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Mini Review

What We Didn't Know About What We Already Knew: Revisiting Cardiovascular Drugs Through a Systems Lens

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Abstract

Classical cardiovascular drugs—including beta-blockers, ACE inhibitors, ARBs, statins, and calcium channel blockers—remain foundational in the management of hypertension, heart failure, and ischemic heart disease. Recent advances in systems pharmacology and network medicine have redefined our understanding of these agents, revealing hidden polypharmacological effects and mechanistic redundancy that extend beyond single-target actions. Integrating multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with network modeling has uncovered how these drugs modulate interconnected pathways, contributing to therapeutic robustness against complex disease networks. This mini-review revisits classical cardiovascular drugs through a systems lens, explores their potential for drug repurposing, and highlights how lessons from these agents can inform the rational design of next-generation, network-informed polypharmacological therapies.

Keywords: Polypharmacology; Systems pharmacology; Network medicine; Multi-omics; Cardiovascular drugs; Beta blockers; ACE inhibitors; Calcium channel blockers (CCBs); Statins; Drug repurposing; Nucleic acid-based therapeutics (NATs)

Highlights

- Classical cardiovascular agents possess multitarget, system level actions—revealed by omics and network pharmacology.
- Mechanistic redundancy provides therapeutic resilience in complex diseases such as heart failure and hypertension.
- Systems driven repurposing opportunities for these drugs span oncology, metabolic, neurologic, and inflammatory disorders.
- Lessons from these agents can guide next generation drugs with network informed polypharmacological profiles.

Introduction

For decades, a small repertoire of drug classes—beta blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), statins, and select diuretics—has underpinned cardiovascular disease (CVD) management. These agents are cost effective, well-studied, and remain first line therapy in hypertension, heart failure, ischemic heart disease, and arrhythmias [1-3].

Until recently, pharmacology of these agents was framed in terms of single target effects—e.g., β_1 adrenergic antagonism, RAAS inhibition, or L type calcium channel blockade. However, in an era of multi omic profiling and network medicine, this reductionist view is obsolete. Instead, these classical agents exhibit polypharmacology—modulating multiple targets and pathways, often via subtle off target or indirect effects that manifest at the network level [3-10]. This enables mechanistic redundancy, providing therapeutic robustness against patient variability and disease complexity.

Systems pharmacology, one of the principles of polypharmacology [7]—the melding of systems biology with pharmacological data—offers a framework to formally analyze these network effects. It leverages transcriptomics, proteomics, metabolomics, and computational modeling to map drug–target–disease interactions.

This review offers (1) a systems level reinterpretation of classical cardiovascular drugs, (2) an exploration of mechanistic redundancy as a therapeutic asset, (3) repurposing opportunities unveiled by network analysis and omics data, and (4) implications for the design of next generation polypharmacological agents.

Systems Pharmacology and Network Pharmacology in Cardiovascular Medicine

Systems pharmacology applies systems biology principles to drug action, emphasizing drug–target networks rather than single interactions. It integrates drug target data, protein protein and gene disease networks, and omics responses to understand drug effects across scales—from molecular to organ system.

A landmark network pharmacology mapping of 254 FDA approved cardiovascular drugs and their 206 known targets revealed an average of ~2.8 targets per drug, with some agents like verapamil and dronedarone engaging over a dozen targets [10]. This confirms widespread drug promiscuity, which in cardiovascular agents often proves beneficial rather than adverse.

Network medicine further frames disease as clusters of interacting genes and pathways. Drugs that modulate multiple nodes in disease networks—rather than single points—may deliver greater efficacy in complex conditions such as heart failure or hypertension, which are marked by redundancy and feedback loops [7,11].

Omics profiling (transcriptomics, proteomics, metabolomics, epigenomics) complements network modeling. For instance, transcriptomic analyses demonstrate that beta blockers modulate gene sets involved in mitochondrial function, oxidative stress, and fibrosis. Proteomics shows ACE inhibitors influence kinase and extracellular matrix pathways beyond RAAS; metabolomics reveals how statins alter bioenergetic and inflammatory metabolites.

Such integrative approaches form the backbone of network pharmacology in cardiovascular research—as documented in multiple reviews focused on both drug discovery and therapeutic repurposing [7,12].

Reinterpreting Classical Cardiovascular Agents

Beta Blockers

Initially targeting β_1 adrenergic receptors to reduce heart rate and myocardial oxygen demand, beta blockers also exhibit anti inflammatory, anti fibrotic, anti arrhythmic, and endocrine modulating effects. Network pharmacology and omics analyses reveal modulation of calcium handling, oxidative phosphorylation, fibrosis related genes, and microRNA expression. For example, carvedilol, beyond β blockade, acts as an antioxidant and inhibits lipid peroxidation, likely via direct radical scavenging and modulation of mitochondrial gene networks (Figure 1).

Beta blockers reduce renin secretion and modulate the RAAS indirectly; they also attenuate stress hormone mediated pathways involved in angiogenesis and inflammation—effects implicated in observed associations with reduced cancer progression.

ACE Inhibitors and ARBs

Beyond inhibiting angiotensin converting enzyme (ACE) or blocking AT_1 receptors, these agents enhance bradykinin and nitric oxide signaling, and modulate extracellular matrix remodeling via MMPs and collagen pathways. Network studies and proteomics mapping show ACE inhibitors alter endothelial kinase pathways and inflammation mediators. Telmisartan, an ARB, also activates PPAR γ, linking it to metabolic regulation and insulin sensitivity—disclosed through systems level analysis.

In heart failure, ACE inhibitors reduce adverse remodeling and fibrosis through pleiotropic signaling beyond classical RAAS blockade and confer endothelial protection via network level cross talk among nitric oxide, TGF β, and inflammatory axes (Figure 1).

Statins

While statins primarily inhibit HMG CoA reductase, metabolomics and transcriptomics have revealed robust anti inflammatory and endothelial protective effects (Figure 1). They downregulate NF κB signaling networks, enhance eNOS activity, stabilize plaques,

reduce oxidative stress, and modulate immune cell transcriptional programs. These pleiotropic, polypharmacologic actions help explain clinical benefits of statins even in normocholesterolemic patients.

Calcium Channel Blockers (CCBs)

CCBs like amlodipine, verapamil, and diltiazem target L type calcium channels to reduce vascular resistance. Network analyses, however, indicate broader effects on mitochondrial function, ROS pathways, and even neuronal circuits regulating autonomic tone. Omics studies show modulation of signaling pathways in vascular smooth muscle beyond calcium influx, suggesting secondary network mechanisms contributing to benefits in ischemia and hypertension (Figure 1).

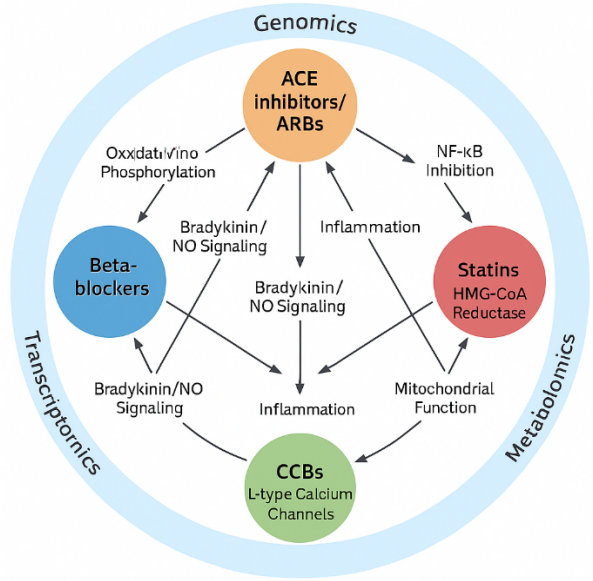

Figure 1: Hidden Polypharmacology of Classical Cardiovascular Drugs.

This systems pharmacology network illustrates the multitarget actions of classical cardiovascular drug classes—beta-blockers, ACE inhibitors/ARBs, statins, and calcium channel blockers (CCBs). Each drug class, originally developed for a single primary target (e.g., β_1-adrenergic receptors, HMG-CoA reductase), also modulates additional pathways including inflammation, oxidative stress, mitochondrial function, and bradykinin/nitric oxide (NO) signaling. The surrounding blue ring highlights the contribution of multi-omics approaches (genomics, transcriptomics, proteomics, and metabolomics) in uncovering these hidden effects. The figure underscores the emergent concept of therapeutic redundancy and polypharmacology revealed through systems-level analyses.

Mechanistic Redundancy as a Therapeutic Strength

Mechanistic redundancy—multiple targets converging on similar disease-relevant endpoints—was once considered pharmacologic clutter. Systems pharmacology repositions redundancy as therapeutic robustness. In multifactorial disease networks, redundant mechanisms enhance resilience to inter individual variability, genetic polymorphisms, and compensatory pathways [7].

Beta blockers, ACE inhibitors, and statins each impact overlapping pathways—RAAS, sympathetic signaling, inflammation, endothelial function, fibrosis—offering redundant suppression of pathogenic circuits. This reduces reliance on any single pathway and increases durability of response, even when disease biology shifts (e.g. heart failure progression) [13-15].

Moreover, redundancy reduces emergence of resistance: mono target agents may lose efficacy through upregulation of alternative routes, whereas polypharmacological drugs deliver network coverage that maintains benefit despite partial escape.

Repurposing Old Drugs Using Systems Pharmacology

Systems driven polypharmacology has uncovered repurposing potential for classical agents [7,8]:

- Beta blockers in cancer: Some epidemiologic data suggest reduced tumor progression, possibly via modulation of β adrenergic stress signalling impacting angiogenesis and invasion.
- Statins in neurodegeneration: Via anti-inflammatory and cholesterol independent network effects, statins may modulate Alzheimer's related pathways.
- ACE inhibitors and ARBs in metabolic disorders: Mechanistic links through PPAR-γ and bradykinin nitric oxide networks suggest benefits in diabetes and insulin resistance.

These associations emerge when mapping drug targets onto disease protein networks and overlaying omics signatures, providing computational hypotheses for clinical repurposing studies.

Lessons for Next Generation Polypharmacological Drug Design

What cardiovascular systems pharmacology teaches us:

1. Design for polypharmacology: Rather than hyper selective molecules, network informed drugs that modulate multiple disease relevant nodes may yield higher efficacy in complex syndromes such as HFpEF, cardiorenal or cardio metabolic disease [7,8].

2. Use omics as drug fingerprints: Profiling transcriptomic, proteomic, and metabolomic responses of classical drugs provides templates for synthetic analogs or combinations aimed at recapitulating beneficial network signatures [16-19].

3. Integrate AI and systems modeling: Machine learning on drug target disease networks can predict multi target effects across patient genotypes and phenotypes, enabling more precise, personalized polypharmacology.

4. Explore rational drug combinations: Fixed or co formulated regimens—e.g. combining beta blockers, ACE inhibitors, and statins—may deliver expanded, synergistic network coverage with reduced toxicity [13-15].

These strategies align with broader trends in quantitative systems pharmacology and network medicine approaches to drug discovery and therapeutic optimization.

Challenges and Future Directions

Despite the transformative promise of systems pharmacology and polypharmacology, several key challenges must be addressed to realize their full clinical potential:

- Data integration: Multi-omics datasets are often noisy, context-dependent, and lack standardization [16-19]. This variability complicates accurate network reconstruction and limits the reproducibility of systems pharmacology models across studies and patient populations.
- Clinical validation: While in silico predictions and omics-based insights are abundant, few multitarget hypotheses have been robustly validated in large-scale clinical trials. Translational bottlenecks remain, particularly for repurposing old drugs based on network-level rationale.
- Regulatory and ethical frameworks: Current drug approval processes are still largely geared toward single-target drugs with clearly defined mechanisms. Multitarget drugs—especially those developed through systems approaches or for off-label indications—require new regulatory paradigms to accommodate complex evidence bases, network models, and polypharmacologic profiles.
- Precision variability: Genetic, epigenetic, and environmental factors shape individual drug responses and network dynamics. Systems pharmacology must increasingly integrate patient-level data to enable precision polypharmacology, ideally through personalized network models.

To overcome these challenges, future efforts should prioritize integrative platforms that combine deep phenotyping, multi-omic profiling, machine learning, and real-world outcome data. Emerging technologies such as digital twins, multiscale computational models of cardiovascular physiology, and AI-guided network therapeutics offer promising tools to optimize drug selection, dosing, and design in a personalized and dynamic manner.

Moreover, while AI-assisted drug discovery has significantly accelerated target identification and compound screening, discovering small molecules that engage multiple targets with favorable pharmacokinetics, low toxicity, and appropriate selectivity remains a largely stochastic and resource-intensive endeavor.

In this context, the emergence of nucleic acid-based therapeutics (NATs)—such as siRNA, antisense oligonucleotides (ASOs), mRNA, and microRNA modulators—has made the discovery and development of multitarget drugs (MTDs) significantly more feasible, programmable, and precise than with traditional small-molecule agents [20-31] (Figure 2). This advantage is grounded in several key features:

1. Intrinsic sequence programmability: NBTs are defined by their nucleotide sequence rather than by rigid chemical structures. This enables deliberate design of multitarget strategies by:

   ○ Creating siRNA cocktails or multiplexed ASOs that silence several genes simultaneously;

   ○ Engineering microRNA mimics or inhibitors that naturally regulate networks of targets [20,23-25,30,31];

   ○ Encoding multiple protein domains using multi-cistronic mRNA constructs.

2. Mechanism of action: Network-level regulation: NATs act upstream at the RNA level, influencing gene expression and regulatory networks before protein synthesis. In contrast to small molecules, which typically modulate one protein, NATs can reprogram entire transcriptional or post-transcriptional networks—ideal for treating polygenic, multifactorial diseases.

3. High-throughput target discovery via omics integration: The fusion of transcriptomics, proteomics, and network biology enables rapid identification of co-regulated or co-dysregulated targets. NATs can then be precisely tailored to these networks, facilitating rational multitarget drug development.

4. Lower structural constraints and more predictable off-target effects: Unlike small molecules, which must fit specific protein pockets and risk unpredictable interactions, NATs bind based on Watson–Crick base pairing, allowing greater specificity and computational prediction of both on- and off-targets. Therapeutic off-targets can even be intentionally harnessed in the design of multitarget interventions.

5. Faster iteration and modular development: NAT development is modular and often follows a design–build–test cycle. Libraries of ASOs, siRNAs, or CRISPR guides can be rapidly screened in parallel. Synthetic sequences can be generated and optimized quickly, shortening development timelines compared to traditional drug discovery.

6. Clinical precedents and regulatory momentum: Several NATs with multitarget implications have reached clinical use:

- Inclisiran (siRNA) targets PCSK9 to lower LDL cholesterol;
- Nusinersen (ASO) modulates SMN2 expression in spinal muscular atrophy;
- Anti-miR-122 therapies regulate lipid and metabolic pathways in the liver.

These examples have laid the foundation for broader regulatory acceptance of nucleic acid-based multitarget therapeutics and are catalyzing the next generation of RNA-based polypharmacology.

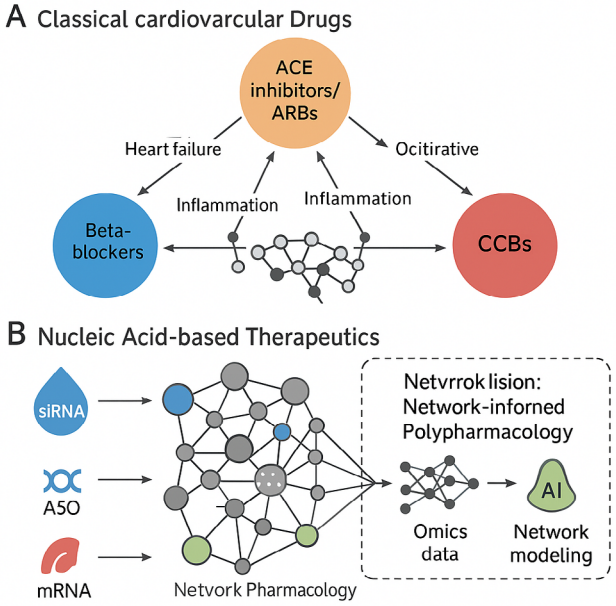

Figure 2. Systems Pharmacology and Future Therapeutics.

A two-panel conceptual diagram depicting the evolution of cardiovascular pharmacotherapy through the lens of systems pharmacology. A: Classical cardiovascular drugs (beta-blockers, ACE inhibitors, and CCBs) are shown acting on interconnected disease networks involving heart failure, inflammation, and oxidative stress, highlighting their pleiotropic and redundant actions. B: Nucleic acid-based therapeutics (NATs), including siRNA, antisense oligonucleotides (ASOs), and mRNA, are shown as programmable agents designed to modulate multiple targets within disease networks. Integration of omics data and AI-powered network modeling supports the rational design of multitarget therapies. This panel emphasizes the synergy between classical insights and modern biotechnologies in developing future network-informed, precision-guided cardiovascular treatments.

Conclusion

Classical cardiovascular drugs, once viewed as mechanistically simple, are now being reinterpreted through the lens of systems pharmacology, which reveals their hidden polypharmacology and mechanistic redundancy. These features provide resilience against network complexity, disease heterogeneity, and adaptive resistance. By mapping omics responses and drug-target networks, opportunities for repurposing emerge and inform strategies for designing next-generation cardiovascular therapeutics. Revisiting these established agents through a systems perspective not only deepens our understanding of their clinical benefits but also offers a framework for future drug discovery, emphasizing network-informed, precision-guided polypharmacology. Moreover, the convergence of systems pharmacology with nucleic acid-based therapeutics (NATs) enhances our ability to design programmable, multitarget therapies that address the syndromic nature of cardiovascular disease. These advances herald a paradigm shift from single-target treatments toward a holistic approach integrating AI, omics, and network medicine.

Classical cardiovascular drugs, long considered fully understood and mechanistically singular, are being rediscovered through a systems pharmacology approach that reveals their hidden polypharmacologic nature and mechanistic redundancy. These features, once deemed pharmacologic excess, now emerge as strengths—providing resilience against network complexity, disease heterogeneity, and compensatory resistance. By systematically mapping omics responses and drug target networks, we uncover opportunities for repurposing and glean lessons to inform design of next-generation cardiovascular therapeutics. Revisiting what we already knew about these agents through a systems lens thus offers both a deeper appreciation of their complexity and a blueprint for future drug discovery strategies.

As cardiovascular disease increasingly reveals its syndromic and network-level complexity, the need for precise, multitarget therapeutics has become urgent. Systems pharmacology, powered by omics, AI, and network modeling, offers the conceptual framework to redefine how we design and deploy therapies. The advent of NATs not only complements this paradigm—it accelerates it, providing tools that are inherently programmable, modular, and well-suited for rational multitarget drug design. Together, these advances may finally shift cardiovascular medicine from a paradigm of single-disease, single-drug thinking to one of network-informed, precision-guided polypharmacology.

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Author Contributions

Wang Z and Zhang X conceptualized the work and drafted the manuscript. Wang J refined the concept and performed editing, polishing, and proofreading of the manuscript.

Conflict of Interest Statement

The author declares no conflict of interest.

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