

Sacubitril/Valsartan for Breast Cancer Therapy-Related Cardiac Dysfunction: An Integrated Meta-Analysis and Bioinformatics Study

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Research Article

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Abstract

Background

Sacubitril/valsartan has proven efficacy in heart failure with reduced ejection fraction, but its role in breast cancer therapy-related cardiac dysfunction (CTRCD) remains unclear. We evaluated its efficacy and therapeutic targets via integrated meta-analysis and bioinformatics.

Methods

We systematically searched PubMed, Embase, Cochrane, Web of Science, and CNKI for sacubitril/valsartan studies in breast cancer CTRCD and performed meta-analysis. Candidate targets from network pharmacology were intersected with GEO differentially expressed genes; LASSO and SVM-RFE identified core targets. Two-sample Mendelian randomization assessed causality, and molecular docking verified binding.

Results

The meta-analysis included 7 studies ($n = 409$). In patients with established CTRCD, sacubitril/valsartan treatment significantly improved LVEF from baseline ($MD = 5.27$, 95% CI: 1.35–9.20, $P = 0.008$) and reduced NT-proBNP ($MD = -2323.96$, 95% CI: -4370.12 to -277.79, $P = 0.03$); in those with normal baseline cardiac function, LVEF also improved ($MD = 1.30$, 95% CI: 0.04–2.56, $P = 0.04$), and the incidence of CTRCD decreased ($RR = 0.11$, 95% CI: 0.01–0.93, $P = 0.04$). Mechanistically, machine learning identified 9 core therapeutic targets from 141 candidate targets. Mendelian randomization suggested causal associations of PIK3CG ($OR = 0.88$, 95% CI: 0.81–0.97, $P = 0.006$) and KEAP1 ($OR = 1.12$, 95% CI: 1.01–1.24, $P = 0.028$) with heart failure as a clinical endpoint of CTRCD. Molecular docking showed binding energies between sacubitril/valsartan and the above targets ranging from -5.7 to -10.0 kcal/mol.

Conclusions

Sacubitril/valsartan improves cardiac function in both therapeutic and preventive settings of breast cancer CTRCD, with PIK3CG and KEAP1 as potential cardioprotective targets. Functional experiments and larger randomized trials are needed to confirm these findings.

1 Introduction

Breast cancer is the most common malignancy among women worldwide[1]. Adjuvant therapy is typically anthracycline-based, and HER2-positive patients additionally receive trastuzumab[2]. The combination of these two agents is associated with a significantly higher incidence of cardiotoxicity than either agent alone, placing breast cancer patients among the highest-risk populations for cancer therapy-related cardiac dysfunction (CTRCD). CTRCD encompasses a spectrum from subclinical myocardial injury to overt heart failure and is a leading cause of morbidity and mortality in long-term breast cancer survivors. Anthracyclines directly damage cardiomyocytes, whereas trastuzumab interferes with cardiac compensatory repair [3]; however, the underlying mechanisms remain incompletely understood. Current guidelines recommend prophylactic or therapeutic use of angiotensin-converting enzyme inhibitors (ACEIs) or beta-blockers in selected high-risk populations or patients[4]. Nevertheless, in the context of modern combination regimens involving targeted agents such as trastuzumab, evidence for the preventive benefits of these strategies remains insufficient. This underscores a clear evidence gap regarding cardioprotective strategies specifically in the breast cancer population.

Sacubitril/valsartan is the first angiotensin receptor-neprilysin inhibitor (ARNI), and the PARADIGM-HF trial demonstrated its superiority over enalapril, changing the treatment landscape for heart failure with reduced ejection fraction [5]. The drug possesses both vasodilatory and natriuretic peptide effects [6]. Its potential application in the field of CTRCD has attracted considerable attention [7]. Bioinformatics analyses and animal studies have suggested possible involvement of the AMPK α -mTORC1 pathway [8] and the MAPK pathway [9], but a systematic screening has not yet been performed. Several clinical trials have begun to explore its therapeutic and preventive roles in CTRCD across different cancer types [10–13]. However, existing evidence is confounded by the inclusion of diverse cancer types and chemotherapy regimens, with no dedicated analysis specifically focusing on the breast cancer population [14]. Therefore, this study integrated meta-analysis, network pharmacology, machine learning, Mendelian randomization, and molecular docking to systematically evaluate the role of sacubitril/valsartan in breast cancer CTRCD at both the molecular mechanism prediction and clinical evidence validation levels, aiming to inform future mechanistic investigations and clinical practice.

2 Materials and Methods

2.1 Meta-Analysis of Sacubitril/Valsartan in Breast Cancer CTRCD

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines, and the protocol was registered with PROSPERO (CRD420261295338). The analyses were based on published aggregate-level data.

We systematically searched PubMed, Embase, Cochrane Library, Web of Science, and CNKI (<https://www.cnki.net/>) on May 31, 2026, without restrictions on publication date or language. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, with core terms including sacubitril/valsartan, anthracycline, trastuzumab, cardiotoxicity, and breast cancer (**Supplementary Material Method**).

Study selection was performed independently by two reviewers based on predefined inclusion and exclusion criteria. The inclusion criteria were as follows: (1) adult breast cancer patients receiving anthracycline and/or trastuzumab-based therapy; (2) intervention with sacubitril/valsartan; (3) reported outcomes including changes in left ventricular ejection fraction (LVEF), NT-proBNP, or incidence of CTRCD; and (4) full-text publications with sufficient data (means, standard deviations, and sample sizes) to allow calculation of primary and secondary outcomes. The exclusion criteria were as follows: (1) nonclinical studies; (2) studies not involving breast cancer patients or breast cancer-related treatments; and (3) incomplete data that precluded effect size extraction or unfinished trials.

Data extraction was performed independently by two reviewers, including study characteristics, patient demographics and baseline clinical features, intervention and control details, and summary data for primary and secondary outcomes. For continuous variables, we preferentially extracted means, standard deviations, and sample sizes at each time point. For studies reporting only medians and interquartile ranges, we applied validated statistical formulas to estimate means and standard deviations [15, 16]. Risk of bias was assessed using the RoB 2.0 tool for randomized controlled trials and the ROBINS-I tool for observational studies [17, 18]. The primary outcome was the absolute change in LVEF from baseline to the main follow-up time point. Secondary outcomes included changes in NT-proBNP and the incidence of CTRCD. Based on baseline cardiac function, studies with normal baseline cardiac function were classified as preventive, while those with established CTRCD at baseline were classified as therapeutic, and meta-analyses were performed separately for each group. Meta-analyses were performed using Review Manager 5.3. Between-study heterogeneity was quantified using the I^2 statistic and supplemented by the P-value from Cochran's Q test: a fixed-effects model was used when $I^2 < 50\%$ and $P > 0.05$; otherwise, a random-effects model was applied. Sensitivity analyses were performed by iteratively excluding each study and recalculating the pooled estimate to assess robustness.

2.2 Data Acquisition and Integration

Disease targets for breast cancer therapy-related cardiac dysfunction were obtained from GeneCards (<https://www.genecards.org/>) and Online Mendelian Inheritance in Man (OMIM, <https://www.omim.org/>). The SDF-formatted structure of sacubitril/valsartan was downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and uploaded to SwissTargetPrediction (<https://swisstargetprediction.ch/>) to identify potential drug targets. The intersection of drug targets and disease targets was taken as a candidate target. Transcriptomic data were obtained from the Gene Expression Omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo/>), with anthracycline-treated transcriptomic data derived from GSE40447 and trastuzumab-treated data from GSE264120. Instrumental variables for Mendelian randomization were derived from genome-wide association study (GWAS) summary statistics, with heart failure GWAS data obtained from the IEU OpenGWAS database (<https://gwas.mrcieu.ac.uk/>). All databases were accessed on May 31, 2026.

2.3 Functional Enrichment Analysis of Targets

Functional enrichment analysis of the candidate targets was performed using the clusterProfiler package in R version 4.4.2, including Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment. GO analysis covered three categories: biological process (BP), cellular component (CC), and molecular function (MF). With a significance threshold of $FDR < 0.05$, the top 10 terms from each GO category and the top 10 KEGG pathways were exported for bioinformatics visualization.

2.4 Screening and Identification of Core Therapeutic Targets

2.4.1 Differential Expression Analysis of Datasets

Differential expression analysis of microarray data (GSE40447) was performed using the limma package in R version 4.4.2. For RNA-seq data (GSE264120), the voom method from the limma package was applied prior to differential analysis. Differentially expressed genes (DEGs) were identified with thresholds of $|\log_2FC| > 1$ and $P < 0.05$. The DEGs were then intersected with candidate targets from network pharmacology, and the overlapping genes were used for subsequent machine learning screening.

2.4.2 Machine Learning for Core Therapeutic Target Screening

From the candidate targets, two machine learning algorithms, the least absolute shrinkage and selection operator (LASSO) and support vector machine recursive feature elimination (SVM-RFE), were applied to identify core therapeutic targets. LASSO regression was performed using the glmnet package in R version 4.4.2 with ten-fold cross-validation (standardize = TRUE, alpha = 1, family = "binomial"), and lambda.min and lambda.1 se were used as the final penalty criteria. Meanwhile, SVM-RFE was conducted in parallel using a linear kernel (svmLinear) with ten-fold cross-validation to evaluate the classification performance of different feature subsets, and the gene set corresponding to the highest cross-validation accuracy was selected as the optimal feature set. The intersection of genes identified by the two algorithms was defined as the core therapeutic target. Based on these core therapeutic targets, a logistic regression model was constructed using GSE40447 and GSE264120 as the training set, and its generalization ability was evaluated by plotting receiver operating characteristic (ROC) curves in the independent validation set GSE243674.

2.4.3 Mendelian Randomization for Causal Inference

Two-sample Mendelian randomization (MR) was performed to evaluate the causal relationship between the core therapeutic targets and heart failure (HF), which was used as a clinical endpoint for CTRCD[19]. Cis-expression quantitative trait loci (cis-eQTLs) for the core therapeutic targets were extracted as instrumental variables (IVs), with a significance threshold of $P < 1 \times 10^{-5}$ and linkage disequilibrium clumping parameters set at $r^2 < 0.01$ within a 5,000-kb window. The F-statistic for each IV was calculated as $F = \beta^2/se^2$, and only those with $F > 10$ were retained to avoid weak instrument bias. MR analyses were performed using the TwoSampleMR package in R version 4.4.2, with inverse variance weighting (IVW) as the primary method for causal estimation. MR-Egger regression, weighted median, and weighted mode were also applied as complementary methods to assess the robustness of the results.

2.5 Molecular Docking Validation of Drug–Target Binding

Three-dimensional crystal structures of the core therapeutic target proteins were obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/>, accessed on May 31, 2026) and then processed in PyMOL 3.0 to remove water molecules and organic ligands. The three-dimensional structures of sacubitril and valsartan were downloaded from PubChem and subjected to energy minimization using Chem3D 23.1.1. Preprocessing of proteins and ligands, including removal of water molecules and addition of hydrogen atoms, was performed using AutoDock Tools 1.5.7. Molecular docking was carried out with AutoDock Vina 1.1.2, with the grid spacing set to 1 Å. A binding energy ≤ -5.0 kcal/mol was used as the threshold for effective binding [20, 21]. The docking results were visualized in PyMOL 3.0.

3 Result

3.1 Meta-Analysis of Sacubitril/Valsartan in Breast Cancer CTRCD

3.1.1 Literature search and quality of included studies

The literature screening flowchart is presented in Fig. 1. A total of 409 patients from 7 studies were finally included after searching five databases, namely, PubMed, Web of Science, Embase, Cochrane Library, and CNKI [10–12, 22–25]. The baseline characteristics of the included studies are summarized in Table 1. Among them, six were randomized controlled trials, and one was an observational study. The publication years ranged from 2020 to 2025. The study populations were breast cancer patients receiving potentially cardiotoxic anticancer therapies, with sacubitril/valsartan doses ranging from 24/26 mg to 97/103 mg per administration. The follow-up duration ranged from 2 to 20 months.

Based on baseline cardiac function, the included studies were classified into therapeutic and preventive studies. Four therapeutic studies involving 149 patients with established CTRCD at baseline all adopted a single-arm pre-post design to evaluate the improvement in cardiac function with sacubitril/valsartan. Three preventive studies involving 260 patients with normal baseline cardiac function compared intervention and control groups to evaluate the preventive effect of sacubitril/valsartan on CTRCD.

Risk of bias assessment showed that among the 6 randomized controlled trials, 3 were rated as low risk and 3 had some concerns (**Supplementary Figure S1a**); one prospective cohort study was rated as moderate risk using the ROBINS-I tool (**Supplementary Figure S1b**).

Table 1 Baseline characteristics of the included studies.										
Study	Study design	Baseline CTRCD	No. of patients	Group(no. of patients)	Age(y)	BMI(kg/m2)	Blood pressure(mmHg)	Heart rate(bpm)	Baseline LVEF(%)	P s
Marcely Gimenes Bonatto et al. (2025) [10]	RCT	No	27	S/V(9) Placebo(18)	-	-	-	-	59.4±4.4, 60.3±4.8	T
Torbjorn Omland et al. (2025) [12]	RCT	No	138	S/V(69) Placebo(69)	53.6±9.2, 54.5±9.7	28.1±5.5, 26.1±4.9	127.0±15.6/79.9±9, 132.4±19.3/81.2±10.2	70.6±11.7, 73.0±12.9	60.6±4.9, 60±4.9	A T
Yu-Ling Hsu et al. (2025)[11]	RCT	No	100	S/V(20) Standard Care(80)	50.1±6.1, 51.5±9.0	24.1±6.9, 24.1±3.7	125.4±13.7/76.8±13.0, 125.3±18.7/76.4±11.7	72.2±10.4, 71.9±10.5	63.5±4.6, 63.8±4.3	A T
Kanorsky et al. (2024)[23]	RCT	Yes	127	S/V(63) Candesartan(64)	-	-	-	-	37.2 ± 4.1, 38.3 ± 4.0	A
Wei et al. (2020)[24]	RCT	Yes	62	S/V(34) Standard Care(28)	47.2 ± 16.1, 47.2 ± 16.1	-	-	-	37.8 ± 8.0, 38.2 ± 7.6	T
Yan et al. (2021)[25]	RCT	Yes	70	S/V(35) Standard Care(35)	52.15 ± 7.84, 53.72 ± 6.11	23.17 ± 2.60, 22.91 ± 1.73	-	79.32 ± 9.41, 79.94 ± 7.13	61.59 ± 3.47, 61.48 ± 3.77	A
Gregoriotti et al. (2020)[22]	Prospective cohort	Yes	28	S/V(28)	56.2 ± 13.4	-	-	-	26.7 ± 5.4	A T

Data are presented as the mean ± SD.

Flow chart showing the identification, screening, and inclusion process of studies for meta-analysis. A total of 498 records were identified from PubMed, Web of Science, Embase, Cochrane Library, and CNKI. After removing 190 duplicate records, 308 records were screened by title and abstract, of which 228 were excluded with 39 animal experiments and 189 irrelevant studies. The remaining 80 reports were sought for retrieval and assessed for eligibility. Ultimately, 7 studies met the inclusion criteria and were included in the meta-analysis.

3.1.2 Meta-Analysis of Therapeutic Studies

To evaluate the therapeutic value of sacubitril/valsartan in breast cancer patients with established CTRCD, four single-arm pre-post studies ($n = 149$) were pooled for analysis. These patients developed CTRCD during anthracycline-based therapy with or without trastuzumab, and changes in cardiac function parameters were compared before and after sacubitril/valsartan treatment. The results showed that LVEF significantly improved from baseline after treatment (MD = 5.27, 95% CI 1.35–9.20, $P = 0.008$, $I^2 = 92\%$) (Fig. 2a). Concurrently, NT-proBNP levels were significantly reduced from baseline (MD = -2323.96, 95% CI -4370.12 to -277.79, $P = 0.03$, $I^2 = 98\%$) (Fig. 2b). Leave-one-out sensitivity analysis (**Supplementary Figure S2**) shows that the direction of the effect remained consistent across iterations. For LVEF, excluding Yan et al. reduced I^2 from 92% to 39%, and for NT-proBNP, excluding Wei et al. reduced I^2 from 98% to 0%.

3.1.3 Meta-Analysis of Preventive Studies

To determine whether sacubitril/valsartan could prevent cardiac dysfunction in breast cancer patients during chemotherapy, we performed a meta-analysis of 3 randomized controlled trials ($n = 260$). All included patients had normal baseline cardiac function. The primary outcomes were LVEF and the incidence of CTRCD. Compared with the control group, the sacubitril/valsartan group showed improved LVEF (MD = 1.30%, 95% CI 0.04–2.56, $P = 0.04$, $I^2 = 0\%$) (Fig. 2c) and a decreased incidence of CTRCD (RR = 0.11, 95% CI 0.01–0.93, $P = 0.04$) (Fig. 2d).

Forest plot of (a) change in LVEF from baseline to follow-up in therapeutic studies. (b) Change in NT-proBNP from baseline to follow-up in therapeutic studies. (c) Difference in LVEF between sacubitril/valsartan and control groups in preventive studies. (d) Risk of CTRCD events between the sacubitril/valsartan and control groups in preventive studies.

3.2 Acquisition and functional enrichment of candidate targets

A total of 8,042 disease targets related to breast cancer therapy-related cardiac dysfunction (CTRCD) were obtained from the GeneCards and OMIM databases. A total of 171 drug targets were predicted for sacubitril/valsartan (molecular structure shown in Fig. 3a) through SwissTargetPrediction. The intersection of disease targets and drug targets yielded 141 candidate targets. (Fig. 3b).

To elucidate the biological processes and signalling pathways involving these candidate targets, KEGG pathway enrichment and GO functional annotation were performed on the 141 targets. KEGG pathway enrichment analysis showed that the candidate targets were mainly enriched in the PI3K-Akt signalling pathway, PPAR signalling pathway, insulin resistance, and atherosclerosis (Fig. 3c). GO analysis revealed that in the biological process (BP) category, the candidate targets were significantly enriched in lipid transport and localization, regulation of inflammatory response, fatty acid metabolic process, and eicosanoid biosynthetic process; in the cellular component (CC) category, they were mainly enriched in focal adhesion, cell-substrate junction, vesicle lumen, and protein kinase complex; and in the molecular function (MF) category, they were enriched in endopeptidase activity, serine-type peptidase activity, nuclear receptor activity, and hormone binding (Fig. 3d).

(a) Chemical structures of sacubitril and valsartan. (b) Venn diagram showing 141 overlapping candidate targets between sacubitril/valsartan and CTRCD. (c) Top 10 enriched KEGG pathways. (d) Top 10 enriched terms for biological process (BP), cellular component (CC), and molecular function (MF) among candidate targets.

3.3 Differential expression analysis and construction of candidate targets

Microarray dataset GSE40447 (anthracycline-treated) and RNA-seq dataset GSE264120 (trastuzumab-treated) were obtained from the GEO database. Differentially expressed genes (DEGs) were identified with thresholds of $|\log_2FC| > 1$ and $P < 0.05$ in each dataset (Fig. 4a). The DEGs from each dataset were then intersected with the 141 candidate targets obtained in Section 3.2. This yielded 13 overlapping targets in the anthracycline-treated group and 10 overlapping targets in the trastuzumab-treated group.

3.4 Machine learning identifies core therapeutic targets

To further identify core therapeutic targets, we applied LASSO regression and SVM-RFE. In the anthracycline-induced cardiotoxicity dataset, LASSO regression identified 4 potential features, while SVM-RFE identified 12 features; the intersection of the two algorithms yielded 4 core therapeutic targets, namely, PIK3CG, KEAP1, RXRA, and KLKB1. Similarly, in the trastuzumab-related cardiotoxicity dataset, LASSO and SVM-RFE identified 5 and 5 features, respectively, and their intersection finally determined 5 core therapeutic targets, namely, PLAUR, TBXA2R, TSPO, PDE3A, and ICAM1 (Fig. 4b–d).

To evaluate the diagnostic performance of these core therapeutic targets, we constructed a logistic regression model using GSE243674 as the validation set. The model was built based on the above targets and tested in the independent validation set GSE243674, with the area under the curve (AUC) reaching 0.736 for the anthracycline group and 0.885 for the trastuzumab group (Fig. 4e).

- (a) Volcano plot displaying the DEGs in the anthracycline and trastuzumab datasets. (b) Results of LASSO regression in groups A and T; the optimal λ corresponds to 4 and 5 genes. (c) SVM results, which reached maximum accuracy with 12 and 5 genes. (d) Venn diagrams showing the intersection of LASSO and SVM results, yielding 4 core therapeutic targets (PIK3CG, KEAP1, RXRA, KLKB1) in the anthracycline group and 5 core therapeutic targets (PLAUR, TBXA2R, TSPO, PDE3A, ICAM1) in the trastuzumab group. (e) ROC curves of the logistic regression models in the external validation set (GSE243674), showing AUCs of 0.736 (A) and 0.885 (T).
- (A) and (T) below denote the anthracycline and trastuzumab groups, respectively.

3.5 Mendelian Randomization Analysis

To genetically evaluate the potential causal relationship between the 9 core therapeutic targets and CTRCD, two-sample Mendelian randomization was performed using heart failure (HF) as the outcome. Summary-level GWAS data for the outcome were obtained from the IEU OpenGWAS database (GWAS ID: ebi-a-GCST009541), comprising 47,309 cases and 930,014 controls with a total of 7,773,021 single nucleotide polymorphisms (SNPs). The results showed that among the 9 core therapeutic targets, genetically predicted expression levels of PIK3CG and KEAP1 were significantly causally associated with HF risk (PIK3CG: OR = 0.88, 95% CI: 0.81–0.97, $P = 0.006$; KEAP1: OR = 1.12, 95% CI: 1.01–1.24, $P = 0.028$). The MR-Egger intercept P -value and Cochran's Q test P -value were both > 0.05 , indicating no significant horizontal pleiotropy or heterogeneity, supporting the robustness of the causal inference (Fig. 5).

Forest plot showing the causal associations between genetically predicted expression levels of nine core therapeutic targets (ICAM1, KEAP1, KLKB1, PDE3A, PIK3CG, PLAUR, RXRA, TBXA2R, and TSPO) and the risk of heart failure. The inverse variance weighted method was used as the primary causal estimate, with MR-Egger, weighted median, simple mode, and weighted mode as complementary methods.

3.6 Molecular docking validation

To validate the potential interactions between sacubitril/valsartan and the core therapeutic targets, molecular docking was performed to simulate the binding modes of its two active components, sacubitril and valsartan, with the proteins encoded by the 9 core therapeutic targets. The docking results showed that the binding energies of sacubitril and valsartan with each of the nine target proteins were all below -5.0 kcal/mol, indicating strong binding affinities (Fig. 6a). The binding poses of sacubitril and valsartan with KEAP1 and PIK3CG, respectively, were visualized in PyMOL 3.0 (Fig. 6b–e).

(a) Heatmap of molecular docking between sacubitril/valsartan and core therapeutic targets. All targets had a total binding energy lower than -5.0 kcal/mol.
(b–e) Docking poses of sacubitril/valsartan with KEAP1 and PIK3CG.

4 Discussion

This is the first study that integrates pooled clinical evidence with molecular target prediction specifically in the breast cancer population. Our findings are as follows: (1) Meta-analysis preliminarily indicated that sacubitril/valsartan was associated with improved cardiac function in both therapeutic and preventive settings; (2) machine learning identified 9 core targets from 141 candidate targets, and Mendelian randomization further suggested PIK3CG and KEAP1 as potential core therapeutic targets; and (3) molecular docking suggested favourable binding potential between the active components of sacubitril/valsartan and the above targets.

In patients with established CTRCD, sacubitril/valsartan treatment was associated with an improvement in LVEF from baseline (MD = 5.27%) and a reduction in NT-proBNP levels (MD = -2323.96 pg/mL), suggesting its potential therapeutic value in those with existing cardiac dysfunction. Previous systematic reviews and cohort studies across pan-cancer populations have reported similar findings. Compared with the approximately 7.3% LVEF improvement reported by Hüntermann et al. [26] and the 7.9% improvement in the single-arm study by Martín-García et al. [27], the pooled effect size in our study was slightly lower. This discrepancy may be attributable to the focus on breast cancer patients and differences in follow-up duration. Further validation through large-scale randomized controlled trials is warranted to confirm its definitive efficacy.

In breast cancer patients with normal baseline cardiac function, the sacubitril/valsartan group showed a statistically significant improvement in LVEF compared with the control group (MD = 1.3%). In the context of preventive intervention, this effect size was similar to the improvement (MD = 1.5%) reported in a previous meta-analysis of ACEIs/ARBs for primary prevention [28]. Sacubitril/valsartan was associated with a reduced risk of CTRCD (RR = 0.11), which differs from previous meta-analyses of ACEI/ARB and beta-blockers that failed to show a significant reduction in CTRCD incidence [29, 30]. These findings suggest that sacubitril/valsartan may offer superior cardioprotective effects, a hypothesis that warrants confirmation in larger prospective studies.

The above clinical evidence suggests that sacubitril/valsartan exerts cardioprotective effects in breast cancer CTRCD, but its molecular basis remains unclear. To address this, we obtained candidate targets through network pharmacology, followed by differential expression analysis using GEO datasets. After intersection, two machine learning algorithms (LASSO and SVM-RFE) were applied, yielding 4 core therapeutic targets (PIK3CG, KEAP1, RXRA, and KLKB1) in the anthracycline group and 5 core therapeutic targets (PLAUR, TBXA2R, TSPO, PDE3A, and ICAM1) in the trastuzumab group. Further two-sample MR analysis revealed causal associations between genetically predicted expression levels of PIK3CG and KEAP1 and heart failure risk. PIK3CG is involved in regulating the PI3K/AKT pathway, which can significantly attenuate anthracycline-induced myocardial injury and dysfunction [31, 32] and further activate the MAPK signalling pathway, consistent with previous findings [9, 33]. Multiple studies have shown that pharmacological agents or interventions can improve anthracycline-induced cardiac dysfunction through modulation of the KEAP1-NRF2 signalling pathway, providing evidence for KEAP1 as a potential target of sacubitril/valsartan [34–37]. Notably, in addition to the two targets validated by MR, some of the other screened targets also have literature support for their potential association with CTRCD. RXRA has been identified as a therapeutic target for anthracycline-induced cardiotoxicity, and its activation exerts cardioprotective effects through restoration of endothelial cell barrier function [38]. Trastuzumab can promote ICAM-1 expression via TLR4-mediated inflammatory pathways, and inhibition of this pathway attenuates cardiac dysfunction and reduces ICAM-1 levels [39]. Furthermore, TSPO and PDE3A were identified as core feature targets in the trastuzumab group. Previous studies have suggested their potential protective roles in anthracycline-induced cardiotoxicity [40–42]; however, their roles in trastuzumab-related cardiotoxicity remain unclear and warrant further investigation.

We performed molecular docking of sacubitril/valsartan with the above 9 core therapeutic target proteins. The binding affinities ranged from -5.7 to -10.0 kcal/mol, all below the conventional threshold of -5.0 kcal/mol, indicating favourable binding potential between most targets and the components of sacubitril/valsartan. Notably, previous studies have suggested that sacubitril/valsartan can regulate the PI3K/AKT pathway [43], activate the NRF2 signalling pathway through downregulation of KEAP1 expression [44], and reduce ICAM-1 expression [37]. The binding potential for the remaining targets warrants further functional validation.

Several limitations should be acknowledged in this study. The included therapeutic studies were all single-arm pre-post designs without concurrent controls, and the pooled results should be interpreted with caution. The limited number of eligible studies and the relatively small overall sample size may have compromised the stability of the effect estimates. The mechanistic findings were derived from computational predictions and lack experimental validation, which cannot substitute for empirical evidence. Of note, several related randomized controlled trials are currently underway [45], and our conclusions remain to be further validated by these ongoing large-scale trials.

5 Conclusions

This is the first study to integrate systematic review, meta-analysis, and multiple computational approaches to evaluate the role of sacubitril/valsartan in breast cancer therapy-related cardiac dysfunction. Our findings preliminarily suggested improvements in cardiac function in both therapeutic and preventive settings and identified PIK3CG and KEAP1 as potential core therapeutic targets. These findings provide exploratory evidence for the application of sacubitril/valsartan in breast cancer CTRCD. However, given the limited sample size in the meta-analysis and the computational nature of the predictions, these conclusions require further experimental validation. Future basic research and large-scale randomized controlled trials are warranted to confirm our findings.

Abbreviations

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; CTRCD, cancer therapy-related cardiac dysfunction; DEGs, differentially expressed genes.

Declarations

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Declaration of Competing Interest

The authors declare no competing interests.

Data availability

All data used in this study were derived from publicly available databases. No new data were generated. Analysis scripts are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

RZ: Conceptualization, methodology, software, formal analysis, data curation, writing – original draft, visualization, writing – review & editing. **QL:** Validation, Formal analysis, Data curation, Writing – review & editing. **HH:** Investigation, Resources, Data curation, Writing – review & editing. **XC:** Investigation, Writing – review & editing.

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Figures

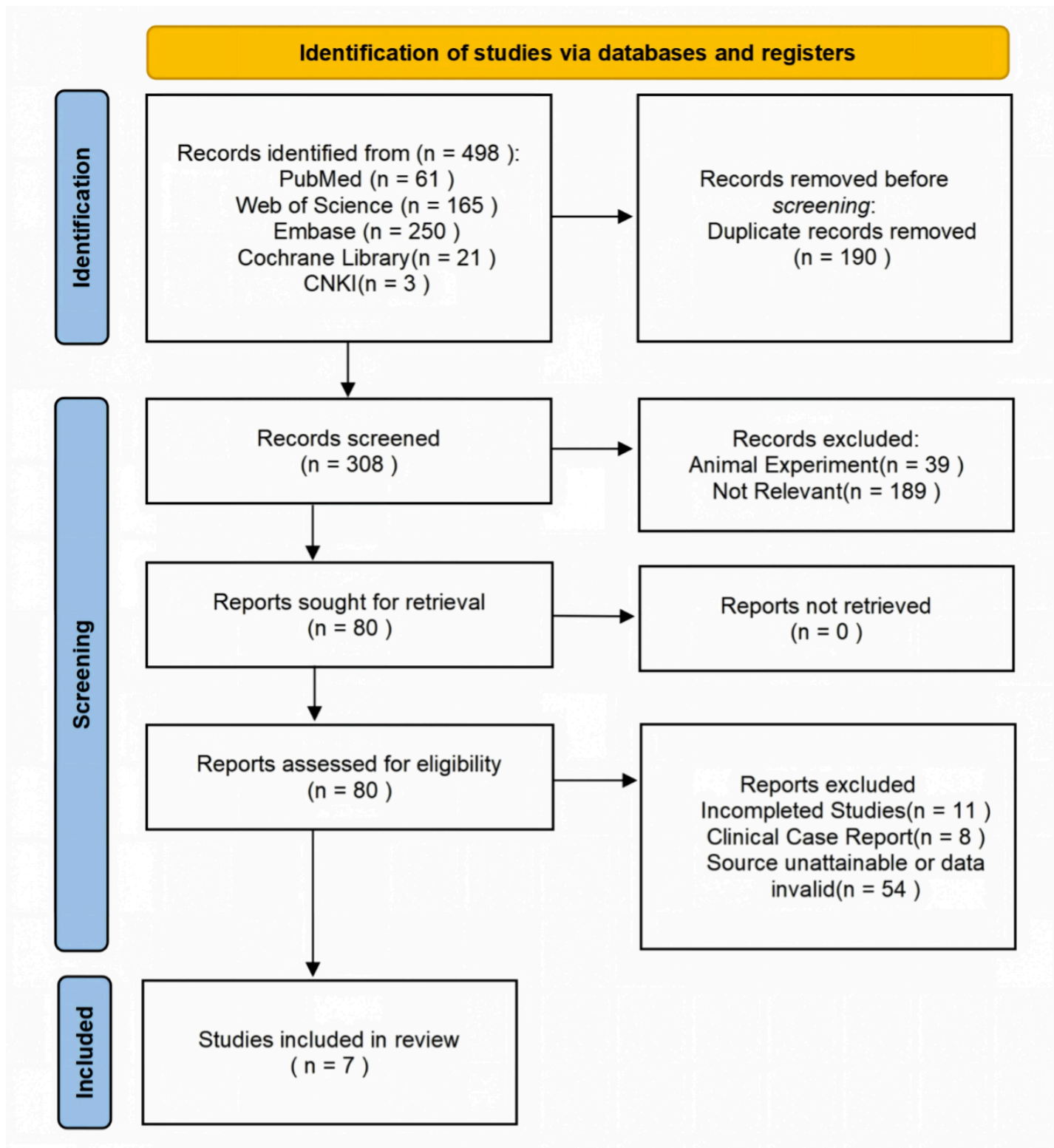


Figure 1

PRISMA flow chart of study selection.

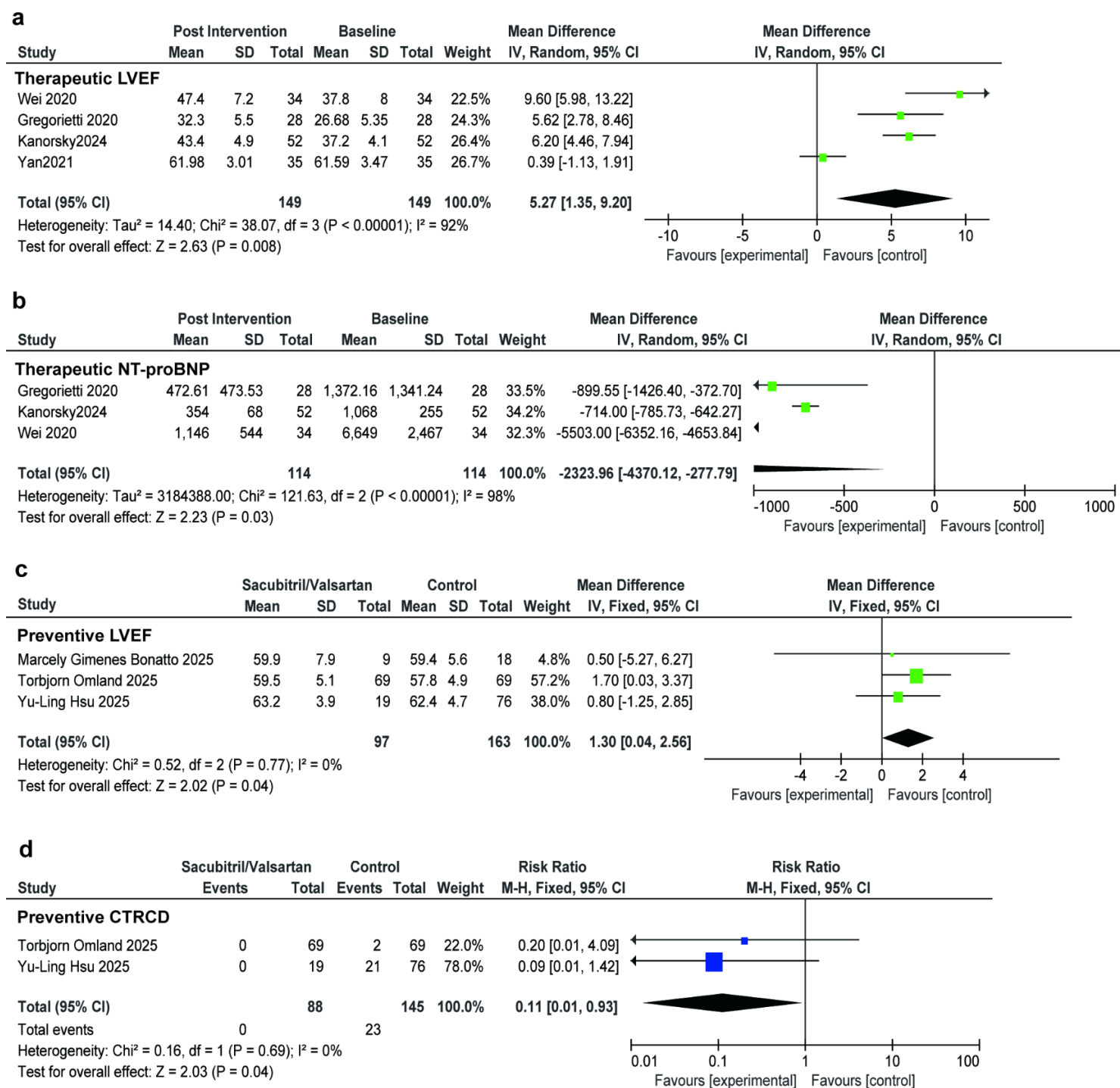
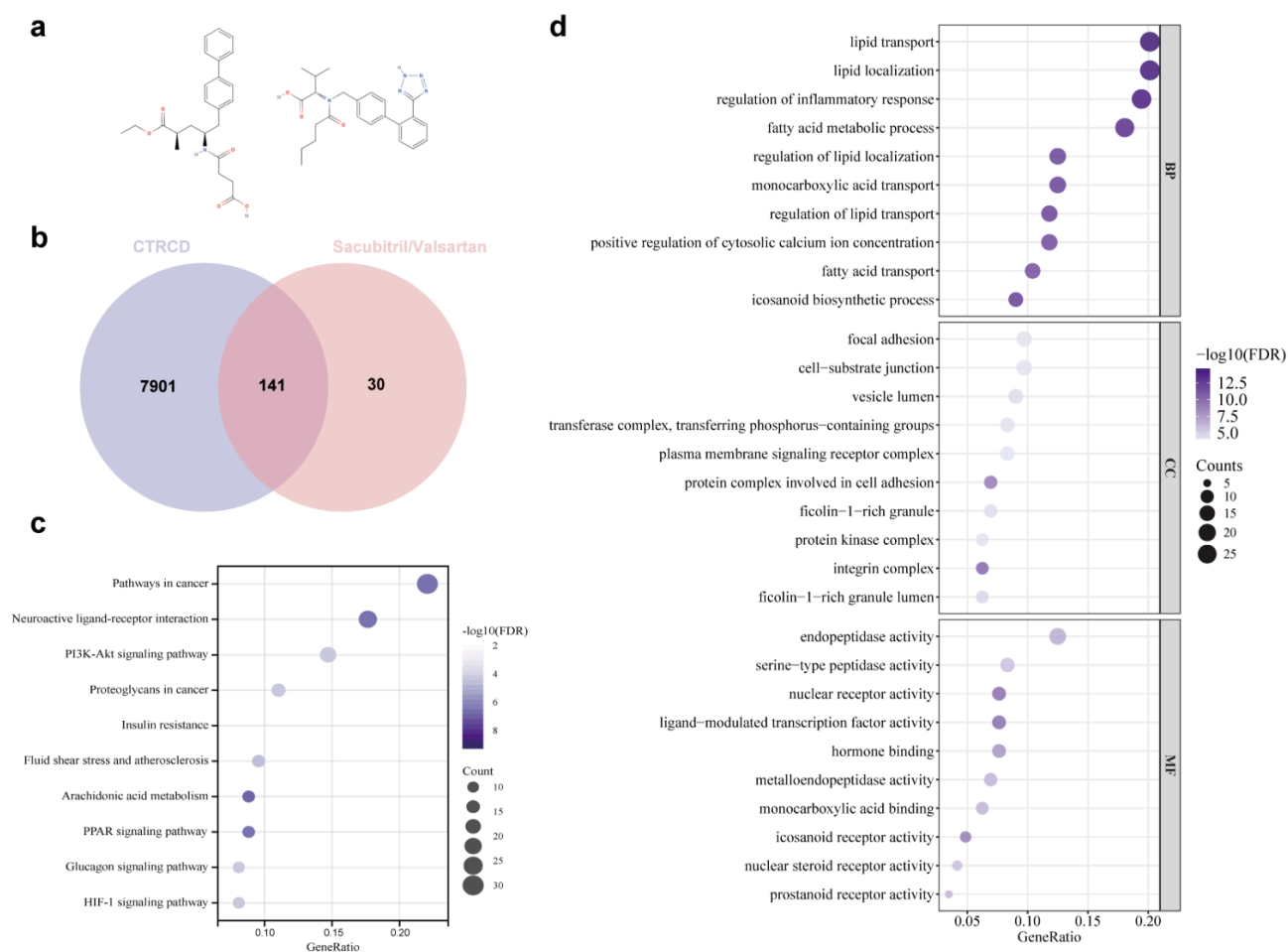


Figure 2

Meta-analysis results of sacubitril/valsartan for breast cancer-related CTRCD.



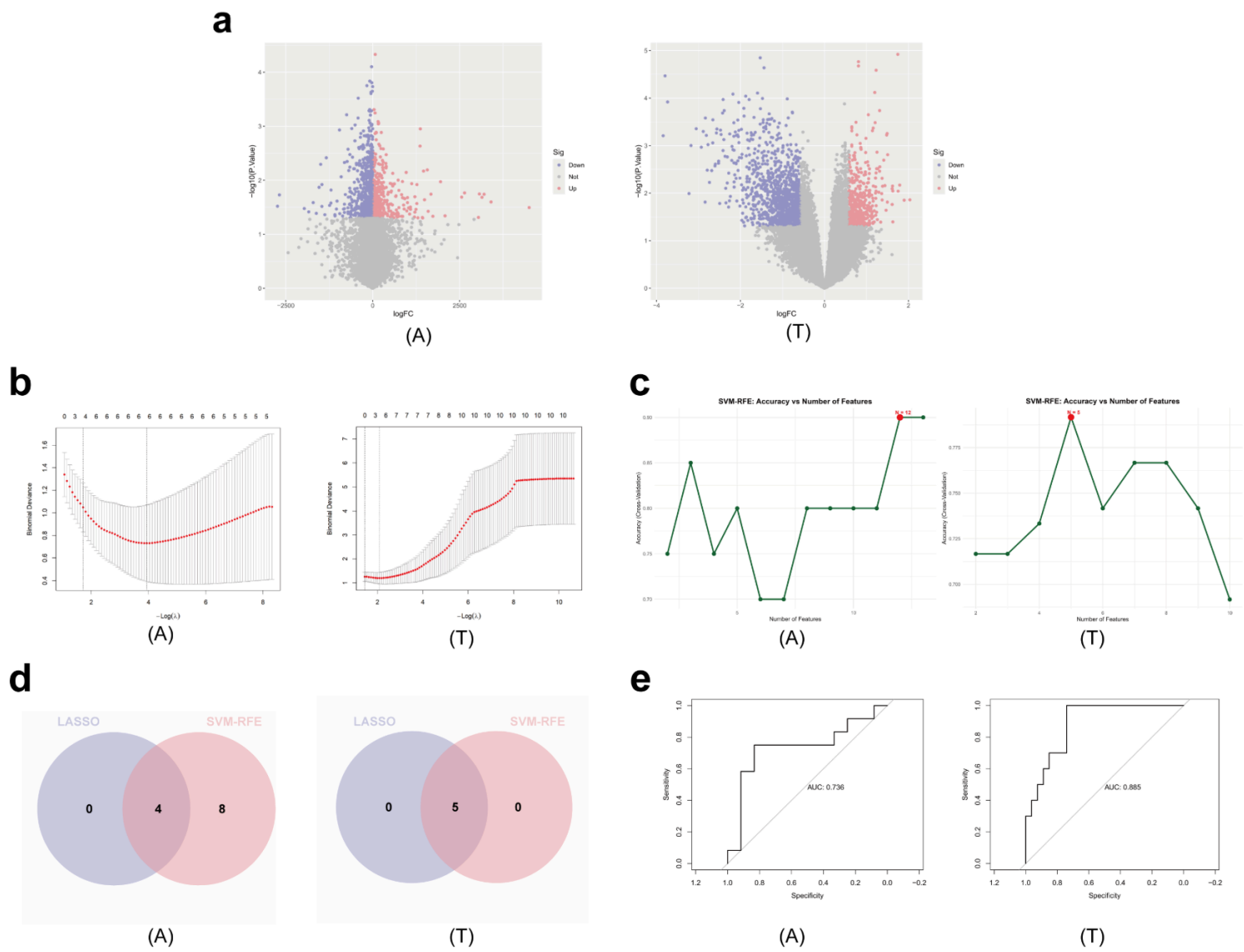


Figure 4

Differential expression analysis and machine learning identification of core therapeutic targets.

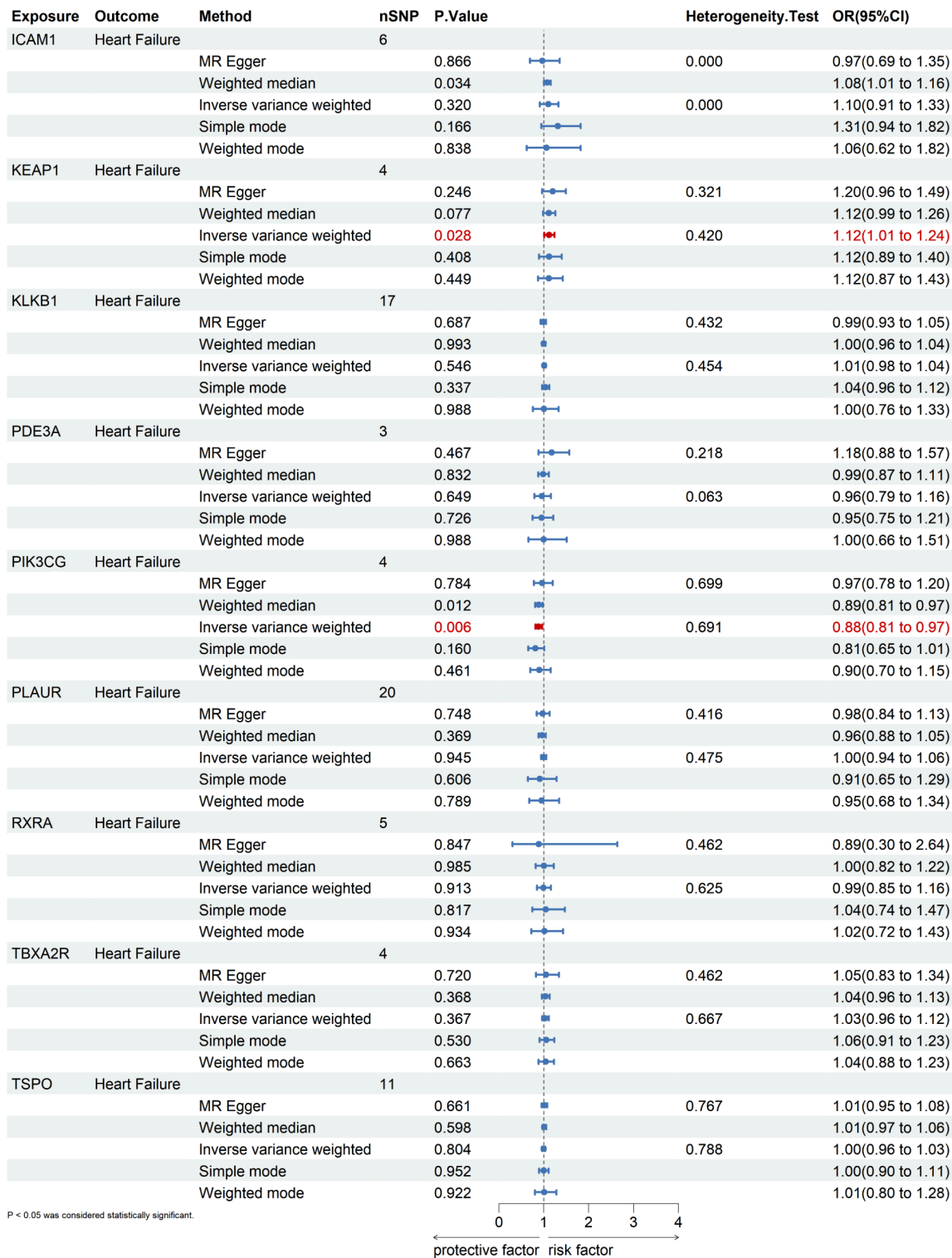


Figure 5

Mendelian randomization analysis

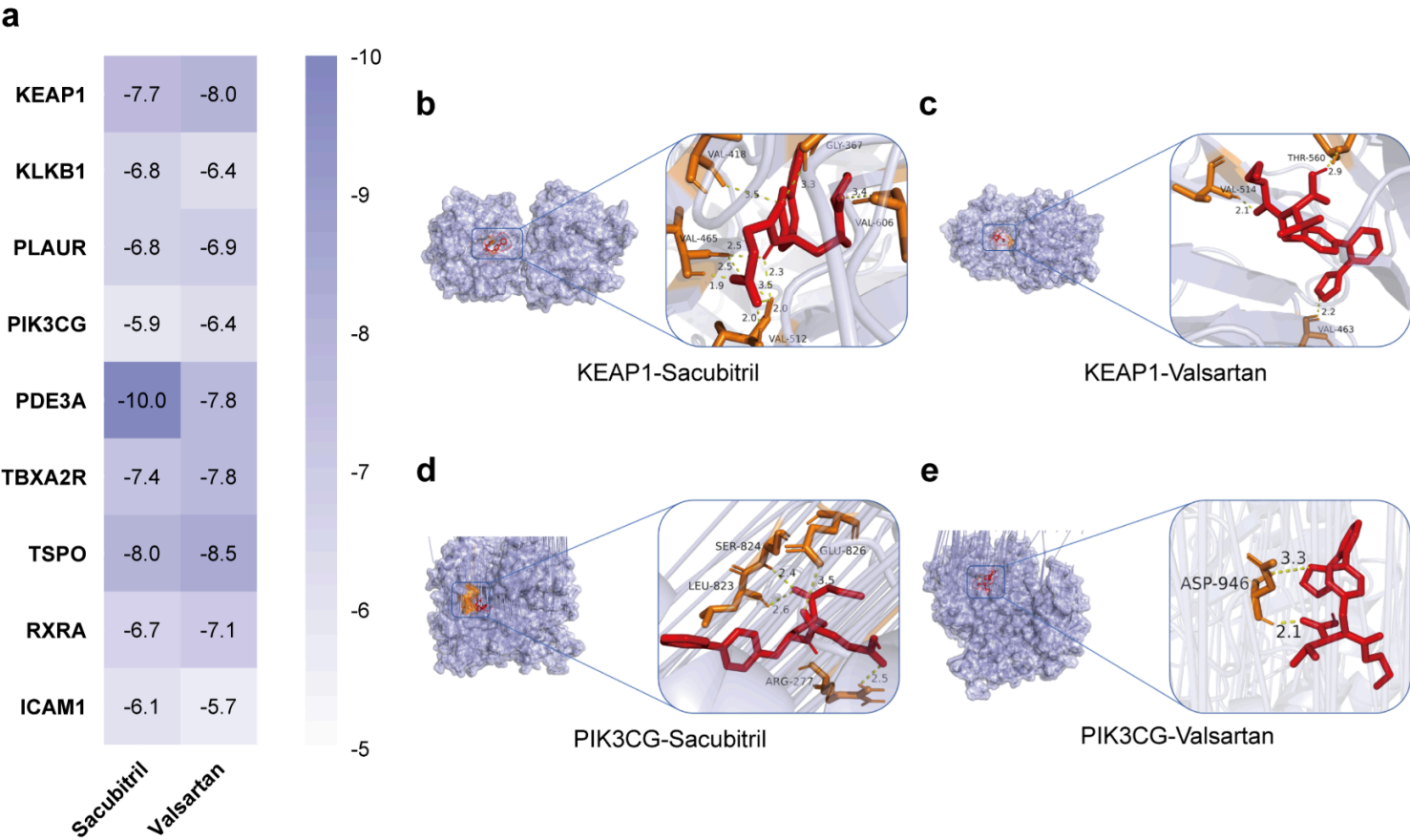


Figure 6

Molecular docking results of sacubitril/valsartan with core therapeutic targets.

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