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INTEGRATED COMPUTATIONAL APPROACH FOR ANALYZING BIOACTIVE COMPOUNDS IN CARDIOVASCULAR DISEASES

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We propose a step-by-step methodological approach for computational analysis of bioactive compounds in cardiovascular diseases (CVD) that integrates network medicine/systems biology, multi-omics integration, AI/ML, QSAR, molecular docking/AlphaFold 3, and chemogenomic resources. The workflow aligns with contemporary clinical stratification (HFrEF/HFmrEF/HFpEF; dyslipidemia; hypertension; coronary artery disease; pulmonary hypertension) and drug classes (statins/ezetimibe/PCSK9 inhibitors and siRNA; SGLT2 inhibitors; ARNI; vericiguat; targeted anti-inflammatories; ATTR-specific therapy). Projects under development include: virtual library, QSAR/early tox filters, target position/affinity (docking), including AlphaFold 3 complex prediction (AF3 for joint complex prediction), network proximity, multi-omics signature matching, prioritized hit list. Representative studies (2014–2025) are synthesized, the effects presented, and a methodological scheme for further research developed.

Keywords**:** *cardiovascular, bioactive, network medicine, multi-omics, ML, QSAR, molecular docking, drug-repositioning, AlphaFold 3.*

ABORDARE COMPUTAȚIONALĂ INTEGRATĂ PENTRU ANALIZA COMPUȘILOR BIOACTIVI ÎN BOLILE CARDIOVASCULARE

Propunem o abordare metodologică, pas cu pas, pentru analiza computațională a compușilor bioactivi în bolile cardiovasculare (BCV), care integrează medicina de rețea/biologia sistemelor, integrarea multi-omică, AI/ML, QSAR, docking molecular/AlphaFold 3 și resursele chemogenomice. Fluxul de lucru se aliniază cu stratificarea clinică contemporană (HFrEF/HFmrEF/HFpEF; dislipidemie; hipertensiune arterială; boală coronariană; hipertensiune pulmonară) și clasele de medicamente (statine/ezetimib/inhibitori PCSK9 și siRNA; inhibitori SGLT2; ARNI; vericiguat; antiinflamatoare țintite; terapie specifică ATTR). Proiectele aflate în dezvoltare includ: bibliotecă virtuală, filtre QSAR/early tox, poziție/afinitate țintă (docking), inclusiv predicție complexă AlphaFold 3 (AF3 pentru predicția complexului articular), proximitate de rețea, potrivire a semnăturilor multi-omice, listă de rezultate prioritizate. Sunt sintetizate studii reprezentative (2014–2025), prezentate efectele și elaborate o schemă metodologică pentru investigațiile ulterioare.

Cuvinte-cheie*: cardiovascular, bioactiv, medicină de rețea, multi-omică, ML, QSAR, andocare moleculară, repoziționare de medicamente, AlphaFold 3.*

Introduction

Cardiovascular diseases caused ~19.8 million deaths (~32%) in 2022, with ~85% from myocardial infarction and stroke [1]. Heart failure subtypes by LVEF-HFrEF (<40%), HFmrEF (40–49%), and HFpEF (≥50%) - per 2021 ESC guidelines, differ in remodeling, inflammation, metabolism, and endothelial function [2].

Atherosclerosis and ischemic heart disease associate lipid-related risks (LDL-C, ApoB, Lp(a)) with IL-1β/NLRP3 signalling and oxidative stress, supported by multi-omics and network studies [7]. Hypertension and vascular remodelling involve RAAS, nitric oxide, oxidative stress, and inflammation [5]. Pulmonary hypertension subtypes align with endothelin, NO-cGMP, and prostacyclin pathways, as shown in PVDOMICS-style phenomics [22–24]. In inherited cases, ATTR cardiomyopathy demonstrates a validated structure-based approach with tafamidis [25].

Network-based computational methods are increasingly applied in CVD [11]. The hypothesis: integrating module-level network proximity with omics-based disease/drug signatures and structure-informed screening enhances mechanistic plausibility and candidate prioritization, including for natural compounds [3, 10–12].

Materials and methods

Design and Sources

We performed a systematic literature review (2014–2025) on computational methods for drug repurposing in CVD, following PRISMA 2020 for transparency and reproducibility [6]. Aligned with open-science principles, we prioritized sources supporting data/code availability. Key sources included PubMed/MEDLINE, AHA Journals, Nature Portfolio, and major cardiology society guidelines; ESC 2021 HF guidelines provided clinical context [2].

Search Strategy

Final searches were completed in mid-2025. Core Boolean queries (PubMed fields in brackets) were designed to capture computational approaches in cardiovascular disease (CVD), for example:

(„cardiovascular disease”[Title/Abstract] AND (repurposing OR “drug reposition*”) AND (network OR „multi-omics” OR QSAR OR docking OR AlphaFold)

(„heart failure” OR atherosclerosis OR “pulmonary hypertension”)[MeSH Terms] AND („machine learning” OR AI OR „drug–target interaction”)

To enhance clinical relevance, we included refinement tokens targeting specific phenotypes (HFrEF, HFmrEF, HFpEF), drug classes (SGLT2 inhibitors, ARNI, vericiguat), rare conditions (ATTR amyloidosis, tafamidis), and anti-inflammatory agents (colchicine, canakinumab).).

Inclusion and Exclusion Criteria

Inclusion: i) CVD focus plus ≥1 method: (A) network medicine; (B) multi-omics; (C) AI/ML for repurposing; (D) QSAR/in silico safety; (E) structural modeling (docking, MD, AlphaFold); (ii) methodological transparency (data/methods available; preference for open code/data); (iii) validation—external or experimental/clinical; QSAR/ML must align with OECD-style principles [9]; (iv) practical relevance (lab/clinical testing or independent cohorts); (v) alignment with clinical context (e.g., ESC 2021 HF) [2].

Exclusion: non-peer-reviewed, outside 2014-2025, or lacking transparency/validation.

QSAR/ML validation principles (per manuscript scope): applicability domain; external validation on independent sets; metrics (e.g., R^2/RMSE for regression; AUC/F1 for classification); model transparency and documentation [9].

Data extraction

We extracted standardized fields into evidence tables.

Clinical studies: population; endpoints; HR/RR; significance.

Network/Systems: proximity metrics; target/protein ranking strategies.

AI/ML: validation metrics (AUC, precision, recall, F1) on internal vs external cohorts; feature families (network proximity, omics signatures, mutational profiles).

QSAR: descriptors/fingerprints; R^2, RMSE; cross-validation; external test sets.

Docking/MD: software (AutoDock, Schrödinger, GROMACS), scoring functions, force fields, simulation timeframes; stability metrics (RMSD; binding free energy).

Resources recorded included PPI, small-molecule libraries, omics datasets, and registries; we noted availability of open code/data.

Synthesis and Comparative Framework

We organized approaches into five operational levels to show vertical integration (molecule → phenotype) and horizontal integration across computational modalities:

(A) network medicine/systems biology; (B) multi-omics integration; (C) AI/ML; (D) QSAR/toxicity; (E) clinical validation. Comparative tables summarize data types, scope, validation, and translational outputs.

Results

We identified computational approaches for drug repositioning and molecular stratification in CVD and grouped them into five levels within a single pipeline (Table 1; Figure 1). Levels progress from in-silico predictions to multi-stage clinical validation.

Table 1. Key computational approaches and their roles in CVD

Level	Method/ module	Purpose	Strength	Limitations	Typical data sources	Examples/ refs*
A	Network medicine; target–disease proximity metrics; disease-module mapping	Identify polytarget nodes; rank targets and candidates for repositioning	Systems-level perspective; integrates multiscale data; detects potential synergies	Incomplete/ noisy networks; static interactome snapshots	PPI networks; gene–disease databases; pathway databases	Network medicine in CVD [11]; multiomics network medicine [7]; network-based repositioning [3]
B	Integration of genomics, transcriptomics, proteomics, metabolomics	Phenotype stratification; identification of mechanistic "hotspots"; disease–drug signature matching	Mechanistic grounding; supports personalisation	Platform heterogeneity; sample-size/ normalisation requirements	GWAS; RNA-seq; proteomic and metabolomic profiles	Multi-omics framework [7]
C	AI/ML models for DTI and candidate ranking; multimodal integration	Prioritise compounds/targets using network and omics features	Scalable; captures non-linear patterns; potentially explainable	Risk of overfitting; label dependence; dataset bias	ChEMBL; LINCS/CMap; EHR/EMR; registries	Foundation model for repurposing [8]
D	QSAR / ML-QSAR; prediction of activity and ADMET (incl. cardiac risks)	Rapid structure–activity–toxicity filtering; early removal of unsuitable candidates	Speed; interpretability (for some models)	Limited applicability domain; dataset quality; need for external validation	Chemical descriptors/fingerprints; in-vitro toxicology	QSAR validation principles [9]
E	Clinical effectiveness (RCTs, meta-analyses, registries, RWE/EHR)	Confirm benefit/safety on clinical outcomes; translate computational hypotheses	RCT/meta-analysis publications; registries; EHR	Time/cost; inclusion criteria constraints	RCT/meta-analysis publications; registries; EHR	Examples in Table 4

Abbreviations: PPI - protein-protein interaction; DTI – drug-target interaction; ADMET - absorption, distribution, metabolism, excretion, toxicity; EHR - electronic health records.

Network-level analysis (Level A). T The network approach applied principles from network biology and medicine to identify therapeutic targets and candidate compounds. Diseases were modeled as modules within the human interactome; drugs were mapped via their target proteins in this network. The core concept was network proximity: drug targets located near disease modules were more likely to have therapeutic effects [3,11].

As shown in Figure 2, overlap or adjacency between drug targets and disease modules indicated potential efficacy, while proximity to adverse-reaction modules suggested side effect risk [3, 11]. We used interactome data and gene–disease association databases to define statistically significant disease modules and retrieve approved drugs linked to them [3,11]. Examples appear in Table 2.

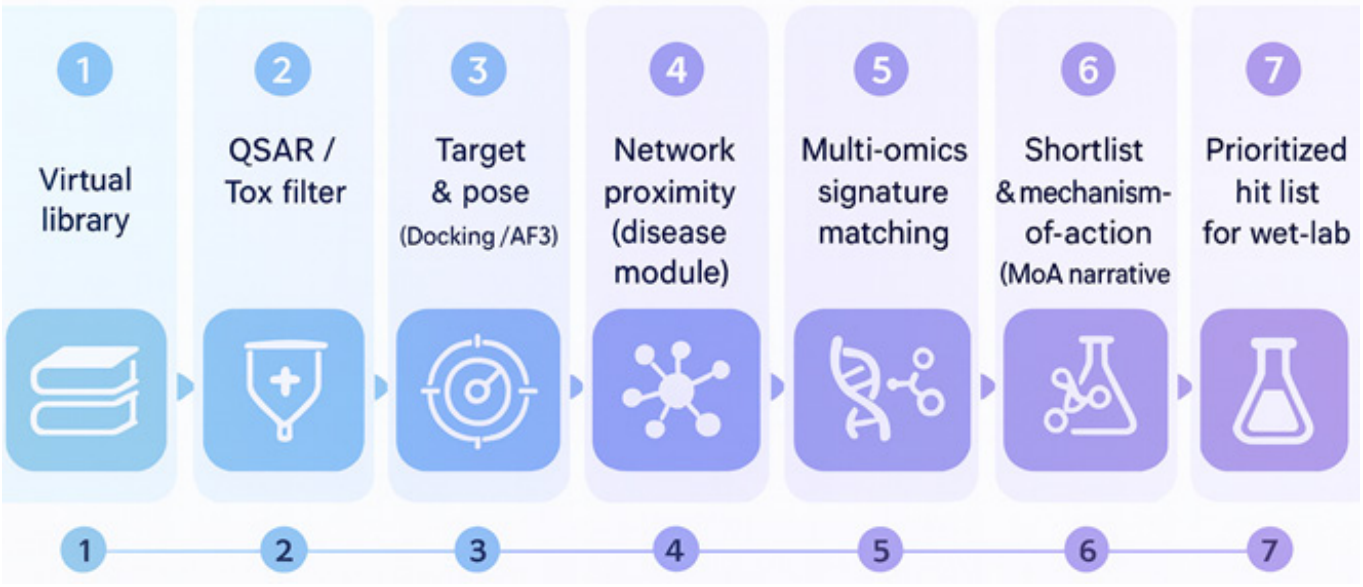

Figure 1. Integrated computational pipeline for drug repositioning in cardiovascular diseases (CVD): Virtual library → QSAR/Tox filter (quantitative structure–activity relationship/toxicity) → Target & pose (Docking/AF3 (AlphaFold 3)) → Network proximity (disease module) → multi-omics signature matching → Shortlist & mechanism-of-action (MoA) narrative → Prioritized hit list for wet-lab.

The aim at this level was to identify multi-target nodes—genes or proteins whose perturbation could modulate entire disease modules. Despite limitations from incomplete or noisy network data, this layer formed the foundation for downstream integration and candidate prioritization (Level A, Table 1).

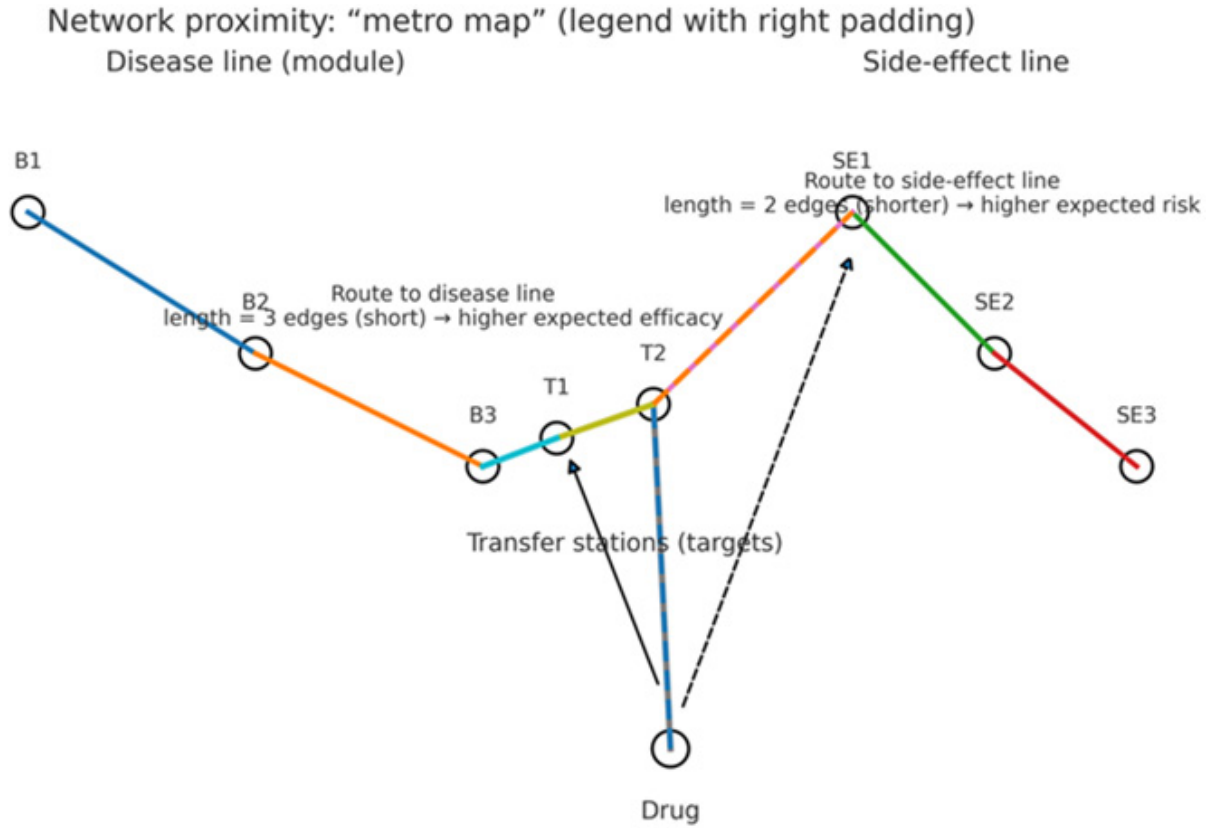

Figure 2. D–T–C (Disease–Target–Compound) schematic: network proximity of drug targets to the disease module and their relationship to modules of adverse effects (author’s schematic).

Table 2. Representative natural compounds and mechanisms in CVD

Compound (source)	Key targets/pathways and proposed effects	Evidence base (type of evidence)
Polyphenols: quercetin, luteolin, naringenin, punicalagin (various plants)	Anti-inflammatory and antioxidant effects; modulation of PI3K/Akt/NRF2; impact on lipid metabolism; possible effects on NLRP3/IL-1β	Integrative review of herbal bioactive in CVD (in silico with in vitro/in vivo confirmations) [15]; herb/target databases used for pathway mapping [16].
Salvianolic acids (Total Salvianolic Acid Injection, Salvia miltiorrhiza)	Cardioprotection in ischaemia-reperfusion: antioxidant/anti-apoptotic actions; pathways linked to oxidative stress and inflammation	Network pharmacology plus experimental verification (cell/animal ischaemia-reperfusion models) [17].
Compounds from Suaeda salsa (candidate ACE inhibitors)	ACE inhibition; potential antihypertensive and anti-remodelling activity	3D-QSAR, metabolomics, docking, and molecular dynamics; prioritisation of natural ACE inhibitors [18].
Imperatorin (Angelica dahurica and others)	Targeting ACE/post-MI remodelling pathways; anti-inflammatory/vasoprotective potential	Network pharmacology plus animal validation in post-infarction remodelling [19].

Multi-omics approaches integrated datasets across genomics, transcriptomics, proteomics, metabolomics, and related layers to support molecular stratification of CVD. Using large biobanks and patient-level data, we derived disease signatures that partitioned heterogeneous syndromes into subtypes sharing pathogenic pathways [7,20]. Table 3 shows examples of multi-omics biomarkers, such as gene-expression signatures linked to heart-failure phenotypes and associated target pathways. At this layer, the goal was to identify regulatory nodes, actionable targets, and match disease and drug signatures e.g., compounds that reverse pathological profiles [8]. Key challenges included high dimensionality, data heterogeneity, and variability.

Table 3. Classification of cardiovascular diseases (CVD) with a molecular focus

Clinical category	Dominant molecular mechanisms/markers	Priority targets/ pathways	Representative evidence
Heart failure: HFrEF / HFmrEF / HFpEF	Myocardial energetic shift (reduced fatty-acid β-oxidation with increased glycolysis), mitochondrial dysfunction, Ca^{2+} homeostasis, inflammation/fibrosis; NT-proBNP	SGLT2-linked metabolic axes; TGF-β/ECM (collagen, MMP/TIMP); Ca^{2+} regulation (SERCA2a/RYR); NO–sGC–cGMP	ESC heart-failure guideline on HF phenotypes [2]; metabolic remodelling in HF [20]
Ischaemic heart disease / atherothrombosis	Lipid cascade (LDL-C, ApoB, Lp(a)); inflammation (IL-1β/NLRP3); thrombosis	HMGCR (statins), PCSK9, NPC1L1; IL-1β / inflammatory cascade; antithrombotic targets (e.g., P2Y12)	Multi-omics/network framework for CVD [7]; anti-inflammatory therapy (CANTOS, IL-1β) [21]
Pulmonary hypertension (predominantly arterial)	Imbalance of vasoactive pathways: endothelin, NO–cGMP, prostacyclin; vascular remodelling	ETA/ETB (endothelin receptors), PDE5, sGC, IP (prostacyclin) receptors	PVDOMICS programme: phenomics and stratification in PH [22–24]

Inherited/rare forms (example: ATTR cardiomyopathy)	TTR amyloidogenesis; myocardial fibril deposition	TTR stabilisation (tafamidis); aggregation inhibition	ATTR-ACT: efficacy of TTR stabilisation [25]

Abbreviations: ECM - extracellular matrix; MMP/TIMP- matrix metalloproteinases / their tissue inhibitors; SERCA2a-sarcoplasmic reticulum Ca^{2+}-ATPase; RYR-ryanodine receptor; NO-sGC-cGMP-nitric oxide / soluble guanylate cyclase / cyclic GMP; ETA/ETB-endothelin receptor subtypes; PDE5-phosphodiesterase-5; IP-prostacyclin receptor; TTR-transthyretin.

Level 3 applied AI/ML to biomedical data, using features like network proximity, omics profiles, and mutations to rank drug candidates for CVD [8]. Strengths included scalability and non-linear modeling; key limitations were data demands, overfitting risk, and low interpretability [8]. Explainable AI (XAI) helped identify molecular features tied to therapeutic effects, though rare diseases and external validation remained challenging. This stage (Table 1) linked upstream network/omics data to cheminformatics, narrowing broad inputs into specific candidates.

Shortlisted compounds were assessed via molecular docking and QSAR to evaluate target binding and ADMET profiles. Docking predicted binding modes and interactions [10,12]; QSAR estimated activity/toxicity from chemical structure [9]. Docking was limited by static models and simplified scoring [10]; QSAR by training-set constraints and strict validation needs [9].

Clinical effectiveness and validation. This level completed the integrated pipeline by converting hypotheses generated at the molecular-target level (docking/AF3), and at the network and omics levels, into testable patient-level clinical effects. We summarized outcomes from large, randomized trials across key drug classes (Table 4) that exemplify repositioning or extension of indications in cardiology.

Table 4. Drug classes, targets, and outcome effects

Class/target	Drug(s) (example)	Population/ context	Key outcome/ effect	Pivotal trial
PCSK9 inhibitors	Evolocumab	ASCVD/CAD on background statins	Primary endpoint: HR = 0.85; LDL-C ↓ ≈ 59%	FOURIER [13]
PCSK9 inhibitors	Alirocumab	Post-ACS on intensive statins	Reduction in composite ischaemic events (MACE) (qualitative)	ODYSSEY OUTCOMES [14]
PCSK9 siRNA	Inclisiran	ASCVD/CAD on standard therapy	Sustained LDL-C ↓ ≈ 50% with twice-yearly dosing	ORION-10/11 [26]
SGLT2 inhibitors	Dapagliflozin	HFrEF	Composite “worsening HF / CV death”: HR = 0.74 (95% CI 0.65–0.85)	DAPA-HF [27]
SGLT2 inhibitors	Empagliflozin	HFrEF	Composite “HF hospitalisation / CV death”: HR = 0.75 (95% CI 0.65–0.86)	EMPEROR-Reduced [28]
ARNI (NEP + AT1)	Sacubitril/valsartan	HFrEF	Superiority to enalapril on the primary endpoint (qualitative)	PARADIGM-HF [30]

sGC stimulator	Vericiguat	Recently decompensated HFrEF	Reduced risk of CV death/HF hospitalisation (qualitative)	VICTORIA [31]
Anti-inflammatory (IL-1β)	Canakinumab	Post-MI with elevated CRP	Recurrent CV events: HR = 0.85 (95% CI 0.74–0.98)	CANTOS [21]
Anti-inflammatory (colchicine)	Colchicine (low dose)	Post-MI	Ischaemic events: HR = 0.77 (95% CI 0.61–0.96)	COLCOT [32]
Anti-inflammatory (colchicine)	Colchicine (low dose)	Chronic CAD	Composite outcome: HR = 0.69 (95% CI 0.57–0.83)	LoDoCo2 [33]
TTR stabiliser	Tafamidis	ATTR cardiomyopathy	↓ all-cause mortality and CV-related hospitalisations (qualitative)	ATTR-ACT [25]

Abbreviations: ASCVD - atherosclerotic cardiovascular disease; CAD - coronary artery disease; ACS - acute coronary syndrome; HF - heart failure; HFrEF- HF with reduced ejection fraction; HFpEF- HF with preserved ejection fraction; NEP - neprilysin; AT1 - angiotensin II type-1 receptor; sGC - soluble guanylate cyclase; CV - cardiovascular; MACE - major adverse cardiovascular events; MI - myocardial infarction; CRP - C-reactive protein; TTR - transthyretin.

PCSK9 Inhibition (Monoclonal Antibodies): In FOURIER, evolocumab plus statins reduced LDL-C by ~59% and CV events by 15% (HR 0.85; 95% CI 0.79–0.92; p<0.001) [13]. In ODYSSEY OUTCOMES, alirocumab reduced MACE post-ACS (HR 0.85; 95% CI 0.78–0.93; p<0.001) [14]. These support network-based prioritization of LDL-catabolic pathways (Table 4).

PCSK9-Targeting siRNA: Inclisiran, in ORION-10/11, showed ~50% LDL-C reduction with twice-yearly dosing (p<0.001) [26], aligning with network/multi-omics predictions for long-term PCSK9 suppression (Table 4).

SGLT2 Inhibitors: DAPA-HF: Dapagliflozin reduced HF worsening/CV death by 26% in HFrEF (HR 0.74; p<0.001) [27].

EMPEROR-Reduced: Empagliflozin reduced CV death or HF hospitalization by 25% (HR 0.75; p<0.001) [28].

EMPEROR-Preserved: Benefit extended to HFpEF (HR 0.79; p<0.001) [29]. These findings support multi-omics signals involving energetic remodelling and inflammation.

ARNI (Sacubitril/Valsartan): In PARADIGM-HF, ARNI outperformed enalapril in HFrEF (HR 0.80; p<0.001), reducing all-cause mortality [30], consistent with network models of cGMP signalling and ECM remodelling.

sGC Stimulation (Vericiguat): VICTORIA showed modest benefit post-HF decompensation (HR 0.90; p=0.02) [31], supporting the NO–sGC–cGMP pathway identified in network analyses.

Anti-inflammatory Strategies: CANTOS: Canakinumab lowered CV events via IL-1β inhibition (HR 0.85; p=0.021) without lipid changes [21]. COLCOT and LoDoCo2: Low-dose colchicine reduced events post-MI (HR 0.77) [32] and in stable CAD (HR 0.69; p<0.001) [33], validating multi-target anti-inflammatory strategies linked to the NLRP3/IL-1β axis.

ATTR Cardiomyopathy (TTR Stabilization): In ATTR-ACT, tafamidis reduced all-cause mortality (HR 0.70) and CV hospitalizations (RR 0.68) over 30 months [25], confirming predictions from structure-based binding models.

Conclusion

We propose a five-tier pipeline for cardiovascular drug repurposing, from chemical filters to phenotypic outputs. QSAR cardiotoxicity, docking/AlphaFold3, and multi-modal ML generate mechanistic hypotheses, which are mapped to disease modules via network proximity and omics signature matching to expose polypharmacology. Benchmarking against trial-validated classes (PCSK9, SGLT2, IL-1β) enhances translational relevance and reduces overfitting (Table 4). Key limitations include omics data variability, the need for interpretable and externally validated ML, and docking/MD constraints from force-field accuracy and limited biological context. Next steps involve longitudinal multi-omics, integration with real-world data (EHRs, registries), rare disease expansion, and coupling with high-throughput ex vivo or organ-on-chip platforms for accelerated validation [34,35]. This framework integrates AI/ML, docking, and network medicine into a scalable, clinically grounded strategy for precision cardiology.

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