and early intervention. Detecting pathology before it manifests clinically, such as subclinical amyloid deposition, elevated Lp(a), or early hypertension, could allow disease-modifying therapies to be introduced at a stage when irreversible organ damage has not yet occurred. In this way, cardiovascular pharmacology could transition from a field focused on managing advanced illness to one dedicated to preserving health and preventing decline.

Together, these converging forces, scientific innovation, clinical vigilance, and systems-level adaptation, will determine whether the current breakthroughs deliver on their promise. The next decade will reveal whether cardiovascular pharmacology can fully embrace this transformation, turning impressive molecular advances into meaningful, accessible, and lasting improvements in patient outcomes.

Conclusions

The recent advances in cardiovascular pharmacology represent a robust and encouraging shift from incremental improvements to disease-modifying therapies, especially in genetic risk domains and previously underserved diseases (like ATTR-CM). While the number of new drug approvals remains relatively modest, the classes emerging (RNAi, antisense, novel stabilizers, upstream hormone inhibitors) and the breadth of potential application suggest that we are entering a new era. The next few years will be critical to see whether biomarker reductions translate into reduced cardiovascular events and better survival, whether safety in the long term is acceptable and whether health systems, diagnostic tools and patient access can keep up. If those align, we may soon witness substantial shifts in how cardiovascular disease is prevented and treated, not simply managed.

References

1. U.S. Food and Drug Administration. FDA approves drug for heart disorder caused by transthyretin-mediated amyloidosis. 2024. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-heart-disorder-caused-transthyretin-mediated-amyloidosis
2. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. N Engl J Med 2024;390:132-42.
3. Judge DP, Gillmore JD, Alexander KM, et al. Long-term efficacy and safety of acoramidis in ATTR-CM: Initial report from the open-label extension of the ATTRibute-CM trial. Circulation 2025;151:601-11.
4. Judge DP, Alexander KM, Cappelli F, et al. Efficacy of acoramidis on all-cause mortality and cardiovascular hospitalization in transthyretin amyloid cardiomyopathy. J Am Coll Cardiol 2025;85:1003-14.
5. Anchouche K, Thanassoulis G. Lp(a): A rapidly evolving therapeutic landscape. Curr Atheroscler Rep 2024;27:7.
6. Nissen SE, Ni W, Shen X, et al. Lepodisiran - A long-duration small interfering RNA targeting lipoprotein(a). N Engl J Med 2025;392:1673-83.
7. Bhatia HS, Bajaj A, Goonewardena SN, Moriarty PM. Pelacarsen: Mechanism of action and Lp(a)-lowering effect. J Clin Lipidol 2025. Online ahead of print.
8. Zheng Z, Chen R, Liu M, Ding Y, Xu S, Hou C, Li S. Identification of novel therapeutic targets for hypertension. Hypertension 2025;82:1056-70.
9. Khan RS, Frishman WH. Zilebesiran: A promising antihypertensive therapy inhibiting angiotensinogen synthesis. Cardiol Rev 2025;33:279-84.
10. Dey S, Frishman WH, Aronow WS. Baxdrostat: An aldosterone synthase inhibitor for the treatment of systemic hypertension. Cardiol Rev 2025;33:243-5.
11. Flack JM, Azizi M, Brown JM, et al. Efficacy and safety of baxdrostat in uncontrolled and resistant hypertension. N Engl J Med 2025;393:1363-74.
12. Mapelli M, Rubbo FM, Costantino S, et al. Pharmacological therapy of HFrEF in 2025: navigating new advances and old unmet needs in an eternal balance between progress and perplexities. Card Fail Rev 2025;11:e18.
13. Ahmed OTF, Ahmed ZT, Dairi AW, et al. The inconclusive superiority debate of allogeneic versus autologous MSCs in treating patients with HFrEF: a systematic review and meta-analysis of RCTs. Stem Cell Res Ther 2025;16:175.
14. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. BMJ 2024;384:e076410.
15. Parhofer KG, Aguiar C, Banach M, et al. Expert opinion on the integration of combination therapy into the treatment algorithm for the management of dyslipidaemia: the integration of ezetimibe and bempedoic acid may enhance goal attainment. Eur Heart J Cardiovasc Pharmacother 2025;11:367-79.
16. Chen X, Xue B, Xu L. Efficacy and safety of treating pulmonary arterial hypertension with imatinib: A meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol 2025;85:177-85.
17. Hermann DM, Bacigaluppi M, Bassetti CL, et al. Most prominent challenges in translational neuroscience and strategic solutions to bridge the gaps: Perspectives from an editorial board interrogation. Explor Neurosci 2025;4:1006106.
18. Cho L, Nicholls SJ, Nordestgaard BG, et al. Design and rationale of Lp(a)HORIZON trial: Assessing the effect of Lipoprotein(a) lowering with pelacarsen on major cardiovascular events in patients with CVD and elevated Lp(a). Am Heart J 2025;287:1-9.
19. Alla SSM, Shah DJ, Meyur S, et al. Small interfering RNA (siRNA) in dyslipidemia: A systematic review on safety and efficacy of siRNA. J Exp Pharmacol 2025 28;17:249-67.

20. Sehgal I, Eells K, Hudson I. A comparison of currently approved small interfering RNA (siRNA) medications to alternative treatments by costs, indications, and medicaid coverage. Pharmacy (Basel) 2024 28;12:58.
21. Vo QD. Gene editing therapy as a therapeutic approach for cardiovascular diseases in animal models: A scoping review. PLoS One 2025;20:e0325330.
22. Zhang C, Du Z, Chen R, et al. Gene- and cell-based therapy in cardiovascular diseases. J Cardiovasc Pharmacol 2025;86: 157-65.
23. Siddiqui E, Siddiqui AH, Moeed A, et al. Advancing hypertension management: the role of zilebesiran as an siRNA therapeutic agent. Ann Med Surg (Lond) 2025;87: 577-82.