Cardio-Oncology

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Prevention and treatment of anthracycline-induced cardiotoxicity: a systematic review and network meta-analysis of randomized controlled trials

Siyu Li[1†], Wenrui Li[1†], Mengfei Cheng[1], Xiaoxiao Wang[1*] and Wanyi Chen[1*]

Abstract

Background Anthracyclines are cornerstone chemotherapeutics, but cardiotoxicity limits their use.

Objective This study aims to evaluate the efficacy of various drugs in preventing and treating anthracycline-induced cardiotoxicity (AIC).

Methods We conducted an extensive search across seven databases to identify randomized controlled trials (RCTs) pertinent to the prevention and treatment of AIC with medications. Subsequently, a Bayesian Model-based network meta-analysis was performed in the R 4.4.0.

Results A total of 128 RCTs involving 10,431 cancer patients treated with anthracyclines and 78 drug regimens were included in this study. The network meta-analysis results showed that, compared with patients who did not receive cardioprotective drugs, those treated with Calcium Dibutyryladenosine Cyclophosphate (Mean Difference [95% Credible Interval], 8.760 [0.5917, 16.92]), Carvedilol (4.024 [0.5372, 7.656]), Carvedilol + Candesartan (7.934 [3.159, 12.91]), Compound Salvia Miltiorrhiza + Levocarnitine (9.087 [0.9160, 17.25]), Dexrazoxane (5.066 [2.589, 7.540]), Dexrazoxane + Cinobufacini (11.61 [4.590, 18.70]), Dexrazoxane + Shenqi Fuzheng (13.05 [4.640, 21.40]), Nicorandil (14.24 [5.122, 23.31]), Qiliqiangxin (11.38 [2.826, 19.91]), and Xinmai Long (6.371 [1.735, 11.02]) experienced less decrease in LVEF after chemotherapy. The SUCRA ranking results indicated that the most effective treatment option for preserving LVEF was Nicorandil (SUCRA 91.76%).

Conclusion Apart from Dexrazoxane, Carvedilol, a β-blocker, also appears to show significant potential in preventing AIC. Furthermore, our results indicate that there is insufficient evidence to support the beneficial effects of statins, Sildenafil, Ivabradine, Levocarnitine, N-acetylcysteine, Glutathione, Coenzyme Q10, Vitamin E, and Vitamin C in preventing LVEF decline and exerting a positive effect on the prevention of AIC.

Key messages

• Anthracyclines are cornerstone chemotherapeutics, but cardiotoxicity limits their use.

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- 128 RCTs/10,431 patients assess 78 drug regimens for AIC prevention/treatment in the network meta-analysis.
- Apart from Dexrazoxane, Carvedilol also appears to show significant potential in preventing AIC.
- Combining Dexrazoxane with certain Chinese patent medicines may enhance cardioprotection.
- Lack of valid evidence for ARBs, ACEIs, MRAs, statins, Sildenafil, etc., in AIC prevention.

Keywords Anthracyclines, Cardiotoxicity, Randomized controlled trials, Network meta-analysis, Systematic review

Introduction

Despite the continuous introduction of novel anti-tumor drugs, anthracyclines remain a cornerstone in various combination chemotherapy regimens due to their notable features such as broad anti-tumor spectrum, favorable clinical efficacy, and effectiveness against hypoxic cells. Anthracyclines are widely used in the treatment of cancers including breast cancer, lymphoma, and leukemia [1]. A dose-limiting and potentially fatal adverse effect of anthracyclines is cardiotoxicity, which can occur at any stage of chemotherapy and manifests primarily as arrhythmias, pericardial effusion, myocardial ischemia, cardiomyopathy, and heart failure [2, 3]. Studies have reported that 6% of patients experience clinically symptomatic cardiac injury and 18% suffer from subclinical cardiac toxicity after anthracycline treatment [4]. Severe cardiotoxicity can significantly impair patients' cardiac function and health-related quality of life, posing substantial limitations on the clinical use of these drugs [5].

Currently, it has been demonstrated that the concomitant use of Dexrazoxane can effectively mitigate anthracycline-induced cardiotoxicity (AIC) [6], and Dexrazoxane has been exclusively recommended by the U.S. Food and Drug Administration (FDA) as a first-line agent for preventing AIC. However, studies have suggested that Dexrazoxane may increase the risk of second primary malignancies in pediatric cancer patients [7–9]. Besides Dexrazoxane, recent studies have successively identified that statins [10, 11], β-blockers [12, 13], renin–angiotensin–aldosterone system (RAAS) inhibitors [14, 15] (including angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], and mineralocorticoid receptor antagonists [MRAs]), as well as some Chinese patent medicines [16], may play a positive role in the primary prevention of AIC.

To date, there has been a lack of large-scale randomized controlled trials (RCTs) conducting head-to-head comparisons of these different medications. This systematic review and network meta-analysis of RCTs aims to evaluate the currently reported drugs for the prevention and treatment of AIC, further update and integrate the latest evidence, and support clinical decision-making.

Method

This study is reported in accordance with the PRISMA statement for systematic reviews [17] and the PRISMA extension for network meta-analysis (PRISMA-NMA) [18], and has been successfully registered on PROSPERO (registration number CRD 42024552106). Patients and the public were not involved in the design, conduct, reporting, and dissemination plans of our study.

Eligibility criteria

We established the eligibility criteria for the literature based on the PICOS (Population, Intervention, Comparator, Outcome, Study design) principle.

Inclusion criteria

1. Population (P): Cancer patients who are receiving or anticipated to receive anthracycline-based chemotherapy;
2. Intervention (I): Chemical drugs or Chinese patent medicines used for the prevention or treatment of AIC;
3. Comparator (C): Placebo, no intervention, or active drugs;
4. Outcome (O): Indicators related to cardiac injury, such as left ventricular ejection fraction (LVEF), electrocardiogram, and myocardial enzymes. During medication or follow-up, the occurrence of arrhythmias (atrial fibrillation, premature beats, tachycardia, bradycardia), low QRS voltage, ST-T abnormalities, prolonged Q-T interval, and conduction blocks are defined as electrocardiographic abnormalities in patients. Additionally, patients who exhibit one of the following: ① LVEF abnormalities, myocardial enzyme abnormalities, or electrocardiographic abnormalities, accompanied by clinical manifestations of cardiac dysfunction such as shortness of breath, fatigue, and dyspnea; ② patients who experience AIC classified as Grade II or higher according to

the World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxicity of Cancer Treatment [19];
5. Study design (S): RCTs.

Exclusion criteria

1. Patients concurrently receiving or anticipating other potentially cardiotoxic agents;
2. Reviews or editorials;
3. Conference abstracts, letters, study proposals, etc., that do not report detailed treatments and outcomes information;
4. Duplicate publications;
5. The full text is unavailable;
6. Non-Chinese and non-English languages.

Search strategy and data sources

A comprehensive search was conducted in the Medline (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials, Web of Science, CNKI, WanFang Data, and VIP databases to collect RCTs on the prevention and treatment of AIC with medications. The search covered the period from the inception of each database up to June 2024. Besides, the reference lists of included studies and relevant reviews were traced as supplementary searches. The search strategies combined subject headings and free-text terms, and were adjusted slightly for each database. The search terms included: anthracycline, daunorubicin, doxorubicin, epirubicin, pirarubicin, aclarubicin, idarubicin, valrubicin, mitoxantrone; cardiotoxicity, arrhythmia, myocardial ischemia, cardiomyopathy, cardiac failure, heart failure, adverse cardiac event, adverse cardiac reaction, adverse cardiac effect; treatment, prevention, management, etc. No language restrictions were applied during the search process. The detailed search strategy is provided in the Supplementary file 1.

Study selection

Before formally screening eligible studies, a preliminary test of the selection process was conducted. Two researchers independently selected potentially eligible studies based on the titles and abstracts, and then confirmed the final inclusion through full-text articles. Inconsistencies were resolved through negotiation between the two researchers or determined by a third one.

Data extraction

Two trained researchers independently extracted data using a standardized form and cross-checked the extracted data. Any disputes were resolved through discussion between the two researchers or determined by a third one. The extracted data included: ① basic information of the literature (first author, title, publication year, etc.); ② study design (study setting, follow-up duration, etc.); ③ basic characteristics of patients (age, gender, cancer type, chemotherapy regimens, etc.); ④ treatments (drug name, dosage form, administration regimen, etc.); ⑤ outcome data (LVEF, electrocardiogram, and other indicators related to cardiac function). This study prioritized the intention-to-treat (ITT) results or adjusted ITT results reported in the studies over per-protocol analysis results. For studies with non-combinable different dose groups of the same treatment, the results of the highest dose data were extracted. For studies with two or more follow-up time points, the results of the longest follow-up time point data were extracted.

Bias risk assessment

Two researchers independently assessed the risk of bias in the studies using the Cochrane Risk of Bias Tool 2.0 (ROB 2.0) [20]. The ROB 2.0 provides a series of signaling questions (with answer options of "yes," "probably yes," "probably no," "no," and "no information") to help assess the risk of bias in the following six domains:"bias arising from the randomization process," "bias due to deviations from intended interventions," "bias due to missing outcome data," "blinding of outcome assessment," and "bias in selection of the reported result"(with risk levels of low, some concerns, and high). The overall risk of bias in the RCTs was assessed with reference to the Cochrane Handbook [20]. A trial was considered to have a low overall risk of bias when all domains were judged as low risk, and a high overall risk of bias when the trial was judged to be at high risk of bias in at least one domain (Table 1).

Data synthesis and statistical analysis

This study conducted a network meta-analysis using a random-effects model within a Bayesian framework. Each node represented a treatment, with the placebo/no treatment group serving as the common control group. For dichotomous outcomes, the odds ratio (OR) and corresponding 95% credible interval (95% CrI) were used to summarize the effects of different treatments. For continuous outcomes, the mean difference (MD) and corresponding 95% CrI were used. A two-sided p-value < 0.05 was considered statistically significant. Besides, for treatment groups using multiple drugs, this study regarded them as a combined regimen and created separate nodes.

The gemtc and ggplot2 packages in R version 4.4.0 were used for network meta-analysis and plotting graphs. In the network relationship graph, the size of nodes represented the number of patients, and the

Table 1 Overall risk of bias

Low risk of bias	Some concerns	High risk of bias
The trial is judged to be at low risk of bias for all domains for this result	The trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain	The trial is judged to be at high risk of bias in at least one domain for this result Or The trial is judged to have some concerns for all domains in a way that substantially lowers confidence in the result

width of each line indicated the number of direct comparisons studies between the two treatments. Based on the ranking probability matrix table generated by the R, cumulative ranking probability curves were plotted, and the surface under the cumulative ranking curve (SUCRA) was calculated. A higher SUCRA value generally indicated a higher-ranking probability for the treatment.

Furthermore, our study conducted sensitivity analyses using different methods (fixed-effects and random-effects models) for combining effect sizes to assess the stability of the results, and we evaluated the agreement of direct and indirect evidence in the studied treatment networks using node-splitting analysis.

Results

Literature search and screening

A total of 6338 articles were searched from various databases, and 5 articles were obtained from reviews and the reference lists of included studies. After removing

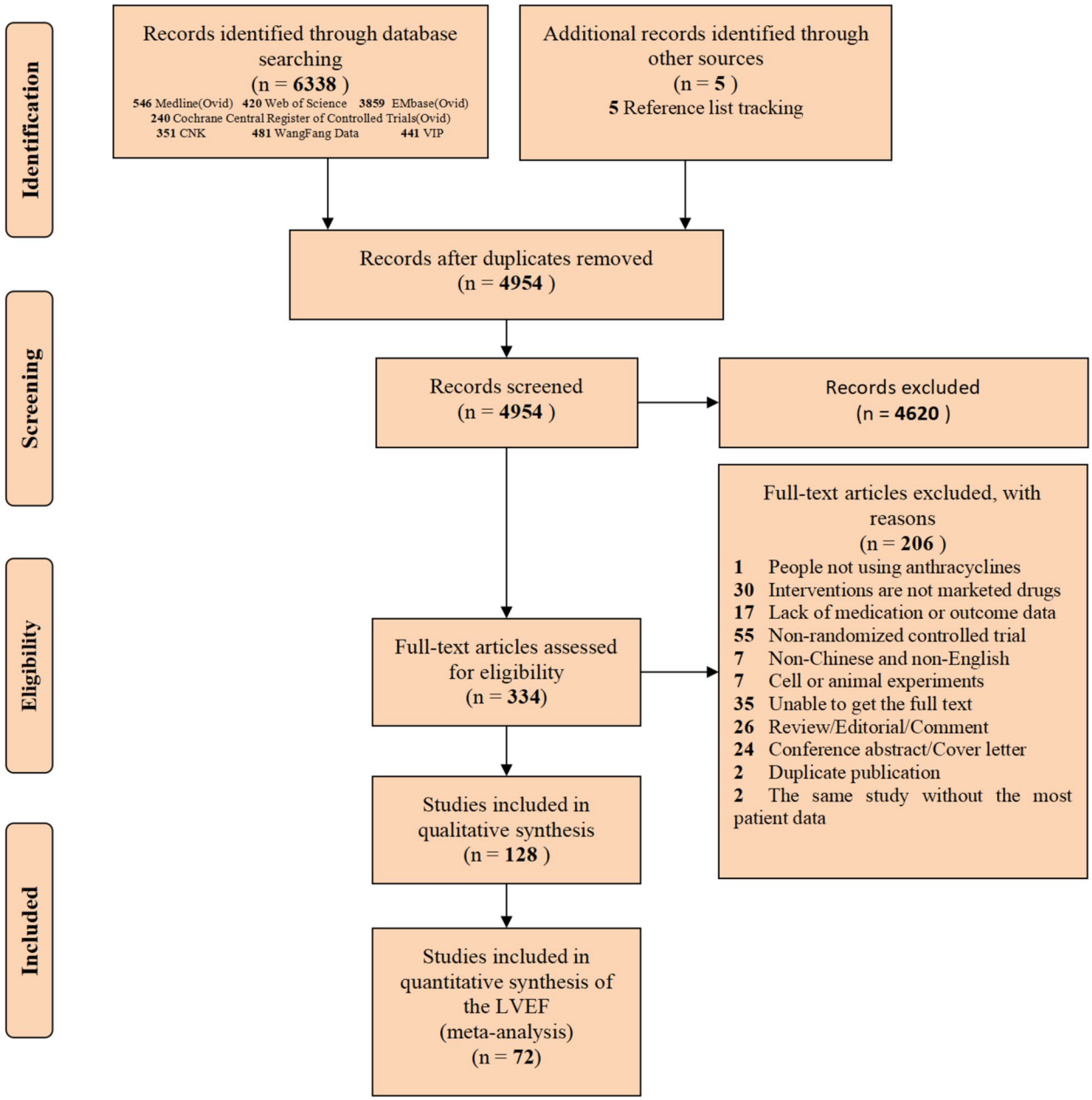


Fig. 1 Research screening process

duplicates, 4954 articles were initially screened by browsing the titles and abstracts. Excluding 4620 irrelevant articles, 334 articles underwent full-text screening, ultimately resulting in the inclusion of 128 studies [10, 21–147] with 10,431 patients (Fig. 1).

Characteristics of studies

The 128 RCTs, published between 1996 and 2024, reported 78 drug regimens (41 chemical drugs, 10 combined chemical and Chinese patent medicines, and 27 Chinese patent medicines). In these RCTs, 3841 patients were randomly assigned to the placebo or no treatment group, while 6590 patients were randomly assigned to cardioprotective drug groups. Only 9 RCTs (7.0%) recruited patients aged ≤ 18 years, and the average age of patients in over half of the studies was between 40 and 60 years. The duration of follow-up ranged from 1 day to 5 years, with a median follow-up time of 4 to 6 months in most studies. In terms of the types of anthracyclines used, 50 RCTs (39.1%) involved doxorubicin, and 29 studies (22.7%) involved epirubicin. The top five countries with the highest number of studies were China (104 RCTs, 81.3%), Iran (3 RCTs, 2.3%), Canada (2 RCTs, 1.6%), Korea (2 RCTs, 1.6%), and Turkey (2 studies, 1.6%) (Supplementary file 2).

Risk of bias assessment

Twelve RCTs (9.4%) were assessed as high risk of bias, 108 RCTs (84.4%) were considered as having "some concerns", and 8 RCTs (6.3%) were assessed as low risk of bias. In the domain of "bias arising from the randomization process", 10 RCTs (7.8%) were assessed as high risk, 48 RCTs (37.5%) were assessed as low risk, and 70 RCTs (54.7%) were deemed to have "some concerns" due to inadequate reporting of the randomization process and lack of details on allocation concealment. In the domain of "bias due to deviations from intended interventions," most studies were assessed as having "some concerns"(114 RCTs [89.1%]). Regarding "blinding of outcome assessment", 23 RCTs (18.0%) were assessed as low risk, while 105 RCTs (82.0%) were considered as having "some concerns" due to insufficient reporting of relevant information. For "bias in selection of the reported result" and "bias due to missing outcome data", 123 RCTs (96.1%) and 125 RCTs (97.7%), respectively, were assessed as low risk of bias (Supplementary file 3).

Prevention of anthracycline-induced cardiotoxicity

Assessments of heterogeneity and consistency for all outcomes are reported in the Supplementary file 4.

Left ventricular ejection fraction

Seventy-two RCTs [10, 21–31, 33–41, 45–49, 51–54, 57–59, 61–64, 67, 68, 71, 75, 76, 80, 85, 86, 88, 89, 93, 95–98, 101, 104, 111, 112, 118–120, 123, 127–131, 133, 134, 136, 139, 140, 144, 146] reporting LVEF were included in the network meta-analysis. These studies reported 46 drug regimens (25 chemical drugs, 4 combined chemical and Chinese patent medicines, and 17 Chinese patent medicines) and involved 5928 patients using anthracyclines (2346 patients were randomly assigned to the placebo or no treatment group, while 3582 patients were randomly assigned to the cardioprotective drug groups).

All treatments, except for Shenmai, Safflower, Glucose-Insulin-Potassium (GIK), Dexrazoxane (DEX) + Shenqi Fuzheng, Shengmai, Vitamin C, and Coenzyme Q10 + Vitamin E, had at least one placebo-controlled trial or no-treatment control trial (Fig. 2).

In terms of preventing LVEF decline after anthracyclines use, the following treatments were more effective than placebo/no treatment: Calcium Dibutyryladenosine Cyclophosphate (Mean Difference [95% CrI], 8.760 [0.5917, 16.92]), Carvedilol (4.024 [0.5372, 7.656]), Carvedilol + Candesartan (7.934 [3.159, 12.91]), Compound Salvia Miltiorrhiza + Levocarnitine (9.087 [0.9160, 17.25]), DEX (5.066 [2.589, 7.540]), DEX + Cinobufacini (11.61 [4.590, 18.70]), DEX + Shenqi Fuzheng (13.05 [4.640, 21.40]), Nicorandil (14.24 [5.122, 23.31]), Qiliqiangxin (11.38 [2.826, 19.91]), and Xinmai Long (6.371 [1.735, 11.02]) (Fig. 3).

Based on the cumulative probability plot and SUCRA rankings, the highest-ranked treatment is Nicorandil (SUCRA, 91.76%), followed by DEX + Shenqi Fuzheng (90.05%), and DEX + Cinobufacini (87.54%). The complete cumulative probability plot and SUCRA are provided in the Supplementary file 6.

Electrocardiographic abnormalities

A total of 70 RCTs [25, 29, 33, 39, 47, 49–51, 53–57, 62, 64, 66–69, 71, 73, 75, 77–81, 83, 85, 88, 89, 91, 93, 95, 97–101, 103, 105, 106, 111–117, 119, 123–134, 136, 137, 139–141, 144, 145, 147] reporting ECG abnormalities in patients were included in the network meta-analysis. These studies evaluated 43 drug regimens (21 chemical drugs, 6 combined chemical and Chinese patent medicines, and 16 Chinese patent medicines) involving 5,504 patients who received anthracyclines (2,061 patients were randomly assigned to the placebo or no treatment group, while 3,443 patients were randomly assigned to the cardioprotective drug groups. See Supplementary file 5 for the network relationship figure).

A total of 28 treatments were found to be more effective than placebo/no treatment in preventing ECG abnormalities following anthracyclines use, except for the

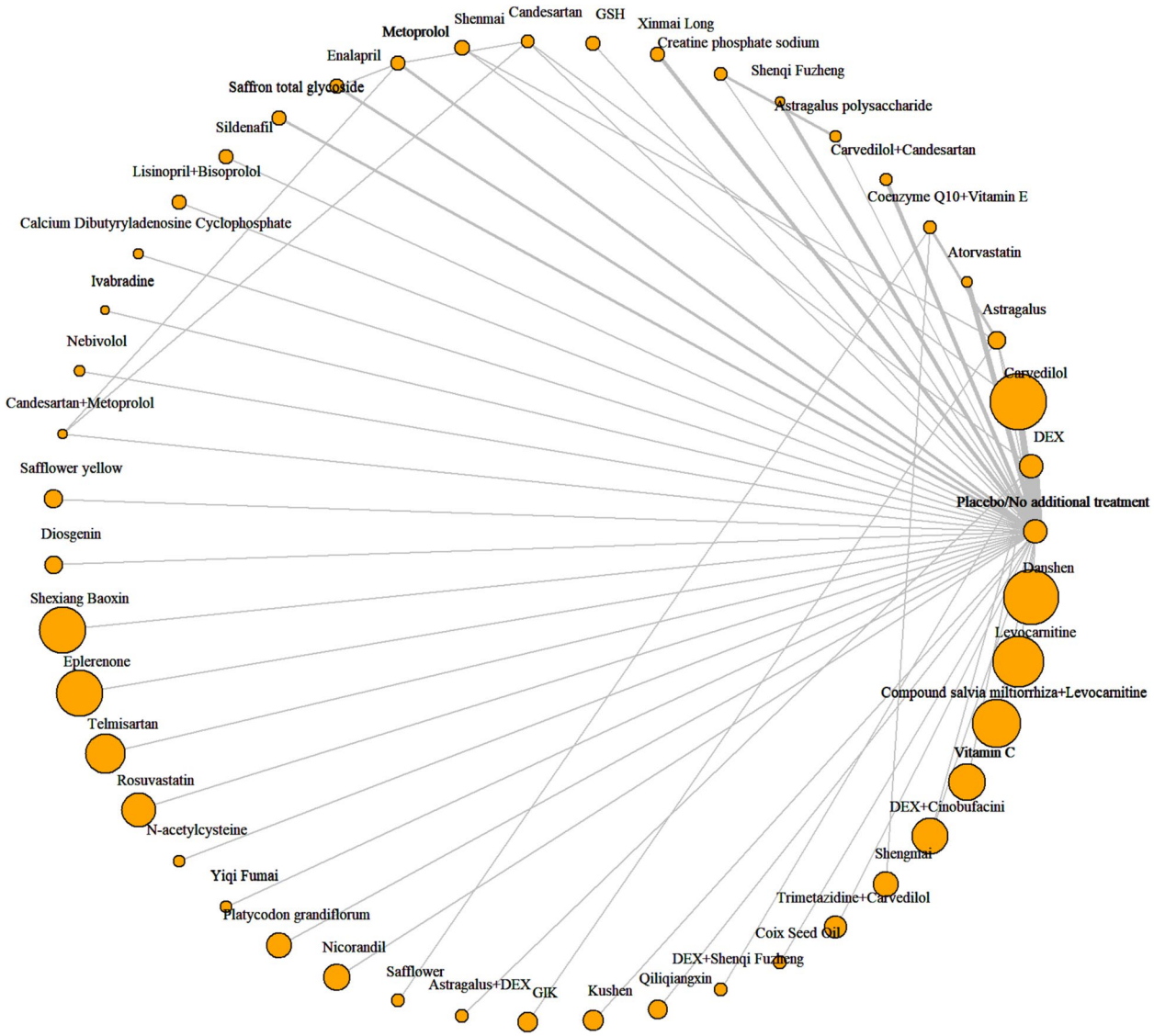


Fig. 2 Network of LVEF. Note: DEX: Dexrazoxane; GSH: Reduced glutathione; GIK: Glucose-insulin-potassium. Astragalus, Astragalus polysaccharide, Coix Seed Oil, Compound salvia miltiorrhiza, Cinobufacini, Danshen, Diosgenin, Kushen, Platycodon grandiflorum, Qiliqiangxin, Safflower, Safflower yellow, Saffron total glycoside, Shengmai, Shenmai, Shenqi Fuzheng, Shexiang Baoxin, Xinmai Long, and Yiqi Fumai are Chinesel Patent Medicines, and most are injections (Diosgenin, Platycodon grandiflorum, Qiliqiangxin, Saffron total glycoside, and Shexiang Baoxin are solid oral dosage forms, including tablets, pills, capsules, and granules)

following: Adenosine Disodium Triphosphate + Coenzyme A (Odds Ratio [95% CrI], 0.6216 [0.0735, 4.730]), Coenzyme Q10 + Vitamin E (0.9552 [0.3413, 2.767]), Enalapril (0.4730 [0.2007, 1.105]), Kushen (0.2572 [0.05848, 1.078]), Metoprolol (0.3931 [0.1243, 1.187]), Platycodon grandiflorum (0.2918 [0.06359, 1.178]), GIK (2.344 [0.7460, 8.061]), Glutathione (GSH) (0.9828 [0.1344, 7.294]), Safflower (0.2706 [0.04311, 1.592]), Shenmai + Compound salvia miltiorrhiza (1.238 [0.1647, 8.904]), Shuxuening (0.5920 [0.05993, 4.906]), Telmisartan (1.317 [0.2941, 5.889]), Trimetazidine + Shensong Yangxin (0.4483 [0.07287, 2.249]), Vitamin C (0.3398 [0.08822, 1.323]), and Vitamin C + Coenzyme Q10 + Vitamin E (0.06460 [0.002149, 1.750]) (Fig. 4).

Based on the cumulative probability plot and SUCRA rankings, the highest-ranked treatment is Potassium aspartate and magnesium aspartate injection (SUCRA, 98.56%), followed by Carvedilol (93.38%), Astragalus + DEX (88.64%), DEX + Shenmai (82.62%), Carvedilol + Candesartan (82.14%), DEX + Levocarnitine (78.94%), DEX + Cinobufacini (78.52%), Shengmai (74.93%), and Diosgenin (74.27%) (Supplementary file 6).

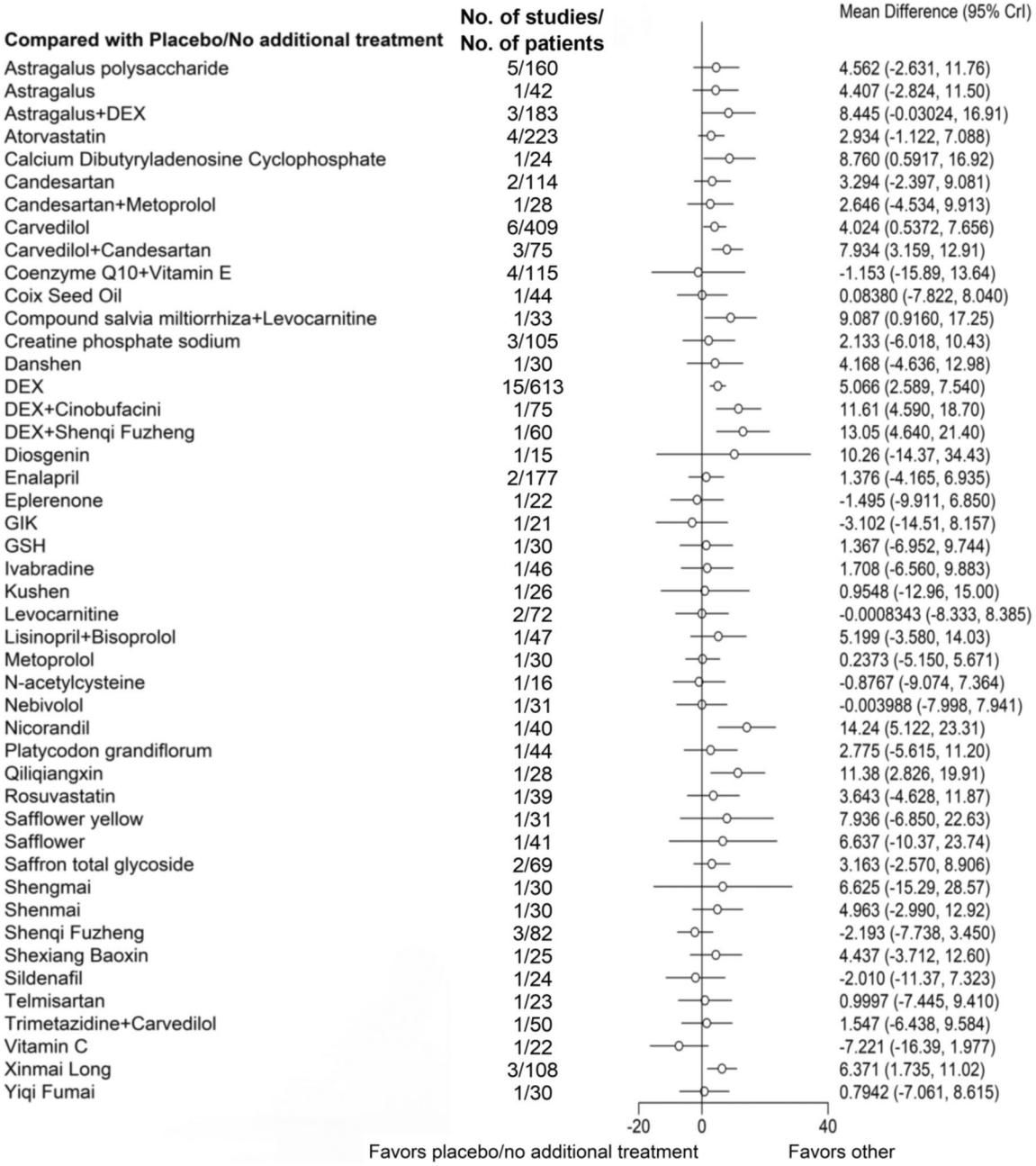


Fig. 3 Network forest plot of LVEF. Note: DEX: Dexrazoxane; GSH: Glutathione; GIK: Glucose-insulin-potassium. Astragalus, Astragalus polysaccharide, Coix Seed Oil, Compound salvia miltiorrhiza, Cinobufacini, Danshen, Diosgenin, Kushen, Platycodon grandiflorum, Qiliqiangxin, Safflower, Safflower yellow, Saffron total glycoside, Shengmai, Shenmai, Shenqi Fuzheng, Shexiang Baoxin, Xinmai Long, and Yiqi Fumai are Chinese Patent Medicines, and most are injections (Diosgenin, Platycodon grandiflorum, Qiliqiangxin, Saffron total glycoside, and Shexiang Baoxin are solid oral dosage forms, including tablets, pills, capsules, and granules)

Creatine Kinase-MB (CK-MB)

A total of 21 RCTs [40, 47, 48, 51, 52, 54, 61, 69, 76, 97, 101, 106, 108, 111, 115, 126, 127, 133, 136, 139, 142] reporting the serum levels of CK-MB before and after chemotherapy were included in the network meta-analysis. These studies evaluated 18 drug regimens (5 chemical drugs, 3 combined chemical and Chinese patent medicines, and 10 Chinese patent medicines) involving 1,933 patients who received anthracyclines (767 patients were randomly assigned to the placebo or no treatment group, while 1,166 patients were randomly assigned to the cardioprotective drug groups;

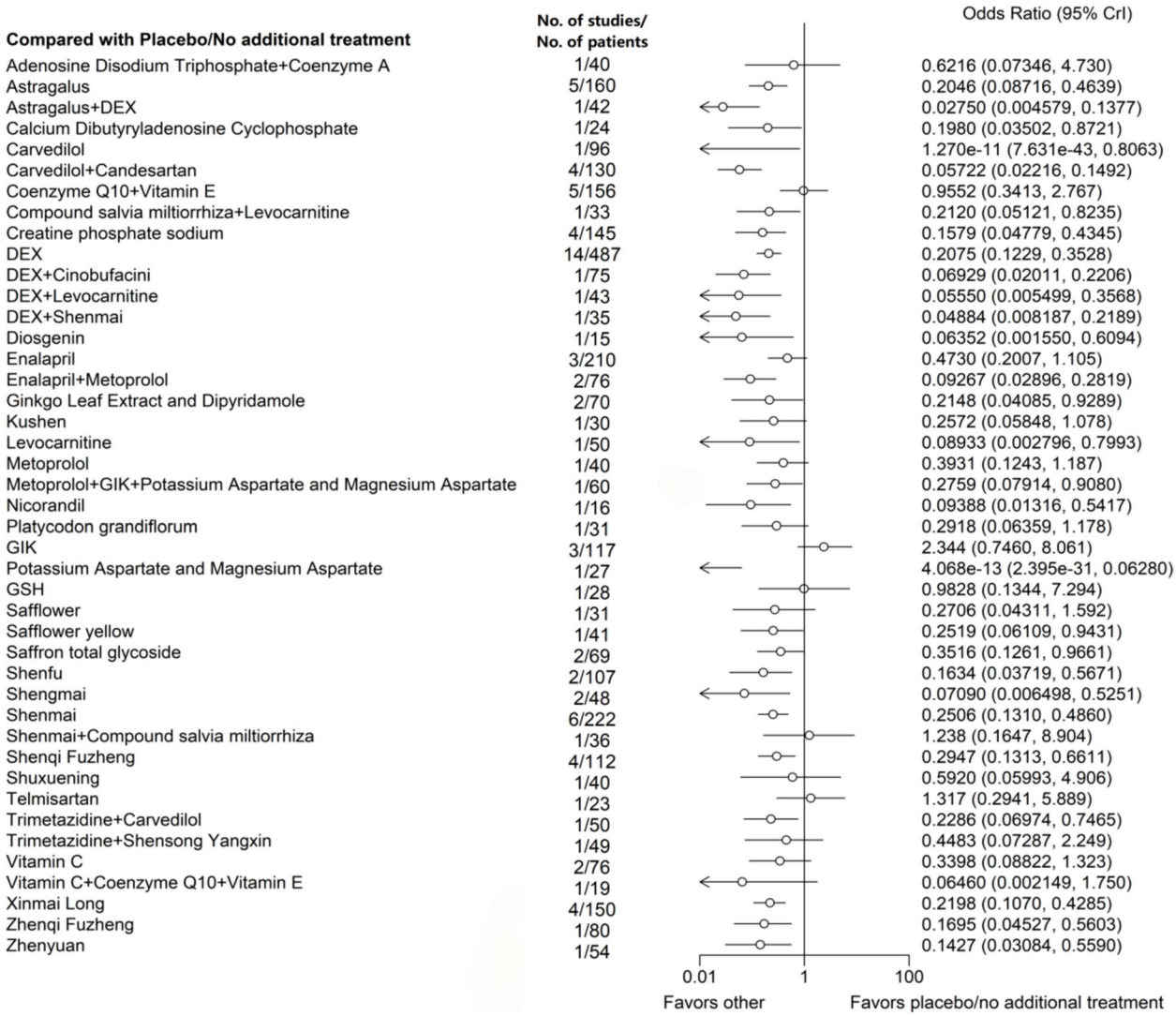


Fig. 4 Network forest plot of electrocardiographic abnormalities. Note: DEX: Dexrazoxane; GSH: Glutathione; GIK: Glucose-insulin-potassium. Astragalus, Compound salvia miltiorrhiza, Cinobufacini, Diosgenin, Ginkgo Leaf Extract and Dipyridamole, Kushen, Platycodon grandiflorum, Safflower, Safflower yellow, Saffron total glycoside, Shenfu, Shengmai, Shenmai, Shenqi Fuzheng, Shuxuening, Shensong Yangxin, Xinmai Long, Zhenqi Fuzheng, and Zhenyuan are Chinese Patent Medicines, and most are injections (Diosgenin, Platycodon grandiflorum, Saffron total glycoside, Shensong Yangxin, Zhenqi Fuzheng, and Zhenyuan are solid oral dosage forms, including tablets, capsules, and granules)

see the Supplementary file 5 for the network relationship figure).

For preventing an increase in serum CK-MB levels after chemotherapy, the following treatments had a beneficial effect compared to placebo/no treatment: Astragalus + DEX (Mean Difference [95% CrI], −11.99 [−17.94, −5.207]), Astragalus polysaccharide (−5.759 [−10.37, −1.056]), Danshen (−5.801 [−10.63, −0.8633]), DEX (−6.158 [−8.938, −2.676]), DEX + Cinobufacini (−9.798 [−14.17, −5.140]), DEX + Levocarnitine (−21.26 [−29.66, −12.38]), DEX + Shenqi Fuzheng (−18.29 [−23.71, −12.11]), Shuxuening (−31.79 [−37.31, −26.33]), and Zhenqi Fuzheng (−36.27 [−41.71, −30.86]) (Fig. 5).

Based on the cumulative probability plot and SUCRA rankings (Supplementary file 6), the top-ranked treatments are Zhenqi Fuzheng (SUCRA, 99.30%), Shuxuening (94.67%), DEX + Levocarnitine (87.05%), DEX + Shenqi Fuzheng (83.99%), Astragalus + DEX (75.02%), DEX + Cinobufacini (70.95%), followed by DEX (58.23%), Danshen (55.89%), Astragalus polysaccharide (55.87%), and Levocarnitine (55.47%).

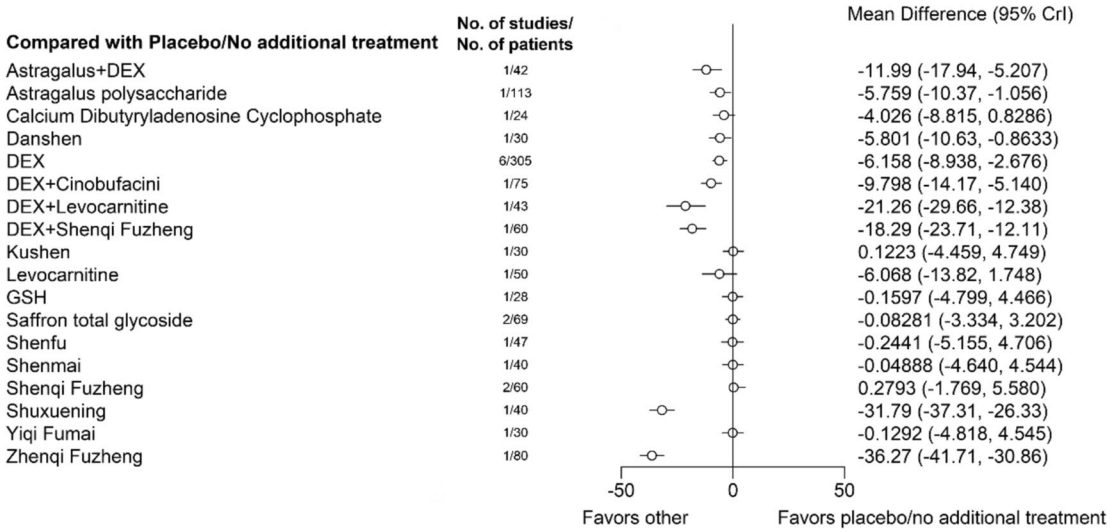


Fig. 5 Network forest plot of CK-MB. Note: DEX: Dexrazoxane; GSH: Glutathione. Astragalus, Astragalus polysaccharide, Cinobufacini, Danshen, Kushen, Saffron total glycoside, Shenfu, Shenmai, Shenqi Fuzheng, Shuxuening, Yiqi Fumai, and Zhenqi Fuzheng are Chinese Patent Medicines, and most are injections (Saffron total glycoside, and Zhenqi Fuzheng are solid oral dosage forms, including tablets and granules)

Symptomatic cardiotoxicity

Forty-four RCTs [25, 26, 30–32, 40, 41, 44, 45, 50, 52–55, 57, 59, 60, 62, 64–66, 68, 77, 79, 80, 82, 84–87, 90, 97, 109, 111, 114, 115, 117, 121, 124, 130–133, 140] reporting symptomatic cardiac dysfunction in patients were included in the network meta-analysis. These studies evaluated 37 drug regimens (18 chemical drugs, 1 combined chemical and Chinese patent medicines, and 18 Chinese patent medicines) involving 3,862 patients who received anthracyclines (1,447 patients were randomly assigned to the placebo or no treatment group, while 2,415 patients were randomly assigned to the cardioprotective drug groups; see the Supplementary file 5 for the network relationship figure).

Regarding the prevention of symptomatic cardiac injury following anthracycline use, our results showed that the following treatments were more effective than placebo/no treatment: Astragalus polysaccharide (Odds Ratio [95% CrI], 0.1302 [0.04025, 0.4502]), Carvedilol (0.06943 [0.001414, 0.6658]), DEX (0.2343 [0.07190, 0.6765]), DEX + Cinobufacini (0.02860 [0.003092, 0.1600]), Diosgenin (0 [0, 0.08773]), Levocarnitine (0.1512 [0.02136, 0.7765]), Rosuvastatin (0 [0, 0.4911]), Shenfu (0 [0, 0.6526]), Shenqi Fuzheng (0.08347 [0.002251, 0.7765]), and Xinmai Long (0.2352 [0.05848, 0.9199]) (Fig. 6).

Based on the cumulative probability plot and SUCRA rankings, the highest-ranked treatment is Shenfu (SUCRA, 88.35%), followed by Rosuvastatin (87.84%), Diosgenin (87.04%), Ivabradine (84.86%), DEX + Cinobufacini (74.13%), Carvedilol (65.12%), Shenqi Fuzheng (61.90%), Candesartan + Metoprolol (59.11%), and Astragalus polysaccharide (58.68%) (Supplementary file 6).

Sensitivity analysis

In the fixed-effects model analysis, the point estimates for most treatments are stable. However, the narrowing of 95% CrIs indicates that some treatments such as Candesartan, Candesartan + Metoprolol, Enalapril, Lisinopril + Bisoprolol, Rosuvastatin, and Astragalus are significantly beneficial compared to placebo. Besides, no inconsistent evidence is detected in the sensitivity analysis for DEX and Carvedilo (Supplementary file 7).

Treatment of anthracycline-induced cardiotoxicity

For patients who have already developed AIC, results from low-quality RCTs with small sample sizes have shown that Sacubitril/Valsartan Sodium, Levocarnitine, and Wenxin granules can achieve effectiveness rates of over 90%, significantly improving patients' symptoms and cardiac function. Additionally, Carvedilol has been found to increase LVEF in patients who experienced a decrease after anthracycline use (Table 2).

Discussion

Anthracyclines are a crucial component in the treatment of cancer, and their safety has been a topic of ongoing concern. Their severe cardiotoxicity limits the use of anthracycline-based chemotherapy regimens, especially in patients with high cardiovascular risk. Our study included 128 RCTs related to the prevention and treatment of AIC, involving 10,431 patients who received

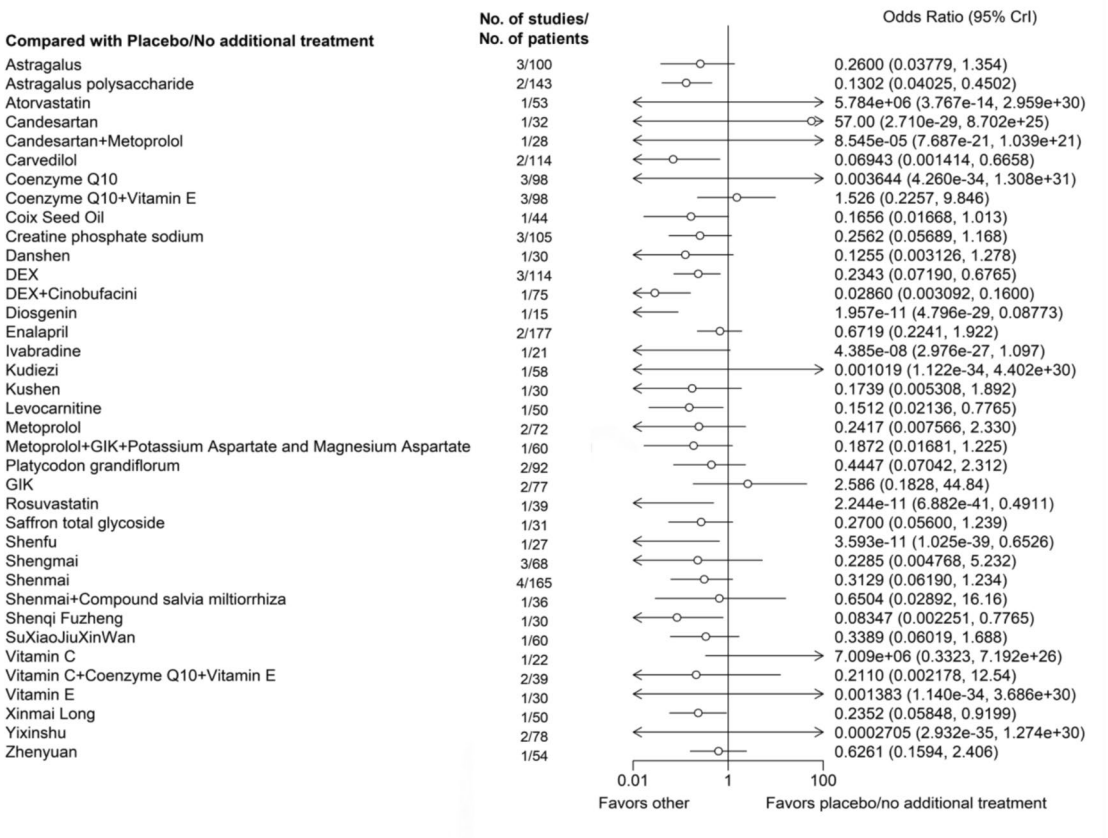


Fig. 6 Network forest plot of symptomatic cardiotoxicity. Note: DEX: Dexrazoxane; GIK: Glucose-insulin-potassium. Astragalus, Astragalus polysaccharide, Coix Seed Oil, Compound salvia miltiorrhiza, Cinobufacini, Danshen, Diosgenin, Kudiezi, Kushen, Platycodon grandiflorum, Saffron total glycoside, Shenfu, Shengmai, Shenmai, Shenqi Fuzheng, SuXiaoJiuXinWan, Xinmai Long, Yiqi Fumai, and Zhenyuan are Chinese Patent Medicines, and most are injections (Diosgenin, Platycodon grandiflorum, Saffron total glycoside, SuXiaoJiuXinWan, and Zhenyuan are solid oral dosage forms, including tablets, capsules, and granules)

anthracyclines and 78 drug regimens (41 chemical drugs, 10 combined chemical and Chinese patent medicines, and 27 Chinese patent medicines).

A Bayesian network meta-analysis was conducted using a random-effects model, incorporating seventy-two RCTs that reported LVEF. The results indicated that, compared to no treatment, patients treated with Calcium Dibutyryladenosine Cyclophosphate, Carvedilol, Carvedilol + Candesartan, Compound Salvia Miltiorrhiza + Levocarnitine, DEX, DEX + Cinobufacini, DEX + Shenqi Fuzheng, Nicorandil, Qiliqiangxin, and Xinmai Long showed less variation in LVEF following anthracycline use. The SUCRA ranking results indicated that the most effective treatment option for preserving LVEF was Nicorandil (SUCRA 91.76%). However, it should be noted that the findings for Calcium Dibutyryladenosine Cyclophosphate, Compound Salvia Miltiorrhiza + Levocarnitine, DEX + Cinobufacini, DEX + Shenqi Fuzheng, Nicorandil, and Qiliqiangxin are derived from a single small-sample RCT.

Our study found that although they all belong to β-blockers, Carvedilol (Mean Difference [95% CrI], 4.024 [0.5372, 7.656]) can prevent the decline of LVEF after anthracycline use, while Metoprolol (0.2373 [−5.150, 5.671]), Nebivolol (−0.003988 [−7.998, 7.941]), and Lisinopril + Bisoprolol (5.199 [−3.580, 14.03]) do not appear to have protective effects against AIC. Our finding aligns with He, D. et al. [148], indicating Carvedilol's superiority over Metoprolol, Bisoprolol, and Nebivolol in preventing LVEF decline after anthracycline use, with Metoprolol showing no significant difference from placebo. Recent RCTs and meta-analyses have consistently supported the positive effects of Carvedilol on AIC [13, 149].

The exact mechanism of AIC remains unclear. Oxidative stress, which promotes the formation of large amounts of reactive oxygen species (ROS), and the inhibition of topoisomerase IIβ in cardiomyocytes leading to

Table 2 RCTs Related to the Treatment of AIC

Study id	Age, y	Male sex n(%)	Anthracyclines	Treatments	No. patients	Duration of follow-up	Cardiac function		Response rate	Overall bias
							Prior treatment	Post treatment		
Chen RY, 2006 [107]	25–68	-	Doxorubicin	Compound Danshen (Salvia miltiorrhiza) dripping pill + Vitamin C + Oryzanol + Vitamin B1; Vitamin C + Oryzanol + Vitamin B1	38; 26	15 days	-	-	89.47%; 69.23%	H
Li H., 2007 [74]	32–72	51 (46.4%)	-	Sodium tanshinone IIA sulfonate + Astragalus injection + Vitamin E + Coenzyme Q_{10}; Astragalus injection + Vitamin E + Coenzyme Q_{10}	58; 52	14 days	-	-	Improvement of symptoms: 94.83%; 84.62% Electrocardiogram improvement: 87.93%; 80.77%	S
Li YQ, 2008a [84]	48.35 ± 8.6	12 (33.3%)	Doxorubicin	Carvedilol; No additional treatment	18; 18	6 months	LVEDD 64.1 ± 9.8 mm; 63.89 ± 9.9 mm LVESD 51.3 ± 9.92 mm; 51.68 ± 9.68 mm LVEF 30.76 ± 8.1%; 31.02 ± 8.2%	LVEDD 57.26 ± 9.32 mm; 62.56 ± 9.89 mm LVESD 40.36 ± 9.65 mm; 49.02 ± 10.68 mm LVEF 44.78 ± 10.2%; 35.4 ± 10.1%	-	S
Wang LH, 2011 [72]	13–71	33 (43.4%)	Daunorubicin/ Doxorubicin/Mitoxantrone	Creatine phosphate sodium; Vitamin C	41; 35	7 days	CK-MB 33.2 ± 3.6 μmol/L; 34.1 ± 2.9 μmol/L LDH 172.5 ± 25.4 U/L; 159.6 ± 23.5 U/L HBDB 285.4 ± 49.3 U/L; 279.6 ± 51.3 U/L	CK-MB 21.3 ± 2.8 μmol/L; 32.5 ± 3.1 μmol/L LDH 112.4 ± 11.8 U/L; 139.2 ± 12.1 U/L HBDB 198.2 ± 45.2 U/L; 211.6 ± 39.6 U/L	-	S
Xu S, 2023 [122]	50.4 ± 2.2	29 (43.9%)	-	Wenxin grannle; Placebo	33; 33	2 months	-	-	93.94%; 75.76%	S
Yan ZM, 2021 [110]	52.9 ± 7.1	0 (0.0%)	Doxorubicin	Sacubitril/Valsartan sodium; No additional treatment	35; 35	3 months	LVEDD 42.10 ± 2.28 mm; 42.19 ± 2.14 mm LVEF 61.59 ± 3.47%; 61.48 ± 3.77%	LVEDD 40.94 ± 1.84 mm; 41.03 ± 1.41 mm LVEF 61.98 ± 3.01%; 62.67 ± 3.21%	94.29%; 74.29%	S
Zhang LQ, 2015 [135]	4.7 ± 1.7	33 (55.0%)	-	Levocarnitine; Vitamin C + Coenzyme Q10 + Vitamin E	30; 30	/	CK 491 ± 75 U/L; 493 ± 79 U/L	CK 245 ± 57 U/L; 286 ± 53 U/L	93.33%; 80.00%	S

Table 2 (continued)

Study id	Age, y	Male sex n(%)	Anthracyclines	Treatments	No. patients	Duration of follow-up	Cardiac function		Response rate	Overall bias
							Prior treatment	Post treatment		
Zhou AM, 2011 [143]	31–74	39 (43.3%)	-	Amiodarone; Wenxin grannle	45; 45	2 months	-	-	82.22%; 95.56%	S

mitochondrial defects, are relatively well-accepted mechanisms [150, 151]. Carvedilol may mitigate AIC by reducing ROS release, inhibiting cell apoptosis, and preventing lipid peroxidation in cardiomyocytes [152, 153].

Nicorandil showed the highest efficacy for LVEF improvement in SUCRA rankings (SUCRA 91.76%), but its single small-sample RCT basis necessitates larger-scale validation. DEX's protective effects on AIC are supported by numerous studies [8], and our study further confirms its positive effects. Additionally, our study found that the combination of DEX with some Chinese patent medicines may be more effective than DEX alone (DEX + Shenqi Fuzheng [SUCRA 90.05%] > DEX + Cinobufacini [87.54%] > DEX [62.06%]). Exploring the mechanisms of the potential cardioprotective effects of these Chinese patent medicines and validating their efficacy through further multicenter, large-sample clinical trials could be promising directions for future research.

Our study also found that, compared to placebo, Candesartan and Telmisartan (ARBs), Enalapril (ACEIs), and Eplerenone (MRAs) did not prevent the decline in LVEF. Moreover, Enalapril and Telmisartan failed to significantly mitigate electrocardiographic abnormalities, while Candesartan and Enalapril did not significantly prevent symptomatic cardiotoxicity, as compared to placebo/no treatment. Histological studies have shown that AT_{1a}-mediated Ang II signaling contributes to doxorubicin-induced cardiac injury [154], exacerbating fibrosis and dysfunction in mice exposed to doxorubicin [155]. Existing RCTs have not found significant differences between ACEIs/ARBs versus placebo/no treatment in preventing AIC, but this does not exclude the possibility of insufficient sample size and statistical power affecting the results.

Statins have shown promising results in preclinical models. They can reduce the incidence of oxidative stress, cardiomyocyte death, and cardiac contractile dysfunction through inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase and activating endothelial nitric oxide synthase [156–158]. However, the results of RCTs and meta-analyses on whether statins can improve patients' LVEF and prevent AIC are controversial [159–162]. Our study shows that there is not enough evidence to prove that statins (Atorvastatin and Rosuvastatin) have a positive effect on preventing the decline in LVEF, and more large-scale RCTs based on hard endpoints are needed to determine the efficacy of statins in preventing AIC.

In addition, Sildenafil, Ivabradine, Levocarnitine, N-acetylcysteine, and Glutathione have not shown beneficial effects on preventing the decline in LVEF. Coenzyme Q10, Vitamin E, and Vitamin C have failed to demonstrate efficacy in preventing the decline in LVEF, electrocardiographic abnormalities, and symptomatic cardiotoxicity.

For the treatment of patients who have already developed AIC, there is currently insufficient evidence to support the beneficial effects of any drugs. Preliminary findings from small-sample, low-quality RCTs hint at potential improvements in cardiac function with Sacubitril/Valsartan Sodium, Levocarnitine, Wenxin Granules, and Carvedilol. However, these observations are hampered by the limited number and quality of studies, necessitating confirmation through larger-scale, rigorously designed RCTs with low risk of bias.

This extensive network meta-analysis, unprecedentedly comprising 128 RCTs involving 10,431 patients and evaluating 78 distinct drug regimens, is the largest network meta-analysis conducted on the prevention and treatment of AIC. This is the greatest advantage and innovation of our study. However, there are also several limitations: 1) Regarding heterogeneity, four intervention pairs demonstrated high heterogeneity ($I^2 > 75\%$) in the LVEF, and one pair in the CK-MB (Supplementary file 4). Potential reasons include bias in study implementation and outcome measurement/assessment, notably the failure of many studies to report blinding of participants, researchers, and outcome assessors, as well as the instruments and methods used for measuring LVEF and CK-MB. Furthermore, due to the limited number of studies and incomplete data (specifically, the omission of anthracycline types and doses in certain studies), it was impractical to further evaluate the influence of sample size, anthracycline types and doses, follow-up duration, and tumor types on heterogeneity using quantitative methods such as subgroup analysis. Considering potential unquantifiable confounding factors influencing the study outcomes, we pre-determined to use the random-effects model for pooling effect sizes, owing to its superior ability to accommodate uncertainty and offer broader confidence intervals than the fixed-effects model. 2) Apart from DEX, almost all other treatments have been evaluated in ≤ 5 RCTs, and more than half in a single RCT. Consequently, the planned meta-regression analyses, stratified by follow-up duration, sample size, and anthracycline type, could not be executed as intended; 3) Given the small number of studies (1–3) for most treatments, methods to assess publication bias, such as funnel plots, Begg's test, and Egger's test, were not employed. This limitation underscores the potential for publication bias in our findings; 4) The overall quality of the included studies was moderate, with 84.4% assessed as having "some concerns". Furthermore, the majority of treatments were evaluated in a limited number of low- and moderate-quality studies with

small sample sizes, necessitating confirmation of our findings through large-scale, higher-quality studies; 5) Besides, by focusing solely on Chinese and English literature, this study may have inadvertently excluded relevant studies published in other languages, introducing a potential source of language bias. Future endeavors should strive for a more comprehensive, multilingual approach to mitigate this limitation.

Conclusions

Apart from DEX, Carvedilol, a β-blocker, also appears to show significant potential in preventing AIC. Furthermore, our results indicate that there is insufficient evidence to support the beneficial effects of statins (Atorvastatin and Rosuvastatin), Sildenafil, Ivabradine, Levocarnitine, N-acetylcysteine, Glutathione, Coenzyme Q10, Vitamin E, and Vitamin C in preventing LVEF decline and exerting a positive effect on the prevention of AIC. However, due to the limited number of studies and small sample sizes for most treatments, our findings await further confirmation by high-quality, large-scale RCTs.

Abbreviations

RCTs	Randomized Controlled Trials
AIC	Anthracycline-induced Cardiotoxicity
LVEF	Left Ventricular Ejection Fraction
SUCRA	Surface Under Cumulative Ranking Curve
DEX	Dexrazoxane
GIK	Glucose-Insulin-Potassium
GSH	Glutathione
ECG	Electrocardiogram
CK-MB	Creatine Kinase-MB

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

Patient consent statement

Not applicable.

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The work described was original research that has not been published previously, and is not under consideration for publication elsewhere, in whole or in part.

Clinical trial registration

Not applicable.

Authors' contributions

SL: Conceptualization, Methodology, Data curation, Visualization, Formal analysis and interpretation of data, and Writing–original draft; WL: Data curation, Writing–review and editing; MCh: Data curation, Writing–review and editing; XW: Supervision, Writing–review and editing, and Funding acquisition; WCh: Supervision, Writing–review and editing, and Funding acquisition.

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Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate

This study does not involve human participants.

Competing interests

The authors declare no competing interests.

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