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Editorial Board Member of *World Journal of Cardiology*, Akash Batta, MD, DM, Assistant Professor, Department of Cardiology, Dayanand Medical College and Hospital, Civil Lines, Ludhiana, Punjab 141001, India. dr_akash_batta@dmch.edu

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EDITORIAL

Recent advances in the diagnostic methods and therapeutic strategies of transthyretin cardiac amyloidosis

Christos Kourek, Alexandros Briasoulis, Dimitrios E Magouliotis, Panagiotis Georgoulias, Grigorios Giamouzis, Filippos Triposkiadis, John Skoularigis, Andrew Xanthopoulos

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Christos Kourek, Clinical Ergospirometry, Exercise and Rehabilitation Laboratory, 1st Critical Care Medicine Department, Evangelismos Hospital, National and Kapodistrian University of Athens, Athens 10676, Greece

Alexandros Briasoulis, Department of Clinical Therapeutics, Alexandra Hospital, Faculty of Medicine, National and Kapodistrian University of Athens, Athens 11528, Greece

Dimitrios E Magouliotis, Department of Cardiothoracic Surgery, University of Thessaly, Larissa Biopolis, Larissa 41110, Greece

Panagiotis Georgoulias, Department of Nuclear Medicine, University Hospital of Larissa, Larissa 41110, Greece

Grigorios Giamouzis, Filippos Triposkiadis, John Skoularigis, Andrew Xanthopoulos, Department of Cardiology, School of Medicine, University Hospital of Larissa, Larissa 41110, Greece

Corresponding author: Andrew Xanthopoulos, MD, PhD, Postdoctoral Fellow, Department of Cardiology, School of Medicine, University Hospital of Larissa, Mezourlo, Larissa 41110, Greece. andrewvxanth@gmail.com

Abstract

Cardiac amyloidosis is a progressive disease characterized by the buildup of amyloid fibrils in the extracellular space of the heart. It is divided in 2 main types, immunoglobulin light chain amyloidosis and transthyretin amyloidosis (ATTR), and ATTR amyloidosis is further divided in 2 subtypes, non-hereditary wild type ATTR and hereditary mutant variant amyloidosis. Incidence and prevalence of ATTR cardiac amyloidosis is increasing over the last years due to the improvements in diagnostic methods. Survival rates are improving due to the development of novel therapeutic strategies. Tafamidis is the only disease-modifying approved therapy in ATTR amyloidosis so far. However, the most recent advances in medical therapies have added more options with the potential to become part of the therapeutic armamentarium of the disease. Agents including acoramidis, eplontersen, vutrisiran, patisiran and anti-monoclonal antibody NI006 are being investigated on cardiac function in large, multicenter controlled trials which are expected to be completed within the next 2-3 years, providing promising results in patients with ATTR cardiac amyloidosis. However, further and ongoing research is required in order to improve diagnostic methods that could provide an early diagnosis, as well as survival and quality of life of these patients.

Key Words: Transthyretin cardiac amyloidosis; Tafamidis; Acoramidis; Eplontersen; Vutrisiran; Patisiran

Core Tip: Transthyretin amyloidosis (ATTR) cardiac amyloidosis is a progressive disease, affecting patients' functional capacity, survival and quality of life. Incidence and prevalence of ATTR cardiac amyloidosis is increasing over the last years while survival rates are improving. Tafamidis is the only disease-modifying approved therapy so far. Novel medical therapies including acoramidis, eplontersen, vutrisiran, patisiran and anti-monoclonal antibody NI006 are being investigated on cardiac function in large, multicenter controlled trials, with the potential to become part of the therapeutic armamentarium of the disease.

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INTRODUCTION

Cardiac amyloidosis is a progressive disease characterized by the buildup of abnormal protein deposits, known as amyloid fibrils, in the extracellular space of the heart[1]. In systemic conditions, protein deposits in the peripheral nervous system can cause peripheral neuropathy, affecting the autonomic nervous system and therefore, blood pressure, heart rate, and cardiac function[1-3]. People with cardiac amyloidosis may have arrhythmias, cardiomegaly, or orthostatic hypertension, abnormalities that lead to progressive heart failure (HF) with increased rates of hospitalizations and mortality[1-3]. The age of the initial symptoms ranges from age 20 years to 70 years, varying widely among individuals[1-3].

Cardiac amyloidosis is divided into 2 main types; immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR)[2]. ATTR cardiac amyloidosis is further divided into 2 subtypes; non-hereditary wild type ATTR (ATTRwt) amyloidosis and hereditary mutant variant (ATTRv) amyloidosis[3]. Cardiac amyloidosis is a progressive disorder with significantly reduced survival and quality of life with ATTR type presenting a better prognosis than AL[4]. Tafamidis is the only approved disease-modifying therapy for ATTR cardiac amyloidosis so far. However, new experimental therapies are being developed through clinical phases worldwide.

The aim of the present editorial is to present all the recent advances on epidemiology, diagnostic techniques and therapeutic methods in ATTR cardiac amyloidosis.

EPIDEMIOLOGY OF ATTR CARDIAC AMYLOIDOSIS

The AC-TIVE study, a large prospective multicentric study that was conducted in Italy, investigated the prevalence of ATTR cardiac amyloidosis among patients with echocardiographic red flags and evaluated their diagnostic accuracy[5]. The main findings of this trial were that: (1) More than 7% of patients ≥ 55 years of age undergoing clinically-indicated echocardiography and 33% of patients with non-dilated, hypertrophic left ventricle (LV) with preserved ejection fraction (EF) have echocardiographic red-flags of cardiac amyloidosis; (2) Patients with a high echocardiographic suspicion of cardiac amyloidosis (≥ 3 red-flags) represent 1% of patients ≥ 55 years of age undergoing clinically-indicated echocardiography and 5% of patients with cardiac amyloidosis-compatible echocardiograms; (3) Patients with highly cardiac amyloidosis-suggestive echocardiograms are more frequently referred to echocardiographic laboratories due to HF with preserved EF (HFpEF); and (4) Thickened interatrial septal is the most frequent possible echocardiographic red-flag of cardiac amyloidosis[5]. The second phase of the study showed that the prevalence of cardiac amyloidosis was 29% in consecutive adults with echocardiographic findings suggestive of cardiac amyloidosis and LVEF ≥ 50%, while combined echocardiographic red flags usually present good diagnostic accuracy[5]. Similarly, Porcari *et al*[6] examined mortality rates between ATTR and AL cardiac amyloidosis over a 30-year period in Italy and found that incidence and prevalence rates of ATTR and AL cardiac amyloidosis are much higher the last decade compared to the previous ones, but the 2-year survival of ATTR amyloidosis has improved over the years compared to AL cardiac amyloidosis.

In a large national study in the French territory[7], authors investigated the prevalence and the incidence of ATTR cardiac amyloidosis between 2011 and 2019. Interestingly, incidence rate was increased from 0.6/100000 person-year to 3.6/100000 person-year within 8 years ($P < 0.001$). Moreover, men were more than women [sex ratios (males/females) increased from 1.52 in 2011 to 2.23 in 2019], as also confirmed from other studies in the French territory[8]. Median age at diagnosis was 85.5 years for women and 83.5 years for men. Finally, survival and prognosis were poor (median survival: 41.9 months [95% confidence interval (CI): (39.6, 44.1)].

A multicenter study in the United States[9] estimated the prevalence and incidence of ATTR cardiomyopathy in 1235 consecutive patients with HFpEF and ventricular wall thickening in southeastern Minnesota. Investigators showed that the prevalence was 2.5% (95%CI: 1.4%-4.0%) in men and 0% (95%CI: 0.0%-0.6%) in women. Moreover, prevalence increased with age from 0% in patients 60 years to 69 years of age to 21% in patients 90 years and older ($P < 0.001$).

In the United Kingdom, Ravichandran *et al*[10] obtained data from the United Kingdom National Amyloidosis Center database, identifying 11,006 patients who received a diagnosis of amyloidosis during the period from 1987 until 2019. Patients diagnosed with cardiac amyloidosis increased by 670% while the incidence of ATTRwt amyloidosis increased from less than 3% of all cases in 1987 to 25% in 2019.

In a cohort in Sweden[11], approximately 20% of 2238 HF patients with increased myocardial wall thickness were diagnosed with ATTRwt, estimating the prevalence for the whole population of HF patients at approximately 1.1% and in total population at 1:6000 people. Lauppe *et al*[12] investigated prevalence of patients with ATTR cardiac amyloidosis in Denmark, Finland, Norway, and Sweden during 2008-2018. The mean average prevalence in Scandinavia was 3.3 per 100000 people in 2018, and most specifically, cases of ATTRwt amyloidosis were higher in Sweden and Norway with 5.0 per 100000 and 3.7 per 100000, respectively, and lower in Finland and Denmark with 1.8 per 100000 and 1.4 per 100000, respectively. Prevalence increased in all of them during the following years. As far as sex is concerned, female patients were 20.3% in Denmark, 24.4% in Norway, 29.9% in Sweden, and 49.5% in Finland while overall, in the Nordic countries, 31.0% of patients were female[12]. Finally, median survival time after ATTR cardiac amyloidosis diagnosis was 25 (CI: 21-30) months in Denmark, 18 (CI: 16-22) months in Finland, 28 (CI: 25-36) months in Norway, and 37 (34-44) months in Sweden.

Finally, Ney *et al*[13] conducted a large retrospective study in Germany from 2009 to 2018, using health claims data of a statutory health insurance. Both prevalence and incidence increased from 15.5 to 47.6 per 100000 person-years and from 4.8 to 11.6 per 100000 person-years, respectively. Risk of death reduced by 9% (95%CI: 2%-15%, $P = 0.008$) in the second compared to the first 5 years of observation.

It seems clear that the incidence and prevalence of ATTR cardiac amyloidosis have significantly increased over time[5-13], due to advancements in non-invasive imaging techniques and heightened clinical awareness. This rise may also be influenced by the aging population, as the diagnosis is more prevalent in older adults. As a result, ATTR cardiac amyloidosis is now considered a critical factor in HF among the elderly, necessitating ongoing research and development of targeted therapies.

CURRENT GUIDELINES AND RECCOMENDATIONS IN DIAGNOSTIC METHODS

ATTR cardiac amyloidosis is a progressive and fatal condition without early diagnosis, leading to cardiomyopathy and end-stage cardiac failure. The main problems in the disease's diagnosis are the increased number of misdiagnosed[14] and underdiagnosed cases[15], as well as the lack of awareness of this disease among healthcare professionals and the community in the United Kingdom and the United States[16,17], countries of South America[18], countries in the Middle East and Gulf Region[19], as well as European countries[20,21].

Diagnosis of cardiac amyloidosis includes two critical phases, the suspicious and the definite diagnosis phase[22]. The diagnostic process of ATTR cardiac amyloidosis begins with clinical history/examination, electrocardiogram (ECG), and transthoracic echocardiogram[3]. Cardiac magnetic resonance (CMR) imaging and endomyocardial biopsy are the diagnostic methods with the highest sensitivity and specificity that may be required in order to make the diagnosis[3].

ECG and echocardiography are primary diagnostic tools which can practically set the initial suspicions of cardiac amyloidosis[23]. Specifically, increased LV wall thickness with low-voltage QRS[24], the lack of progression of the R wave in the anterior precordial leads[25], left ventricular hypertrophy (LVH) morphology[26], and conduction defects including atrioventricular (AV) or bundle branch block and conduction delay[27] seem to be the most characteristic findings in the ECG so far. Ventricular tachycardia and ventricular fibrillation are those arrhythmias which can lead to sudden death in patients with ATTR amyloidosis[27]. However, the absence of these findings does not exclude the diagnosis[28]. The new insight in the ECG is the development of novel machine learning techniques with specific ECG algorithms which use patterns from detailed electroanatomic mappings of patients with cardiac amyloidosis[29]. Echocardiography includes standard diagnostic clues such as increased LV wall thickness (≥ 1.2 cm), thickening of AV valves, right ventricle free wall and interatrial septum, diastolic dysfunction, decreased mitral annular systolic velocity, enlargement of both atrials, and decreased global longitudinal strain with relative apical sparing[22,30-32]. However, neither this technique can set the diagnosis alone. Machine learning techniques combining ECG and echocardiography could present promising results in detecting ATTR cardiac amyloidosis in early stages, as shown through a large multicenter study where the machine learning model combining ECG and echo was capable to detect cardiac amyloidosis 1 year before diagnosis, and discriminate it from other differential diagnoses causing LVH[33].

CMR provides detailed cardiac tissue characterization and it is very useful in excluding amyloidosis from other diagnoses. The most characteristic findings are expansion of the extracellular volume, abnormal gadolinium contrast kinetics, and diffuse late gadolinium enhancement[30,31]. However, CMR has also disadvantages as it is not sufficient to establishing the diagnosis of cardiac amyloidosis alone, and cannot distinguish between AL and ATTR cardiac amyloidosis without endomyocardial biopsy[34].

Cardiac scintigraphy with intravenous injection of pyrophosphate, followed by the acquisition of planar and single-photon emission computed tomography (SPECT) or SPECT images after 1 and 3 hours, is considered as a cornerstone of ATTR amyloidosis diagnosis, especially in the absence of a monoclonal protein screen comprising 3 laboratory tests: Serum immunofixation electrophoresis (SIFE), urine immunofixation electrophoresis (UIFE) and serum free light chain

(sFLC) assay[35,36]. Diagnostic criteria for positive planar scintigraphy include a Perugini score ≥ 2, and/or a heart/contralateral chest ratio ≥ 1.5 on a 1-hour scan or > 1.3 on a 3 hours scan[22,32,37,38]. In patients with suspected cardiac amyloidosis and an abnormal monoclonal protein screen, endomyocardial biopsy may be required to establish the diagnosis.

Finally, genetic testing for the presence or absence of a transthyretin (TTR) variant in the patient *via* TTR gene sequencing, in combination with genetic counseling and cascade testing of at-risk relatives, can distinguish ATTRv from ATTRwt, therefore, defining the appropriate treatment strategy[3].

The appropriate diagnostic steps of ATTR cardiac amyloidosis after clinical or ECG/echo suspicions (Figure 1), according to the most updated recommendations are[3,22]: (1) Exclusion of AL amyloidosis by the absence of a monoclonal protein screen comprising sFLC assay, SIFE, and UIFE, with a negative predictive value of > 99%, or establishment of the diagnosis if present[32,35,37,38]; (2) Bone avid tracer scintigraphy to assess for ATTR amyloidosis and, if positive and grade 2 or 3 then TTR genetic testing so that to distinguish ATTRv from ATTRwt amyloidosis[2], or (3) Endomyocardial biopsy if there is ongoing clinical suspicion of cardiac amyloidosis including findings in the ECG, echocardiography and CMR, and low suspicion in the bone avid tracer scintigraphy[2].

NEW INSIGHTS INTO THERAPEUTIC ARMAMENTARIUM OF ATTR CARDIAC AMYLOIDOSIS

Treatment management of ATTR cardiac amyloidosis is focused in either the symptoms of the clinical syndrome or its modification[22]. Classic symptom therapy may include HF medication such as diuretics, beta-blockers and calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blocker and sacubitril/valsartan, digoxin, sodium-glucose cotransporter type 2 inhibitors, antiarrhythmic treatment and anticoagulant therapy for atrial fibrillation, norepinephrine replacers such as midodrine, droxidopa, fludrocortisone or octreotide for orthostatic hypotension, device implantation such as pacemakers and defibrillators, and more complex therapies such as heart transplantation in advanced HF[2]. Disease-modifying therapy includes drugs that act on different phases of amyloidogenesis: (1) Silencing of the gene encoding TTR (small interfering RNA: Patisiran, vutrisiran; antisense oligonucleotides: Inotersen, eplontersen; new CRISPR Cas-9 drug technology for editing *in vivo* DNA); (2) Stabilization of circulating TTR to inhibit its dissociation and subsequent assembly of the resulting monomers in amyloidotic fibrils (tafamidis, acoramidis, and tolcapone), and (3) Destruction and re-absorption of already formed amyloid tissue deposits (monoclonal antibodies)[39].

The only approved medication for ATTR cardiac amyloidosis by the United States Food and Drug Administration (FDA) so far, is tafamidis at a dosage of 61 mg or tafamidis meglumine of 80 mg. Tafamidis acts as a TTR stabilizer, slowing the dissociation of TTR, and prevents amyloidogenesis and cardiac deposition by binding to transthyretin[3]. The beneficial effects of tafamidis were demonstrated through a large clinical trial in 2018, the ATTR-ACT trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial)[40]. In this multicenter, international, double-blind, placebo-controlled, phase 3 trial, authors randomly assigned 441 patients with ATTR cardiomyopathy in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months and assessed all-cause mortality, cardiovascular (CV)-related hospitalizations, changes in the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire (KCCQ)-Overall Summary. Patients who received tafamidis presented lower all-cause mortality [78 of 264 (29.5%) *vs* 76 of 177 (42.9%); hazard ratio: 0.70; 95%CI: 0.51-0.96] and lower rates of CV-related hospitalizations [relative risk ratio 0.68 (0.48 per year *vs* 0.70 per year; 95%CI: 0.56-0.81)] compared to placebo. Moreover, tafamidis was associated with reduction in the decline of functional capacity and quality of life in these patients[41]. Benefits from tafamidis in mortality and functional decline are regardless of ATTR status, as shown by a subsequent analysis of the ATTR-ACT trial[42]. Moreover, Elliot *et al*[43] showed that patients initially treated with tafamidis in the ATTR-ACT trail, had better long-term survival up to 58 months than patients who were initially treated with placebo. As far as safety profile of tafamidis is concerned, adverse events were mild to moderate in severity[40], while monitoring is usually not necessary in the clinical environment.

The new insights in ATTR cardiac amyloidosis include promising targeted medical therapies which are being investigated in significant clinical trials (Table 1). Specifically, acoramidis, a novel TTR stabilizer, has currently been investigated in a phase 3 clinical trial, the ATTRIBUTE-CM trial[44]. In this double-blind trial, authors randomly assigned patients with ATTR cardiomyopathy in a 2:1 ratio to receive acoramidis hydrochloride at a dose of 800 mg twice daily or matching placebo for 30 months and evaluated 4 main outcomes; death from any cause, CV-related hospitalization, the change from baseline in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and the change from baseline in the 6-minute walk distance. Moreover, the score on the KCCQ-Overall Summary, and the serum TTR level were also evaluated. Acoramidis resulted in significantly improved rates of mortality, morbidity, and function compared to placebo [win ratio: 1.8 (95%CI: 1.4-2.2; $P < 0.001$), while adverse events were similar between the two groups (98.1% *vs* 97.6%, respectively)][44]. The new insight in the treatment of cardiac amyloidosis is that the FDA has accepted a New Drug Application for acoramidis for the treatment of transthyretin amyloid cardiomyopathy and set a Prescription Drug User Fee Act action date of November 29, 2024.

Eplontersen, a TTR silencer and antisense oligonucleotide, has also been assessed on cardiac structure and function in the NEURO-TTRansform trial[45]. This trial involved 144 adults with ATTRv polyneuropathy receiving eplontersen throughout and compared with a historical placebo group. Sixty-five weeks of eplontersen treatment was associated with improved LVEF by 4.3% (95%CI 1.40-21.01; $P = 0.049$) and stroke volume by 10.64 mL (95%CI 3.99-17.29; $P = 0.002$) while the remainder of echocardiographic parameters remained stable. Eplontersen's effect on ATTR cardiomyopathy is being investigated in a global, double-blind, randomized, placebo-controlled Phase 3 CV outcome study in more than 1400

Table 1 Novel promising targeted medical therapies of transthyretin amyloidosis cardiac amyloidosis which are being investigated in large clinical trials

Clinical trial	Intervention per group	Duration	Endpoints	Outcomes
ATTR-ACT NCT01994889	I_1: 80 mg of tafamidis; I_2: 20 mg of tafamidis; C: Placebo	30 months	Primary: All-cause mortality; Frequency of CV-related hospitalizations. Secondary: 6MWT; KCCQ-OS; CV-related mortality; Stabilized TTR after 1 month	Tafamidis was associated with: (1) Lower all-cause mortality than placebo [78 of 264 (29.5%) *vs* 76 of 177 (42.9%); HR, 0.70; 95%CI: 0.51-0.96]; (2) Lower rate of cardiovascular-related hospitalizations [relative risk ratio of 0.68 (0.48 per year *vs* 0.70 per year; 95%CI: 0.56-0.81)]; (3) Lower rate of decline in distance for the 6-minute walk test ($P < 0.001$); (4) Lower rate of decline in KCCQ-OS score ($P < 0.001$); and (5) Similar incidence and types of adverse events between groups
ATTRIBUTE-CM NCT03860935	I: 800 mg of acoramidis BID; C: Placebo	30 months	Primary: (1) 6MWT after 12 months; (2) All-cause mortality; (3) CV-related hospitalizations; (4) NT-proBNP; (5) 6MWT after 30 months; and (6) KCCQ-OS	(1) All-cause mortality, cumulative frequency of CV-related hospitalization, change in NT-proBNP, and change in 6-6MWT, had an overall win ratio favoring *acoramidis* (win ratio 1.8, 95%CI: 1.4-2.2, $P < 0.0001$); (2) All-cause mortality: 25.7% *vs* 29.5%; HR: 0.77, 95%CI: 0.54-1.10 ($P = 0.15$); (3) Adjusted mean factor change in NT-proBNP from baseline: 0.529 (95%CI: 0.46-0.60, $P < 0.05$); (4) Improvement from baseline in 6-minute walk distance: 39.6 m (95%CI: 21.1-58.2, $P < 0.001$); (5) CV-related hospitalization: 26.7% *vs* 42.6% ($P < 0.0001$); (6) Least means square change in KCCQ-OS: 9.94 points (95%CI: 5.97-13.91, $P < 0.001$); and (7) Composite of all-cause mortality and CV-related hospitalization: HR: 0.65, 95%CI: 0.50-0.83 ($P = 0.0008$; number needed to treat = 7)
CARDIO-TTRansfor NCT04136171	I: Eplontersen (sc) once every 4 weeks; C: Placebo	140 weeks	Primary: CV mortality and recurrent CV clinical events up to week 140. Secondary: 6MWT at week 121; KCCQ at week 121; all-cause mortality up to week 140	The trial is estimated to be completed by 2025
HELIOS-B NCT04153149	I: 25 mg of vutrisiran (sc) once every 3 months C: Placebo	30-36 months	Primary: All-cause mortality and recurrent CV clinical events at 30-36 months. Secondary: (1) 6MWT at month 30; (2) KCCQ at month 30; (3) Mean (LV) wall thickness at month 30; (4) GLS at month 30; (5) All-cause mortality; (6) Recurrent all-cause hospitalizations and urgent HF visits; and (7) NTproBNP at month 30	The trial is estimated to be completed by 2026
APOLLO-B NCT03997383	I: 0.3 mg/kg of patisiran once every 3 weeks; C: Placebo	12 months	Primary: 6MWT. Secondary: (1) KCCQ-OS; (2) Composite of death from any cause, CV events, and 6MWT; and (3) Composite of death from any cause, hospitalizations for any cause, and urgent HF visits	Patisiran was associated with: (1) Lower decline in the 6MWT (Hodges-Lehmann estimate of median difference, 14.69 m; 95%CI: 0.69-28.69; $P = 0.02$); (2) Increase of the KCCQ-OS (least-squares mean difference, 3.7 points; 95%CI: 0.2-7.2; $P = 0.04$); and (3) Infusion-related reactions, arthralgia, and muscle spasms more often in the patisiran group compared to placebo
NI006 phase 1 NCT04360434	I: 0.3 to 60 mg/kg of NI006 IV every 4 weeks; C: Placebo	4 months	Safety and pharmacokinetic profile; Cardiac imaging studies	NI006 was associated with no apparent drug-related serious adverse events in this phase 1 trial

6MWT: 6-minute walk test; BID: Bis in die; C: Control group; CI: Confidence interval; CV: Cardiovascular; GLS: Global longitudinal strain; HF: Heart failure; HR: Hazard ratio; I: Intervention group; IV: Intravenous; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Summary; LV: Left ventricular; NTproBNP: N-terminal prohormone B-type Natriuretic Peptide; SC: Subcutaneous; TTR: Transthyretin.

patients, the CARDIO-TTRansform trial (NCT04136171). This trial investigates CV mortality and recurrent CV clinical events up to week 140, change in the 6-minute walk test, the KCCQ scores at week 121, and the rates of CV mortality, CV clinical events and all-cause mortality at week 140 (NCT04136171). The trial is estimated to be completed by 2025.

Another targeted agent under investigation is vutrisiran, a TTR silencer and a small interfering RNA. HELIOS-B, a phase 3, randomized, double-blind, placebo-controlled, multicenter study will evaluate the efficacy and safety of vutrisiran 25 mg administered subcutaneously once every 3 months compared to placebo in patients with ATTR amyloidosis (NCT04153149). The major endpoints are all-cause mortality, recurrent CV events, CV hospitalizations and urgent HF visits at 30-36 months. Other endpoints are changes in the 6-minute walk test, the KCCQ Overall Summary, mean LV wall thickness by echocardiographic assessment, global longitudinal strain and NT-proBNP. The trial is estimated to be completed by 2026. However, an exploratory analysis with data from the HELIOS-A clinical trial[46] demonstrated evidence of the potential benefit of vutrisiran on cardiac manifestations in patients with ATTRv amyloidosis with polyneuropathy, with an acceptable safety profile. Specifically, vutrisiran showed improvements on NT-proBNP and echocardiographic parameters after 18 months compared to external placebo of the APOLLO study.

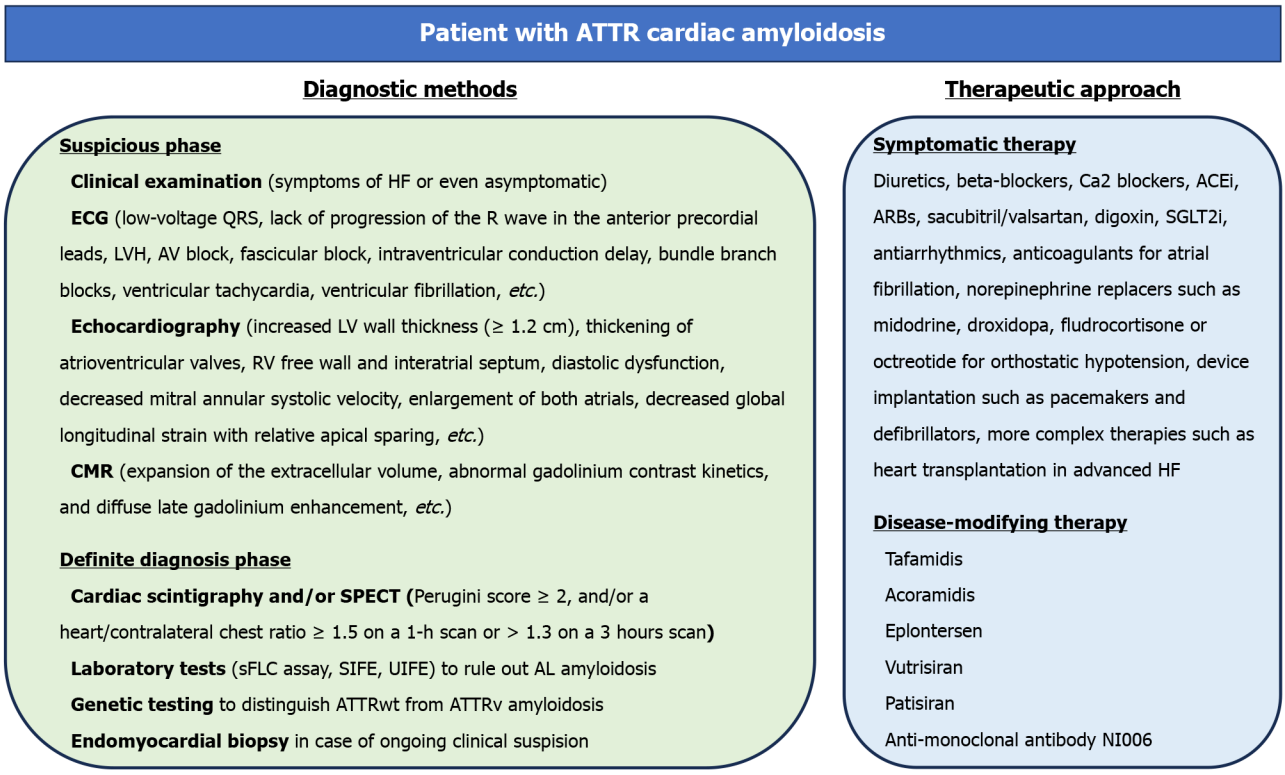

Figure 1 Diagnostic approach and therapeutic strategies in transthyretin amyloidosis cardiac amyloidosis. ACEi: Angiotensin-converting enzyme inhibitors; AL: Immunoglobulin light chain amyloidosis; ARBs: Angiotensin receptor blockers; ATTR: Transthyretin amyloidosis; ATTRv: Mutant variant transthyretin amyloidosis; ATTRwt: Wild type transthyretin amyloidosis; AV: Atrioventricular; CMR: Cardiac magnetic resonance; ECG: Electrocardiogram; HCL: Heart/contralateral; HF: Heart failure; LV: Left ventricular; LVH: Left ventricular hypertrophy; RV: Right ventricular; sFLC: Serum free light chain; SGLT2i: Sodium-glucose cotransporter-2 inhibitors; SIFE: Serum immunofixation electrophoresis; SPECT: Single-photon emission computed tomography; UIFE: Urine immunofixation electrophoresis.

Patisiran is a molecule encapsulated in lipid nanoparticles, administered by intravenous infusion, and internalized specifically by hepatocytes, which was investigated in ATTR cardiac amyloidosis[47]. APOLLO-B trial (NCT03997383), a phase 3, double-blind, randomized trial, randomized patients with ATTRv or ATTRwt cardiac amyloidosis, in a 1:1 ratio, to receive patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks for 12 months. Authors assessed changes in the KCCQ-Overall Summary score, death from any cause, CV events, changes in the 6-minute walk test distance, hospitalizations for any cause, and urgent HF visits over 12 months. They concluded that patisiran was associated with a lower decline in the 6-minute walk distance (Hodges-Lehmann estimate of median difference, 14.69 m; 95%CI: 0.69-28.69; P = 0.02) and increased KCCQ-Overall Summary score (least-squares mean difference, 3.7 points; 95%CI: 0.2-7.2; P = 0.04) compared to the placebo.

Finally, anti-monoclonal antibody NI006 (ALXN2220), a recombinant human anti-ATTR antibody that was developed for the removal of ATTR by phagocytic immune cells, has been evaluated in a phase 1, double-blind trial in 40 patients with ATTRv or ATTRwt cardiomyopathy and chronic HF[48]. Authors compared intravenous infusions of either NI006 or placebo every 4 weeks for 4 months, assessing safety and pharmacokinetic profiles, and showed that the use of NI006 was associated with no apparent drug-related serious adverse events. Additionally, it seemed to reduce surrogate markers of cardiac amyloid load from scintigraphy and CMR imaging, median NT-proBNP and troponin T levels over a period of 12 months.

LIMITATIONS AND FUTURE PERSPECTIVES

Due to limited data in ATTR cardiac amyloidosis, more randomized controlled trials are required in order to demonstrate better diagnostics methods and more efficient therapeutic options. Although there are guidelines for cardiac amyloidosis management, there are still gaps in the awareness of this disease. The existing diagnostic methods cannot provide early diagnosis yet. It is characteristic that for ATTRwt amyloidosis, median time from symptoms to diagnosis remains similar during the last few years[49]. Therapeutically, the only disease-modifying therapy of ATTR-cardiomyopathy, tafamidis, is not available in most countries all over the world, even highly developed ones, due mainly to its high cost[50], resulting in missed opportunity for timely treatment or even no treatment in most patients.

There is need for educational programs and campaigns regarding cardiac amyloidosis in the future, in order to increase clinical awareness and early diagnosis, so that patients receive timely treatment[18]. It has been shown that healthcare professionals would benefit from information on the latest advances in ATTR cardiac amyloidosis as far as

screening, diagnosis and therapy of patients is concerned[21]. Moreover, the development of cardiac amyloidosis networks and reference centers all over the world, as well as the creation of registries including patients' demographics, clinical, imaging and laboratory exams, and medication, would also be helpful to increase scientific knowledge of this disease. The development and establishment of novel, more efficient therapeutic options would increase functional capacity, limit symptoms, improve prognosis, survival and, therefore, improve quality of life in patients with ATTR cardiac amyloidosis.

CONCLUSION

It seems that incidence and prevalence of ATTR cardiac amyloidosis is increasing over the last few years and patients who remained undiagnosed, are finally being diagnosed, probably due to the improvements in sensitivity of diagnostic methods and imaging techniques. Moreover, survival rates are getting higher due to the development of therapeutic strategies. Awareness of this disease still remains at low levels among healthcare professionals and within the community, but, with increasing trends during the last decade. The most recent advances in medical therapies have added more options with potential to become part of the therapeutic armamentarium of ATTR amyloidosis. However, tafamidis, as well as other potential disease modifying treatments, are widely unavailable in most countries due to their high cost, resulting in missed opportunities for timely treatment in most patients. Further and ongoing research is required in order to improve survival and quality of life for these patients.

FOOTNOTES

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Country of origin: Greece

ORCID number: Christos Kourek 0000-0003-4348-2153; Alexandros Briasoulis 0000-0002-5740-9670; Dimitrios E Magouliotis 0000-0001-5417-6392; Grigorios Giamouzis 0000-0002-7406-5427; John Skoularigis 0000-0001-7159-2478; Andrew Xanthopoulos 0000-0002-9439-3946.

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EDITORIAL

Excess cardiovascular mortality in men with non-alcoholic fatty liver disease: A cause for concern!

Akash Batta, Juniali Hatwal

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Akash Batta, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana 141001, Punjab, India

Juniali Hatwal, Department of Internal Medicine, Post Graduate Institute of Medical Education & Research, Chandigarh 160012, India

Corresponding author: Akash Batta, MD, Assistant Professor, Senior Scientist, Department of Cardiology, Dayanand Medical College and Hospital, Tagore Nagar, Civil Lines, Ludhiana 141001, Punjab, India. akashbatta02@gmail.com

Abstract

Non-alcoholic fatty liver disease (NAFLD) has emerged as the commonest cause of chronic liver disease worldwide in recent years. With time, our understanding of NAFLD has evolved from an isolated liver condition to a systemic disease with significant manifestations beyond the liver. Amongst them, cardiovascular diseases (CVDs) are the most important and clinically relevant. Recent research supports a strong independent link between NALFD and CVD beyond the shared risk factors and pathophysiology. Female sex hormones are well known to not only protect against CVD in pre-menopausal females, but also contribute to improved adipose tissue function and preventing its systemic deposition. Recent research highlights the increased risk of major adverse cardiovascular-cerebral events (MACCE) amongst male with NAFLD compared to females. Further, racial variation was observed in MACCE outcomes in NAFLD, with excess mortality in the Native Americans and Asian Pacific Islanders compared to the other races.

Key Words: Non-alcoholic fatty liver disease; Cardiovascular diseases; Male sex; Major adverse cardiovascular-cerebral events; Inflammation; Endothelial dysfunction

Core Tip: Non-alcoholic fatty liver disease (NAFLD) has emerged as the commonest cause of chronic liver disease worldwide in recent years. In recent years, our understanding of NAFLD has evolved from an isolated liver condition to a systemic disease with significant manifestations beyond the liver. Amongst them, cardiovascular diseases (CVDs) are the most important and clinically relevant. Recent research supports a strong independent link between NALFD and CVD beyond the shared risk factors and pathophysiology. The findings from translational research and recent clinical data support the heightened risk of major adverse cardiovascular-cerebral events (MACCE) amongst male with NAFLD compared to females. Further, there was racial variation in MACCE outcomes in NAFLD, with excess mortality in the Native Americans and Asian Pacific Islanders compared to the other races largely attributable to the increased comorbidity burden and unfavorable genetics.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as the commonest cause of chronic liver disease worldwide in recent years. The current estimates indicate that the prevalence is expected to rise logarithmically in the coming years especially so in the developing world[1,2]. Recent evidence has improved our understanding of the disease and appropriately it is now being viewed as truly a multisystem disease. Significant systemic implications of the disease necessitate a comprehensive multidisciplinary approach to improve outcomes[3,4]. Amongst the systemic manifestations of NAFLD, notable mentions include cardiovascular diseases (CVDs), chronic kidney disease, type 2 diabetes mellitus and certain malignancies[5]. Accordingly, it is imperative for clinicians taking care of patients with NAFLD to be aware of these associations and identify those at increased risk so that appropriate measures can be instituted in a timely manner.

PATHOPHYSIOLOGICAL BASIS OF INTERACTION BETWEEN NAFLD AND CVD

NAFLD is characterized by dysfunction of the adipose tissue and its deposition in visceral organs including both the liver and the heart[6,7]. This ectopic/visceral deposition of adipose tissue results in activation of inflammatory cytokines and oxidative stress which underlies a common theme between NAFLD and CVD[8]. Despite the overwhelming evidence supporting the excess CVD in NAFLD, the exact pathophysiological mechanisms involved have remained speculative. Arguably, the common lifestyle risk factors between the two diseases like cigarette smoking, poor nutritional habits, sedentary life style together with other triggers in the form of oxidate stress, alterations in gut microbiome, and inflammation culminate in obesity, hypertension, dyslipidaemia and diabetes which in turn are common grounds for both NAFLD and CVD[9,10]. Further, the most validated pathogenic mechanism in NAFLD which predispose to CVD are a combination of endothelial dysfunction, systemic inflammation, altered glucose metabolism and atherogenic dyslipidaemia which results in increased progression to microvascular dysfunction and macrovascular atherosclerotic CVD. The low-grade inflammation attributable largely to the unhealthy lifestyle habits and exposure to carbohydrate and fat rich diet results in altered endothelial function and increased predisposition for deposition of oxidized low-density lipoprotein into the visceral arterial bed. In particular, pro-inflammatory cytokines (IL-6, IL-17, IL-1B and TNF-a) and hepatokines (FGF-21 and fetuin-A) together with pro-coagulant cytokines (TGF-B, FVIII, FGF-21) remain central to the pathophysiology and contribute to enhanced systemic atherosclerosis and its deleterious effects[11,12]. Ultimately, this contributes to excess hypertension, coronary artery disease, heart failure (both reduced and with preserved ejection fraction) and cardiac arrythmias (most notably atrial fibrillation) which confers increased CVD related mortality in NAFLD patients. Even beyond the shared risk factors and pathophysiology, there is clear evidence supporting the independent CVD risk due to NAFLD[9]. Arguably most of the imminent guidelines recommend that the diagnosis of NAFLD should be followed by a careful and comprehensive cardiovascular risk assessment and evaluation for subclinical atherosclerosis where indicated[13]. To this end, there have been development of certain unique risk scores including Fibrosis-4 index, NAFLD activity and NAFLD fibrosis scores all of which may help in early identification of high-risk group who are at a heightened risk for developing CVD[12].

INFLUENCE OF SEX ON NAFLD RELATED CVD OUTCOMES

There is abundant evidence supporting the protective influence of female sex hormones when regards to initiation and progression of NAFLD. In general, NAFLD is diagnosed 5 years later in females compared to their male counterparts [14]. Further, it is well established that estrogen also has a positive effect on CVD profile in pre-menopausal women and after menopause, the risk for both NAFLD and CVD are comparable to men.

Consistently, most recent reports support the excess CVD related mortality in males with NAFLD compared to age and comorbidity matched females. The increased risk and accelerated progression of NAFLD resulting in heightened systematic inflammation is in part linked to the differences adipocyte metabolism in the male sex. In the reproductive years, female sex is largely protected from the adverse metabolism due to their preferential partitioning of free fatty acids towards the ketone body pathway as opposed to the very low-density lipoprotein-triacylglycerol pathway (more prevalent in males) which has a tendency for visceral deposition and initiation of inflammatory cascade. Further, sex-specific browning of white adipose tissue also adds to the protection against NAFLD in females[14-16]. Indeed, estrogen plays a crucial role in steatogenesis and lipidomics. Experimental rat models have consistently demonstrated estrogen deficiency results in reduced concentrations of peroxisome proliferator-activated receptor and upregulation of genes mediating endogenous synthesis of cholesterol and free fatty acids culminating in hepatic steatosis[17,18]. Post menopause, as the protective effect of estrogen weans, the risk of developing NAFLD becomes similar to males. In females, estrogen deficiency is often paralleled by development of cardio-metabolic risk factors including diabetes, dyslipidemia and obesity which often facilitates accelerated steatosis in the hepatocytes which may soon progress to fibroses and ultimately chronic liver disease[19,20].

IMPACT OF SEX AND RACE ON MAJOR ADVERSE CARDIOVASCULAR-CEREBRAL EVENTS IN NAFLD

In the recent retrospective analysis by Desai *et al*[21], adult hospitalizations for NAFLD were analyzed on the National Inpatient Sample (2019), in particular looking into the age, sex and racial determinants of major adverse cardiovascular-cerebral events (MACCE) amongst these patients. In their analysis of 409130 hospitalizations for NAFLD, these found out that females had a higher prevalence of obesity and uncomplicated diabetes compared to male gender. Likewise, male gender was associated with a greater prevalence of hypertension, dyslipidemia and complicated diabetes that their female counterparts. Overall, MACCE was strongly linked to advancing age ($P < 0.001$) which seems logical as with advancing age, the burden of atherosclerosis and its attendant complications are expected to increase. Notably, they also concluded that after adjusting for all variables, male sex was associated with higher odds of having MACCE, myocardial infarction and cardiac arrest compared to females. The higher CVD risk amongst males with NAFLD has been observed before and the usual reasons cited include the higher consumption of calorie-rich energy drinks and alcohol coupled with a greater likelihood of developing insulin resistance[22,23]. The index study together with prior research clearly indicates the greater degree of dysmetabolism and inflammation in males with NAFLD and makes a strong case for aggressive risk profile assessment and correction in this population.

Another observation from the study was the excess mortality in the Native Americans and Asian Pacific Islanders with NAFLD compared to the other races. Perhaps a higher prevalence of chronic diseases including diabetes, hypertension and dyslipidemia, a sedentary lifestyle and unfavorable genetic make-up are likely to be responsible for the same[24,25].

Despite the important and relevant conclusions from the index paper, one must also acknowledge the key limitations of the study which are likely to impact its generalizability to other parts to the world. Firstly, the retrospective design is inherently prone to numerous biases which could have altered the study results. Secondly, one must appreciate the fact that the index study only applies to NAFLD patients who required admissions. As such, the findings of this study do not apply to vast majority of NAFLD patients who are ambulatory and have not needed a hospitalization. Thirdly, the study solely looked in to the NAFLD patients across the United States and hence its validity needs to be established in other parts of the world.

CONCLUSION

NAFLD is a systemic disease with significant manifestations beyond the liver. Amongst them, CVDs are the most important and clinically relevant. Recent research supports a strong independent link between NALFD and CVD beyond the shared risk factors and pathophysiology. The findings from translational research and recent clinical data support the heightened risk of MACCE amongst male with NAFLD compared to females. Further, there was racial variation in MACCE outcomes in NAFLD, with excess mortality in the Native Americans and Asian Pacific Islanders compared to the other races.

FOOTNOTES

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Country of origin: India

ORCID number: Akash Batta 0000-0002-7606-5826; Juniali Hatwal 0000-0001-5433-0433.

Corresponding Author's Membership in Professional Societies: American College of Cardiology, 3445007; European Society of Cardiology, 1036629; Cardiological Society of India, L-5249.

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EDITORIAL

Misinterpretation of sleep-induced second-degree atrioventricular block

S Serge Barold

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S Serge Barold, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, United States

Corresponding author: S Serge Barold, MD, Professor, Department of Medicine, University of Rochester School of Medicine and Dentistry, 601 Elmwood Av, Rochester, NY 14642, United States. ssbarold@aol.com

Abstract

A number of publications have claimed that Mobitz type II atrioventricular block (AVB) may occur during sleep. None of the reports defined type II AVB and representative electrocardiograms were either misinterpreted or missing. Relatively benign Wenckebach type I AVB is often misdiagnosed as Mobitz type II which is an indication for a pacemaker. Review of the published reports indicates that Mobitz type II AVB does not occur during sleep when it is absent in the awake state. Conclusion: There is no proof that sleep is associated with Mobitz type II AVB.

Key Words: Wenckebach type I atrioventricular block; Mobitz type II atrioventricular block; Vagal tone; Heart block; Cardiac pacemaker

Core Tip: A number of publications have claimed that Mobitz type II atrioventricular block (AVB) may occur during sleep. None of the reports defined it and representative electrocardiograms were either misinterpreted or missing. Sleep-induced relatively benign narrow QRS-Mobitz type I AVB must be differentiated from serious Mobitz type II AVB. This depends solely on strict electrocardiograms definitions and behavior of the sinus rate where slowing rules out Mobitz type II AVB even if all the PR intervals are constant. Mobitz type II AVB does not occur solely during sleep when it is absent in the awake state.

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INTRODUCTION

Second-degree and third-degree atrioventricular block (AVB) not uncommonly occur during ordinary sleep and sleep apnea. They are caused by enhanced vagal tone and generally considered benign. During sleep, second-degree AVB can be manifested by Wenckebach type I AVB block, 2:1 AVB or high grade AVB almost always with a narrow QRS complex. A number of publications have claimed that Mobitz type II AVB may also occur during sleep[1-5]. These reports have been largely discredited because none of the reports defined type II AVB and representative electrocardiograms (ECG) were either misinterpreted or missing[6]. Vagally-induced type I second-degree AVB during sleep occurs in the atrioventricular (AV) node and is reversible. Mobitz type II second-degree AVB is far more serious and irreversible because it is caused by structural changes in the His-Purkinje conduction system of the heart. Therefore, type II AVB is often associated with a broad QRS complex. It is therefore important especially for sleep-health care workers to be familiar with the strict definitions of the various manifestations of second-degree AVB to avoid diagnostic or even therapeutic errors.

Type I AVB is defined as intermittent failure of AV conduction in which a single blocked sinus P wave is preceded by prolongation of conduction time relative to the first conducted P wave after the block. There must be at least two consecutive conducted P waves (*i.e.*, 3:2 AV block), thereby ruling out 2:1 AVB. This definition accommodates all forms of typical and atypical type I block and is valid with variations of the sinus rate[7,8]. Narrow QRS-type I AVB is almost always localized in the AV node.

Mobitz type II second-degree AVB is defined as the occurrence of a single non-conducted sinus P wave associated with constant PR intervals before and after the blocked impulse, provided the sinus rate or the P-P interval is constant and there are at least two consecutive conducted P waves (*i.e.*, 3:2 AVB) to determine behavior of the PR intervals[7-10]. Therefore, type II block appears to represent an all-or-none phenomenon (Figure 1A). Mobitz type II AVB is always localized in the His-Purkinje conduction system and is an indication for a permanent pacemaker[9,11]. Stability of the sinus rate is an important criterion of type II AVB. A vagal surge causing type I AVB by simultaneously slowing of the sinus rate and depression of AV nodal conduction can superficially resemble type II AVB especially when the PR interval before the block is equal to that of the first conducted beat after the block[12,13] (Figure 1B).

Two to one AVB or higher degrees of AVB cannot be classified into Wenckebach type I or Mobitz type II AVB. A common mistake is to equate 2:1 and higher degree of AVB with type II infranodal block when block can be either in the AV node or the His-Purkinje system.

HOW TO AVOID THE MISDIAGNOSIS OF MOBITZ TYPE II BLOCK

Misdiagnosis may can occur in the following situations

First, ignoring the presence of a vagal surge with sinus slowing that may be subtle (at least 0.04 second) either before and/or after the block of a single blocked P wave. Vagally-induced AVB may sometimes present with an ECG pattern that superficially resembles type II block because the PR interval(s) before and after the block are constant (Figure 1B). Note that only the behavior of the sinus rate differentiates Figure 1A (type II AVB) from Figure 1B (type I AVB).

Second, in the presence of 2:1 or higher degrees of AV block.

Third, when narrow QRS- type I block exhibits miniscule increments, a situation mimicking type II block. This pattern may be seen during ECG monitoring or Holter recordings and is associated with sinus slowing which rules out type II block. Furthermore, repeated ECGs or further monitoring should reveal more obvious runs of type I AVB. In this situation, type II AVB can then be safely excluded because type I and II blocks almost never occur together in a single ECG recording or one done at separate times.

Fourth, less commonly during stable sinus rhythm when there is a string of constant PR intervals before the block of a single P wave and the PR interval of the first conducted beat is shorter.

Szajerska-Kurasiewicz *et al*[5] recently warned that sleep-disordered breathing is a risk factor for unnecessary pacemaker implantation based on a study involving 207 patients hospitalized in a general cardiology ward. Paradoxically, about 5% of patients exhibited so called type II block but none received a pacemaker. As type II is rare, their reported incidence is excessive and suggests an incorrect diagnosis.

CONCLUSION

In conclusion, the separate diagnosis of relatively benign narrow QRS- type I AVB from that of serious type II AVB depends solely on strict ECG definitions and behavior of the sinus rate. A suspected diagnosis of true type II AVB during sleep mandates a detailed cardiology evaluation. As a rule, type II AVB does not occur solely during sleep when it is absent in the awake state.

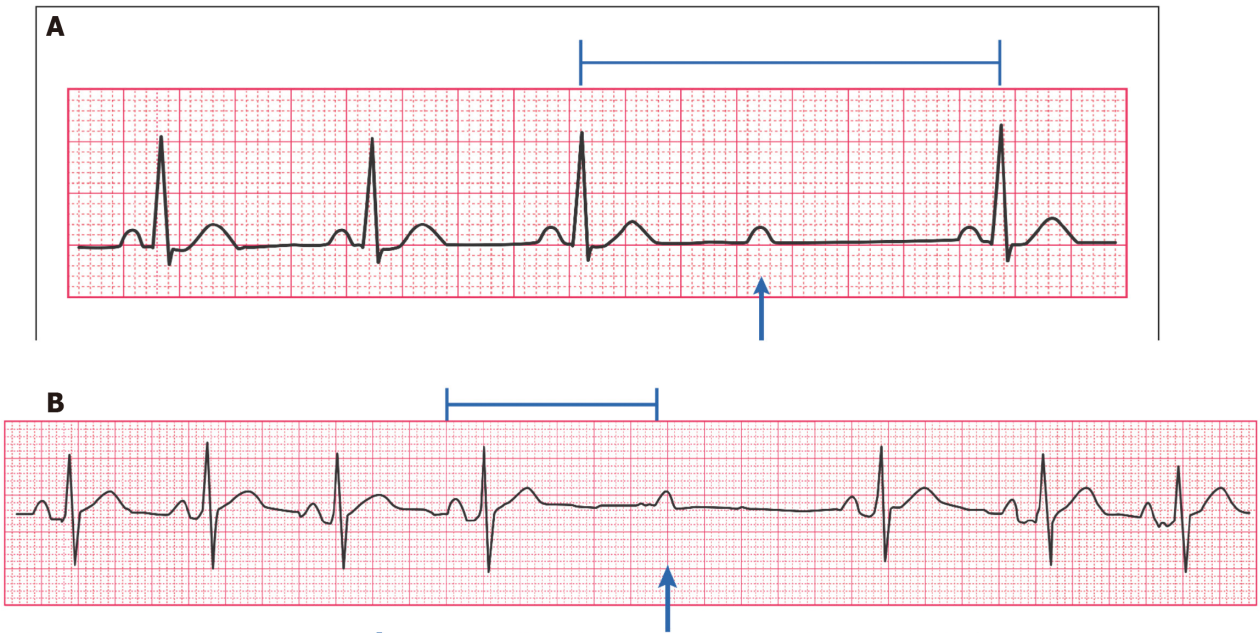

Figure 1 Mobitz type II atrioventricular block and vagally-induced type I atrioventricular block[14]. A: Mobitz type II atrioventricular block (AVB). There is regular sinus rhythm with a single non-conducted P wave. The PR intervals before and after the block are constant. The sinus rate is constant. The RR interval encompassing the blocked P wave is twice the RR interval prior to the blocked P wave; B: Vagally-induced type I AVB. There is sinus slowing shown by the long PP interval. The PR intervals before and after a single blocked P wave are constant simulating Mobitz type II block. However, type II AVB is ruled out because of sinus slowing consistent with vagally induced AVB. Citation: Barold DC, Barold SS. ECG Simplified. Facts You will Never Forget. San Marcos: Conductivity Press, 2022. Copyright ©The Author(s) 2019. Published by Conductivity Press.

FOOTNOTES

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Country of origin: United States

ORCID number: S Serge Barold 0000-0003-4951-6465.

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OPINION REVIEW

Coronary artery disease and heart failure: Late-breaking trials presented at American Heart Association scientific session 2023

Avilash Mondal, Sashwath Srikanth, Sanjana Aggarwal, Naga R Alle, Olufemi Odugbemi, Ikechukwu Ogbu, Rupak Desai

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Avilash Mondal, Department of Internal Medicine, Nazareth Hospital, Philadelphia, PA 19152, United States

Sashwath Srikanth, Department of Internal Medicine, East Carolina University Greenville, Greenville, NC 27834, United States

Sanjana Aggarwal, Department of Internal Medicine, Hamdard Institute of Medical Sciences and Research, New Delhi 110062, India

Naga R Alle, Department of Medicine, Narayana Medical College, Nellore, Andhra Pradesh 524003, India

Olufemi Odugbemi, Department of Internal Medicine, Lincoln Medical Center, Bronx, NY 10451, United States

Ikechukwu Ogbu, Department of Internal Medicine, Mountainview Hospital Sunrise GME, Las Vegas, NV 89108, United States

Rupak Desai, Independent Researcher, Atlanta, GA 30079, United States

Corresponding author: Ikechukwu Ogbu, MD, Doctor, Department of Internal Medicine, Mountainview Hospital Sunrise GME, 2880 N Tenaya Way, Las Vegas, NV 89108, United States. iogbu832267@gmail.com

Abstract

The late-breaking science presented at the 2023 scientific session of the American Heart Association paves the way for future pragmatic trials and provides meaningful information to guide management strategies in coronary artery disease and heart failure (HF). The dapagliflozin in patient with acute myocardial infarction (DAPA-MI) trial showed that dapagliflozin use among patients with acute MI without a history of diabetes mellitus or chronic HF has better cardiometabolic outcomes compared with placebo, with no difference in cardiovascular outcomes. The MINT trial showed that in patients with acute MI and anemia (Hgb < 10 g/dL), a liberal transfusion goal (Hgb ≥ 10 g/dL) was not superior to a restrictive strategy (Hgb 7-8 g/dL) with respect to 30-day all-cause death and recurrent MI. The ORBITA-2 trial showed that among patients with stable angina and coronary stenoses causing ischemia on little or no antianginal therapy, percutaneous coronary intervention results in greater improvements in anginal frequency and

exercise times compared with a sham procedure. The ARIES-HM3 trial showed that in patients with advanced HF who received a HeartMate 3 levitated left ventricular assist device and were anticoagulated with a vitamin K antagonist, placebo was noninferior to daily aspirin with respect to the composite endpoint of bleeding and thrombotic events at 1 year. The TEAMMATE trial showed that everolimus with low-dose tacrolimus is safe in children and young adults when given ≥ 6 months after cardiac transplantation. Providing patients being treated for HF with reduced ejection fraction (HFrEF) with specific out-of-pocket (OOP) costs for multiple medication options at the time of the clinical encounter may reduce 'contingency planning' and increase the extent to which patients are taking the medications decided upon. The primary outcome, which was cost-informed decision-making, defined as the clinician or patient mentioning costs of HFrEF medication, occurred in 49% of encounters with the checklist only control group compared with 68% of encounters in the OOP cost group.

Key Words: Heart failure; Coronary artery disease; Clinical trials; Myocardial infarction; Cardiovascular outcome; Percutaneous coronary intervention; Blood transfusion; Cardiac transplant

Core Tip: In this review paper, we discuss the late-breaking trials featured in the American Heart Association 2023, spanning various cardiac conditions and interventions. The review sheds light on treatment nuances and underscore the importance of evidence-based medicine.

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INTRODUCTION

Cardiovascular research on heart failure (HF) and coronary artery disease, including always-evolving interventional techniques, continually shapes therapeutic approaches, elucidating optimal strategies and challenging established norms. In this review paper, we discuss the late-breaking trials featured in the American Heart Association 2023, held in Philadelphia, Pennsylvania, United States, in November 2023. Dapagliflozin in patient with acute myocardial infarction (DAPA-MI) investigated dapagliflozin's effect on post-MI without diabetes. MINT tried to elucidate transfusion thresholds in anemic MI patients, while ORBITA-2 assessed percutaneous coronary intervention (PCI)'s efficacy for angina relief. ARIES-HM3 scrutinized aspirin's role in levitated left ventricular assist device (LVAD)-treated HF. The TEAMMATE trial assessed everolimus in post-heart transplant care for children (Table 1).

Additionally, integrating cost data into shared decision-making for (HF with reduced ejection fraction) HFrEF treatments emerges as a patient-centered approach. These trials, spanning various cardiac conditions and interventions, shed light on treatment nuances and underscore the importance of evidence-based medicine. The findings contribute crucial insights into optimizing therapeutic strategies, enhancing patient outcomes, and guiding clinical decision-making. As these trials unravel, they offer novel perspectives and potential paradigm shifts in managing cardiovascular ailments, reshaping how we approach cardiac care and highlighting the evolving landscape of cardiovascular research and practice.

CORONARY ARTERY DISEASE

DAPA-MI–A registry-based randomized trial of dapagliflozin in patient with acute myocardial infarction without diabetes

Study summary: The DAPA-MI trial is a multicenter, parallel-group, registry-based, randomized, double-blind, placebo-controlled phase 3 trial integrating existing national clinical registries (SWEDEHEART and NICOR in Sweden and the United Kingdom, respectively) which aimed to assess the effect of dapagliflozin (10 mg daily) *vs* placebo in patients recently hospitalized for myocardial infarction without known diabetes or established HF[1].

Clinical implications: Patients with acute MI without diabetes mellitus or chronic HF have better cardiometabolic outcomes with dapagliflozin than placebo. Over two years, dapagliflozin patients lost 1.65 kg and were less likely to acquire diabetes.

Because the primary composite results were lower than predicted, the trial design was revised to focus on clinically important cardiometabolic outcomes using a hierarchical composite outcome method using the win ratio. However, with

Table 1 Summary of coronary artery disease and heart failure trials from the late-breaking trials presented at the American Heart Association 3 scientific sessions

Trial name	Ref.	Type of study	Sample size	Follow-up duration	Inclusion criteria	Exclusion criteria	Study findings	Study highlights
DAPA-MI	James *et al*[1]	Randomized control Trial	4017	24 months	NSTEMI or STEMI < 10 days, impaired LV systolic function or q-wave MI, hemodynamically stable	Type 1 or type 2 DM, chronic symptomatic HF with a prior HF hospitalization within the last year and known LVEF ≤ 40%, eGFR) < 20 mL/min/1.73 m^2	The primary endpoint for dapagliflozin *vs* placebo was a win ratio of 1.34, 95%CI 1.20–1.50; $P < 0.001$[b]	The DAPA-MI trial indicated that for acute MI patients, without diabetes or chronic heart failure, the use of dapagliflozin results in improved cardiometabolic outcomes while it does not lead to any changes in cardiovascular outcomes
MINT trial	Carson *et al* [2]	Randomized control trial	3504	30 days	Age ≥ 18 years, STEMI or NSTEMI, Hgb < 10 g/dL	Uncontrolled bleeding requiring blood transfusion, declined transfusion, anticipated cardiac surgery, palliative treatment intent	The primary outcome, composite of all-cause death or recurrent nonfatal MI, for restrictive *vs* liberal transfusion strategies at 30 days, was: 16.9% *vs* 14.5%; RR: 1.15, 95%CI: 0.99-1.34; $P = 0.07$	The MINT trial showed that in patients with acute MI and Hgb < 10 g/dL, a liberal transfusion goal (Hgb ≥ 10 g/dL) was not superior to a restrictive strategy (Hgb 7-8 g/dL) with respect to 30-day all-cause death and recurrent MI
ORBITA-2	Rajkumar *et al*[5]	Randomized control trial	301	12 weeks	PCI eligible, had angina or angina equivalents, had anatomical evidence of at least one severe coronary stenosis that was identified on invasive diagnostic coronary angiography or CCTA, had evidence of ischemia on the basis of noninvasive imaging or invasive coronary physiological test	Age < 18 years and age > 85 years, recent ACS, Previous CABG, significant left main stem CAD, chronic total occlusion in the target vessel, contraindication to PCI or drug-eluting stent implantation, contraindication to antiplatelet therapy, severe valvular disease, severe LV dysfunction, severe respiratory disease, life expectancy < 2 years, pregnancy	The primary outcome, mean angina symptom score for PCI *vs* placebo, was: 2.9 *vs* 5.6, OR: 2.21, 95%CI: 1.41-3.47; $P < 0.001$[b]. Mean daily angina frequency: 0.3 *vs* 0.7 (OR: 3.44, 95%CI: 2.00-5.91)	The ORBITA-2 trial showed that among patients with stable angina on little or no antianginal therapy, PCI results in greater improvements in anginal frequency and exercise times compared with a sham procedure
ARIES-HM3	Mehra *et al* [10]	Randomized control trial	628	24 months	Age ≥ 18 years, first durable LVAD implantation with HM3 for an approved indication per local guidelines	Additional MCS in addition to HM3, alternative indication or contraindication for antiplatelet therapy, inability to take oral medications through day 7 postoperatively, aspirin allergy	The primary outcome, survival free from nonsurgical hemocompatibility-related adverse event (*i.e.*, stroke, pump thrombosis, major bleeding, or arterial thromboembolism > 14 days post-implant), for placebo *vs* aspirin at 1 year, was: 74.2 *vs* 68.1 events per 100 patient-years (P for noninferiority < 0.0001[b])	The ARIES-HM3 trial demonstrated that for patients with advanced heart failure treated with a HeartMate 3 LVAD and anticoagulated with a vitamin K antagonist, aspirin did not surpass placebo in terms of the combined incidence of bleeding and clotting events after one year
TEAMMATE	Almond *et al* [11]	Randomized control trial	211	30 months	Cardiac transplantation at age ≤ 21 years, ≥ 6 months after heart transplantation, stable immunosuppression	Recurrent rejection/graft dysfunction, steroid dose > 0.1 mg/kg/day eGFR < 30 mL/min/1.73 m^2, active infection or wound healing problem, severe hyperlipidemia or proteinuria	The co-primary outcomes, median MATE-6 score at 30 months, was 1.96 in everolimus group *vs* 2.18 in tacrolimus group, median MATE-3 score at 30 months, was 0.93 in everolimus group *vs* 1.25 in tacrolimus group (P = NS)	The TEAMMATE trial showed that everolimus + low-dose tacrolimus is safe in children and young adults when given ≥ 6 months after cardiac transplantation
POCKET-COST-HF	Montembeau *et al*[12]	Randomized control trial	247	-	LVEF ≤ 40%		The primary outcome, which was cost-informed decision-making, defined as the clinician or patient mentioning costs	Providing detailed cost information had notable effect on discussions about costs during

		of HFrEF medication, occurred in 49% of encounters with the checklist only control group compared with 68% of encounters in the OOP cost group (P = 0.021[a])	medical appointments for patients with HFrEF

[a]$P < 0.05$.
[b]$P < 0.001$.
NSTEMI: Non-ST segment elevation myocardial infarction; STEMI: Segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; CCTA: Coronary computed tomography angiography; ACS: Acute coronary syndrome; CABG: Coronary artery bypass graft; HF: Heart failure; LVEF: Left ventricular ejection fraction; eGFR: Estimated glomerular filtration rate; DM: Diabetes mellitus; MI: Myocardial infarction; LVAD: Left ventricular assist device; VKA: Vitamin K antagonist; MATE: Major adverse transplant event; HFrEF: Heart failure with reduced ejection fraction; OOP: Out-of-pocket; MCS: Mechanical circulatory support.

longer follow up we might be able to see favorable outcomes.

MINT: Restrictive vs liberal blood transfusion in patients with myocardial infarction and anemia: Results of the MINT trial

Study summary: Several pivotal trials have attempted to delineate the optimal transfusion thresholds for acute myocardial infarction (AMI) patients[2-4], but none have been able to conclude a clear consensus. The theoretical benefit of preventing ischemic injury by improving oxygen delivery and reducing the risk of reinfarction or death needs to be weighed against the potential harm from fluid overload, transfusion-related infection, and thrombotic and inflammatory processes.

Of 3504 patients were included in the analysis. The primary outcome was defined as a 30-day composite of myocardial infarction or all-cause mortality which occurred in 16.9% of the restrictive-strategy group and 14.5% of the liberal-strategy group [RR: 1.15; 95% confidence interval (CI): 0.99-1.34, P = 0.07]. Additionally, there were no significant differences in secondary outcomes like death (RR: 1.19; 95%CI: 0.96-1.47) or recurrent non-fatal MI (RR: 1.19; 95%CI: 0.94-1.49), combined death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition (RR: 1.13; 95%CI: 0.98-1.29), risk of HF (RR: 0.92; 95%CI: 0.71-1.20) at 30 days, pulmonary embolism, or deep venous thrombosis (RR: 0.77; 95%CI: 0.46-1.27) in the restrictive *vs* liberal strategy group. However, cardiac death was more frequent in the restrictive-strategy group (RR: 1.74; 95%CI: 1.26-2.40), while there was less risk of transfusion-associated cardiac overload events in the restrictive-strategy group than in the liberal-strategy group (RR: 0.35; 95%CI: 0.16-0.78). Subgroup analyses of primary outcome revealed trend favoring the liberal strategy for patients with type 1 myocardial infarction (RR: 1.32; 95%CI: 1.04-1.670 and in chronic or acute HF or reduced ejection fraction patients (RR: 1.25; 95%CI: 1.02-1.52).

Clinical implications: Despite not reaching statistical significance, the trial demonstrated an observed effect favoring the liberal strategy by approximately 15%, although the trial was powered to detect a 20% difference. This smaller-than-anticipated difference might be attributed to enrolling a diverse group of AMI patients, including a substantial proportion of type 2 MI patients.

Limitations included lack of masking of intervention, potential influence on healthcare decisions, unadjudicated outcomes, moderate adherence to the liberal strategy's hemoglobin threshold, and lack of adjustment for multiple comparisons in analyses.

ORBITA-2: PCI for stable angina: A randomized, placebo-controlled trial

Study summary: Patients with stable coronary artery disease seek PCI[5], primarily for angina relief. Past unblinded trials show PCI's effect on symptoms, involving both physical changes and a placebo effect[6-9]. Understanding the actual physical impact after subtracting the placebo is crucial for informed clinical choices, especially for costly and risky procedures. Previous trials, like ORBITA mandated antianginal medications, found no significant PCI effect on exercise time. ORBITA-2, however, explores PCI's effect without these medications in stable angina patients.

The ORBITA-2 trial was a double-blind, randomized, placebo-controlled investigation across 14 sites in the United Kingdom. The study enrolled patients deemed suitable for PCI involving severe coronary stenosis and ischemic symptoms, evaluating the efficacy of PCI *vs* a placebo procedure.

Three hundred and one patients were subsequently randomly assigned to PCI (151 patients, mean age 65 ± 5 years) or placebo (150 patients, mean age 64 ± 9 years). Patients underwent an initial phase of symptom assessment and cessation of antianginal medications. They reported symptoms *via* a smartphone application and underwent assessments, including treadmill tests and stress echocardiography. Subsequently, patients were randomized to either PCI or a placebo procedure. Blinding was meticulously maintained throughout.

At the 12-week follow-up, the mean angina symptom score was 2.9 in the PCI group and 5.6 in the placebo group [odds ratio (OR): 2.21; 95%CI: 1.41-3.47; $P < 0.001$], the mean daily angina frequency was 0.3 episodes in the PCI group and 0.7 in the placebo group (OR: 3.44; 95%CI: 2.00-5.91), and the mean daily use of antianginal medication was 0.2 and 0.3 units in the PCI and placebo groups, respectively (OR: 1.21; 95%CI: 0.70-2.10). Secondary endpoints, including quality of life measures, treadmill exercise time, and physician-assessed angina severity, aligned with the primary outcome.

Clinical implications: The angina symptom score was considerably lower in the PCI group than the placebo group at 12 weeks. Angina frequency and antianginal drug usage favored PCI.

ORBITA-2 stressed the importance of double-blinded placebo-controlled studies for PCI evaluation. The experiment showed that PCI for angina relief is effective without baseline antianginal medication, contradicting the idea that PCI is best utilized in individuals with inadequate antianginal responses.

HF

ARIES-HM3: Aspirin and hemocompatibility events with a left ventricular assist device in advanced HF, randomized clinical trial

Study summary: ARIES-HM3 was an international, randomized, double-blind, placebo-controlled trial that aimed to investigate the safety of excluding aspirin from the antithrombotic regimen in patients with advanced HF utilizing LVADs, along with its potential to reduce bleeding incidents[10].

The primary endpoint, assessing survival without major hemocompatibility-related adverse events (such as stroke, pump thrombosis, significant nonsurgical bleeding, and arterial peripheral thromboembolism) at 12 months, was achieved for placebo *vs* aspirin at 1 year, was: 74.2 *vs* 68.1 events *per* 100 patient-years (P for noninferiority < 0.0001). The trial met the noninferiority criterion (with a margin of -10%) showing a 6.0% absolute between-group difference (lower 1-sided 97.5%CI: -1.6%) with a significant P value of less than 001.

Notably, the placebo group demonstrated a lower incidence of bleeding events (22.5% *vs* 28.2% in the aspirin group). Analyzing the time to the first event showed a lower occurrence of deaths or major hemocompatibility-related adverse events in the placebo group compared to the aspirin group over 24 months (36.9% *vs* 45.9%; HR: 0.73, 95%CI: 0.55-0.97, $P = 0.03$).

Clinical implications: The antithrombotic regimen for patients with advanced HF treated with a fully magnetically levitated LVAD without the use of aspirin is not inferior to that with the use of aspirin and shows reduced bleeding events.

The TEAMMATE trial: Everolimus to prevent rejections in children after cardiac transplantation

Study summary: The TEAMMATE Trial evaluated the safety and efficacy of Everolimus and low-dose tacrolimus to prevent rejection, cardiac allograft vasculopathy[11], and renal dysfunction in children and young adults when introduced at 6 months post-heart transplant.

There was no significant difference in major adverse transplant events in the Everolimus group compared to the mycophenolate mofetil (MMF) group. The pre-specified safety criterion was met successfully by the Everolimus group. The cumulative burden of cardiac allograft vasculopathy, chronic kidney disease, and cellular rejection at 30 months was not different in the Everolimus group when compared to the MMF group. A higher glomerular filtration rate, a lower rate of anti-human leukocyte antigen antibody development, and less cytomegalovirus infection were seen in patients receiving Everolimus, but more hyperlipidemia and higher liver transaminases were also seen.

Clinical implication: Everolimus combined with low-dose tacrolimus is safe in children and young adults when initiated six months after transplant.

Integrating cost into shared decision-making for HFrEF: A trial providing out-of-pocket costs for HF medications during clinical encounters POCKET-COST-HF

Clinical implications: Providing detailed cost information had a moderate but notable effect on discussions about costs during medical appointments for patients with HFrEF[12]. This preliminary evidence indicates that such cost disclosures might decrease the need for emergency planning and improve patient adherence to chosen medications.

To better understand the effects of detailed out-of-pocket (OOP) cost information on medication selection, prescribing habits, and patient adherence, larger studies with more participants and extended follow-up periods are necessary.

Additional research is required to explore effective methods for integrating cost information into clinical practice and to develop new tools that can be incorporated into Electronic Health Record systems.

CONCLUSION

DAPA-MI investigated the effects of dapagliflozin after MI in individuals who do not have diabetes or HF. The study included a substantial sample of 4017 people and showed a trend in decrease in the combined mortality, hospitalization for HF, nonfatal myocardial infarction, atrial fibrillation/flutter, type 2 diabetes mellitus, and New York Heart Association class ($P < 0.001$) in the form of a win-ratio, which is being used by a number of newer trials. However, there are inherent limitations to using the win ratio for composite outcomes, such as overestimation of clinical benefits, flawed assessment of patient-reported outcomes, imbalance in the risk profiles of analyzed pairs, and the problematic dismissal of "ties" in treatment outcomes. These issues challenge the accuracy of the win ratio and clinical meaningfulness, suggesting a need for more reliable analytical methods in cardiovascular trials. However, this trial did have effects on the new diagnosis of diabetes and its effect on weight. Maybe with longer follow-up times, we might be able to see a reduction in hard endpoints. We also investigated transfusion thresholds in individuals with myocardial infarction. Prior randomized controlled trials did not offer a definitive consensus. The MINT trial compared restrictive and liberal transfusion strategies in patients with myocardial infarction and anemia[2]. It found no significant difference in 30-day myocardial infarction or death rates between strategies, suggesting that a liberal strategy might not reduce these risks more effectively than a restrictive approach. However, the liberal strategy slightly favored primary outcomes and death rates, indicating potential benefits. There was a 2013 pilot trial in 110 patients by the same author, which showed the liberal transfusion strategy was associated with a trend for fewer major cardiac events and deaths than a more restrictive strategy[2]. In comparison, other trials like REALITY, TRICS, and TITRe2 explored similar themes with varying findings. REALITY favored a restrictive transfusion strategy for patient's post-acute coronary syndrome, challenging the traditional 10/30 rule[4]. TRICS, involving patients undergoing cardiac surgery, found a restrictive strategy noninferior to a liberal one[13]. Contrarily, TITRe2 reported more deaths in the restrictive group[14]. MINT's strengths include its large sample size and practical approach, making its findings broadly applicable. However, the trial had limitations like non-blinding of interventions and moderate adherence to transfusion protocols. Future directions could involve confirming MINT's conclusions and exploring the implications of transfusion strategies in different patient subgroups, considering the nuanced results across various trials. Considering these data, the trend toward clinical benefit observed in MINT suggests that a liberal transfusion strategy in MI may be reasonable to consider without an appreciably increased risk of harm. The ORBITA-2 trial, a follow-up study of the original ORBITA study, enrolled 301 patients to evaluate PCI for stable angina in individuals who did not receive any antianginal medicines at the beginning of the study. At the 12-week mark, PCI demonstrated a substantial reduction in angina symptoms and frequency when compared to the administration of a placebo. Nevertheless, there was no discernible difference in the daily usage of antiangiogenic drugs. The results contradict those of the ORBITA study[15], which found no benefit of PCI in addition to appropriate medical treatment for the primary endpoint of treadmill exercise duration. This research aims to validate the antianginal advantage of PCI for stable coronary artery disease using a sham-controlled strategy, like the original ORBITA study. Patients were taken off anti-anginal medications. Limitations of the study include a brief 12-week period of monitoring and the relatively small size of the sample, which evaluates significant clinical outcomes. The trial's use of blinding emphasizes the notable placebo effect of PCI for angina. This questions the necessity of performing PCI in stable angina patients who are not taking baseline antianginal medications and emphasizes the importance of reevaluating the need for this procedure.

The ARIES-HM3 study examines aspirin use in patients with advanced HF using a fully magnetically LVAD[10]. This randomized, double-blind, placebo-controlled trial evaluated the necessity and impact of aspirin in combination with vitamin K antagonists. The study found that avoiding aspirin is not inferior to using it and is associated with a reduction in bleeding events without increasing thromboembolic risk. This finding challenges the traditional inclusion of aspirin in antithrombotic regimens for LVAD patients. The study suggests potential shifts in managing patients with advanced HF and LVADs, emphasizing personalized approaches to antithrombotic therapy. The TEAMMATE Trial explores the use of everolimus combined with low-dose tacrolimus in preventing transplant complications in pediatric heart transplant recipients[11]. This phase III open-label randomized clinical trial was conducted at 25 sites in the United States, with a primary endpoint focusing on major adverse transplant event. Strengths of the study include a robust sample size and the inclusion of a pediatric population, often underrepresented in clinical trials. Limitations include its open-label design and potential variations in standard care practices across multiple sites. This study opens pathways for future research in pediatric transplant immunosuppression, particularly regarding balancing efficacy and side effects in this vulnerable population. Finally, The POCKET-COST-HF study focuses on integrating OOP cost information into clinical decision-making for HFrEF treatments[12]. Key findings suggest that tailored cost disclosure modestly increases discussions about costs in clinical encounters. Limitations include a small sample size and potential biases in the stepped-wedge design.

This study paves the way for further research on implementing cost-disclosure strategies in clinical practice, highlighting the importance of cost considerations in patient care.

These studies together highlight the need for subtle and refined treatment techniques, question existing standards, and create opportunities for future research, influencing the changing field of cardiovascular care.

FOOTNOTES

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Country of origin: United States

ORCID number: Naga R Alle 0009-0007-4867-1769; Olufemi Odugbemi 0009-0003-6025-6374; Ikechukwu Ogbu 0000-0002-7911-833X; Rupak Desai 0000-0002-5315-6426.

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MINIREVIEWS

Proprotein convertase subtilisin/kexin type 9 inhibitors in peripheral artery disease: A review of efficacy, safety, and outcomes

Moiud Mohyeldin, Ahmed S Abuelgasim, Ahmed MG Mustafa

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Moiud Mohyeldin, Ahmed S Abuelgasim, Ahmed MG Mustafa, Department of Internal Medicine, University of Medical Sciences and Technology, Khartoum 11111, Sudan

Corresponding author: Moiud Mohyeldin, MD, Doctor, Staff Physician, Department of Internal Medicine, University of Medical Sciences and Technology, Ebed Khatim St, Khartoum 11111, Sudan. moiudahmed@gmail.com

Abstract

Peripheral artery disease (PAD) is a common condition characterized by atherosclerosis in the peripheral arteries, associated with concomitant coronary and cerebrovascular diseases. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a class of drugs that have shown potential in hypercholesterolemic patients. This review focuses on the efficacy, safety, and clinical outcomes of PCSK9 inhibitors in PAD based on the literature indexed by PubMed. Trials such as FOURIER and ODYSSEY demonstrate the efficacy of evolocumab and alirocumab in reducing cardiovascular events, offering a potential treatment option for PAD patients. Safety evaluations from trials show few adverse events, most of which are injection-site reactions, indicating the overall safety profile of PCSK9 inhibitors. Clinical outcomes show a reduction in cardiovascular events, ischemic strokes, and major adverse limb events. However, despite these positive findings, PCSK9 inhibitors are still underutilized in clinical practice, possibly due to a lack of awareness among care providers and cost concerns. Further research is needed to establish the long-term effects and cost-effectiveness of PCSK9 inhibitors in PAD patients.

Key Words: Peripheral artery disease; Proprotein convertase subtilisin/kexin type 9 inhibitors; Cardiovascular risk reduction; Evolocumab; Alirocumab; Lipid-lowering therapy; Major adverse limb events; Clinical outcomes; Cost-effectiveness; Safety profile

Core Tip: Evolocumab and alirocumab, which belong to the class of proprotein convertase subtilisin/kexin type 9 inhibitors, are effective in reducing cardiovascular events and major adverse limb events in peripheral artery disease patients. Despite their proven benefits, these inhibitors are underutilized in clinical practice, often due to providers' lack of awareness and concerns about cost. This highlights the need for further research to assess the long-term effects of these inhibitors and their cost-effectiveness for specific patient groups.

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INTRODUCTION

Peripheral artery disease (PAD) is a common condition characterized by atherosclerosis in the peripheral arteries, which reduces blood flow to the limbs. It is a debilitating condition affecting approximately 200 million people worldwide[1]. PAD symptoms include intermittent claudication, variable claudication, and limb pain. However, many PAD patients may present with atypical symptoms that do not align with the classic definition of claudication or remain asymptomatic; in some cases, the blood flow is severely compromised, requiring urgent surgical intervention[2]. PAD is associated with significant morbidity and mortality, as it increases the risk of cardiovascular events and limb amputation and reduces the quality of life. The prevalence of PAD is rising globally, fueled by an aging population and the growing prevalence of risk factors, including diabetes, hypertension, and smoking[3]. PAD can be managed through medical or procedural endovascular approaches such as revascularization with percutaneous angioplasty, stents, and arterectomy[4]. Medical management includes the use of statins; angiotensin-converting enzyme inhibitors; or angiotensin receptor blockers, antiplatelet therapy, and prostaglandins[5]. Our study reinforces the substantial potential benefits of the new innovative giant proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor and its role in PAD.

PCSK9 INHIBITORS

Drugs that inhibit the enzyme PCSK9 have shown promise in the treatment of hypercholesterolemia, particularly in familial hypercholesterolemia patients. These drugs work by inhibiting the PCSK9 enzyme, which, in turn, increases the clearance of low-density lipoprotein cholesterol (LDL-C) from the bloodstream, thereby reducing the risk of atherosclerosis and its complications[6]. The Food and Drug Administration has approved two PCSK9 inhibitors, evolocumab and alirocumab, for use in hypercholesterolemia patients[7]. Evolocumab and alirocumab are administered subcutaneously twice a week; alirocumab can also be used once every 4 wk[8,9]. Given the role of atherosclerosis in the development of PAD, there is a growing interest in exploring the potential benefits of PCSK9 inhibitors in the management of PAD.

In addition to antibody-based therapies, alternative approaches targeting PCSK9, including small molecules and peptides, are being explored[10,11]. Small-molecule inhibitors offer potential advantages over antibodies, such as lower manufacturing costs, oral bioavailability, and better cell permeability. These small molecules can inhibit PCSK9 through various mechanisms, such as preventing its synthesis, secretion, or interaction with LDL receptors[10]. Peptide-based strategies, such as epidermal growth factor precursor homology domain A mimetic peptides, represent another approach to blocking PCSK9-LDLR from binding with high specificity[10,11]. However, despite progress in developing these alternative PCSK9 inhibitors, challenges remain in optimizing their selectivity and potency, elucidating their effects on Lp (a) levels, and using them in homozygous familial hypercholesterolemia patients[10].

While PCSK9 inhibitory antibodies have demonstrated much clinical success thus far, small-molecule and peptide PCSK9 inhibitors are emerging as promising complementary strategies that may expand future treatment options[10,11]. This review focuses on the efficacy, safety, and clinical outcomes of PCSK9 inhibitory antibodies (evolocumab and alirocumab) in the management of PAD.

EFFICACY OF PCSK9 INHIBITORS IN PAD

The FOURIER trial investigated the efficacy of evolocumab in PAD patients. The study included 27564 atherosclerotic disease patients receiving statin therapy, of whom 3642 (13.2%) had PAD. The researchers assessed a composite primary endpoint consisting of cardiovascular mortality, stroke, myocardial infarction, hospitalization for unstable angina, or coronary revascularization. The results showed that evolocumab significantly reduced the primary endpoint in PAD patients, yielding a hazard ratio (HR) of 0.79 and a 95% confidence interval[12]. In addition, alirocumab has demonstrated efficacy in reducing cardiovascular events in these patients. In the ODYSSEY Outcomes trial, treatment with alirocumab was associated with a 15% reduction in the risk of coronary heart disease-related death, ischemic stroke, myocardial

infarction, and unstable angina necessitating hospitalization[8].

EFFICACY OF PCSK9 INHIBITORS IN REDUCING LDL LEVELS

Despite the significant adverse limb and cardiovascular outcomes observed in PAD patients, less attention has been paid to risk factor modification compared to other atherosclerotic diseases such as stroke or coronary artery disease. PAD patients have been consistently undertreated with lipid-lowering therapies[12].

The FOURIER trial concluded that at 48 wk, evolocumab treatment led to a 59% reduction in LDL cholesterol levels compared to placebo, with a decrease from a median baseline of 92 mg/dL (2.4 mmol/L) to 30 mg/dL (0.78 mmol/L) (P < 0.001). Compared to the placebo treatment, evolocumab significantly reduced the risk of the primary endpoint (1344 patients [9.8%] *vs* 1563 patients [11.3%]; HR, 0.85; 0.79 to 0.92; P < 0.001) and the secondary endpoint (816 [5.9%] *vs* 1013 [7.4%]; HR, 0.80; 0.73 to 0.88; P < 0.001) (Table 1)[9]. The ODYSSEY trial highlighted greater LDL-C reduction by alirocumab compared to a placebo treatment, with a decrease from 93.3 mg/dL to 37.6 mg/dL (62.7%) at 4 mo and from 101.4 mg/dL to 53.3 mg/dL (54.7%) at 48 mo (Table 1)[8].

PCSK9 inhibitors may treat PAD through several mechanisms other than their potent LDL-C-lowering effects, as illustrated in Figure 1. These include anti-inflammatory effects, improved endothelial function, plaque stabilization, and anti-thrombotic effects. These pleiotropic effects could contribute to the efficacy of these inhibitors in PAD.

COST-EFFECTIVENESS OF PCSK9 INHIBITORS

An analysis of data collected from the ODYSSEY and OSLER trials showed that the use of PCSK9 inhibitors in atherosclerotic cardiovascular disease patients failed to reach generally acknowledged benchmarks for incremental cost-effectiveness and was anticipated to lead to a notable rise in healthcare costs in the United States. This illustrates that the use of PCSK9 inhibitors outside of clinical trial settings could be challenging, as it may not be affordable for most healthcare systems and private insurance payers[13,14]. A systematic review of the cost-effectiveness of PCSK9 inhibitors in cardiovascular disease demonstrated that the economic evaluation of PCSK9 inhibitors has predominantly focused on direct medical costs while neglecting the potential impact of indirect costs, thereby offering an incomplete perspective. While studies have shown that PCSK9 inhibitors have unclear lifetime outcomes, particularly in younger patients, their high economic burden, owing to being priced at $7000 in developed countries and $15000 in the United States, makes them generally ineffective for the broader population. However, their use may have a better cost-effectiveness profile in specific populations, such as patients with familial hypercholesterolemia and statin intolerance. In response to concerns about high costs, Amgen Inc. reduced the price of PCSK9 inhibitors in the United States in October 2018. Future studies conducted after price reductions may yield different outcomes, and a complementary systematic review to compare the results is recommended[15].

SAFETY OF PCSK9 INHIBITORS IN PAD

Various studies have evaluated the safety of PCSK9 inhibitors. The FOURIER trial found evolocumab to be safe in PAD patients[12]. Injection-site reactions were the only significant adverse events reported in the FOURIER and ODYSSEY trials. In the evolocumab group, 2.1% of patients experienced injection-site reactions, compared to 1.6% in the placebo group. Approximately 90% of these reactions in both groups were mild, and only 0.1% of patients in each group discontinued the study drug due to an injection-site reaction[8,12]. Furthermore, the OSLER trial, a study reporting the efficacy and safety of evolocumab for hypercholesterolemic patients over 1 year, reported no significant adverse events between the study and control groups[13].

CLINICAL OUTCOMES OF PCSK9 INHIBITORS IN PAD

In the FOURIER trial, evolocumab reduced the incidence of major adverse limb events, which included acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia. Evolocumab also consistently reduced the primary endpoint in PAD patients, regardless of their prior myocardial infarction or stroke history[12]. In the ODYSSEY Outcomes trial, alirocumab also significantly reduced the risk of myocardial infarction (14%), coronary revascularization (12%), and ischemic stroke (27%)[8].

LIMITATIONS AND FUTURE RESEARCH

While the current research on PCSK9 inhibitors in PAD shows promising results, some limitations must be considered. Most of the trials have focused on short-term outcomes, and there is a need for longer-term studies to establish the long-term effects of PCSK9 inhibitors in PAD patients. Additionally, the cost-effectiveness of these drugs remains a concern,

Table 1 Efficacy of proprotein convertase subtilisin/kexin type 9 inhibitors in reducing low-density lipoprotein levels and cardiovascular events in peripheral artery disease patients

	Drug	LDL-C reduction	CV event reduction
FOURIER	Evolocumab	59% at 48 wk[a]	15%; (HR: 0.85; 95%CI: 0.79 to 0.92[a])
ODYSSEY	Alirocumab	55% at 4 mo; 63% at 48 mo	15% reduction in the composite of CHD death, MI, ischemic stroke, or unstable angina requiring hospitalization

[a]$P < 0.001$. CHD: Coronary heart disease; CI: Confidence interval; CV: Cardiovascular; HR: Hazard ratio; LDL-C: Low-density lipoprotein cholesterol; MI: Myocardial infarction.

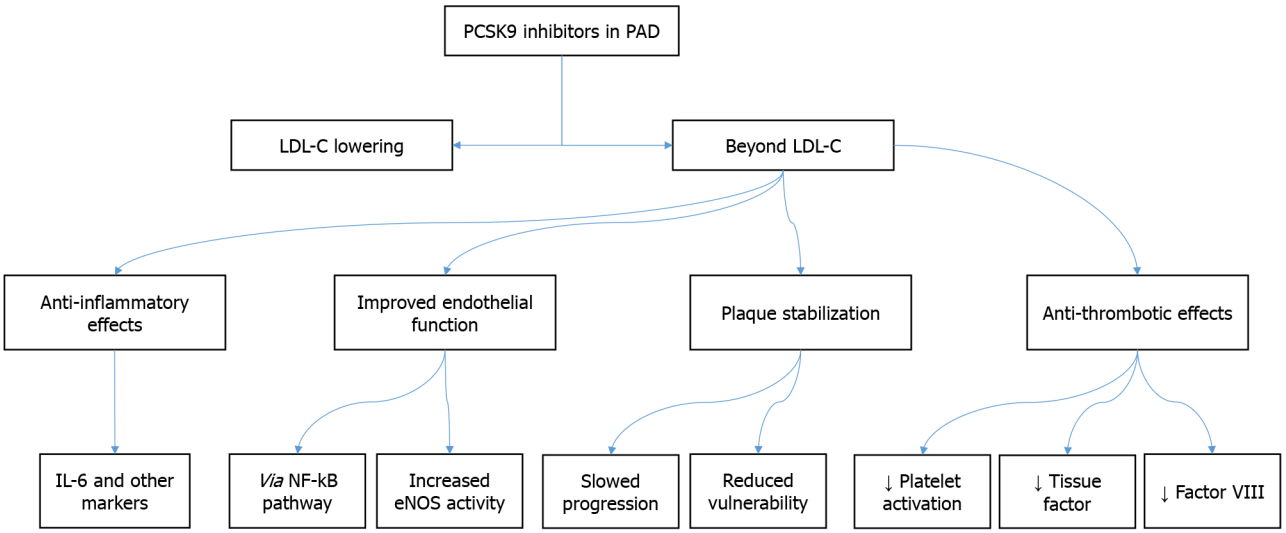

Figure 1 How proprotein convertase subtilisin/kexin type 9 inhibitors enhance low-density lipoprotein (LDL) receptor recycling on hepatocytes, thereby reducing plasma LDL cholesterol levels and mitigating atherosclerosis risks in peripheral artery disease. Key actions include blocking proprotein convertase subtilisin/kexin type 9-low-density lipoprotein receptor interactions and promoting anti-inflammatory and plaque-stabilizing effects, which collectively decrease cardiovascular events in peripheral artery disease (PAD) patients.

and more research is needed to identify the patient population that would benefit the most from this therapy while minimizing the economic burden.

Furthermore, the impact of PCSK9 inhibitors on other clinical outcomes in PAD, such as walking performance and plaque volume, remains unclear[16]. Future research should address these gaps in knowledge and provide a more comprehensive understanding of the role of PCSK9 inhibitors in the management of PAD.

CONCLUSION

According to the available literature, PCSK9 inhibitors, such as evolocumab and alirocumab, have demonstrated efficacy in reducing cardiovascular events and major adverse limb events in PAD patients. These drugs have also shown a favorable safety profile, with injection-site reactions being the most frequently reported adverse event. Despite these positive findings, PCSK9 inhibitors continue to be underutilized in clinical practice, possibly due to providers' lack of awareness and cost concerns. Further research is needed to establish knowledge and provide a more comprehensive understanding of the role of PCSK9 inhibitors in the management of PAD, to investigate the long-term effects and cost-effectiveness of PCSK9 inhibitors in PAD patients, and to identify the patient population that would benefit the most from this therapy. Overall, PCSK9 inhibitors represent a promising therapeutic option for internal medicine physicians, cardiologists, and vascular surgeons managing PAD patients.

FOOTNOTES

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Country of origin: Sudan

ORCID number: Moiud Mohyeldin 0000-0002-5373-2163.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Rates, predictors, and causes of readmission after transcatheter aortic valve replacement in patients with chronic kidney disease

Taha Teaima, Gianfranco Bittar Carlini, Rohan A Gajjar, Imran Aziz, Sami J Shoura, Abdul-Rahim Shilbayeh, Naim Battikh, Tareq Alyousef

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Taha Teaima, Gianfranco Bittar Carlini, Rohan A Gajjar, Imran Aziz, Sami J Shoura, Abdul-Rahim Shilbayeh, Naim Battikh, Tareq Alyousef, Division of Cardiology, Department of Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL 60612, United States

Corresponding author: Tareq Alyousef, MD, Staff Physician, Department of Cardiology, John H. Stroger, Jr. Hospital of Cook County, 1969 W Ogden Ave, Chicago, IL 60612, United States. talyousef@cookcountyhhs.org

Abstract

BACKGROUND

Transcatheter aortic valve replacement (TAVR) is a revolutionary procedure for severe aortic stenosis. The coexistence of chronic kidney disease (CKD) and TAVR introduces a challenge that significantly impacts patient outcomes.

AIM

To define readmission rates, predictors, and causes after TAVR procedure in CKD stage 1-4 patients.

METHODS

We used the national readmission database 2018 and 2020 to look into readmission rates, causes and predictors after TAVR procedure in patients with CKD stage 1-4.

RESULTS

Out of 24758 who underwent TAVR and had CKD, 7892 (32.4%) patients were readmitted within 90 days, and had higher adjusted odds of being females (adjusted odds ratio: 1.17, 95%CI: 1.02-1.31, P = 0.02) with longer length of hospital stay > 6 days, and more comorbidities including but not limited to diabetes mellitus, anemia, and congestive heart failure (CHF).

CONCLUSION

Most common causes of readmission included CHF (18.0%), sepsis, and complete atrioventricular block. Controlling readmission predictors with very close follow-up is warranted to prevent such high rate of readmission.

Key Words: Chronic kidney disease; Transcatheter aortic valve replacement; Readmission;

Predictors; Rates

Core Tip: Our analysis of national readmission database for year 2018 to 2020 for 90 days readmissions for patients with chronic kidney disease stage 1-4 undergoing transcatheter aortic valve replacement showed considerably higher readmission rate to 32.4%. Majority were females and had higher comorbidity burden. Most common cause of 90 days readmission was congestive heart failure. Hence, we recommend optimization of co-morbidities and close follow up after index admission to prevent high rate of readmissions.

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has emerged over the years as a revolutionary less invasive option than surgical aortic valve replacement (SAVR) for the treatment of severe aortic stenosis (AS) in patients who are either above 65 years of age or deemed intermediate to high-risk or inoperable for traditional open-heart surgery[1-3]. This ground-breaking technique offers a ray of hope for individuals with multiple medical co-morbidities who suffer from aortic valve degeneration.

However, the convergence of chronic kidney disease (CKD) and TAVR introduces a complex interplay of medical challenges that significantly impact patient outcomes. As the prevalence of both CKD and AS continue to rise[4,5], understanding the multifaceted relationship between these conditions becomes paramount in optimizing treatment strategies and improving patient care.

The prevalence of CKD is particularly high in elderly populations[6], a demographic that frequently coincides with AS. One study reported a pooled estimate of 12.4% in patients aged ≥ 75 years due to age-related valve degeneration[7,8]. As such, the encounter between CKD and AS is becoming increasingly common. Available literature indicates that presence of CKD or end-stage renal disease (ESRD) is associated with a higher risk of mortality[9,10].

To our knowledge, our study is the first to utilize a large population-based database to describe the effects of co-existence of CKD stage 1-4 on the readmission after TAVR procedure in conjunction with causes and predictors of readmission. Identifying these predictors and causes, and addressing them can establish a base-ground to limit readmission rates after TAVR in patients with CKD.

MATERIALS AND METHODS

The national readmission database (NRD) 2018 and 2020 was employed for this retrospective cohort study. NRD is one of the largest publicly available all-payer inpatient healthcare databases in the United States. The database is sustained by the Agency for Healthcare Research and Quality. It is structured as a weighted probability sample to obtain an approximate sample that statistically represents all hospitalizations in all non-federal acute care hospitals nationwide, excluding rehabilitation facilities and long-term acute care hospitals. Data was obtained from billing data submitted by hospitals to statewide data organizations, representing about 97% of the United States populace. These hospitalizations are then classified based on urban/rural divisions, hospital teaching status, geographic location, and bed size. Data from 20% of all hospitalizations in these strata are then collected, pooled, and weighted to guarantee that it is representative of the United States population.

The NRD database is entirely coded using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)/Procedure Coding System. It includes patient and hospital-level information such as primary diagnosis, secondary diagnosis, median household income, primary payer type, hospital teaching status, hospital bed size, geographic region, and urban/rural location. Diagnoses are then sorted into a single principal diagnosis, and the remaining diagnoses are considered secondary diagnoses. The principal diagnosis corresponds to the main International Classification of Diseases, Tenth Revision (ICD-10) code for hospitalization, and the secondary diagnoses are any other ICD-10 codes besides the principal diagnosis that were tied to the hospitalization.

The study population exclusively consists of adult patients over 18 years hospitalized for TAVR procedure and had co-diagnosis of CKD stage 1-4. Multiple ICD-10-CM codes for TAVR procedure (02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ) and CKD stage 1-4 (N181, N182, N183, N184) were used to create our subpopulation. ICD-10 codes used in this study were obtained from a literature review of similar validated analyses. The population included in the analysis is outlined in

(Figure 1).

The study variables include demographic characteristics such as age, gender, mean household income, and medical insurance status. Hospital characteristics such as teaching status, and bed size are also included in the database. Comorbidity burden was assessed using the Charlson comorbidity index (CCI), adjusted for population-based research, and ICD-10-CM coding for each comorbidity to generate baseline patient characteristics**.**

The primary study outcome in our analysis was the readmission rates after TAVR procedure in patients with CKD stage 1-4 and most common causes of readmission. Secondary outcomes include adjusted odds of readmission predictors. Analysis STATA® (StataCorp, College Station, TX, United States) version 17 was utilized to perform the statistical analysis. Year-based discharge weights provided by the Healthcare Cost and Utilization Project (HCUP) were used to calculate weighted national estimates. Categorical variables proportions were compared using the Chi-square test. An independent sample *t*-test was used to evaluate the means of continuous data. The unadjusted odds ratio (OR) was calculated using univariate regression analysis for each outcome. Based on the significance of each univariate screen ($P < 0.2$), we selected variables to perform the multivariable logistic regression analysis to adjust for possible confounders. Other essential variables based on the literature review were included in the model. Logistic regression was used for binary or categorical outcomes, and linear regression analysis was used for continuous outcomes. All *P*-values were two-tailed, and we used a threshold of 0.05 to determine significance.

This manuscript is exempt from Institutional Review Board approval, as NRD is a de-identified national administrative database and is readily available online at https://www.hcup-us.ahrq.gov. Based on this exemption and according to the HCUP guidelines, our study did not require Cook County Health Institutional Review Board approval.

RESULTS

Out of 24758 adults who underwent TAVR and had co-diagnosis of CKD stage 1-4, 24375 (98.4%) discharged alive. Out of these and within 90 days of discharge, 7892 (32.4%) patients were readmitted (Figure 1). Readmitted patients were more likely to be females (42.5 % *vs* 39.3%, $P = 0.018$) with longer length of stay (LOS) > 6 days during index admission (34.8% *vs* 19.0%, $P < 0.001$), and had 3 or more comorbidities according to CCI (36.7% *vs* 26.0%, $P < 0.001$). Readmitted patients were more likely to have chronic obstructive pulmonary disease (COPD) (28.0% *vs* 23.3%, $P < 0.001$), diabetes mellitus (DM) (52.9% *vs* 46.9%, $P < 0.001$), malignancy (10.2% *vs* 6.5%, $P < 0.001$), peripheral arterial disease (PAD) (12.3% *vs* 10.6%, $P = 0.013$), atrial flutter or atrial fibrillation (33.4% *vs* 24.9%, $P < 0.001$), anemia (49.3% *vs* 37.7%, $P < 0.001$), and to be malnourished (4.5% *vs* 2.6%, $P < 0.001$) (Table 1). Most common causes of readmission were congestive heart failure (CHF) (18.0%), sepsis (4.6%), acute kidney injury (AKI) (3.4%), complete atrioventricular block (3.2%), paroxysmal atrial fibrillation (1.4%), pneumonia (1.2%), and gastrointestinal bleeding (1.2%) (Figure 2).

On multivariate regression analysis, readmitted patients had higher adjusted odds of longer hospital stay during index admission > 6 days [adjusted OR (aOR): 1.3, 95%CI: 1.15-1.40, $P < 0.001$], higher adjusted odds of being admitted to skilled nursing facility after index admission (aOR: 1.37, 95%CI: 1.22-1.52, $P < 0.001$), and females had higher adjusted odds of readmission (aOR: 1.17, 95%CI: 1.02-1.31, $P = 0.02$). Readmitted patients had also higher adjusted odds of having DM (aOR: 1.27, 95%CI: 1.17-1.39, $P < 0.001$), anemia (aOR: 1.25, 95%CI: 1.14-1.37, $P < 0.001$), CHF (aOR: 1.25, 95%CI: 1.11-1.41, $P < 0.001$), atrial flutter or atrial fibrillation (aOR: 1.32, 95%CI: 1.20-1.45, $P < 0.001$), AKI during index admission (aOR: 1.18, 95%CI: 1.05-1.34, $P = 0.006$), and cardiac complications during index admission (aOR: 1.6, 95%CI: 1.22-2.04, $P < 0.001$) (Figure 3).

Covariates of the multivariate regression analysis included age, sex, length of hospital stay, discharge destination, DM, COPD, PAD, malnutrition, anemia, CHF, coronary artery disease, atrial flutter or atrial fibrillation, AKI during index admission, cardiac, respiratory, and vascular complications during index admission.

DISCUSSION

In our study, readmission rate post TAVR in CKD stage 1-4 patients was 32.4% with the most common cause being CHF (18.0%). Readmitted patients had higher adjusted odds of longer hospital stay during index admission > 6 days, higher adjusted odds of being discharged to skilled nursing facility, and females had slightly higher adjusted odds of readmission as compared to men. Readmitted patients also had higher adjusted odds of having DM, Anemia, CHF, atrial flutter or atrial fibrillation, AKI during index admission, and cardiac complications during index admission.

Our findings suggest a substantial coexistence of CHF and CKD in patients undergoing TAVR. Given that both CHF and CKD are independently associated with increased readmission rates in various medical contexts, it is plausible to hypothesize that their confluence significantly amplifies the risk of readmissions post TAVR. The intricate interplay between cardiac and renal functions might create a synergistic effect, resulting in a higher likelihood of adverse outcomes.

Moreover, CKD may complicate the management of CHF, influencing post-TAVR readmission rates. Patients with compromised renal function may exhibit altered responses to standard CHF therapies, potentially affecting the management of their cardiac condition. This prompts consideration of tailored treatment strategies for CHF in patients with CKD, aiming to optimize cardiac health, volume status before discharge to potentially reduce readmission rates.

In the current published literature, the rates for readmissions post-TAVR after 30-days and 90-days ranged around 14.6-20.9% and 24.1%-25.1%[11,12]**.** If analyzed on a system-based approach, cardiovascular causes represent the most common causes of readmission, estimated to represent 38%, of which a wide range of variation, 22.8%-30.4% represent

Table 1 The baseline characteristics of the patients who were readmitted, and those who were not readmitted during index admission, *n* (%)

Patient population	Patients underwent TAVR and were discharged alive with no readmission in 90 days (*n* = 16483) (67.6)	Patients underwent TAVR and were discharged alive with readmission in 90 days (*n* = 7892) (32.4)	*P* value
18-44	0 (0)	0 (0)	0.2890
45-64	544 (3.3)	229 (2.9)	
≥ 65	15939 (96.7)	7663 (97.1)	
Female	6478 (39.3)	3354 (42.5)	0.0018
Male	10005 (60.7)	4538 (57.5)	
Insurance status			
Medicaid	15395 (93.4)	7426 (94.1)	0.5559
Medicare	164 (1.0)	71 (0.9)	
Private	890 (5.4)	379 (4.8)	
Self-pay	33 (0.2)	16 (0.2)	
Length of stay			
Less than 3 days	10285 (62.4)	3528 (44.7)	< 0.001
3 to 6 days	3065 (18.6)	1618 (20.5)	
More than 6 days	3131 (19.0)	2746 (34.8)	
Hospital bed size			
Small	807 (4.9)	379 (4.8)	0.9935
Medium	3955 (24.0)	1894 (24.0)	
Large	11719 (71.1)	5619 (71.2)	
Teaching hospital	14653 (88.9)	7000 (88.7)	0.7673
Non-teaching hospital	1830 (11.1)	892 (11.3)	
Urban hospital	16335 (99.1)	7805 (98.9)	0.3680
Rural hospital	148 (0.9)	87 (1.1)	
CCI			
No comorbidity	1830 (11.1)	1634 (20.7)	< 0.001
1 comorbidity	5011 (30.4)	1847 (23.4)	
2 comorbidities	5357 (32.5)	1515 (19.2)	
≥ 3 comorbidities	4286 (26.0)	2896 (36.7)	
Median household income			
First quartile ($1-$49999)	3395 (20.6)	1673 (21.2)	0.3420
Second quartile ($50000-$64999)	4928 (29.9)	2352 (29.8)	
Third quartile ($65000-$85999)	4401 (26.7)	2186 (27.7)	
Fourth quartile ($86000+)	3758 (22.8)	1681 (21.3)	
Hypertension	181 (1.1)	79 (1.0)	0.9876
Congestive heart failure	13104 (79.5)	6740 (85.4)	< 0.001
Coronary artery disease	12329 (74.8)	5974 (75.7)	0.3283

History of cerebrovascular accidents	462 (2.8)	260 (3.3)	0.2142
Malnutrition	429 (2.6)	355 (4.5)	< 0.001
COPD	3841 (23.3)	2210 (28.0)	< 0.001
Obesity	4055 (24.6)	2036 (25.8)	0.2091
Diabetes mellitus	7731 (46.9)	4175 (52.9)	< 0.001
Dyslipidemia	12873 (78.1)	5769 (73.1)	< 0.001
Cancer	1071 (6.5)	805 (10.2)	< 0.001
Anemia	6214 (37.7)	3891 (49.3)	< 0.001
Smoking	6560 (39.8)	3038 (38.5)	0.2631
Peripheral arterial disease	1747 (10.6)	971 (12.3)	0.0133
Cirrhosis	280 (1.7)	174 (2.2)	0.0745
Alcohol abuse	165 (1.0)	95 (1.2)	0.1668
Atrial fibrillation or flutter	4104 (24.9)	2636 (33.4)	< 0.001
Vascular complications	577 (3.5)	450 (5.7)	< 0.001
Pericardial complications	82 (0.5)	110 (1.4)	< 0.001
Cardiac complications	346 (2.1)	316 (4)	< 0.001
Respiratory complications	214 (1.3)	189 (2.4)	< 0.001
Infectious complications	742 (4.5)	576 (7.3)	< 0.001
Gastrointestinal complications	143 (0.87)	77 (0.97)	0.4053
Neurological complications	59 (0.36)	36 (0.46)	0.3743
Skin related complications	138 (0.84)	118 (1.5)	0.0012
Cardiac tamponade	59 (0.36)	70 (0.89)	0.0001
Post operative bleeding	155 (0.94)	89 (1.13)	0.4053

CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; TAVR: Transcatheter aortic valve replacement.

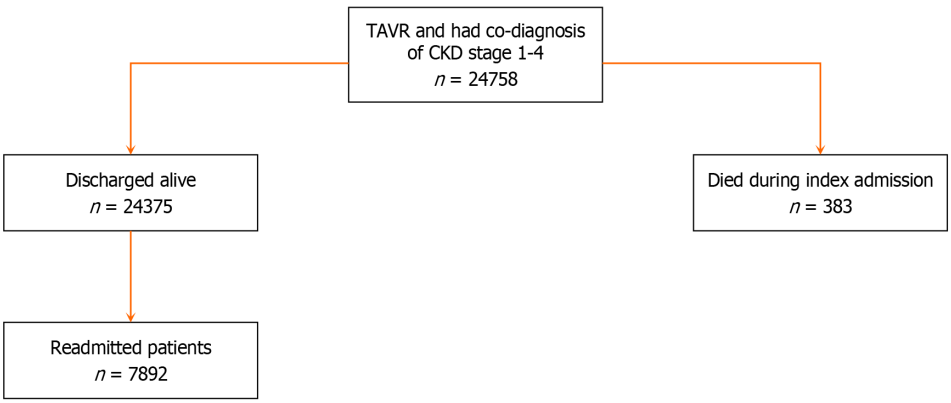

Figure 1 Flow chart of Readmission rates after transcatheter aortic valve replacement in chronic kidney disease stage 1-4 patient. TAVR: Transcatheter aortic valve replacement; CKD: Chronic kidney disease.

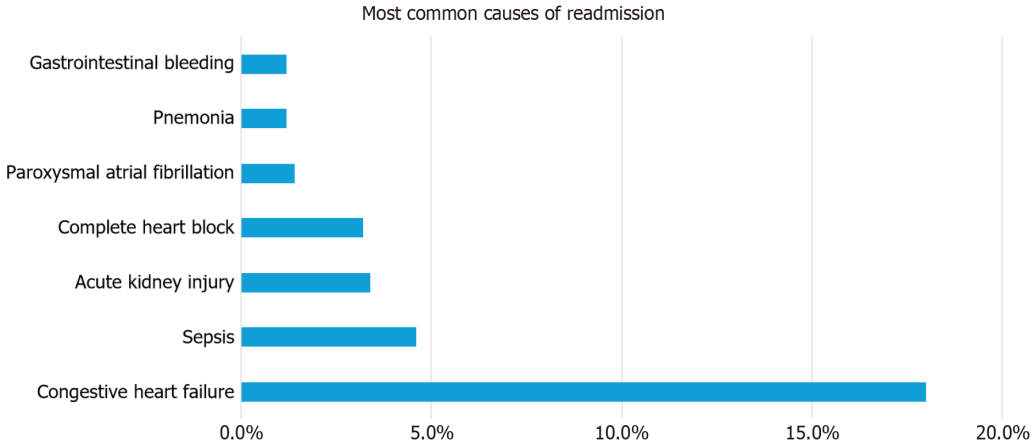

Figure 2 Most common causes of readmission.

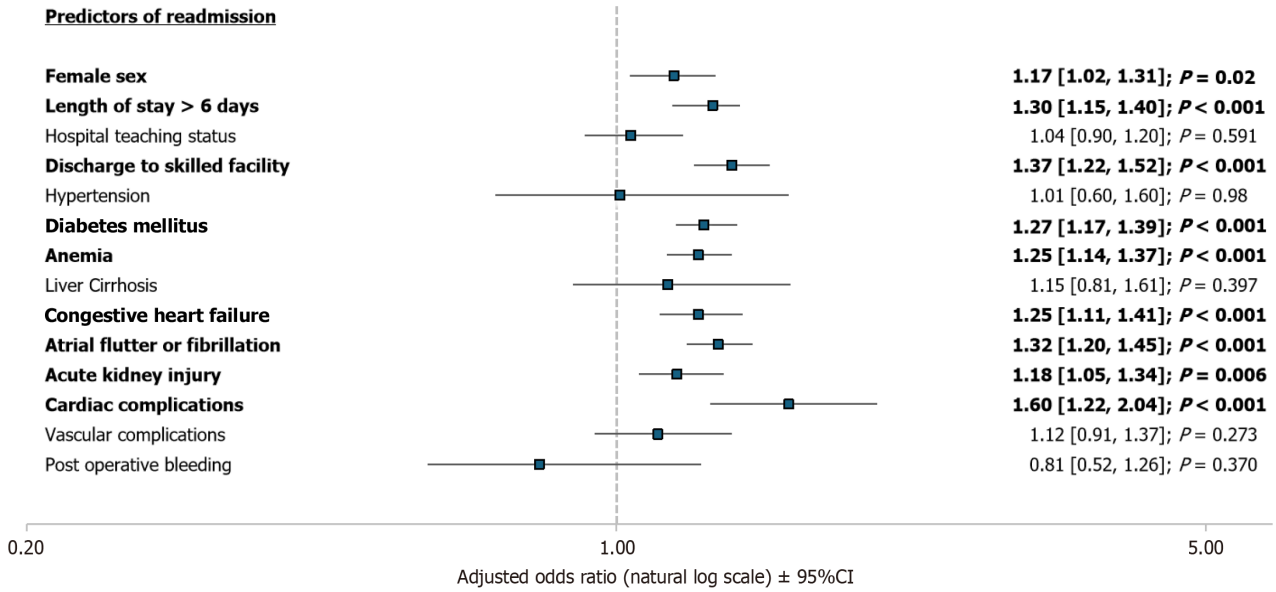

Figure 3 Forrest plot for predictors of readmission when adjusted for patient demographics, comorbidities, and hospital characteristics.

heart failure readmissions[11,12], which is similar to our findings that CHF is the most common cause of readmission post TAVR in non-ESRD CKD patients (18.0%). TAVR readmissions have decreased in the past 5-6 years. This is attributed to the advancement of imaging, provider experience, and later-generation devices for valve deployment. Other reports describe a progressive increase in readmissions due to noncardiac causes by up to 34% within a mean 1.96-year follow-up. In contrast, cardiac causes progressively decreased to 20.5%[13-15]. Our study revealed a 32.4% readmission rate for patients with CKD but not ESRD, whereas ESRD patients showed a readmission rate of 34.4% in a separate study [16]. The continuity and progression of readmission rates across the renal disease continuum favor a direct correlation between worse renal function and higher readmission rates post TAVR. A major contributor could be the difficulty in optimizing fluid status in those patients. Efficient fluid management is critical in both CHF and CKD. Based on our findings, we think that appropriate fluid balance during and after TAVR is crucial, particularly for patients with concurrent CHF and CKD. An imbalance could exacerbate cardiac and renal stress, potentially contributing to readmissions. Tailoring fluid management protocols might be beneficial in mitigating this risk.

In our study, female sex carried a higher adjusted odds of readmission. Cardiovascular disparities between males and females have been widely described in the literature. These differences include medical therapy for heart failure, interventional and surgical procedures, anticoagulation, and even preventative cardiovascular care[17-19]. Higher rates of readmissions, in-hospital mortality during index presentation, and increased LOS in 90 days post-TAVR analysis in women compared to men in this setting are well supported and attributed to complex interactions between longevity, comorbidities, and disparities in care. Common comorbidities reported among women include pulmonary hypertension, hypertension, diabetes, and anemia[17]. Proposed mechanisms in the setting of AS include a higher incidence of concentric hypertrophy than men, diastolic dysfunction, and reduced preload and stroke volume[20-22].

Trend analyses have shown progressive decrease in in-hospital mortality, overall fatality, and LOS in patients undergoing TAVR for the past years[23,24]. Previous multivariate analyses have characterized LOS greater than 5 days

and multiple comorbidities as predictors of early readmission post TAVR**.** The same report also found periprocedural AKI and CKD as predictors of both early readmissions and increased mortality[11]. Among readmitted patients our analysis showed a bimodal distribution where 44.7% of readmissions had index-LOS shorter than 3 days followed by 34.8% with LOS beyond 6 days. Considering that 62.4% of patients were discharged within 3 days post procedure, only patients with LOS > 6 days ties a statistically significant increase in 90-day readmission risk.

Decreased renal reserve predisposing to periprocedural AKI on CKD, decreased glomerular filtration rate, and higher diastolic dysfunction in patients with CKD have been demonstrated to play a role in longer admissions for these patients [16].

The prevalence of heart failure in patients with AS is estimated at 10% and represents the sole most common cause of readmissions post-TAVR[25,26]**.** Systolic dysfunction, as measured by stress-corrected midwall shortening, is an unfavorable prognostic factor in AS. An echographic study demonstrated left ventricular myocardial systolic dysfunction is common in asymptomatic AS patients with increased valvuloarterial afterload, whereas ejection fraction is generally preserved[21]**.** Despite known data with worse outcomes for SAVR in this population, TAVR has emerged as a reasonable alternative for afterload reduction in patients with severe AS associated with left ventricular ejection fraction < 50%, regardless of their surgical risk, and life expectancy < 20 years[27-30]**.** Heart failure readmissions post TAVR are associated with increased mortality and decreased quality of life compared to patients who do not require readmission. Additionally, the incidence of CHF readmissions 1 year post TAVR ranges from 9%-24%, and correlates with that of major trials for chronic systolic heart failure[31-33]**.**

Our study showed that CKD patients with underlying CHF were more likely to experience all-cause 90-day readmissions post-TAVR (79.5% *vs* 85.4%). The proportion of patients with concomitant CHF in CKD patients occupies the higher half of the spectrum, regardless of risk for readmission. Readmitted patients significantly surpassed literature descriptions. Altogether, these findings support the coexistence of heart failure in CKD-patients as a particularly high-risk relationship for readmissions post TAVR[34]**.** Despite the mortality impact aortic valve replacement has brought into the natural course of disease for patients with AS, systolic dysfunction carries a baseline prognosis non-modifiable by TAVR. Ongoing clinical trials aim to determine net benefit from TAVR in patients with moderate AS and severe heart failure[35]**.**

In our cohort, readmitted patients were more likely to have COPD. The incidence of COPD in patients undergoing aortic valve replacement is estimated to be around 22.7%-36%, with an approximate of 12%-13% with severe disease[36]**.** COPD significantly increases adverse outcomes in patients with TAVR, especially if associated with chronic hypoxic respiratory failure requiring home O_2 supplementation**.** In such patients, mortality was 2.5-fold higher compared to their non-oxygen users counterparts[37,38]**.** Conflicting evidence exists regarding COPD and oxygen supplementation and readmissions in TAVR-patients as an independent variable[39].

Limitations

We encountered some limitations based on the nature of the NRD database. It is a retrospective database collected based on ICD-10 codes, which may not-in some cases - be the best representative of the actual figures due to possible human errors. NRD also has limitations regarding therapeutic medications, actual investigations, and lab values, which are not accounted for in this study, with the possibility of confounding. Despite these limitations, the long study period, huge sample size, and analysis techniques empowered this study to shed light on TAVR readmissions in CKD patients stage 1-4, which is encouraging for more large prospective, multicenteric and controlled studies.

CONCLUSION

Finally, with the increased utility of TAVR for AS in an aging patient population with multiple comorbidities, physicians should consider very early and close follow up for patients with CKD post TAVR especially those with higher number of readmission predictors or with more complications during index admission. Future studies are encouraged to investigate the utility of earlier follow up, and other preventative measures that can mitigate the increased rates of readmission experienced by this patient population.

FOOTNOTES

Author contributions: Teaima T and Alyousef T conceptualized the research idea and designed the study; Teaima T curated data from database and performed statistical anylysis, Gajjar RA contributed with data analysis; Teaima T, Carlini GB, Gajjar RA, Aziz I, Shoura SJ wrote the original manuscript draft; Shilbayeh AR and Battikh N contributed with manuscript review and further editing; Teaima T and Alyousef T supervised all the tasks. All authors have read and approve the final manuscript.

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Informed consent statement: National readmission database is a de-identified national administrative database and is readily available online no informed consent was required.

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Country of origin: United States

ORCID number: Sami J Shoura 0000-0001-5015-0814; Tareq Alyousef 0000-0002-7437-1600.

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ORIGINAL ARTICLE

Observational Study

Impact of depression on in-hospital outcomes for adults with type 2 myocardial infarction: A United States population-based analysis

Sivaram Neppala, Himaja Dutt Chigurupati, Shaylika Chauhan, Mrunal Teja Chinthapalli, Rupak Desai

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Sivaram Neppala, Department of Internal Medicine, University of Texas at San Antonio, San Antonio, TX 78249, United States

Himaja Dutt Chigurupati, Department of Internal Medicine, New York Medical College at Saint Michael's Medical Center, Newark, NJ 07102, United States

Shaylika Chauhan, Department of Internal Medicine, Geisinger Health System, Wikes-Barre, PA 18702, United States

Mrunal Teja Chinthapalli, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States

Rupak Desai, Independent Researcher, Atlanta, GA 30079, United States

Corresponding author: Shaylika Chauhan, FACP, MD, Clinical Assistant Professor (Honorary), Department of Internal Medicine, Geisinger Health System, 1000 E Mountain Blvd, Wikes-Barre, PA 18702, United States. drshaylikachauhan@gmail.com

Abstract

BACKGROUND

Type 2 myocardial infarction (T2MI) is an ischemic myocardial injury in the context of oxygen supply/demand mismatch in the absence of a primary coronary event. However, though there is a rising prevalence of depression and its potential association with type 1 myocardial infarction (T1MI), data remains non-existent to evaluate the asso-ciation with T2MI.

AIM

To identify the prevalence and risk of T2MI in adults with depression and its impact on the in-hospital outcomes.

METHODS

We queried the National Inpatient Sample (2019) to identify T2MI hospitalizations using Internal Classification of Diseases-10 codes in hospitalized adults (≥ 18 years). In addition, we compared sociodemographic and comorbidities in the T2MI cohort with *vs* without comorbid depression. Finally, we used multivariate regression analysis to study the odds of T2MI hospitalizations with *vs* without depression and in-hospital outcomes (all-cause mortality, cardiogenic shock, cardiac arrest, and stroke), adjusting for confounders. Statistical significance was

achieved with a *P* value of < 0.05.

RESULTS

There were 331145 adult T2MI hospitalizations after excluding T1MI (median age: 73 years, 52.8% male, 69.9% white); 41405 (12.5%) had depression, the remainder; 289740 did not have depression. Multivariate analysis revealed lower odds of T2MI in patients with depression *vs* without [adjusted odds ratio (aOR) = 0.88, 95% confidence interval (CI): 0.86-0.90, *P* = 0.001]. There was the equal prevalence of prior MI with any revascularization and a similar prevalence of peripheral vascular disease in the cohorts with depression *vs* without depression. There is a greater prevalence of stroke in patients with depression (10.1%) *vs* those without (8.6%). There was a slightly higher prevalence of hyperlipidemia in patients with depression *vs* without depression (56.5% *vs* 48.9%), as well as obesity (21.3% *vs* 17.9%). There was generally equal prevalence of hypertension and type 2 diabetes mellitus in both cohorts. There was no significant difference in elective and non-elective admissions frequency between cohorts. Patients with depression *vs* without depression also showed a lower risk of all-cause mortality (aOR = 0.75, 95%CI: 0.67-0.83, *P* = 0.001), cardiogenic shock (aOR = 0.65, 95%CI: 0.56-0.76, *P* = 0.001), cardiac arrest (aOR = 0.77, 95%CI: 0.67-0.89, *P* = 0.001) as well as stroke (aOR = 0.79, 95%CI: 0.70-0.89, *P* = 0.001).

CONCLUSION

This study revealed a significantly lower risk of T2MI in patients with depression compared to patients without depression by decreasing adverse in-hospital outcomes such as all-cause mortality, cardiogenic shock, cardiac arrest, and stroke in patients with depression.

Key Words: Type 2 myocardial infarction; Depression; Major adverse cardiovascular events; Mortality; Stroke; Cardiac arrest; Outcomes

Core Tip: We studied the prevalence and risk of type 2 myocardial infarction (T2MI) in adults with depression and its impact on the in-hospital outcomes which revealed a significantly lower risk of T2MI in patients with depression compared to patients without depression by decreasing adverse in-hospital outcomes. Our study revealed decreased risks of all-cause mortality, cardiogenic shock, and cardiac arrest during T2MI hospitalization in patients with depression.

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INTRODUCTION

Coronary heart disease (CHD) and depression have become a global health problem[1,2]. In 2020, in the United States, CHD was the leading cause of morbidity and mortality (41.2%), with approximately 382800 deaths[3]. CHD is a syndrome characterized by myocardial cell death caused by ischemia resulting from the imbalance of supply and demand[4]. Myocardial infarction has been subclassified according to pathogenesis in 2007[4]. Type 1 myocardial infarction (T1MI) is a spontaneous episode occurring due to atherothrombosis or thrombus from an atherosclerotic plaque[4,5] or in the absence of acute atherothrombosis, known as T2MI[3,4]. Although disrupted atherosclerotic thrombus has remained the hallmark cause of acute MI, multiple other mechanisms are known to cause myocardial injury. However, definitive diagnostic and therapeutic strategies are yet to be defined[4,6].

Depression is one of the most common, debilitating illnesses, affecting around 26% of women and 18% of men in the United States[7]. Depression is more common in patients with acute MI, affecting approximately 20% of patients during the hospitalization with MI and over the first year after hospitalization[8], and has been classified as a significant risk factor for poor prognosis among patients with CHD[9]. Both mental illness and CHD have been imposing a significant economic and social burden due to their higher prevalence in high- and middle-income countries[10]. Several studies in recent years have reported growing evidence of links between depression and CHD[11,12], with a higher prevalence of depression among patients following acute myocardial infarction hospitalizations ranging from 15%-32%[13,14], which is also an independent predictor of increased mortality after acute MI[14,15]. Recently, a multicenter cohort observational study (TRIUMPH trial) done by Smolderen *et al*[8] showed that depression in patients with acute MI has been associated with long-term mortality but is mainly confined to untreated depression. A meta-analysis done by Barth *et al*[16] found that depression in MI is associated with a 2.5 times higher risk of mortality. Similarly, a meta-analysis done by van Melle *et al*[17] and Nicholson *et al*[11] found an increased risk of 2.0-2.5 times poor cardiac and mortality outcomes in 2 years after an MI in depression patients.

Although the majority of CHD trials were focused mainly on the role of biological risk factors, including smoking, hyperlipidemia, obesity, hypertension, diabetes mellitus, and lifestyle, more recently, stress, anxiety, and depression have been reported as the most significant risk factors for the coronary artery disease (CAD) even after controlling biological factors[18]. However, previous research studies have several limitations concerning causal interference. Despite the increasing occurrence of depression and its potential link to T1MI, there is a lack of data to assess this relationship with T2MI. Our objective is to determine the prevalence and risk of T2MI in adults with depression, as well as to examine its influence on in-hospital outcomes.

MATERIALS AND METHODS

Design and data source

In this retrospective observational study, we analyzed the National Inpatient Sample datasets for 2019, which are available through the Healthcare Cost and Utilization Project. The National Inpatient Sample is a large publicly available database representing 95% of hospitalizations in the United States, covering 48 states and the District of Columbia. We utilized the Internal Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) code I21.A1 to identify the principle of T2MI hospitalizations. This is an observational study looking at the prevalence and risk of T2MI in adults with depression and its impact on in-hospital outcomes. Comorbid depression was identified using these codes - F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2. Primary outcomes, including cardiovascular events, were identified using previously reported and validated ICD-10-CM codes or clinical classification software codes (The Clinical Classifications Software Refined groups ICD-10-CM/PCS codes into practical categories).

Study population and characteristics

Using the ICD-10 codes for 2019, we included hospitalized adult patients with a diagnosis of T2MI, excluding cases with T1MI.

Outcome measures

The primary outcome of this study is to assess the odds of T2MI and subsequent major adverse cardiovascular events (MACE: All-cause mortality, cardiogenic shock, cardiac arrest, and stroke) in T2MI patients with *vs* without comorbid depression. Secondary outcomes included health care utilization and length of hospitalization stay. We compared socio-demographic and comorbidities in the T2MI cohorts with *vs* without comorbid depression. Patient confounders were adjusted with multivariable regression analyses, which are known to have prognostic implications for our outcomes.

Statistical analysis

Patient characteristics and in-hospital outcomes were compared among patients with depression who were admitted with T2MI. Categorical data was displayed in percentages, and continuous data was represented using the median and interquartile range for non-normally distributed data. A P value below 0.05, determined through a two-tailed test, was deemed to show significance. National estimates were generated by leveraging the database's discharge weight and utilizing sample modules for analysis. Odds ratios (OR) and their 95% confidence intervals (CI) were obtained using multivariable logistic regression for in-hospital mortality and outcomes. The multivariable logistic regression was adjusted for covariates such as age, gender, race, zip code-based income quartile, primary payer, and a range of co-morbidities and prior conditions, including acquired immunodeficiency syndrome, alcohol and drug abuse, arthritis, hypertension (complicated and uncomplicated), diabetes (complicated and uncomplicated), hyperlipidemia, obesity, peripheral vascular disease, prior myocardial infarction with or without revascularization, tobacco use disorder, chronic lung disease, hypothyroidism, other thyroid disorders, previous MI or transient ischemic attack/stroke, and cancer. All reported P values are two-sided, with a value of < 0.05 considered significant. Statistical analyses were conducted using IBM SPSS Statistics 25.0 software (IBM Corp, Armonk, NY, United States).

RESULTS

Baseline characteristics

We identified 331145 adult T2MI hospitalizations after excluding T1MI cases. The median age was 73 years, 52.8% male and 69.9% white. Among these hospitalizations, 41405 (12.5%) had depression, leaving the remaining 289740 without depression. The T2MI+D+ cohort, in comparison with the T2MI-D- cohort, often consisted of younger (median age, 71 *vs* 73) females (59.9% *vs* 45.4%), with both cohorts predominantly including white (78.4, 68.7) (Table 1). T2MI-D+ had 4530 (11.2%), and T2MI-D- had 47880 (16.9%) black patients. The Hispanic population comprised 2490 (6.1%) in the T2MI+D+ cohort and 22790 (8.1%) in the T2MI+D- cohort. Both groups primarily had medicare-enrolled patients, 207830 (71.8%) in the T2MI-D- *vs* 30400 (73.5%) in T2MI+D+. Private insurance, including Health Maintenance Organization, was the next most common-36125 (12.5%) in T2MI+D- while medicaid was next most common in T2MI-D+ 4575 (11.1%).

Elective and non-elective admissions frequency did not differ significantly between cohorts. The prevalence of prior MI with any revascularization and peripheral vascular disease was comparable among cohorts with and without depression. However, patients with depression showed a higher prevalence of stroke at 10.1% compared to those without depression at 8.6%. Additionally, patients with depression exhibited a slightly higher prevalence of hyperlipidemia (56.5% *vs* 48.9%)

Table 1 Demographic characteristics and comorbidities in type 2 myocardial infarction-related hospitalizations with *vs* without depression

	Depression		Total T2MI, *n* = 331145	*P* value
	No, *n* = 289740	Yes, *n* = 41405		
Age at admission				
Median (IQR)	73 (62-83)	71 (61-81)	73 (62-82)	< 0.001
18-44 years	5.4%	5.0%	5.3%	
45-64 years	24.1%	27.6%	24.6%	
≥ 65 years	67.3%	70.1%	70.5%	
Sex				< 0.001
Male	54.6%	40.1%	52.8%	
Female	45.4%	59.9%	47.2%	
Race				< 0.001
White	68.7%	78.4%	69.9%	
Black	16.9%	11.2%	16.2%	
Hispanic	8.1%	6.1%	7.8%	
Asian or Pacific Islander	2.8%	1.4%	2.6%	
Native American	0.8%	0.9%	0.9%	
Others	2.8%	2.0%	2.7%	
Median household income quartile for patient zip code				< 0.001
0-25th	32.9%	31.2%	32.7%	
26-50th	26.5%	27.2%	26.6%	
51-75th	23.1%	23.6%	23.2%	
76-100th	17.5%	17.9%	17.5%	
Primary expected payer				< 0.001
Medicare	71.8%	73.5%	72.0%	
Medicaid	10.4%	11.1%	10.5%	
Private including HMO	12.5%	10.8%	12.3%	
Self-pay	2.9%	2.1%	2.8%	
No charges	0.2%	0.1%	0.2%	
Others	2.2%	2.4%	2.2%	
Type of admission				0.985
Non-elective	97.0%	97.0%	97.0%	
Elective	3.0%	3.0%	3.0%	
Location/teaching status of hospital				< 0.001
Rural	8.4%	9.0%	8.5%	
Urban non-teaching	15.6%	15.2%	15.5%	
Urban teaching	76.0%	75.8%	76.0%	
Region of hospital				< 0.001
Northeast	22.9%	21.7%	22.8%	
Midwest	23.1%	27.9%	23.7%	
South	35.0%	33.4%	34.8%	

West	19.0%	17.0%	18.7%	
Comorbidities				
Alcohol abuse	4.9%	0.6%	5.0%	< 0.001
Arthropathies	4.1%	5.8%	4.3%	< 0.001
Dementia	10.9%	15.8%	11.6%	< 0.001
Hypertension, complicated	49.9%	49.2%	49.8%	0.006
Hypertension, uncomplicated	19.9%	22.6%	20.2%	< 0.001
Diabetes with chronic complications	31.5%	32.4%	31.6%	< 0.001
Diabetes without chronic complications	9.0%	8.9%	9.0%	0.244
Hyperlipidemia	48.9%	56.5%	49.9%	< 0.001
Obesity	17.9%	21.3%	18.4%	< 0.001
Peripheral vascular disease	11.3%	11.6%	11.3%	0.095
Prior MI	12.2%	13.2%	12.3%	< 0.001
Prior TIA/stroke	8.6%	10.1%	8.8%	< 0.001
Drug abuse	5.0%	7.4%	5.3%	< 0.001
Tobacco use disorder	15.5%	19.4%	16.0%	< 0.001
Chronic pulmonary disease	31.4%	38.9%	32.3%	< 0.001
Hypothyroidism	15.0%	21.3%	15.8%	< 0.001
Other thyroid disorders	1.5%	1.9%	1.5%	< 0.001
Anxiety & fear related disorders	9.0%	39.3%	9.0%	< 0.001
Cancer	9.3%	7.7%	9.1%	< 0.001

$P < 0.05$ indicates statistical significance. IQR: Interquartile range; HMO: Health Maintenance Organization; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; TIA: Transient ischemic attack; T2MI: Type 2 myocardial infarction.

and obesity (21.3% *vs* 17.9%) compared to those without depression. Nonetheless, there was generally an equal prevalence of hypertension and type 2 diabetes mellitus in both cohorts.

Primary outcomes

Table 2 reveals significant differences in in-hospital outcomes for T2MI patients with versus without depression. Notably, patients with depression exhibited a lower all-cause mortality rate (5.8%) compared to those without depression (8.4%), alongside reduced incidences of cardiogenic shock, dysrhythmias, cardiac arrest, and stroke, with all differences being statistically significant ($P < 0.001$). After adjusting for potential confounders in a multivariable logistic regression analysis, the findings revealed that patients with depression had significantly lower odds of experiencing T2MI compared to those without depression [adjusted OR (aOR) = 0.88, 95%CI: 0.86-0.90, $P = 0.001$] (Table 3). Additionally, patients with depression were found to have lower risks of all-cause mortality (aOR = 0.75, 95%CI: 0.67-0.83, $P = 0.001$), cardiogenic shock (aOR = 0.65, 95%CI: 0.56-0.76, $P = 0.001$), cardiac arrest (aOR = 0.77, 95%CI: 0.67-0.89, $P = 0.001$), and stroke (aOR = 0.79, 95%CI: 0.70-0.89, $P = 0.001$) compared to patients without depression.

Secondary outcomes

For patients without depression, hospitalizations are associated with higher costs compared to patients with depression (median $53592 and $50156, respectively) without any change in length of stay with a median of 5 days. In contrast, patients with depression were most frequently transferred to skilled nursing facilities compared to patients without depression (32.7% *vs* 27.7%). This difference could reflect a need for more extended care or rehabilitation services in patients with depression (Table 2).

DISCUSSION

This study is one of the most extensive population-based outcome studies to explore the association between depression and the risks of T2MI, as well as its impact on incidence, demographics, and in-hospital outcomes. The study included a total of 331415 patients from the publicly available National Inpatient Sample 2019 database, of whom 41405 (12.5%) had depression. The clinical findings from this large observational study indicate that patients with depression showed an

Table 2 In-hospital outcomes in type 2 myocardial infarction hospitalizations in patients with *vs* without depression

	No depression (*n* = 289740)	Depression (*n* = 41405)	Total T2MI (*n* = 331145)	*P* value
All-cause mortality	8.4%	5.8%	8.1%	< 0.001
Cardiogenic shock	3.5%	2.2%	3.4%	< 0.001
Dysrrhythmia	43.8%	40.2%	43.3%	< 0.001
Cardiac arrest including ventricular fibrillation	3.4%	2.4%	3.3%	< 0.001
Stroke	5.3%	4.1%	5.2%	< 0.001
Disposition of patient				< 0.001
Routine	39.9%	36.4%	39.5%	
Transfers to short-term hospitalization	3.5%	2.9%	3.4%	
Transfer other includes: Skilled nursing facility, intermediate care facility, another type of facility	27.7%	32.7%	28.3%	
Home health care	19.0%	20.7%	19.2%	
Length of stay (days), median (IQR)	5 (3-9)	5 (3-8)	5 (3-9)	0.243
Total charges USD, median (IQR)	53592 (29003-105279)	50156 (28249-90301)	53139 (28872-103331)	< 0.001

P < 0.05 indicates statistical significance. IQR: Interquartile range; T2MI: Type 2 myocardial infarction.

Table 3 Multivariable odds ratios for type 2 myocardial infarction and subsequent major adverse cardiac outcomes associated with depression

Outcome	Predictor	Odds ratio	95% confidence interval	*P* value
T2MI	Depression	0.88	0.86-0.90	< 0.001
In T2MI patients				
In-hospital all-cause mortality	Depression	0.75	0.67-0.83	< 0.001
Cardiogenic-shock	Depression	0.65	0.56-0.76	< 0.001
Cardiac arrest including ventricular fibrillation	Depression	0.77	0.67-0.89	0.001
Stroke	Depression	0.79	0.70-0.89	< 0.001

The multivariable logistic regression analysis was adjusted for a comprehensive set of covariates, including age category, gender, race, income quartile based on zip code, primary payer, and a variety of comorbidities and prior conditions. These comorbidities encompassed acquired immunodeficiency syndrome, alcohol abuse, arthritis, both complex and uncomplicated hypertension, complex and uncomplicated diabetes, hyperlipidemia, obesity, peripheral vascular disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, drug abuse, tobacco use disorder, chronic lung disease, hypothyroidism, other thyroid disorders, prior transient ischemic attack or stroke without neurologic deficit, and cancer. T2MI: Type 2 myocardial infarction.

inverse correlation with T2MI compared to patients without depression. It was observed that patients with depression had lower odds of all-cause mortality, cardiogenic shock, cardiac arrest, and stroke. Additionally, the study found that patients with depression had lower hospitalization costs with a similar mean length of stay compared to patients without depression. Previous studies have shown that depression is a significant risk factor for the development of CAD. Still, there is limited evidence for the impact of depression on T2MI.

This study also identified significant variations in the prevalence of depression among T2MI patients based on gender, with potential explanations including disparities in biological factors such as hormones, as well as psychosocial factors [19]. Another study indicated that female cohorts with CHD were at a 1.77-fold higher risk of experiencing depression compared to male cohorts[20]. Furthermore, we observed notable differences in the prevalence of depression in T2MI admissions based on race and region, with higher rates in white patients and increased prevalence in urban teaching hospitals, possibly reflecting variances in socioeconomic and sociocultural characteristics, as seen in other studies[21].

The presence of major depressive disorder has been associated with increased susceptibility to CAD, which raises the risk of illness and death despite advancements in medical and interventional treatments[3,9,14,15,18,22]. The precise mechanisms by which depression contributes to a heightened risk of CAD are not entirely understood[11,12]. However,

several potential causes of CAD in individuals with depression have been suggested, including heightened platelet aggregation[23,24], increased levels of inflammatory markers, elevated catecholamine levels, alterations in cortisol levels, heightened sympathetic tone, potential variability in heart rate, sedentary lifestyle, and non-adherence to prevention and treatment of risk factors. A meta-analysis by Barth *et al*[16] and Nicholson *et al*[11] disclosed an increased probability of CAD in people with depression, as well as a twofold rise in mortality over two years. However, our study discovered that the occurrence of depression among admissions for T2MI is roughly 12.5%. Additionally, we noted that patients with depression have a higher prevalence of obesity (21.3% *vs* 17.9%) and hyperlipidemia (56.5% *vs* 48.9%), likely due to changes in lifestyle and diet.

Patients with depression were at a two to fourfold increased risk of developing CAD at some point in their lifetime[25,26]. Several other epidemiological studies have emphasized the higher incidence of depression in patients with ischemic heart diseases, particularly within the first one to two years[27,28]. While there have been no studies in the literature examining the impact of depression on T2MI and outcomes, our study revealed decreased risks of all-cause mortality, cardiogenic shock, and cardiac arrest during T2MI hospitalization in patients with depression. This contrasts previous studies on T1MI and depression, as several meta-analyses have previously indicated a 10%-25% increased risk of all-cause mortality and cardiovascular mortality in patients with T1MI and depression[29,30]. The exact mechanism of how there is a protective effect with depression and T2MI is unknown. However, Serebruany *et al*[31] demonstrated that patients who are on anti-depressants have a favorable impact on the outcomes, possibly due to changes in serotonin activity, which we couldn't access in our study, which might impact the outcomes.

Several theories have been proposed in the literature regarding the potential link between depression, atherosclerosis, and stroke. One theory involves neuroendocrine dysfunction resulting from the dysregulation of the hypothalamic-pituitary-adrenocortical axis, platelet aggregation dysfunction[32], and immunological/inflammatory effects[33], which may elevate the risk of stroke. In recent years, studies have indicated that inflammatory cytokines, such as interleukins (IL-1, IL-2, IL-6), C-reactive protein, tumor necrosis factor α, IL-1β, and P-selectin, play a significant role in the development and rupture of atherosclerosis plaques, which are major contributors to CAD and stroke[34]. Our study has suggested a paradoxical lower risk of stroke in patients admitted with depression and T2MI. This could be attributed to variations in neurotransmitters or pathways in T2MI patients. Additionally, selective serotonin reuptake inhibitor medication may have protective effects against stroke, as indicated in previous research, beyond its antidepressant effects [35]. However, some other studies found a positive association between anti-depressants and stroke risk[36].

In this research, the unexpected discovery that depression may be linked to improved clinical outcomes in a cardiac context could be influenced by various factors. Patients with a depression diagnosis might receive careful monitoring and treatment due to perceived higher risks, leading to early identification and management of complications. Furthermore, the unique psychological traits of these individuals could affect their perception of pain and reporting, potentially influencing the nature and timing of the care they receive. Additionally, there is a possibility that certain antidepressant medications might unintentionally have beneficial effects on the heart, as suggested by studies exploring the cardiovascular impacts of psychiatric therapies. This surprising association emphasizes the complexity of mental health's influence on cardiovascular health outcomes. It underscores the need for further research to fully understand the underlying mechanisms and potential clinical implications for patients with depression or other mental health disorders in the context of T2MI.

Future directions

This study examining the link between depression and T2MI and associated subsequent MACE provided preliminary insights and paved the way for future prospective investigations. Its strength lies in analyzing a large dataset with more generalizable findings, minimized selection bias and controlled confounders in comprehensive multivariable analysis ensuring the reliability of its findings. Additionally, future longitudinal research could address limitations by exploring stages and severity of depression, medication adherence and social influences to enhance our knowledge of the link between depression and T2MI outcomes.

Limitations

Our study has several limitations. Firstly, we focused our analysis on T2MI hospitalizations using ICD-10 codes in adults aged 18 and above, which helped minimize selection bias by narrowing down the study population. We utilized the National Inpatient Sample for 2019 and identified cohorts admitted with T2MI using ICD-10 codes. However, this approach may introduce the possibility of misclassification, particularly regarding height and weight measurements. Nonetheless, this potential misclassification should be consistent among survivors and non-survivors, thus not significantly affecting the interpretation of the results. We did not consider different stages of depression, which could potentially impact the population in various ways. Furthermore, it is crucial to have access to more comprehensive data concerning the medication status, social determinants, and adherence of the cohorts. These variables have the potential to serve as confounding factors, especially about mortality within the demographic afflicted by depression. However, it is essential to note that the substantial sample size of our study enhances its statistical robustness, helping to mitigate the limitations above.

CONCLUSION

This study revealed a significantly lower risk of T2MI related admissions in patients with depression compared to patients without depression and lower odds of adverse in-hospital outcomes such as all-cause mortality, cardiogenic

shock, cardiac arrest, and stroke in T2MI patients with depression. It's important to consider potential confounding variables that could influence the study outcomes, such as medication usage, psychosocial factors, and the different stages of depression, all of which play a crucial role in the progression of the disease and the outcomes. Previous studies have not explored the impact of depression on T2MI outcomes, and further prospective studies are needed to evaluate the influence of depression on various in-hospital outcomes across different stages of depression. Additionally, it is essential to investigate the effects of medication, duration, and serotonin levels on T2MI.

FOOTNOTES

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Country of origin: United States

ORCID number: Himaja Dutt Chigurupati 0000-0003-3885-8515; Shaylika Chauhan 0000-0002-0253-3973; Rupak Desai 0000-0002-5315-6426.

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ORIGINAL ARTICLE

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Network pharmacology-based exploration of molecular mechanisms underlying therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure with spleen Qi deficiency syndrome

Si-Qi Li, Dong-Yu Min, Jun-Wen Jiang, Xiao-Ying Li, Xu-Na Yang, Wen-Bo Gu, Jia-Hui Jiang, Li-Hao Chen, Han Nan, Ze-Yu Chen

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Si-Qi Li, Dong-Yu Min, Jun-Wen Jiang, Xiao-Ying Li, Xu-Na Yang, Wen-Bo Gu, Jia-Hui Jiang, Li-Hao Chen, Han Nan, Ze-Yu Chen, Second Department of Cardiology, The Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang 110000, Liaoning Province, China

Corresponding author: Si-Qi Li, MD, Chief Physician, Second Department of Cardiology, The Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, No. 33 Beiling Street, Huanggu District, Shenyang 110000, Liaoning Province, China. pangdun66@163.com

Abstract

BACKGROUND

Chronic heart failure is a complex clinical syndrome. The Chinese herbal compound preparation Jianpi Huatan Quyu recipe has been used to treat chronic heart failure; however, the underlying molecular mechanism is still not clear.

AIM

To identify the effective active ingredients of Jianpi Huatan Quyu recipe and explore its molecular mechanism in the treatment of chronic heart failure.

METHODS

The effective active ingredients of eight herbs composing Jianpi Huatan Quyu recipe were identified using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform. The target genes of chronic heart failure were searched in the Genecards database. The target proteins of active ingredients were mapped to chronic heart failure target genes to obtain the common drug-disease targets, which were then used to construct a key chemical component-target network using Cytoscape 3.7.2 software. The protein-protein interaction network was constructed using the String database. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed through the Metascape database. Finally, our previously published relevant articles were searched to verify the results obtained *via* network pharmacology.

RESULTS

A total of 227 effective active ingredients for Jianpi Huatan Quyu recipe were

identified, of which quercetin, kaempferol, 7-methoxy-2-methyl isoflavone, formononetin, and isorhamnetin may be key active ingredients and involved in the therapeutic effects of TCM by acting on STAT3, MAPK3, AKT1, JUN, MAPK1, TP53, TNF, HSP90AA1, p65, MAPK8, MAPK14, IL6, EGFR, EDN1, FOS, and other proteins. The pathways identified by KEGG enrichment analysis include pathways in cancer, IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, cAMP signaling pathway, NF-kappaB signaling pathway, AMPK signaling pathway, *etc.* Previous studies on Jianpi Huatan Quyu recipe suggested that this Chinese compound preparation can regulate the TNF-α, IL-6, MAPK, cAMP, and AMPK pathways to affect the mitochondrial structure of myocardial cells, oxidative stress, and energy metabolism, thus achieving the therapeutic effects on chronic heart failure.

CONCLUSION

The Chinese medicine compound preparation Jianpi Huatan Quyu recipe exerts therapeutic effects on chronic heart failure possibly by influencing the mitochondrial structure of cardiomyocytes, oxidative stress, energy metabolism, and other processes. Future studies are warranted to investigate the role of the IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, and other pathways in mediating the therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure.

Key Words: Jianpi Huatan Quyu recipe; Traditional Chinese medicine; Chronic heart failure; Data mining; Network pharmacology; Bioinformatics; Spleen Qi deficiency syndrome

Core Tip: Based on the clinical characteristics of patients, the dialectical treatment of chronic heart failure is often performed primarily by strengthening Qi and nourishing Yin, promoting blood circulation and removing blood stasis, resolving phlegm and alleviating water retention, and warming and tonifying heart Yang. In this study, the authors found that the Chinese medicine compound preparation Jianpi Huatan Quyu recipe exerts therapeutic effects on chronic heart failure possibly by influencing the mitochondrial structure of cardiomyocytes, oxidative stress, energy metabolism, and other processes.

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INTRODUCTION

Chronic heart failure is a complex clinical syndrome due to abnormal changes in cardiac structure and/or function caused by multiple factors, resulting in ventricular systolic and/or diastolic dysfunction[1]. Its main manifestations are dyspnea, fatigue, and fluid retention. As the end-stage manifestation of cardiovascular disease and the main cause of death, chronic heart failure is thought to belong to "chest impediment", "palpitation", "true heart pain", and other categories in traditional Chinese medicine (TCM). Based on the clinical characteristics of patients, the dialectical treatment of chronic heart failure is often performed primarily by strengthening Qi and nourishing Yin, promoting blood circulation and removing blood stasis, resolving phlegm and alleviating water retention, and warming and tonifying heart Yang[2]. We have been studying the curative effect and mechanism of the Chinese herbal compound preparation Jianpi Huatan Quyu recipe, which has the effects of strengthening the spleen, dissolving phlegm, and removing blood stasis, in the treatment of chronic heart failure. In order to further explore the therapeutic mechanism of this compound recipe, network pharmacology was applied in the present study to identify the effective active ingredients of eight herbs composing Jianpi Huatan Quyu recipe, as well as common target proteins shared by Jianpi Huatan Quyu recipe and chronic heart failure. In addition, our previous studies on the mechanism of action of Jianpi Huayu Qutan recipe in different conditions were searched to provide support for the results obtained *via* network pharmacology.

MATERIALS AND METHODS

Analysis of effective active components of Jianpi Huatan Quyu recipe

Jianpi Huatan Quyu recipe is composed of eight Chinese herbs: Dangshen, Fuling, Baizhu, Zhigancao, Danshen, Qingbanxia, and Gualou. The effective active components of these eight herbs were searched using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)[3]. Oral bioavailability ≥ 30% and

drug-likeness ≥ 0.18 were used as the screening criteria to ensure that the selected active ingredients have good oral absorption and high druggability.

Identification of common targets shared by Jianpi Huatan Quyu recipe and chronic heart failure

The TCMSP database was used to identify the targets of the effective active ingredients as mentioned above. Human gene names and corresponding target proteins were downloaded from the UniProt database (https://www.uniprot.org/)[4]. The target genes of chronic heart failure were searched in the Genecards database (https://www.genecards.org/)[5]. The target proteins of active ingredients were mapped to chronic heart failure target genes to obtain the common drug-disease targets and to find out the key chemical components corresponding to these targets.

Key chemical component-target network construction

Common drug-disease targets and their corresponding key chemical components were sorted into a table, which was then imported into Cytoscape 3.7.2 software to obtain their relationship network.

Protein-protein interaction network construction

Protein-protein interaction (PPI) networks can graphically describe the interactions between common drug-disease targets. The common drug-disease targets identified above were input into the String database (https://string-db.org/ Version 10.5)[6] to obtain the PPI network. The protein interaction score was further set to 0.9 to optimize the network diagram. Data on protein interactions were downloaded to screen out the top 15 core proteins.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis

The common drug-disease targets identified above were imported into the Metascape database (http: //metascape.org/gp/index.html)[7] for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, with the parameters set as follows: *P* value = 0.01, minimum overlap = 3, and minimum enrichment = 1.5, GO biological process (BP), cellular component (CC), and molecular function (MF) and KEGG pathways were enriched, respectively. Bubble maps were generated online using the ImageGP website tool. The target-pathway network was constructed with Cytoscape software.

Confirmatory study

According to the key targets and proteins belonging to the signal pathways identified above, our previously published relevant articles were analyzed to verify the therapeutic mechanism of Jianpi Huatan Quyu recipe in the treatment of chronic heart failure.

RESULTS

Identification of effective active ingredients of Jianpi Huatan Quyu recipe

There are eight herbs in the Chinese herbal compound preparation Jianpi Huatan Quyu recipe: Huangqi, Dangshen, Fuling, Baizhu, Zhigancao, Danshen, Qingbanxia, and Gualou. As shown in Table 1, a total of 227 active ingredients were identified in the TCMSP database according to the oral bioavailability and drug-likeness.

Identification of common drug-disease targets

A total of 4123 genes were downloaded from the Genecard database and screened for genes with a score of 5 or greater, which might be associated with chronic heart failure. Mapping of the target proteins of active ingredients of Jianpi Huatan Quyu recipe to chronic heart failure target genes led to the identification of 201 common targets. The Venn diagram indicating these common targets is shown in Figure 1.

Construction of key chemical component-target network

Cytoscape software was used to construct the relationship network of key active components in Jianpi Huatan Quyu recipe and chronic heart failure associated genes. As shown in Figure 2, the top 5 key chemical components are as follows: Quercetin (MOL000098, degree = 236), kaempferol (MOL000422, degree = 94), 7-methoxy-2-methyl isoflavone, (MOL003896, degree = 60), formononetin (MOL000392, degree = 53), and isorhamnetin (MOL000354, degree = 47). The top 15 common target proteins are as follows: PTGS2, ESR1, AR, PTGS1, NOS2, SCN5A, PRSS1, GSK3B, PPARG, CCNA2, ESR2, ADRB2, DPP4, F10, and RXRA.

PPI network analysis

The PPI network was obtained by inputting the common drug-disease targets into the String database. As shown in Figure 3, the PPI network contains 200 nodes and 906 edges. Among them, the interacting protein pairs with a PPI score equal to 0.999 are AKT1-NOS3, AKT1-GSK3B, BCL2 L1-TP53, BCL2 L1-CASP8, CASP3-CASP8, CASP7-CASP8, CCNA2-CDK2, CCNA2-CDKN1A, CCND1-CDKN1A, CCND1-CDK2, CDK2-RB1, CDK2-CDKN1A, CDKN1A-TP53, CDKN1A-PCNA, E2F1-RB1, EDN1-EDNRA, EGF-EGFR, F3-F7, FOS-JUN, IKBKB-NFKBIA, IKBKB-TNF, JUN-MAPK8, KDR-VEGFA, MDM2-TP53, PLAT-SERPINE1, and PLAU-SERPINE1. By calculating the number of connection points in the network, the top 15 core proteins were identified: STAT3, MAPK3, AKT1, JUN, MAPK1, TP53, TNF, HSP90AA1, RELA,

Table 1 Active ingredients of herbs composing Jianpi Huatan Quyu recipe

Molecule ID	Molecule name	Drug(s)	Molecule ID	Molecule name	Drug(s)
MOL007059	3-β-hydroxymethyllenetanshiquinone	Danshen, Dangshen	MOL001792	DFV	Gancao
MOL004355	Spinasterol	Dangshen, Gualou	MOL001484	Inermine	Gancao
MOL003896	7-methoxy-2-methyl isoflavone	Dangshen, Gancao	MOL000500	Vestitol	Gancao
MOL002776	Baicalin	Banxia, Danshen	MOL000497	Licochalcone a	Gancao
MOL000449	Stigmasterol	Banxia, Dangshen	MOL000359	Sitosterol	Gancao
MOL000422	Kaempferol	Gancao, Huangqi	MOL000300	Dehydroeburicoic acid	Fuling
MOL000417	Calycosin	Gancao, Huangqi	MOL000292	Poricoic acid C	Fuling
MOL000392	Formononetin	Gancao, Huangqi	MOL000291	Poricoic acid B	Fuling
MOL000354	Isorhamnetin	Gancao, Huangqi	MOL000290	Poricoic acid A	Fuling
MOL000296	Hederagenin	Fuling, Huangqi	MOL000289	Pachymic acid	Fuling
MOL000239	Jaranol	Gancao, Huangqi	MOL000287	3-β-hydroxy-24-methylene-8-lanostene-21-oic acid	Fuling
MOL000211	Mairin	Gancao, Huangqi	MOL000285	(2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15,16,17-octahydrocyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	Fuling
MOL000098	Quercetin	Gancao, Huangqi	MOL000283	Ergosterol peroxide	Fuling
MOL000033	(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	Baizhu, Huangqi	MOL000282	Ergosta-7,22E-dien-3beta-ol	Fuling
MOL000006	Luteolin	Danshen, Dangshen	MOL000280	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	Fuling
MOL000442	1,7-dihydroxy-3,9-dimethoxy pterocarpene	Huangqi	MOL000279	Cerevisterol	Fuling
MOL000439	Isomucronulatol-7,2'-di-O-glucosiole	Huangqi	MOL000276	7,9(11)-Dehydropachymic acid	Fuling
MOL000438	(3R)-3-(2-hydroxy-3,4-dimethoxyphenyl)chroman-7-ol	Huangqi	MOL000275	Trametenolic acid	Fuling
MOL000433	FA	Huangqi	MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	Fuling
MOL000398	Isoflavanone	Huangqi	MOL008411	11-Hydroxyrankinidine	Dangshen
MOL000387	Bifendate	Huangqi	MOL008407	(8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-1,2,4,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one	Dangshen
MOL000380	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	Huangqi	MOL008406	Spinoside A	Dangshen
MOL000379	9,10-dimethoxypterocarpan-3-O-β-D-glucoside	Huangqi	MOL008400	Glycitein	Dangshen
MOL000378	7-O-methylisomucronulatol	Huangqi	MOL008397	Daturilin	Dangshen

MOL000374	5'-hydroxyiso-muronulatol-2',5'-di-O-glucoside	Huangqi	MOL008393	7-(β-xylosyl)cephalomannine_qt	Dangshen
MOL000371	3,9-di-O-methylnissolin	Huangqi	MOL008391	5α-Stigmastan-3,6-dione	Dangshen
MOL007180	Vitamin E	Gualou	MOL007514	Methyl icosa-11,14-dienoate	Dangshen
MOL007179	Linolenic acid ethyl ester	Gualou	MOL006774	Stigmast-7-enol	Dangshen
MOL007175	Karounidiol 3-O-benzoate	Gualou	MOL006554	Taraxerol	Dangshen
MOL007172	7-oxo-Dihydrokaro-unidiol	Gualou	MOL005321	Frutinone A	Dangshen
MOL007171	5-Dehydrokarounidiol	Gualou	MOL004492	Chrysanthemaxanthin	Dangshen
MOL007165	10α-cucurbita-5,24-diene-3β-ol	Gualou	MOL003036	ZINC03978781	Dangshen
MOL006756	Schottenol	Gualou	MOL002879	Diop	Dangshen
MOL005530	hydroxygenkwanin	Gualou	MOL002140	Perlolyrine	Dangshen
MOL002881	Diosmetin	Gualou	MOL001006	Poriferasta-7,22E-dien-3β-ol	Dangshen
MOL001494	Mandenol	Gualou	MOL007156	Tanshinone VI	Danshen
MOL005020	Dehydroglyasperins C	Gancao	MOL007155	(6S)-6-(hydroxymethyl)-1,6-Dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	Danshen
MOL005018	Xambioona	Gancao	MOL007154	Tanshinone iia	Danshen
MOL005017	Phaseol	Gancao	MOL007152	Przewaquinone E	Danshen
MOL005016	Odoratin	Gancao	MOL007151	Tanshindiol B	Danshen
MOL005013	18α-hydroxyglycyrrhetic acid	Gancao	MOL007150	(6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone	Danshen
MOL005012	Licoagroisoflavone	Gancao	MOL007149	NSC 122421	Danshen
MOL005008	Glycyrrhiza flavonol A	Gancao	MOL007145	Salviolone	Danshen
MOL005007	Glyasperins M	Gancao	MOL007143	Salvilenone I	Danshen
MOL005003	Licoagrocarpin	Gancao	MOL007142	Salvianolic acid J	Danshen
MOL005001	Gancaonin H	Gancao	MOL007141	Salvianolic acid G	Danshen
MOL005000	Gancaonin G	Gancao	MOL007140	(Z)-3-[2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid	Danshen
MOL004996	Gadelaidic acid	Gancao	MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	Danshen
MOL004993	8-prenylated eriodictyol	Gancao	MOL007130	Prolithospermic acid	Danshen
MOL004991	7-acetoxy-2-methylisoflavone	Gancao	MOL007127	1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	Danshen
MOL004990	7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin	Gancao	MOL007125	Neocryptotanshinone	Danshen
MOL004989	6-prenylated eriodictyol	Gancao	MOL007124	Neocryptotanshinone II	Danshen
MOL004988	Kanzonol F	Gancao	MOL007123	Miltirone II	Danshen
MOL004985	Icos-5-enoic acid	Gancao	MOL007122	Miltirone	Danshen
MOL004980	Inflacoumarin A	Gancao	MOL007121	Miltipolone	Danshen
MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol	Gancao	MOL007120	Miltionone II	Danshen
MOL004974	3'-methoxyglabridin	Gancao	MOL007119	Miltionone I	Danshen
MOL004966	3'-hydroxy-4'-O-methylglabridin	Gancao	MOL007118	Microstegiol	Danshen
MOL004961	Quercetin der.	Gancao	MOL007115	Manool	Danshen
MOL004959	1-methoxyphaseollidin	Gancao	MOL007111	Isotanshinone II	Danshen
MOL004957	HMO	Gancao	MOL007108	Isocryptotanshi-none	Danshen
MOL004949	Isolicoflavonol	Gancao	MOL007107	C09092	Danshen
MOL004948	Isoglycyrol	Gancao	MOL007105	Epidanshenspiroketallactone	Danshen

MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	Gancao	MOL007101	Dihydrotanshinone I	Danshen
MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	Gancao	MOL007100	Dihydrotanshinlactone	Danshen
MOL004935	Sigmoidin-B	Gancao	MOL007098	Deoxyneocryptotanshinone	Danshen
MOL004924	(-)-medicocarpin	Gancao	MOL007094	Danshenspiroketallactone	Danshen
MOL004917	Glycyroside	Gancao	MOL007093	Dan-shexinkum d	Danshen
MOL004915	Eurycarpin A	Gancao	MOL007088	Cryptotanshinone	Danshen
MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	Gancao	MOL007085	Salvilenone	Danshen
MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone	Gancao	MOL007082	Danshenol A	Danshen
MOL004912	Glabrone	Gancao	MOL007081	Danshenol B	Danshen
MOL004911	Glabrene	Gancao	MOL007079	Tanshinaldehyde	Danshen
MOL004910	Glabranin	Gancao	MOL007077	Sclareol	Danshen
MOL004908	Glabridin	Gancao	MOL007071	Przewaquinone f	Danshen
MOL004907	Glyzaglabrin	Gancao	MOL007070	(6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	Danshen
MOL004905	3,22-dihydroxy-11-oxo-delta(12)-oleanene-27-α-methoxycarbonyl-29-oic acid	Gancao	MOL007069	Przewaquinone C	Danshen
MOL004904	Licopyranocoumarin	Gancao	MOL007068	Przewaquinone B	Danshen
MOL004903	Liquiritin	Gancao	MOL007064	Przewalskin B	Danshen
MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one	Gancao	MOL007063	przewalskin a	Danshen
MOL004891	Shinpterocarpin	Gancao	MOL007061	Methylenetanshinquinone	Danshen
MOL004885	Licoisoflavanone	Gancao	MOL007058	Formyltanshinone	Danshen
MOL004884	Licoisoflavone B	Gancao	MOL007051	6-O-syringyl-8-o-acetyl shanzhiside methyl ester	Danshen
MOL004883	Licoisoflavone	Gancao	MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	Danshen
MOL004882	Licocoumarone	Gancao	MOL007049	4-methylenemiltirone	Danshen
MOL004879	Glycyrin	Gancao	MOL007048	(E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	Danshen
MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone	Gancao	MOL007045	3α-hydroxytanshinone IIa	Danshen
MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	Gancao	MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	Danshen
MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone	Gancao	MOL007036	5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	Danshen
MOL004860	Licorice glycoside E	Gancao	MOL006824	α-amyrin	Danshen
MOL004857	Gancaonin B	Gancao	MOL002651	Dehydrotanshinone IIA	Danshen
MOL004856	Gancaonin A	Gancao	MOL002222	Sugiol	Danshen
MOL004855	Licoricone	Gancao	MOL001942	Isoimperatorin	Danshen
MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	Gancao	MOL001771	Poriferast-5-en-3β-ol	Danshen
MOL004848	Licochalcone G	Gancao	MOL001659	Poriferasterol	Danshen
MOL004841	Licochalcone B	Gancao	MOL001601	1,2,5,6-tetrahydrotanshinone	Danshen
MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	Gancao	MOL000569	Digallate	Danshen

MOL004835	Glypallichalcone	Gancao	MOL006967	β-D-Ribofuranoside, xanthine-9	Banxia
MOL004833	Phaseolinisoflavan	Gancao	MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone	Banxia
MOL004829	Glepidotin B	Gancao	MOL006937	12,13-epoxy-9-hydroxynonadeca-7,10-dienoic acid	Banxia
MOL004828	Glepidotin A	Gancao	MOL006936	10,13-eicosadienoic	Banxia
MOL004827	Semilicoisoflavone B	Gancao	MOL005030	Gondoic acid	Banxia
MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one	Gancao	MOL003578	Cycloartenol	Banxia
MOL004820	Kanzonols W	Gancao	MOL002714	Baicalein	Banxia
MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethyl-chromen-6-yl)prop-2-en-1-one	Gancao	MOL002670	Cavidine	Banxia
MOL004814	Isotrifoliol	Gancao	MOL001755	24-ethylcholest-4-en-3-one	Banxia
MOL004811	Glyasperin C	Gancao	MOL000519	Coniferin	Banxia
MOL004810	Glyasperin F	Gancao	MOL000358	β-sitosterol	Banxia
MOL004808	Glyasperin B	Gancao	MOL000072	8β-ethoxy atractylenolide III	Baizhu
MOL004806	Euchrenone	Gancao	MOL000049	3β-acetoxyatractylone	Baizhu
MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one	Gancao	MOL000028	α-amyrin	Baizhu
MOL004328	Naringenin	Gancao	MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	Baizhu
MOL003656	Lupiwighteone	Gancao	MOL000021	14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol	Baizhu
MOL002565	Medicarpin	Gancao	MOL000020	12-senecioyl-2E,8E,10E-atractylentriol	Baizhu
MOL002311	Glycyrol	Gancao			

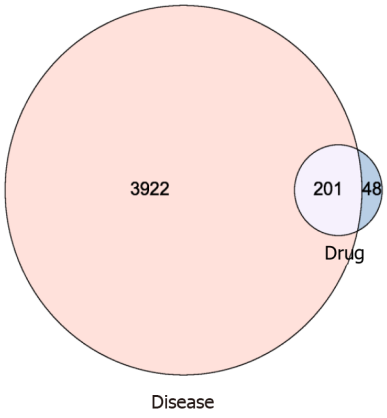


Figure 1 Venn diagram showing common targets of chronic heart failure and Jianpi Huatan Quyu recipe.

MAPK8, MAPK14, IL6, EGFR, EDN1, and FOS, which may be the core proteins mediating the therapeutic effects of Jianpi Huatan Quyu recipe in treating chronic heart failure (Figure 4).

GO enrichment analysis

BP enrichment analysis results are shown in Figure 5A. The BPs enriched include response to lipopolysaccharide, inflammatory response, response to drug, reactive oxygen species metabolic process, response to wounding, cellular response to organic cyclic compound, response to inorganic substance, cellular response to nitrogen compound, circulatory system process, positive regulation of cellular component movement, response to oxygen levels, apoptotic signaling pathway, response to extracellular stimulus, positive regulation of ion transport, regulation of MAPK cascade, regulation of DNA-binding transcription factor activity, regulation of cell adhesion, response to growth factor, response to steroid hormone, fine negative regulation of cell differentiation, *etc.*

Figure 5B shows the results of CC enrichment analysis. The CCs enriched are membrane raft, receptor complex, vesicle lumen, postsynaptic membrane, dendrite, perinuclear region of cytoplasm, side of membrane, extracellular matrix, protein kinase complex, cytoplasmic vesicle membrane, organelle outer membrane, focal adhesion, basal part of cell,

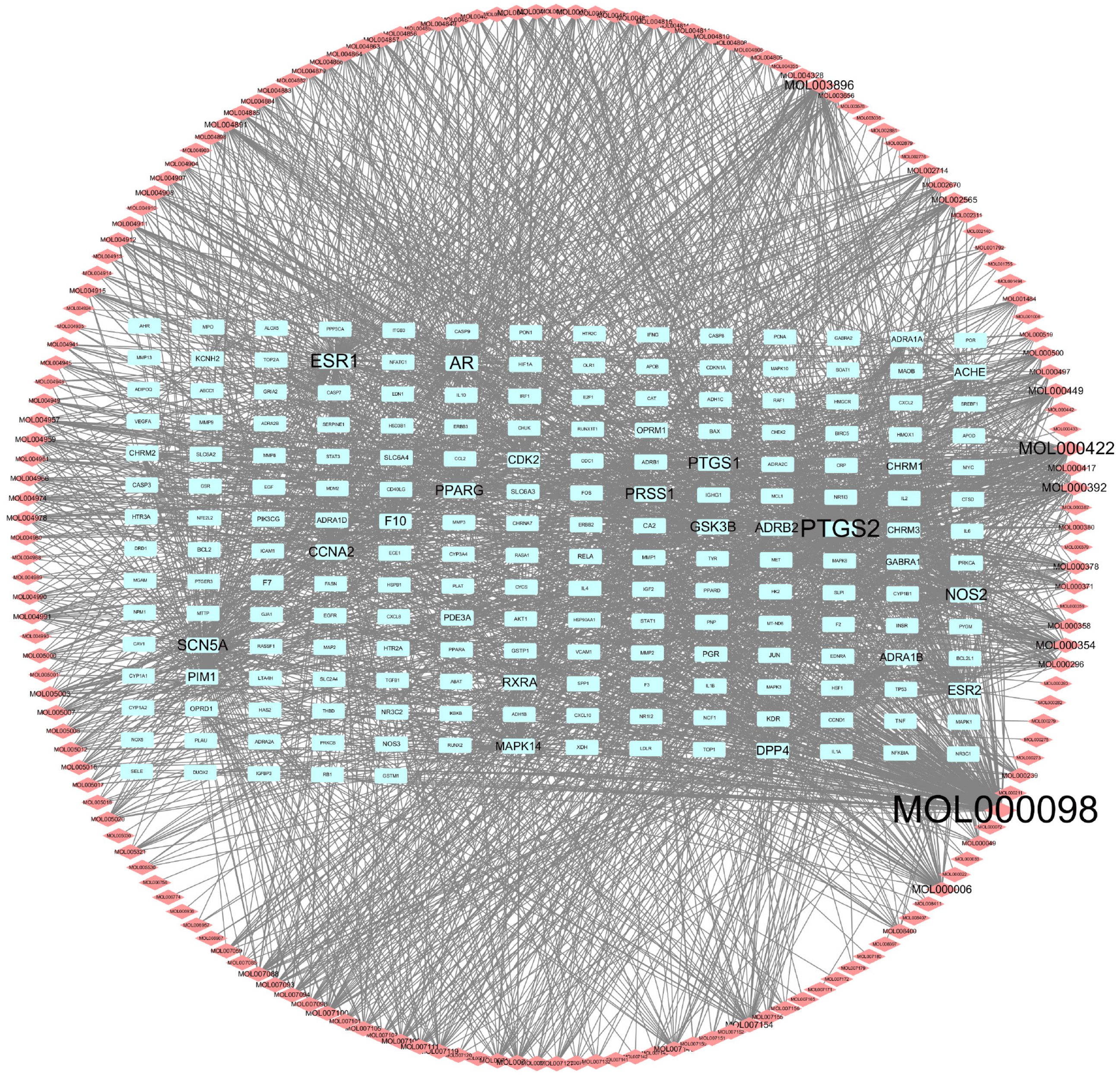


Figure 2 Network of target proteins shared by key active components in Jianpi Huatan Quyu recipe and chronic heart failure. Boxes represent target genes, and diamonds represent active ingredients. The size of the text in boxes and diamonds indicates "degree".

RNA polymerase II transcription regulator complex, dendrite membrane, endocytic vesicle, dopaminergic synapse, *etc*.

Figure 5C shows the results of MF enrichment analysis. The MFs enriched include nuclear receptor activity, protein homodimerization activity, DNA-binding transcription factor binding, G protein-coupled amine receptor activity, protein domain specific binding, protein kinase activity, cytokine receptor binding, protein heterodimerization activity, oxidoreductase activity, transcription coactivator binding, amide binding, neurotransmitter receptor activation activity, endopeptidase activity, drug binding, phosphatase binding, protease binding, core promoter sequence-specific DNA binding, MAP kinase activity, repressing transcription factor binding, kinase regulator activity, *etc*.

KEGG pathway enrichment analysis

KEGG pathway enrichment analysis demonstrated that the pathways enriched include pathways in cancer, IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, cAMP signaling pathway, NF-kappaB signaling pathway, AMPK signaling pathway, *etc*. (Figure 5D).

Target-pathway network construction

The target-pathway network constructed is shown in Figure 6. The selected core targets are IKBKB, RELA, AKT1, MAPK8, MAPK10, CHUK, JUN, MAPK1, TNF, CASP3, IL6, MAPK3, NFKBIA, MAPK14, TP53, CASP8, *etc*.

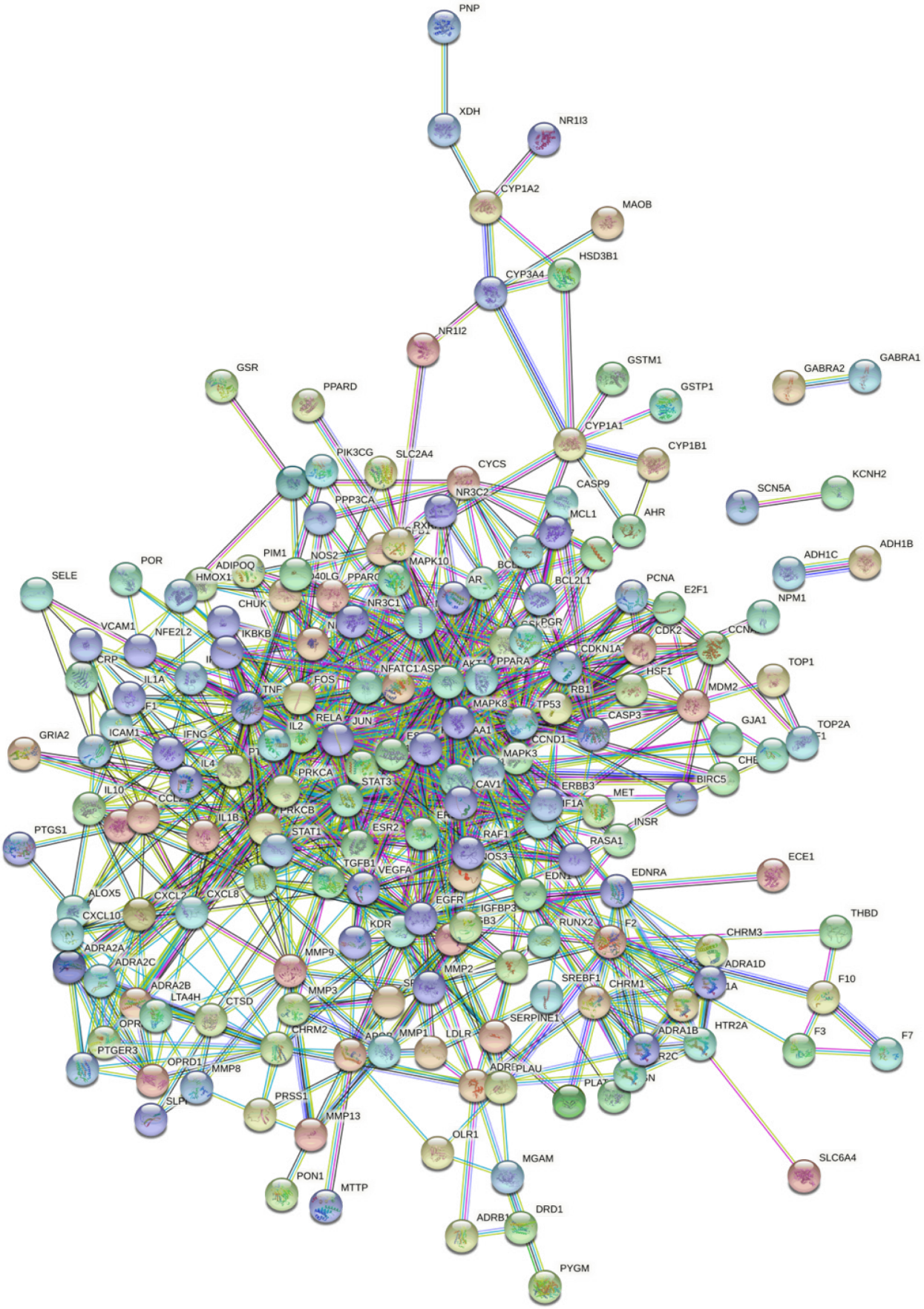


Figure 3 Protein-protein interaction protein interaction network.

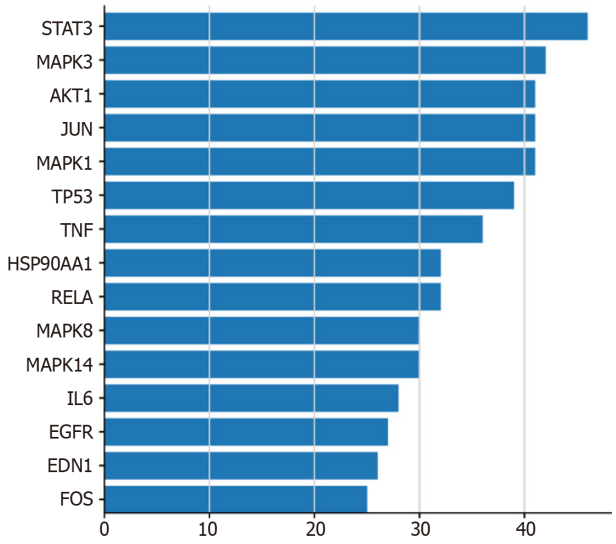


Figure 4 Core proteins identified by protein-protein interaction.

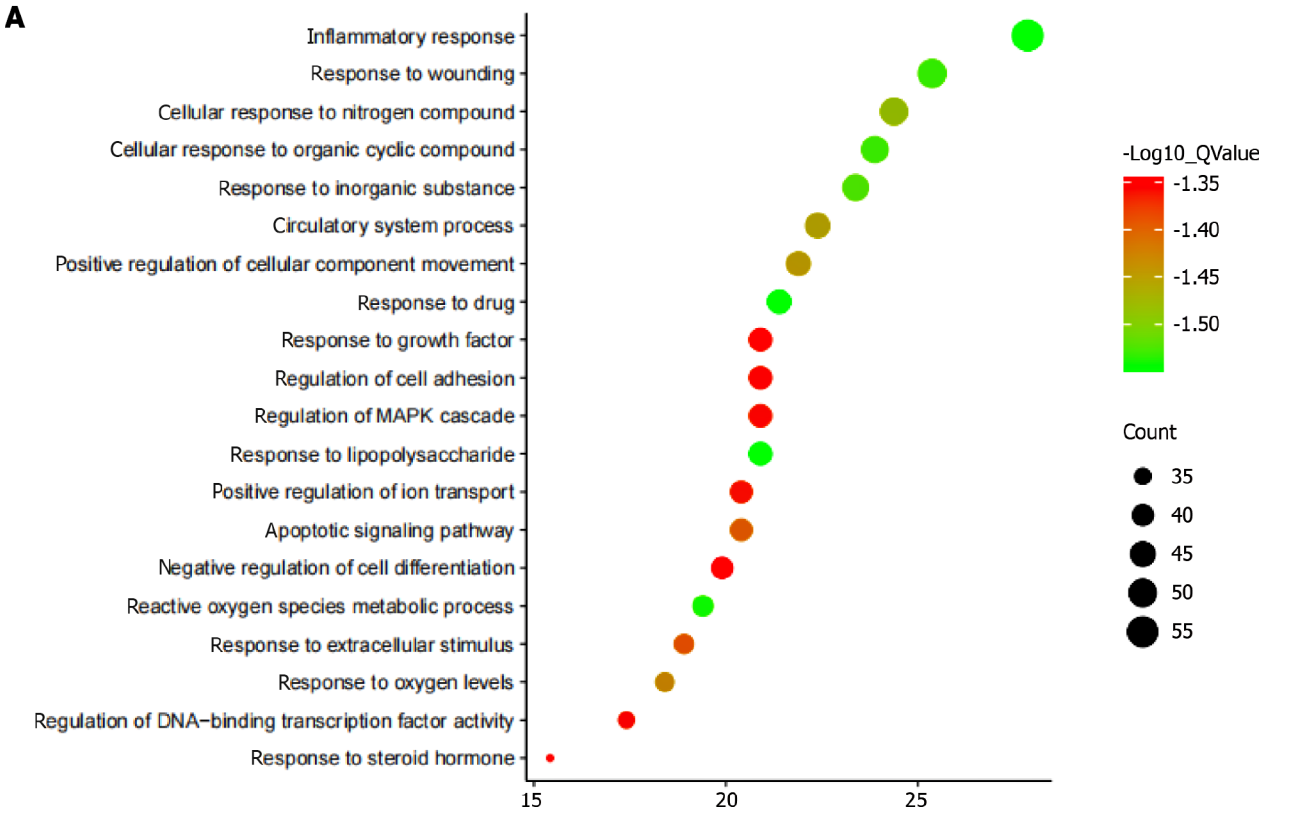
Confirmatory results of our previous studies

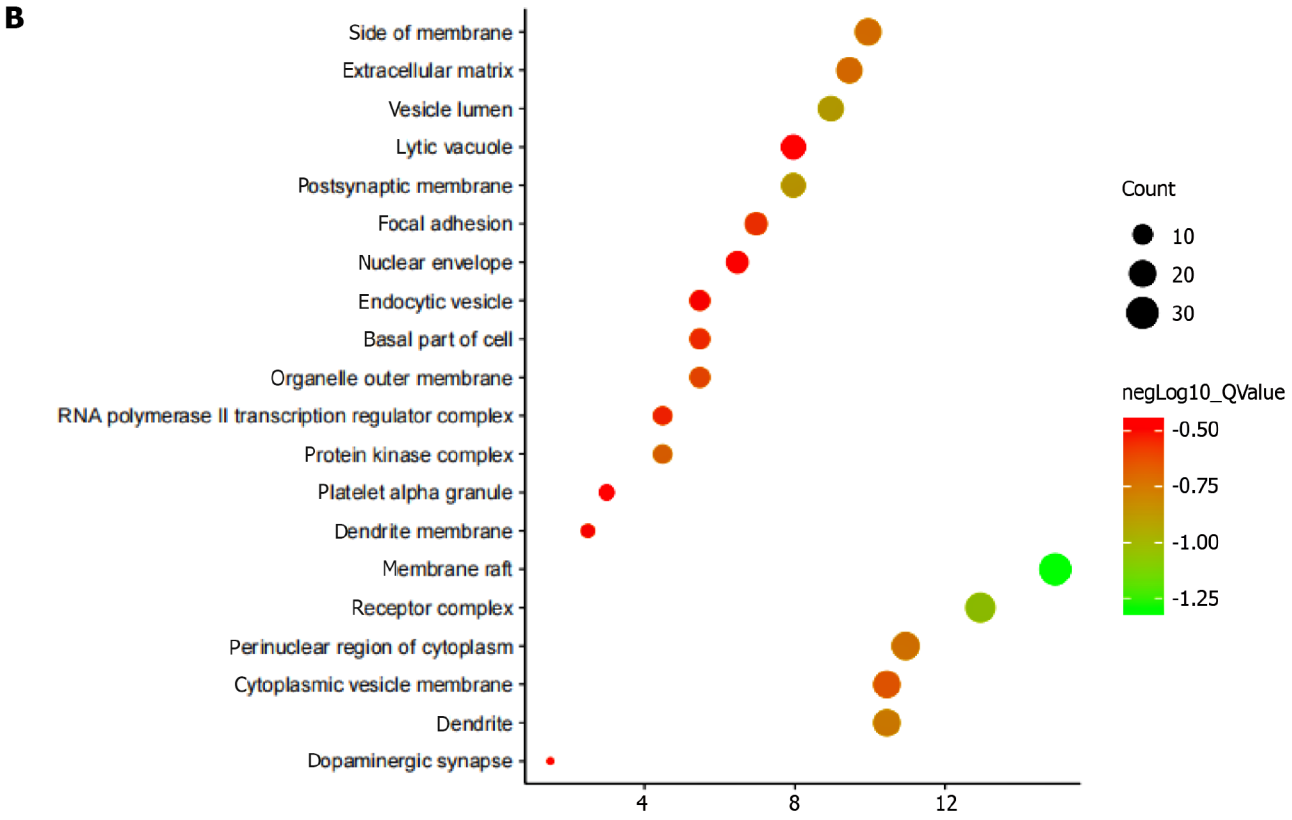
Our previous studies have explored the mechanism of action of Jianpi Huayu Qutan recipe in different conditions, which demonstrated that this recipe functions by regulating the expression of proteins involved in the TNF-α, IL-6, MAPK, cAMP, and AMPK pathways[8-11].

DISCUSSION

From the perspective of TCM, chronic heart failure is a disease characterized by deficiency in origin and excess in superficiality, which initially occurs in the heart, and then involves the lungs, spleen, and kidneys. With deficiency of heart Qi as the root cause, chronic heart failure mainly manifests as phlegm turbidity, fluid retention, and blood stasis[12]. The Chinese herbal compound preparation Jianpi Huatan Quyu recipe, derived from the TCM preparation Sijunzi decoction, was initially used to treat the syndrome of deficiency of spleen Qi[13]. Correcting the deficiency of Qi and blood is essential for the treatment of diseases. The spleen and stomach are the sources of Qi and blood. In Jianpi Huatan Quyu recipe, Huangqi, Dangshen, Baizhu, Fuling, and Zhigancao have strong spleen-strengthening effects and can promote blood circulation by flourishing the spleen Qi. Spleen dysfunction will lead to the accumulation of phlegm, so Qingbanxia is included in the recipe for removing dampness to reduce phlegm, and Gualou is used to relieve depression in the chest and regulate the flow of Qi, both of which can help eliminate the phlegm accumulated in the chest. Qi deficiency results in poor blood circulation and stagnation of blood stasis. Zhang *et al*[14] wrote in the ancient book "Thoroughly Revised Materia Medica" that "Danshen tonifies the heart, removes blood stasis, and promotes fresh blood production.....having multiple therapeutic effects". Therefore, Danshen is included in the Jianpi Huatan Quyu recipe to tonify the heart, promote blood circulation, and remove blood stasis. Combined use of all these herbs can achieve the effects of strengthening the spleen, tonifying the heart, eliminating phlegm, and removing blood stasis. Our previous studies have shown that Jianpi Huatan Quyu recipe can effectively improve patients' blood lipids, improve myocardial function, and affect patients' myocardial mitochondrial energy metabolism[15,16]. This study further explored the molecular mechanism underlying the therapeutic effects of Jianpi Huatan Quyu recipe in chronic heart failure.

In the present study, according to oral bioavailability and drug-likeness, 227 active ingredients of eight herbs composing Jianpi Huatan Quyu recipe were identified, among which quercetin, kaempferol, 7-methoxy-2-methyl isoflavone, formononetin, and isorhamnetin may be the key active ingredients. These chemical components can be highly matched with the following targets of chronic heart failure: PTGS2, ESR1, AR, PTGS1, NOS2, SCN5A, PRSS1, GSK3B, PPARG, CCNA2, ESR2, ADRB2, DPP4, F10, and RXRA. Further analysis of the relationship between these targets and chronic heart failure revealed that STAT3, MAPK3, AKT1, JUN, MAPK1, TP53, TNF, HSP90AA1, p65, MAPK8, MAPK14, IL6, EGFR, EDN1, and FOS may be involved in the development and progression of chronic heart failure. These proteins may also play an important role in the treatment of chronic heart failure. The molecular mechanisms that are involved in the therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure include nuclear receptor activity, protein homodimerization activity, DNA-binding transcription factor activity, G protein-coupled amine receptor activity, protein domain specific binding, protein kinase activity, cytokine receptor binding, protein heterodimerization activity, oxidoreductase activity, transcription coactivator binding, amide binding, and neurotransmitter receptor activity, endopeptidase activity, drug binding, phosphatase binding, protease binding, core promoter sequence-specific DNA binding, MAP kinase activity, repressing transcription factor binding, kinase regulator activity, *etc*. KEGG signaling pathway enrichment analysis indicated that the compound may act on multiple pathways, such as pathways in cancer, IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, cAMP signaling


A
Inflammatory response
Response to wounding
Cellular response to nitrogen compound
Cellular response to organic cyclic compound
Response to inorganic substance
Circulatory system process
Positive regulation of cellular component movement
Response to drug
Response to growth factor
Regulation of cell adhesion
Regulation of MAPK cascade
Response to lipopolysaccharide
Positive regulation of ion transport
Apoptotic signaling pathway
Negative regulation of cell differentiation
Reactive oxygen species metabolic process
Response to extracellular stimulus
Response to oxygen levels
Regulation of DNA−binding transcription factor activity
Response to steroid hormone
15
20
25
-Log10_QValue
-1.35
-1.40
-1.45
-1.50
Count
35
40
45
50
55


B
Side of membrane
Extracellular matrix
Vesicle lumen
Lytic vacuole
Postsynaptic membrane
Focal adhesion
Nuclear envelope
Endocytic vesicle
Basal part of cell
Organelle outer membrane
RNA polymerase II transcription regulator complex
Protein kinase complex
Platelet alpha granule
Dendrite membrane
Membrane raft
Receptor complex
Perinuclear region of cytoplasm
Cytoplasmic vesicle membrane
Dendrite
Dopaminergic synapse
4
8
12
Count
10
20
30
negLog10_QValue
-0.50
-0.75
-1.00
-1.25

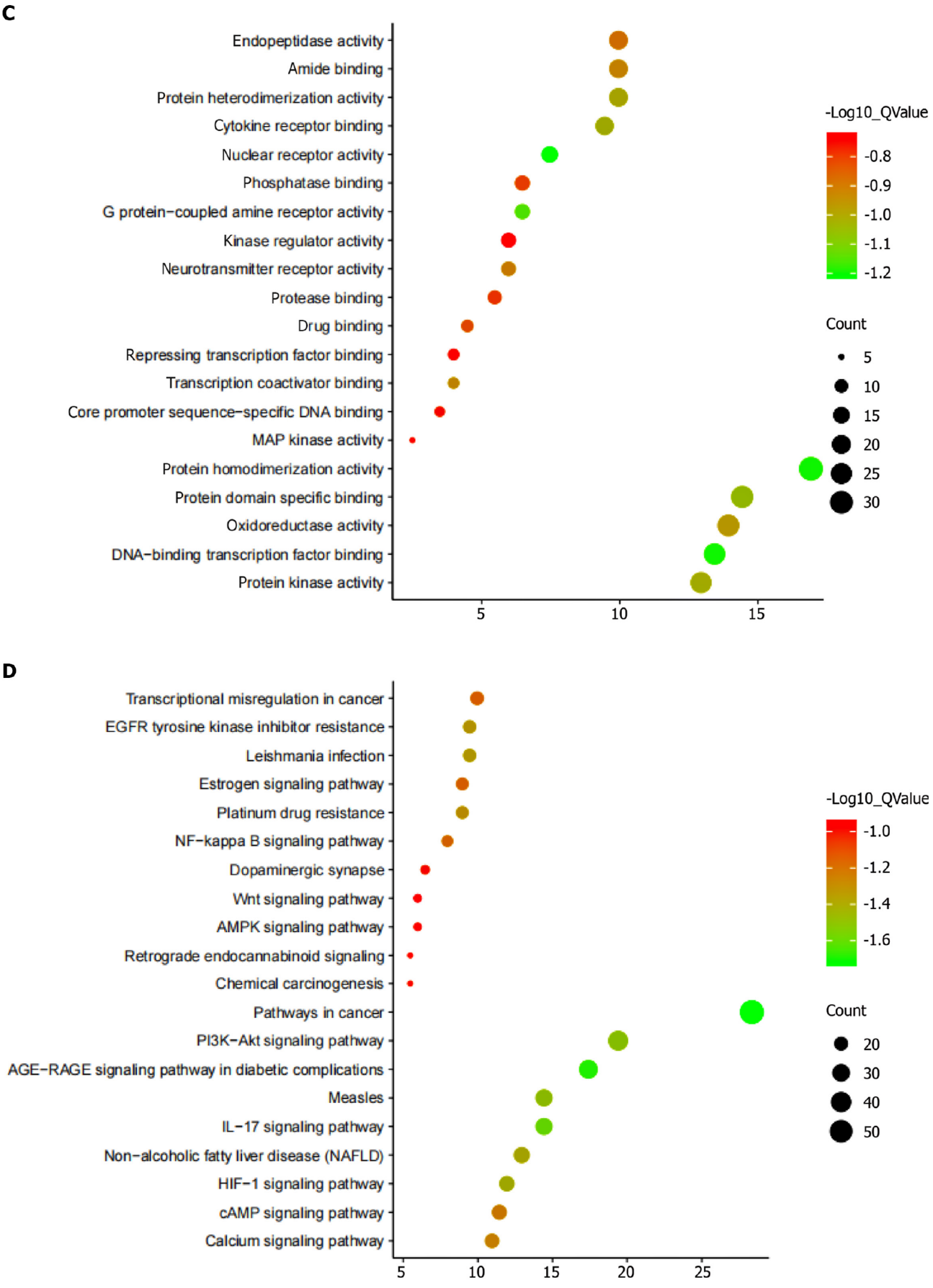


Figure 5 GO and KEGG enrichment analyses. A: GO biological process enrichment analysis; B: GO cellular component enrichment analysis; C: GO molecular function enrichment analysis; D: KEGG enrichment analysis.

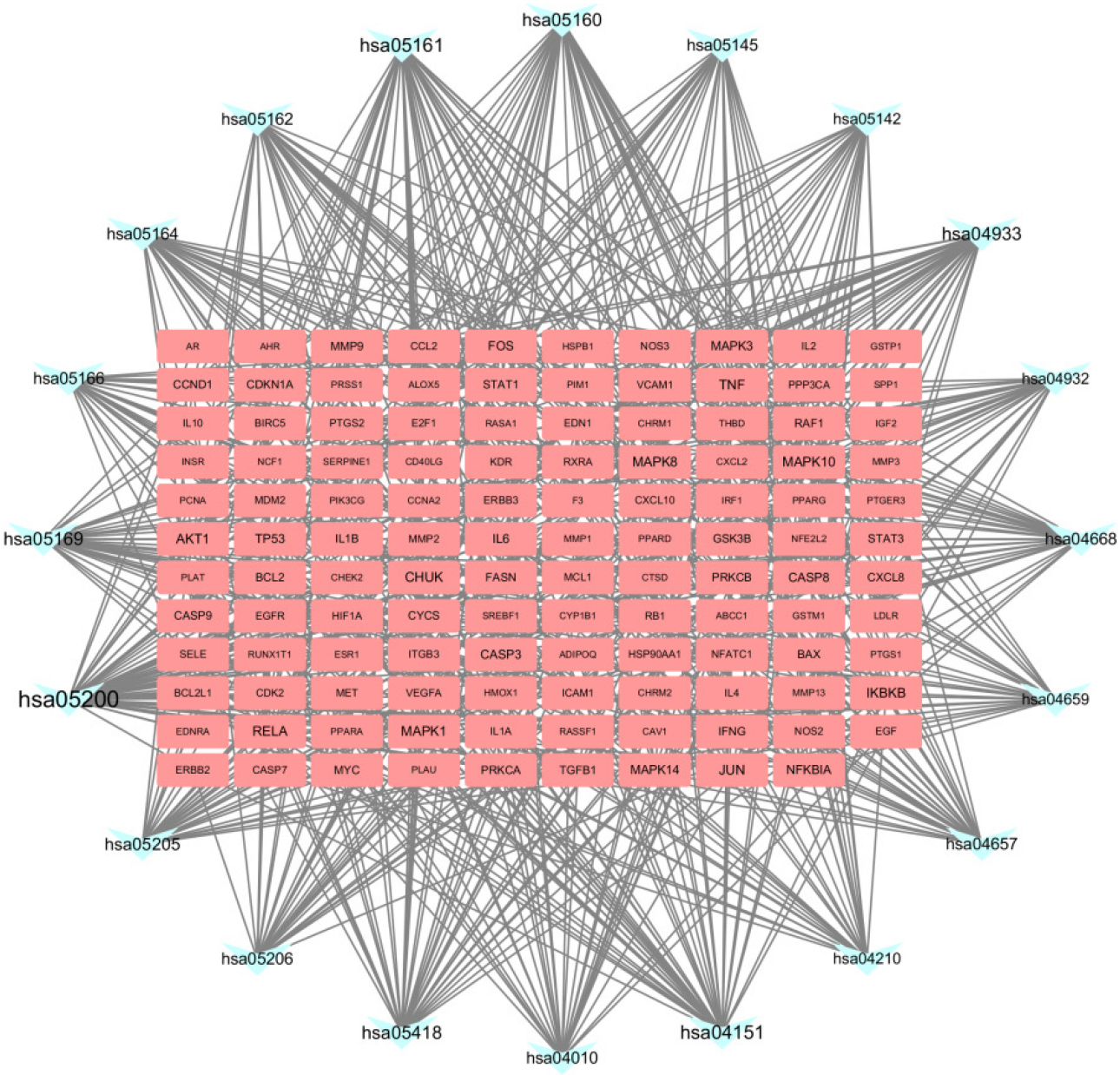


Figure 6 Target-pathway network diagram. The size of the node text is proportional to the number of lines connecting the node, with larger text indicating more targets or pathways associated with the target.

pathway, NF-kappaB signaling pathway, and AMPK signaling pathway. Among these pathways, IKBKB, RELA, AKT1, MAPK8, MAPK10, CHUK, JUN, MAPK1, TNF, CASP3, IL6, MAPK3, NFKBIA, MAPK14, TP53, CASP8, *etc.* may be the key protein targets of Jianpi Huatan Quyu recipe.

CONCLUSION

To sum up, the Chinese herbal compound preparation Jianpi Huatan Quyu recipe acts on multiple targets through a variety of active ingredients, exerting therapeutic effects on chronic heart failure *via* multiple pathways. The TNF-α, IL-6, MAPK, cAMP, and AMPK pathways have been experimentally verified to be involved in the therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure in previous studies. The pathways such as the IL-17, PI3K-Akt, and HIF-1 signaling pathways can be used as the targets in the treatment of chronic heart failure. Future research is warranted to further explore the mechanism of Jianpi Huatan Quyu recipe in the treatment of chronic heart failure.

FOOTNOTES

Author contributions: Li SQ designed the study and drafted the manuscript; all authors contributed to revising and proofreading the manuscript.

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