Int J Clin Exp Med 2026;19(2):41-54
www.ijcem.com /ISSN:1940-5901/IJCEM0166648

Original Article

Associated genetic molecular pathway analysis for the current precision medicines of cardiovascular disease

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Received June 8, 2025; Accepted January 8, 2026; Epub February 15, 2026; Published February 28, 2026

Abstract: Purpose: To thoroughly explore the functions and underlying associated signaling pathways of currently emerging precision medicines for cardiovascular disease, a series of analyses were conducted. Methods: In this study, currently available precision medicines for cardiovascular disease were categorized into 6 types. Specific drug-target interaction profiles were constructed, and correlated molecular pathways were further identified through enrichment analysis. Results: The precision medicines were divided into 6 categories, namely calcium channel blockers, lipid-lowering drugs, antihypertensive drugs, antithrombotic drugs, antiarrhythmic drugs, and diuretics. For calcium channel blockers: 18 agents were selected, and their target genes were identified. CACNA1C emerged as the most frequently targeted gene, while Benidipine targeted the largest number of genes (13 genes). For lipid-lowering drugs: 29 drugs were included, with HMGCR recognized as the most promising target gene. For antihypertensive drugs: A total of 72 drugs were collected. ADRB1 was found to be the most targeted gene, with 10 drugs targeting it. For antithrombotic drugs: PTGIR and P2RY12 were the most frequently targeted genes, each with five related drugs. For antiarrhythmic drugs: 18 drugs and their corresponding target genes were identified, with SCN5A being the most targeted gene. For diuretics: Approximately 14 drugs and their target genes were obtained, and SLC12A3 was the target gene which was most interacted with. Conclusions: Based on this innovative study, currently emerging precision medicines for cardiovascular disease can be classified into 6 types. The functions of their targeted genes were also investigated, collectively providing valuable references for future clinical drug administration.

Keywords: Cardiovascular disease, drug, genetic interacting network, targeted genes, signaling pathways

Introduction

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality globally. It accounts for roughly one-third of deaths worldwide, with 17.8 million fatalities in 2017 - representing a 21.1% increase from 2007 [1]. The root cause of most cardiovascular diseases is atherosclerosis. Cardiovascular diseases arising from atherosclerosis presents as acute and chronic ischemic syndromes, such as acute coronary syndromes, aneurysms, angina pectoris, claudication, ischemic stroke, congestive heart failure, and both sudden and non-sudden cardiac death [2].

Atherosclerosis is characterized by the formation of lipid- and cell-rich plaques in mid- to large-sized arteries [3]. After initiation, leukocytes infiltrate the arterial wall, triggering vascular inflammation, plaque expansion, calcification, and instability. Eventually, this leads to plaque rupture or erosion, which causes catastrophic arterial thrombosis. Such thrombosis results in partial or complete occlusion of the affected artery, thereby inducing clinical symptoms [4].

Another major type of cardiovascular disease is hypertension. As one of the most prevalent diseases worldwide, hypertension can cause multi-organ damage. Its incidence is approximately 47% in the United States and 55% in Europe [5]. Hypertension is defined differently by various guidelines: according to the American Heart Association (AHA) and the American College of Cardiology (ACC), it refers to persistent systolic blood pressure (SBP) ≥130 mm Hg

https://doi.org/10.62347/XWJF1774

and/or diastolic blood pressure (DBP) ≥80 mm Hg; per the International Society of Hypertension (ISH), it is defined as persistent SBP ≥140 mm Hg and/or DBP ≥90 mm Hg; it also includes patients taking antihypertensive medication [6]. As detailed in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), the objective of antihypertensive therapy is to minimize morbidity and mortality using the least invasive approaches available. The primary goal of long-term treatment is not only to reduce overall mortality but also to decrease cardiovascular deaths by mitigating the risks of stroke and myocardial infarction [7].

Arrhythmia is another key component of cardiovascular diseases. Manifesting as single or multiple irregular heartbeats, arrhythmia is one of the most common cardiovascular conditions [8]. Risk factors for life-threatening cardiac arrhythmias include myocardial infarction, cardiac ischemia, cardiomyopathy, and certain medications. Abnormal heart rhythms - particularly atrial fibrillation and ventricular fibrillation - are significant contributors to both disability and mortality. In the Western world, sudden cardiac death (SCD) accounts for 10-20% of adult deaths, causing 0.5 to 1 million fatalities annually among North Americans and Europeans, with ventricular fibrillation being the primary underlying cause [9].

Pharmacotherapy is a crucial approach for treating cardiovascular diseases. Currently, personalized precision medicine has been arising as a great potential to reduce the burden of this common and complex disease cluster. Its key pillars are diagnostics; prediction (of the primary disease); prevention (of the primary disease); prognosis (prediction of complications of the primary disease); treatment (of the primary disease or its complications); and monitoring (of risk exposure, treatment response, and disease progression or remission). However, the underlying molecular mechanisms as well as correlated genetic networks are still under controversial. For most researchers, there is a lack of systematic study for better understanding of these complicated medicines.

To this end, in this study, we classify cardiovascular disease drugs into 6 types and explore their target genes and corresponding functions.

Material and methods

Drug searching and drug-gene network construction

We divided cardiovascular disease related drugs into 6 categories mainly according to Anatomical Therapeutic Chemical (ATC) classification based on previously published work [10].

The ATC classification of unknown compounds is a multi-label classification system, which was created by the World Health Organization (WHO). This system categorizes drugs into classes based on their therapeutic effects as well as characteristics. The ATC classification system simultaneously considers anatomical distribution, therapeutic effects, and chemical characteristics as well.

We have selected the target genes with positive pharmacological effects for these drug's targeting. The drug searching and their target gene chosen was used by DrugBank database. Then using cytoscape v3.10.0 we visualized interactions between drug and target gene with a threshold with $P<0.05$.

Enrichment analysis

Over-representation analysis (ORA) was used to determine the enrichment pathway by using a list of genes through the clusterProfiler R package [11]. Gene ontology (GO) and KEGG (Kyoto Encyclopedia of Genes and Genomes) terms with adjusted *p*-values <0.05 were selected. The enrichplot R package (https://github.com/GuangchuangYu/enrichplot) was used to visualize the results.

Protein-protein interaction analysis

The proteins identified in the intersection were entered into the STRING database (https://string-db.org/) to gather information about the protein interaction network [12]. The organism screening condition was set to "Homo sapiens", and the minimum necessary interaction score was set to "highest confidence (0.9)" [13]. The protein-protein interaction (PPI) data was loaded into Cytoscape 3.10.0 for display and used to form a PPI network.

Results

Calcium channel blockers

In this study, we searched for and selected 18 calcium channel blockers. Their corresponding target genes were also identified, and the interaction network between these 18 drugs and 18 target genes was constructed (**Figure 1A**). We found that CACNA1C was the most frequently targeted gene, followed by CACNA1D as the second most targeted gene. Meanwhile, benidipine targeted the largest number of genes (13 genes).

Subsequently, to analyze the functions of these target genes, enrichment analyses - including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses - were performed. For the GO analysis: The most enriched biological process (BP) terms were "calcium ion transmembrane transport" and "calcium ion transport". The most enriched cellular component (CC) terms were "voltage-gated calcium channel complex" and "calcium channel complex". The most enriched molecular function (MF) terms were "voltage-gated calcium channel activity" and "high-voltage-gated calcium channel activity" (**Figure 1B**).

The KEGG analysis revealed that the most enriched pathways included "MAPK signaling pathway", "Arrhythmogenic right ventricular cardiomyopathy", and "Cardiac muscle contraction" (**Figure 1C**). Protein-protein interaction (PPI) analysis was also conducted, and results showed that all calcium channel-related genes among the target genes interacted with one another (**Figure 1D**, **1E**).

Lipid-lowering drugs

Atherosclerosis progression, which leads to coronary heart disease (CHD), stroke, and stenosis in carotid and femoral arteries (peripheral vascular disease), is associated with multiple cardiovascular disease risk factors, including hyperlipidemia [14]. Current evidence indicates that hyperlipidemia arises from elevated low-density lipoprotein cholesterol (LDL-C) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels. Thus, the urgent priority in treating hyperlipidemia is to lower LDL-C levels [15].

In this study, 29 lipid-lowering drugs were examined, 25 target genes were identified, and drug-target interactions were established (**Figure 2A**). The findings revealed that HMGCR was the most frequently targeted gene, with 10 drugs found to target it; PPARA was the second most targeted gene. Meanwhile, icosapent targeted the largest number of genes among all the drugs studied.

Subsequently, enrichment analyses - including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses - were performed. For the GO analysis: The most enriched biological process (BP) terms included "lipid localization", "cholesterol metabolic process", and "secondary alcohol metabolic process". The most enriched molecular function (MF) terms included "nuclear receptor activity", "ligand-activated transcription factor activity", and "transcription coregulator binding" (**Figure 2B**).

The KEGG analysis results showed that the most enriched pathways were "Cholesterol metabolism" and "PPAR signaling pathway" (**Figure 2C**). Protein-protein interaction (PPI) analysis of the target genes was also conducted (**Figure 2D**, **2E**). PPARA interacted with the largest number of proteins (16 proteins), while HMGCR, PPARG, and SREBF1 interacted with the second largest number of proteins (13 proteins each).

Anti-hypertension drugs

Anti-hypertensive medication is a well-established approach for lowering blood pressure (BP) and preventing myocardial infarction, heart failure, ischemic or hemorrhagic stroke, and end-stage renal disease [16].

In this study, we identified the target genes of 72 anti-hypertensive drugs and subsequently constructed drug-target interaction networks (**Figure 3A**). The results showed that ADRB1 was the most frequently targeted gene, with 10 drugs found to target it, while ACE was the second most targeted gene.

Subsequently, enrichment analyses - including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses - were performed. For the GO analysis: The most enriched biological process (BP) terms includ-

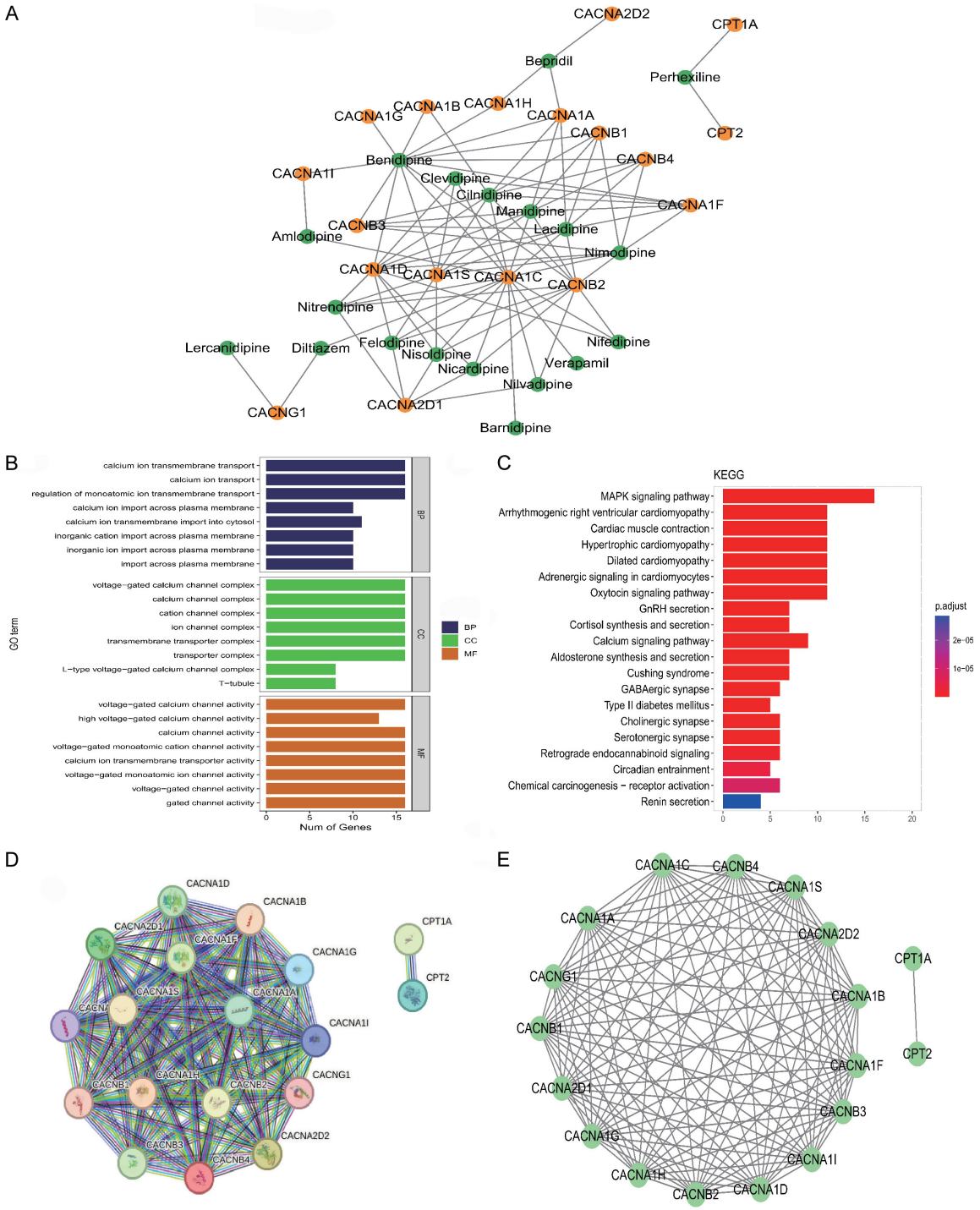

Figure 1. The genetic molecular mechanism examination for calcium channel blockers of cardiovascular disease. A. The target genes analysis with positive pharmacological effects chosen from DrugBank database using cytoscap. B, C. The GO and KEGG analysis. D. The Protein-protein interaction (PPI) analysis. E. The network diagram between all calcium channel-related genes.

ed “regulation of blood circulation”, “regulation of tube diameter”, and “blood vessel diameter maintenance”. The most enriched cellular component (CC) terms included “dopaminergic synapse”, “synaptic membrane”, and “axon terminus”. The most enriched molecular function

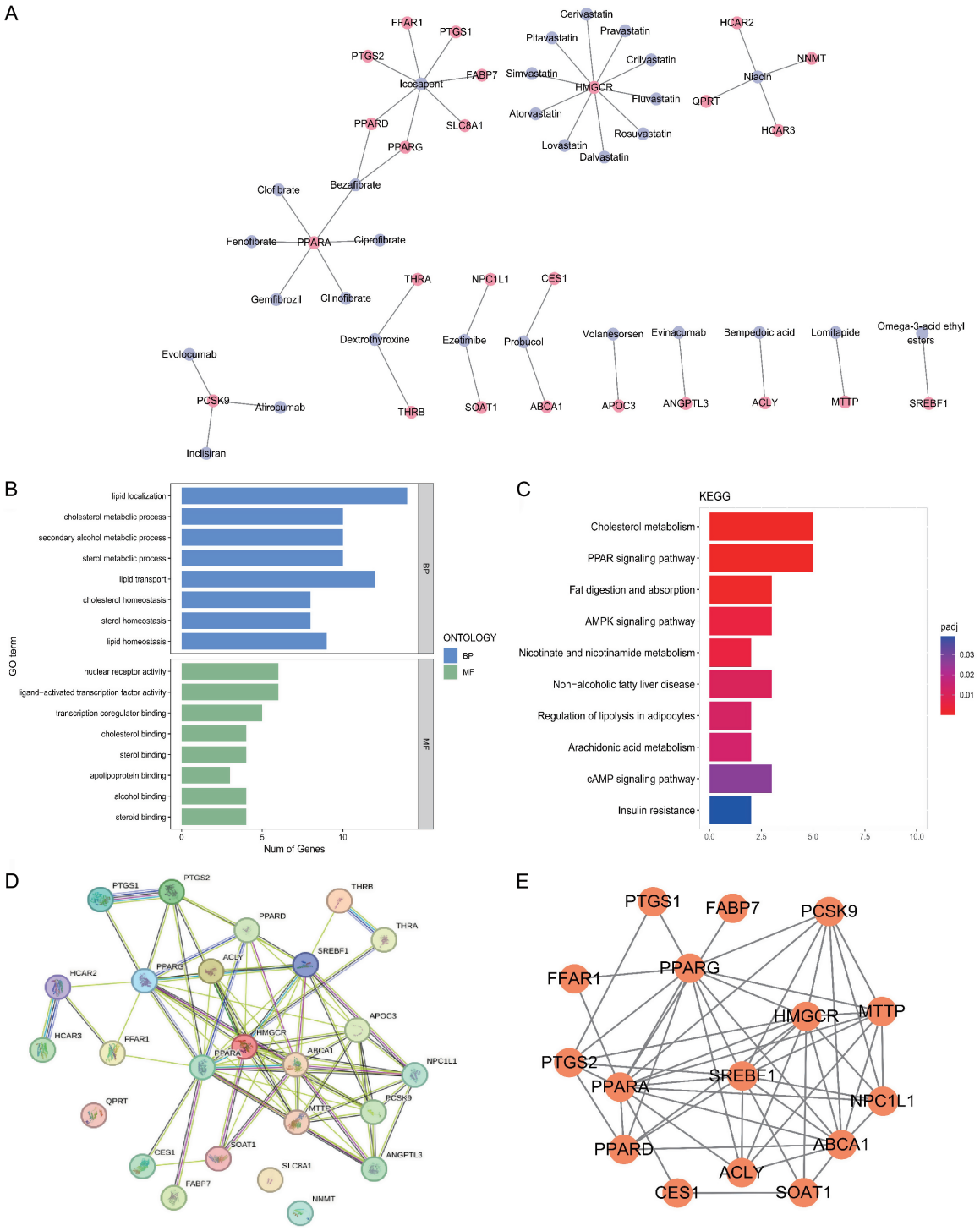

Figure 2. The genetic molecular mechanism examination for lipid-lowering drugs of cardiovascular disease. A. The target genes analysis with positive pharmacological effects chosen from DrugBank database using cytoscap. B, C. The GO and KEGG analysis. D. The Protein-protein interaction (PPI) analysis. E. The network diagram between all lipid-lowering drugs-related genes.

(MF) terms included “G protein-coupled amine receptor activity”, “catecholamine binding”, and “ligand-gated monoatomic cation channel activity” (**Figure 3B**).

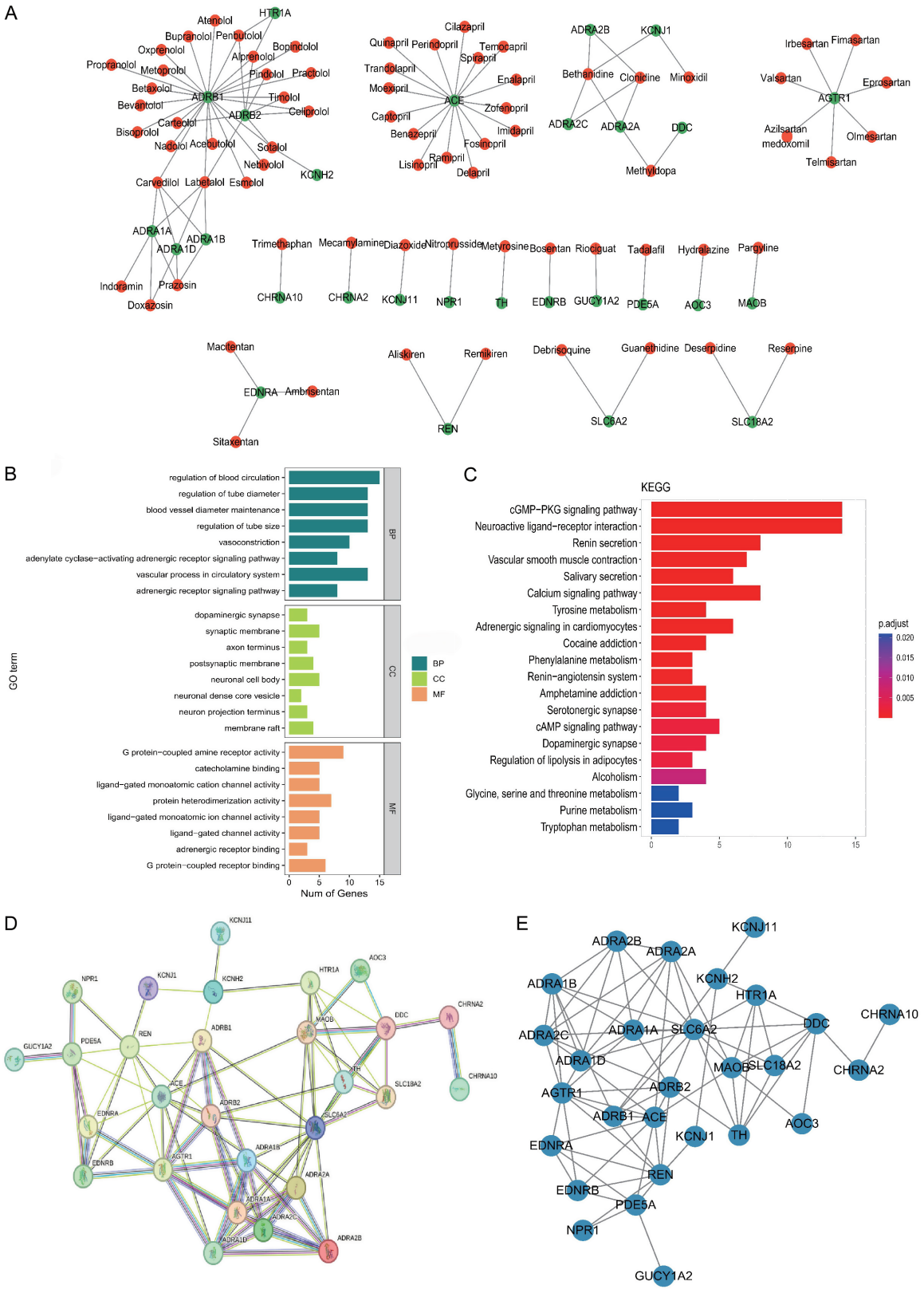

Figure 3. The genetic molecular mechanism examination for anti-hypertension drugs of cardiovascular disease. A. The target genes analysis with positive pharmacological effects chosen from DrugBank database using cytoscap. B, C. The GO and KEGG analysis. D. The Protein-protein interaction (PPI) analysis. E. The network diagram between all anti-hypertension drugs-related genes.

The KEGG analysis results revealed that the most enriched pathways were “cGMP-PKG signaling pathway”, “Neuroactive ligand-receptor interaction”, and others (**Figure 3C**). Protein-protein interaction (PPI) analysis of the target genes was also conducted (**Figure 3D**, **3E**). SLC6A2 interacted with the largest number of proteins (13 proteins), while ACE and AGTR1 interacted with the second largest number of proteins (10 proteins each).

Anti-thrombotic drugs

Blood clots in the body, known as thrombosis, are the leading cause of a quarter of deaths worldwide. Thrombosis is classified into two types: arterial thrombosis (AT) and venous thrombosis (VT) [17]. Hyperlipidemia, smoking, diabetes, hypertension, chronic kidney disease, and obesity are the main causes of arterial thrombosis. Patients with arterial thrombosis have a higher risk of developing venous thrombosis, and vice versa [18].

In this study, we identified the target genes of 26 drugs used to prevent blood clotting and subsequently explored the drug-target interactions (**Figure 4A**). We found that PTGIR and P2RY12 were the most frequently targeted genes, with five drugs targeting each. The second most targeted genes were F10, FLG, and FGA.

Subsequently, enrichment analyses - including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses - were performed. For the GO analysis: the most enriched biological process (BP) terms included “blood coagulation”, “coagulation”, and “hemostasis”. The most enriched cellular component (CC) terms included “external side of plasma membrane”, “blood microparticle”, and “platelet alpha granule”. The most enriched molecular function (MF) terms included “prostanoid receptor activity”, “prostaglandin receptor activity”, and “icosanoid receptor activity” (**Figure 4B**).

The KEGG analysis results showed that the most enriched pathways were “Platelet activation” and “Complement and coagulation cascades” (**Figure 4C**). Protein-protein interaction (PPI) analysis of the target genes was also conducted (**Figure 4D**, **4E**). PTGS1 interacted with the largest number of proteins (10 proteins), while ITGA2B, PTGS2, and F2 interacted with the second largest number of proteins (9 proteins each).

Anti-arrhythmic drugs

Cardiac arrhythmias are a major cause of morbidity and mortality worldwide. In this study, we first identified 18 drugs for preventing cardiac arrhythmia and their corresponding target genes, then explored the drug-target interactions (**Figure 5A**). We found that SCN5A was the most frequently targeted gene, with 13 drugs targeting it.

Subsequently, enrichment analyses - including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses - were performed. For the GO analysis: the most enriched biological process (BP) terms included “regulation of monoatomic ion transmembrane transport” and “action potential”. The most enriched cellular component (CC) terms included “cation channel complex” and “ion channel complex”. The most enriched molecular function (MF) terms included “voltage-gated monoatomic cation channel activity” and “voltage-gated monoatomic ion channel activity” (**Figure 5B**).

The KEGG analysis results showed that the most enriched pathways were “Adrenergic signaling in cardiomyocytes” and “cGMP-PKG signaling pathway” (**Figure 5C**). Protein-protein interaction (PPI) analysis of the target genes was also conducted (**Figure 5D**, **5E**). KCNH2 interacted with the largest number of proteins (20 proteins), while CACNA1C interacted with the second largest number of proteins (19 proteins).

Diuretics

Diuretics are one of the most common prescription drugs. They are defined as drugs that promote the excretion of water and electrolytes by the kidneys, thereby increasing the flow rate of urine [19].

In this study, firstly, we found 14 diuretics and their target genes were also obtained. Then, we explored the connection between the drugs and their target genes (**Figure 6A**). We found that SLC12A3 is the gene most often targeted, with 8 drugs having been found to target SLC12A3.

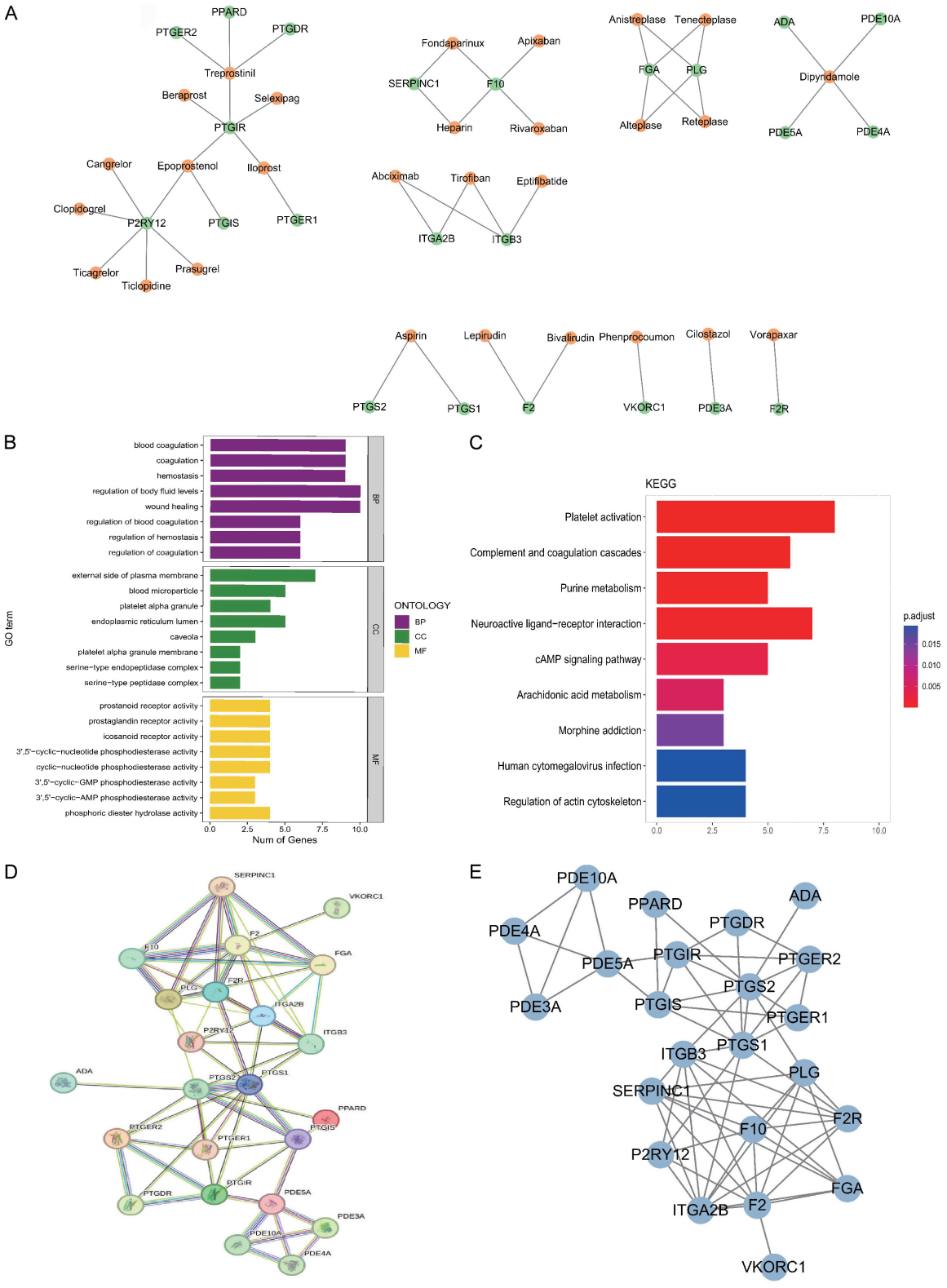

Figure 4. The genetic molecular mechanism examination for anti-thrombotic drugs of cardiovascular disease. A. The target genes analysis with positive pharmacological effects chosen from DrugBank database using cytoscap. B, C. The GO and KEGG analysis. D. The Protein-protein interaction (PPI) analysis. E. The network diagram between all anti-thrombotic drugs-related genes.

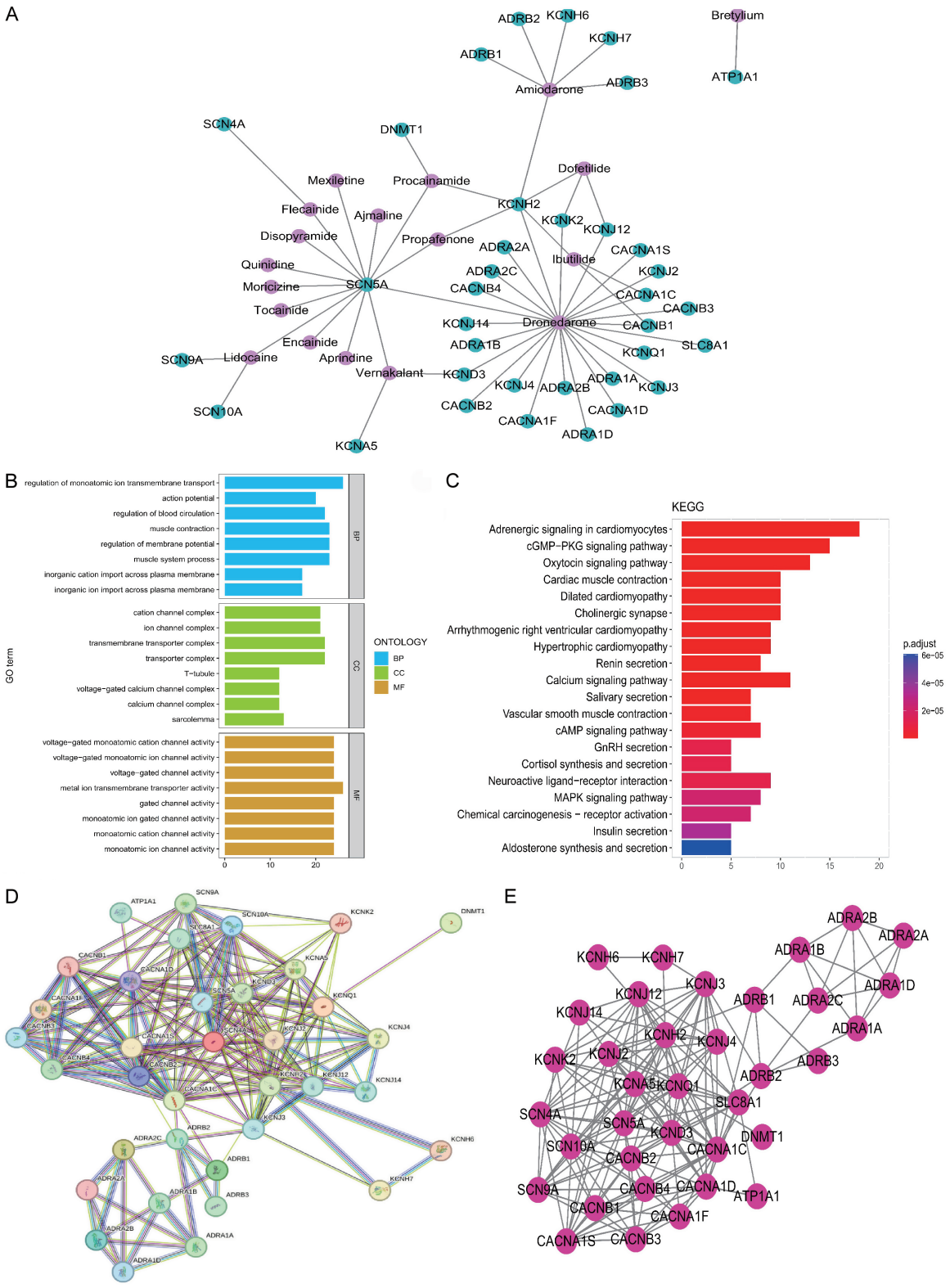

Figure 5. The genetic molecular mechanism examination for anti-arrhythmic drugs of cardiovascular disease. A. The target genes analysis with positive pharmacological effects chosen from DrugBank database using cytoscap. B, C. The GO and KEGG analysis. D. The Protein-protein interaction (PPI) analysis. E. The network diagram between all anti-arrhythmic drugs-related genes.

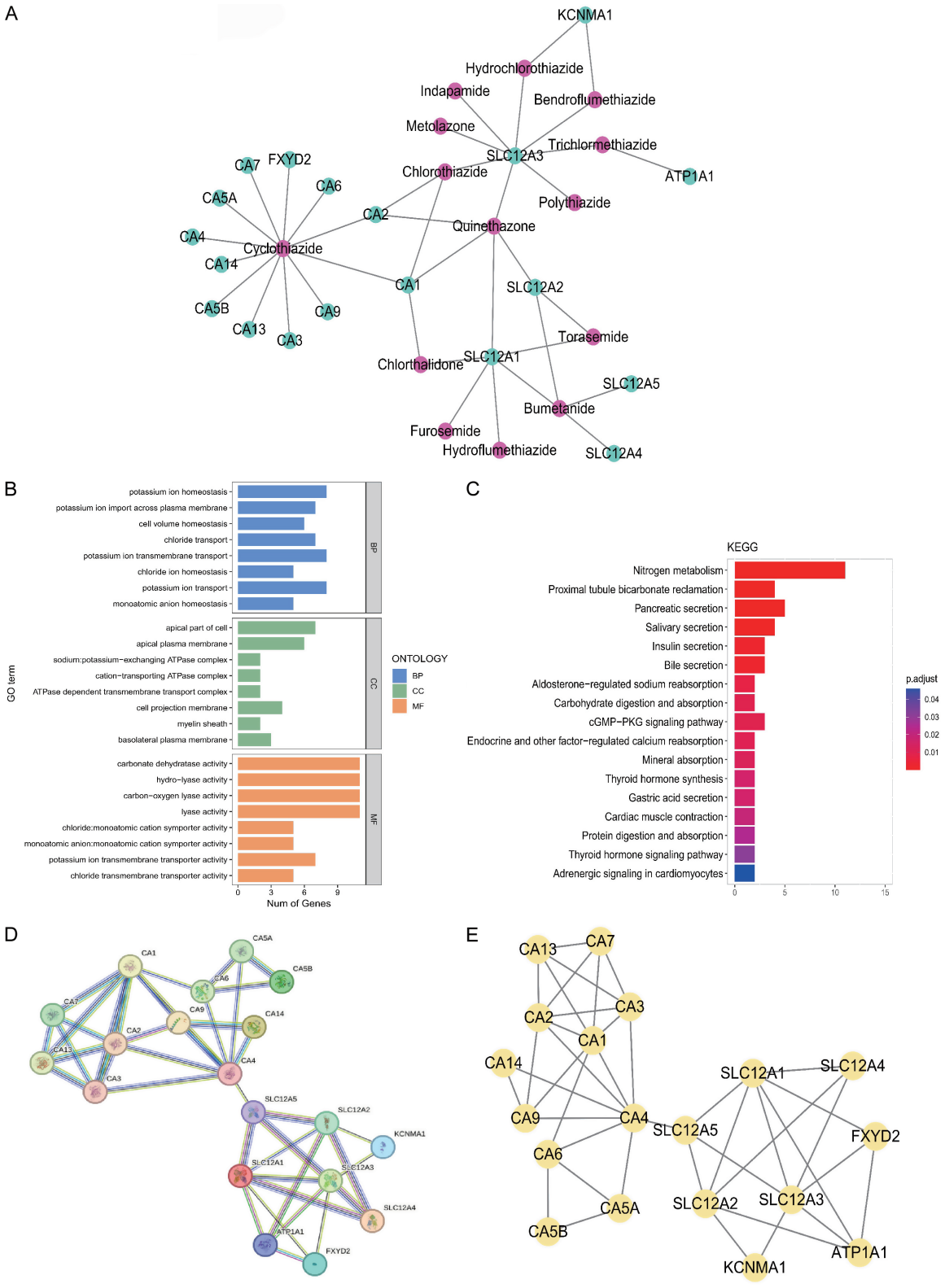

Figure 6. The genetic molecular mechanism examination for diuretics of cardiovascular disease. A. The target genes analysis with positive pharmacological effects chosen from DrugBank database using cytoscap. B, C. The GO and KEGG analysis. D. The Protein-protein interaction (PPI) analysis. E. The network diagram between all diuretics-related genes.

Enrichment analysis, including GO analysis and KEGG analysis, was then performed. GO analysis show that the most enriched BP item was "potassium ion homeostasis", "potassium ion import across plasma membrane". The most enriched CC items were "apical part of cell", "apical plasma membrane" and other entries. The most enriched MF items were "carbonate dehydratase activity", "hydro-lyase activity" and so on (**Figure 6B**). KEGG results show that the most enriched KEGG items were "Nitrogen metabolism", "Proximal tubule bicarbonate reclamation" and others (**Figure 6C**).

Protein-protein interaction of target gene was also conducted (**Figure 6D**, **6E**). CA4 can interact with the most proteins, interacting with 8 proteins. CA1 can interact with the second most proteins, interacting with 7 proteins.

Discussion

Cardiovascular disease (CVD), encompassing heart disease and vascular disorders, stands as a leading cause of morbidity and mortality globally and constitutes a major public health challenge. In the present study, based on the targeted diseases, pharmacological functions, and action sites of the drugs, we classified CVD-related precision medicines into 6 categories. Subsequently, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on the target genes of each drug category.

Based on their target site, calcium channel blockers were grouped into a single category. Calcium ions entering cells via calcium channels bind to calmodulin [20]. The calcium-calmodulin complex then binds to and activates myosin light chain kinase (MLCK), which catalyzes the phosphorylation of the regulatory light chain subunit of myosin - a crucial step in muscle contraction. Calcium channel blockers inhibit the extracellular calcium influx through ion-specific transmembrane channels. Although multiple channel subtypes have been identified, clinically available calcium channel blockers primarily target L-type channels in humans. Blockade of inward calcium flux induces relaxation of vascular smooth muscle cells, resulting in vasodilation and reduced blood pressure (BP) [21]. In cardiac muscle, this leads to decreased contractility, slowed sinus node pacemaker activity, and reduced atrioventricular conduction velocity. In the kidneys, calcium channel blockers promote natriuresis by increasing renal blood flow, dilating afferent arterioles, and enhancing glomerular filtration pressure [22]. Non-dihydropyridine calcium channel blockers alleviate albuminuria by improving glomerular permselectivity and/or reducing renal perfusion pressure.

Notably, our findings demonstrated that CACNA1C is the most frequently targeted gene for calcium channel blocker-based precision medicine. The CACNA1C gene encodes the pore-forming subunit of the CaV1.2 L-type Ca^{2+} channel, a critical component of membrane physiology in multiple tissues including the heart, brain, and immune system. The first identified mutations in CACNA1C were shown to cause Timothy syndrome (TS), a severe multisystem disorder characterized by neurodevelopmental deficits, long-QT syndrome, life-threatening cardiac arrhythmias, craniofacial abnormalities, and immune impairments [23]. Moreover, patients with CACNA1C mutations predominantly present with cardiac or neurological symptoms.

In addition to calcium channel blockers, in this study, 25 target genes were identified among 29 lipid-lowering drugs, and drug-target interaction networks were established. HMGCR emerged as the most frequently targeted gene, with 10 drugs interacting with it. Drugs targeting HMGCR are known as statins, which act as competitive inhibitors of HMG-CoA reductase and are widely used as highly effective lipid-lowering agents. They directly block the enzyme's active site, inhibiting the conversion of HMG-CoA to mevalonate - the rate-limiting step in the upstream pathway of cholesterol biosynthesis [24]. In humans, plasma cholesterol is derived from dietary intake or de novo cellular synthesis. Statins reduce serum cholesterol levels by suppressing de novo cholesterol production and modulating the expression of low-density lipoprotein (LDL) receptors [25]. All statins exert a non-linear, dose-dependent effect on lowering serum LDL but differ in their absorption, excretion, and solubility profiles [26].

Following HMGCR, PPARA was the second most frequently targeted gene. Peroxisome proliferator-activated receptor-α (PPAR-α) belongs to the ligand-activated nuclear hormone receptor

superfamily and plays a pivotal role in lipid metabolism and glucose homeostasis [27, 28]. Fibrates act as PPAR-α agonists, and their tolerability, safety, lipid-lowering efficacy, and ability to inhibit atherosclerosis progression have been extensively investigated [29]. Clinically, fibrates reduce plasma triglyceride (TG) or TG-rich lipoprotein (TRL) levels and increase high-density lipoprotein (HDL) concentrations through multiple PPAR-α-mediated mechanisms, including: (1) enhanced lipolysis via activation of lipoprotein lipase (LPL) and suppression of apolipoprotein C-III (ApoC-III); (2) increased hepatic fatty acid uptake through induction of fatty acid transporter protein (FATP) and acyl-CoA synthetase; and (3) upregulated synthesis of apolipoprotein A-I (ApoA-I) and apolipoprotein A-II (ApoA-II) [30].

Our results identified ADRB1 as the most frequently targeted gene associated with antihypertensive medications. Both α- and β-adrenoceptors belong to the G protein-coupled receptor (GPCR) superfamily, which transduces signals into cells via coupling to guanine nucleotide regulatory proteins (G proteins). Regarding α-adrenoceptors: postsynaptic α_1 receptors on vascular smooth muscle mediate smooth muscle contraction, whereas presynaptic α_2 receptors on sympathetic nerve endings regulate neurotransmitter release [31]. β-receptors are classified into β_1, β_2, and potentially β_3 subtypes based on their tissue distribution, distinct agonist/antagonist selectivity, and biological functions [32].

Based on their adrenoceptor targets, we claim that the drugs can be classified as follows: α_1-adrenoceptor blockers: indoramin, doxazosin, and prazosin; α_2-adrenoceptor agonists (note: corrected from "blockers" based on pharmacological accuracy): bethanidine, clonidine, and methyldopa; α_1/β-adrenoceptor blockers: carvedilol and labetalol; β_2/β_2-adrenoceptor blockers: penbutolol, alprenolol, pindolol, timolol, celiprolol, sotalol, and carteolol; β_1-adrenoceptor blockers: nebivolol, esmolol, bevantolol, betaxolol, acebutolol, atenolol, metoprolol, practolol, bupranolol, bopindolol, bisoprolol, nadolol, propranolol, oxprenolol, and carvedilol.

Antithrombotic agents are categorized into three classes: antiplatelet agents, anticoagulants, and fibrinolytics [33]. Four main FDA-approved antiplatelet agents are currently available: cyclooxygenase inhibitors (e.g., aspirin), $P2Y_{12}$ antagonists (e.g., prasugrel, clopidogrel, and ticagrelor), $\alpha IIb\beta_3$ antagonists (e.g., abciximab), and protease-activated receptor 1 (PAR1 or F2R) antagonists (e.g., vorapaxar) [34]. Aspirin irreversibly acetylates a serine residue in cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2), thereby inhibiting the synthesis of prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2), and subsequently reducing thromboxane A_2 (TXA_2) production [35]. For patients with established atherosclerotic disease, aspirin is the preferred antiplatelet agent for both acute and long-term secondary prevention of ischemic events.

$P2Y_{12}$ is a G protein-coupled receptor that binds adenosine diphosphate (ADP). This binding activates intracellular signaling pathways and induces conformational changes in GPIIb/IIIa receptors, enhancing sustained platelet aggregation and increasing the receptors' affinity for their primary ligand, soluble fibrinogen. Currently available $P2Y_{12}$ inhibitors are divided into two families: thienopyridines (i.e., ticlopidine, clopidogrel, and prasugrel) and nucleoside-nucleotide derivatives (i.e., ticagrelor and cangrelor) [36].

Class I antiarrhythmic drugs, such as quinidine, procainamide, and disopyramide - antagonize fast sodium channels, leading to prolonged depolarization (QRS complex widening) and slowed cardiac conduction. Abnormal activity of these channels can trigger certain tachyarrhythmias. The cardiac sodium channel is voltage-dependent and consists of a transmembrane pore-forming α-subunit (Nav1.5, encoded by the SCN5A gene) linked to auxiliary modulatory β-subunits. Activation (opening) of sodium channels allows sodium ion influx into cardiomyocytes, depolarizing the cell membrane and thereby promoting the activation of L-type calcium channels, calcium influx, and myocardial contraction. Our study identified SCN5A as a key target among all class I antiarrhythmic drugs.

Diuretics are extensively used in cardiovascular medicine and are currently recommended as one of the first-line therapeutic options for uncomplicated essential hypertension. They are formally indicated for hypertension complicated by congestive heart failure and/or renal

insufficiency, and are considered mandatory for all types of congestive heart failure in the absence of definite contraindications [37]. Diuretics are typically classified based on their primary site of action along the nephron and their underlying inhibitory mechanisms. Loop diuretics, such as furosemide, bumetanide, and torsemide, act on the luminal side of the thick ascending limb of the loop of Henle and the macula densa, where they inhibit the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2, encoded by SLC12A1). As organic anions, these agents bind to the translocation pocket of the transporter by interacting with the chloride-binding site; due to their larger molecular size compared to chloride ions, they cannot traverse the pocket, thereby abrogating transporter function [38]. Distal convoluted tubule diuretics, specifically thiazides and thiazide-like drugs, are also organic anions that exert their effects via the thiazide-sensitive Na^+-Cl^- cotransporter (NCC), encoded by SLC12A3, in the distal convoluted tubule. Importantly, the luminal site of action is a key mechanistic feature underlying the functionality of both loop and distal convoluted tubule diuretics.

In summary, the present study classified emerging CVD precision medicines into 6 categories based on their pharmacological functions. For each category, we identified the corresponding target genes, constructed drug-target interaction networks, and performed enrichment analyses of the target genes. These findings provide valuable insights and a foundation for future cardiovascular pharmacogenetics research.

Disclosure of conflict of interest

None.

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