Open Access Journal of Clinical Trials

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Advancements in Managing Anthracycline-Induced Cardiotoxicity: Insights from Interventional Clinical Trials

Mei Zhao[1], Xiaohong Zhang[1], Dongyang Zhou[2], Junxian Song[3–5]

[1]Department of Pharmacy, Peking University People's Hospital, Beijing, People's Republic of China; [2]Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, UK; [3]Department of Cardiology, Peking University People's Hospital, Beijing, People's Republic of China; [4]Beijing Key Laboratory of Early Prediction and Intervention of Acute Myocardial Infarction, Peking University People's Hospital, Beijing, People's Republic of China; [5]Center for Cardiovascular Translational Research, Peking University People's Hospital, Beijing, People's Republic of China

Correspondence: Junxian Song, Department of Cardiology, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing, 100044, People's Republic of China, Email sjx221@163.com

Purpose: Anthracycline-induced cardiotoxicity (AIC) is a significant complication in cancer treatment, impacting long-term health outcomes. This study aimed to evaluate interventional clinical trials targeting AIC and identify effective strategies.

Methods: We reviewed clinical trials on AIC from International Clinical Trial Registration Platform (ICTRP), focusing on intervention strategies. We assessed the publication status and effectiveness of cardioprotective agents, monitoring techniques, and exercise interventions.

Results: A total of 100 trials were identified, with 35% published. Most studies were conducted in the United States, China, and Italy, highlighting geographical disparities. Effective interventions included dexrazoxane for primary prevention, ACEI/ARB combination with β blockers for long-term cardioprotection. Advanced monitoring techniques, including global longitudinal strain (GLS)-guided echocardiography, cardiac magnetic resonance (CMR) and novel biomarkers (cfDNA, microRNA), showed promise in early AIC detection. Exercise interventions demonstrated significant cardiovascular benefits.

Conclusion: Cardioprotective agents, early detection methods, and exercise interventions are key to managing AIC. Dexrazoxane and ACEI/ARB combination with β blockers are promising. Exercise interventions can improve cardiovascular health and reduce AIC risk. Larger trials with long-term follow-up are essential for refining these strategies.

Keywords: anthracycline-induced cardiotoxicity, clinical trials, cardiovascular toxicity, cancer therapy safety

Introduction

The discovery of anthracycline marked a significant milestone in cancer treatment, becoming essential in managing cancers such as breast cancer, lymphoma, and leukemia.[1,2] However, their use has brought a formidable challenge due to their cardiovascular complications.[3,4]

Cardiomyocytes, being terminally differentiated, are prone to anthracycline-induced toxicities. These toxicities are primarily driven by oxidative stress, mitochondrial dysfunction and topoisomerase IIβ disruption, which result in cell death and impaired cardiac function.[5,6] These pathophysiological changes lead to a broad spectrum of complications, collectively termed "anthracycline-induced cardiotoxicity" (AIC), ranging from subclinical damage to severe conditions like arrhythmias and heart failure.[7,8] Doxorubicin, the most widely used anthracycline, has a well-established association with cardiotoxicity. Other drugs, such as daunorubicin and epirubicin, also contribute significantly to AIC, with effects varying by dosage and individual susceptibility.[9–11]

Given the therapeutic benefits of anthracyclines, strategies to mitigate cardiotoxicity are essential, driving global efforts to develop interventions through clinical trials. While reviews have summarized the mechanisms and clinical impact of AIC, few

Received: 17 October 2024
Accepted: 18 January 2025
Published: 30 January 2025

have synthesized data from global interventional clinical trial. Existing analyses often lack comprehensive coverage of trial designs, populations and outcomes, limiting the identification of effective clinical strategies.

In this context, the International Clinical Trials Registration Platform (ICTRP) provides a valuable resource by consolidating evidence-based information on clinical studies worldwide.[12] This study aimed to present a comprehensive overview of interventional clinical trials on AIC, offering actionable insights to optimize cardiac monitoring strategies, tailor regimens, and develop prophylactic measures to improve patient outcomes and quality of life for cancer survivors. These findings can guide personalized treatment adjustments, early detection strategies, ultimately aiding clinicians in balancing cancer treatment efficacy with cardiovascular safety.

Methods

Data Source

The data source for this study was the ICTRP (http://trialsearch.who.int), a public free database maintained by the World Health Organization (WHO). Accessed on December 21, 2022, the ICTRP facilitates the establishment of ethical and scientific standards for conducting clinical trials.[13] It comprises 18 registries: European Union, Africa, ClinicalTrials.gov and countries such as Australia, Brazil, China, Cuba, India, South Korea, Japan and so on.

Search Strategy and Selection Criteria

On December 21, 2022, two investigators independently conducted a standard search on ICTRP to identify all clinical trials related to AIC. Doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone are commonly employed in the anthracycline family.[14] Search terms encompassed "anthracycline", "doxorubicin", "mitoxantrone", "epirubicin", "idarubicin", "daunorubicin" and "cardiotoxicity" as well as "cardiovascular disease" or "heart failure" without any restrictions.

We excluded observational trials, mechanisms and epidemiology studies, and adjustment of chemotherapy regimens such as anthracycline derivatives and infusion protocols. Inclusion in the study required agreement by at least two of the investigators, with a third investigator reviewing outcomes. Discrepancies were resolved by consensus or by referring to the fourth investigator. A total of 100 trials were identified for further analysis (Figure 1). Information from these identified interventional trials was recorded manually using a standardized form.

Data Collection and Extraction

Two researchers extracted the data from each clinical trial independently using a predefined data extraction design. The collected data consisted of two primary parts:

1. Intervention methods: agents including chemicals and traditional Chinese medicine, monitoring test including biomarker, computed tomography (CT), cardiac magnetic resonance (CMR), ultrasonography, positron emission tomography (PET), exercise and lifestyle changes including exercise and dietary supplement, device and stem cell therapy.
2. Additional important variables: unique identification number, registration date, country, recruitment status, design, sample size, participants, phase of the trial, conditions being treated, primary outcomes and publications.

Retrieving Publication Status

Two investigators searched PubMed, Embase and Google Scholar using the registry number. The search was updated to include studies published until November 2024, considering the typical duration of clinical trials and their publication timelines. To ensure the relevance of publications, they were verified by comparing the descriptions in the manuscript with the characteristics listed in the ICTRP database. Study protocols, commentaries and other non-relevant articles were excluded. A third investigator reconfirmed the publication search for trials without publications by the first two investigators. In cases where multiple research articles were available for the same

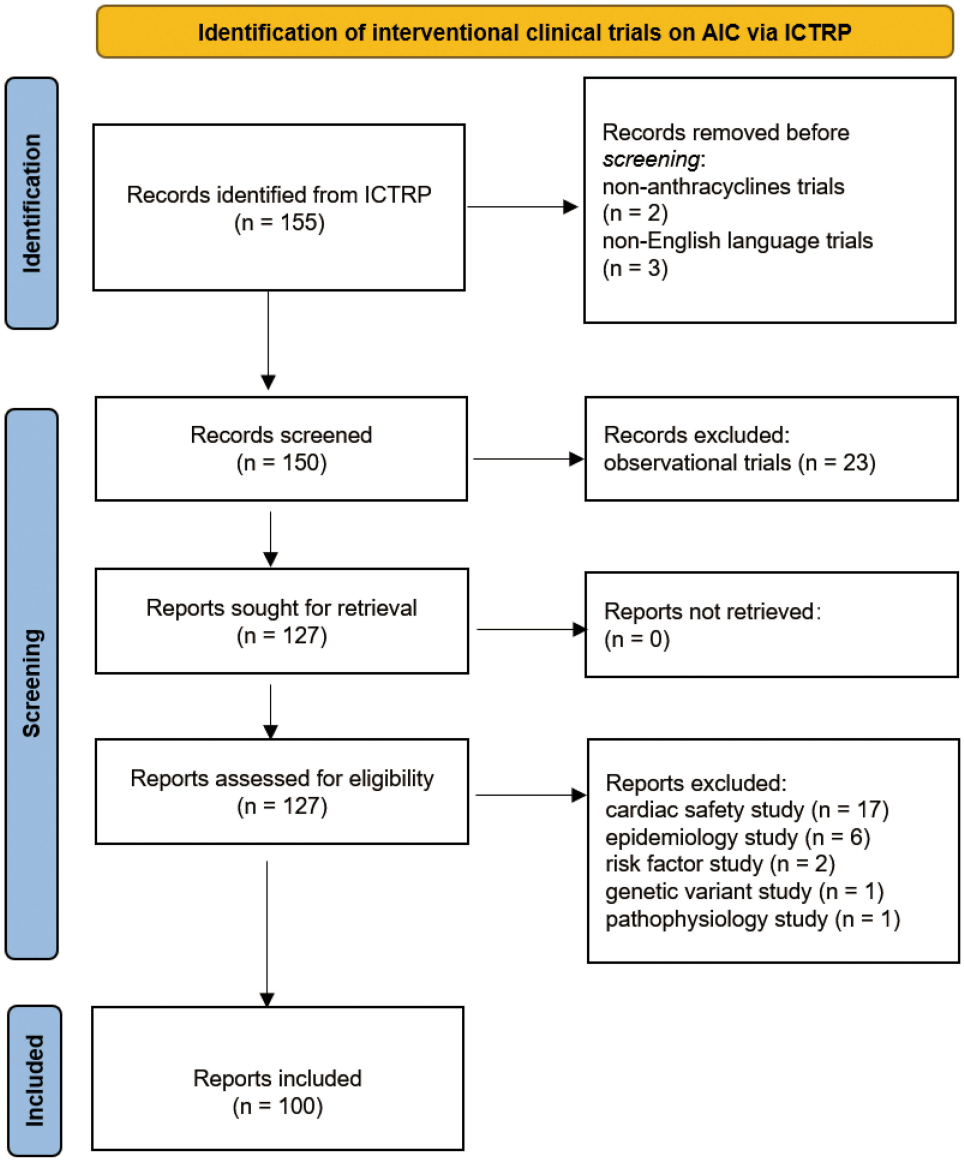

Figure 1 Flow chart of clinical research selection.
Abbreviations: AIC, anthracycline-induced cardiotoxicity; ICTRP, international clinical trials registry platform.

registry number, all results were included. Identified publications were reviewed by two investigators by matching the description with study characteristics outlined in ICTRP database.

Statistical Analysis

Categorical variables and continuous variables were presented as the number (percentage) and median (interquartile range), respectively. IBM SPSS 23.0 software was used for statistical analysis.

Results

General Characteristics

The distribution of registration years was summarized in Figure 2A. The earliest recorded clinical trial began in 1999. The total number of registered trials increased steadily across the seven time-periods, with a notable 55.0% (55/100) commencing between 2014 and 2019.

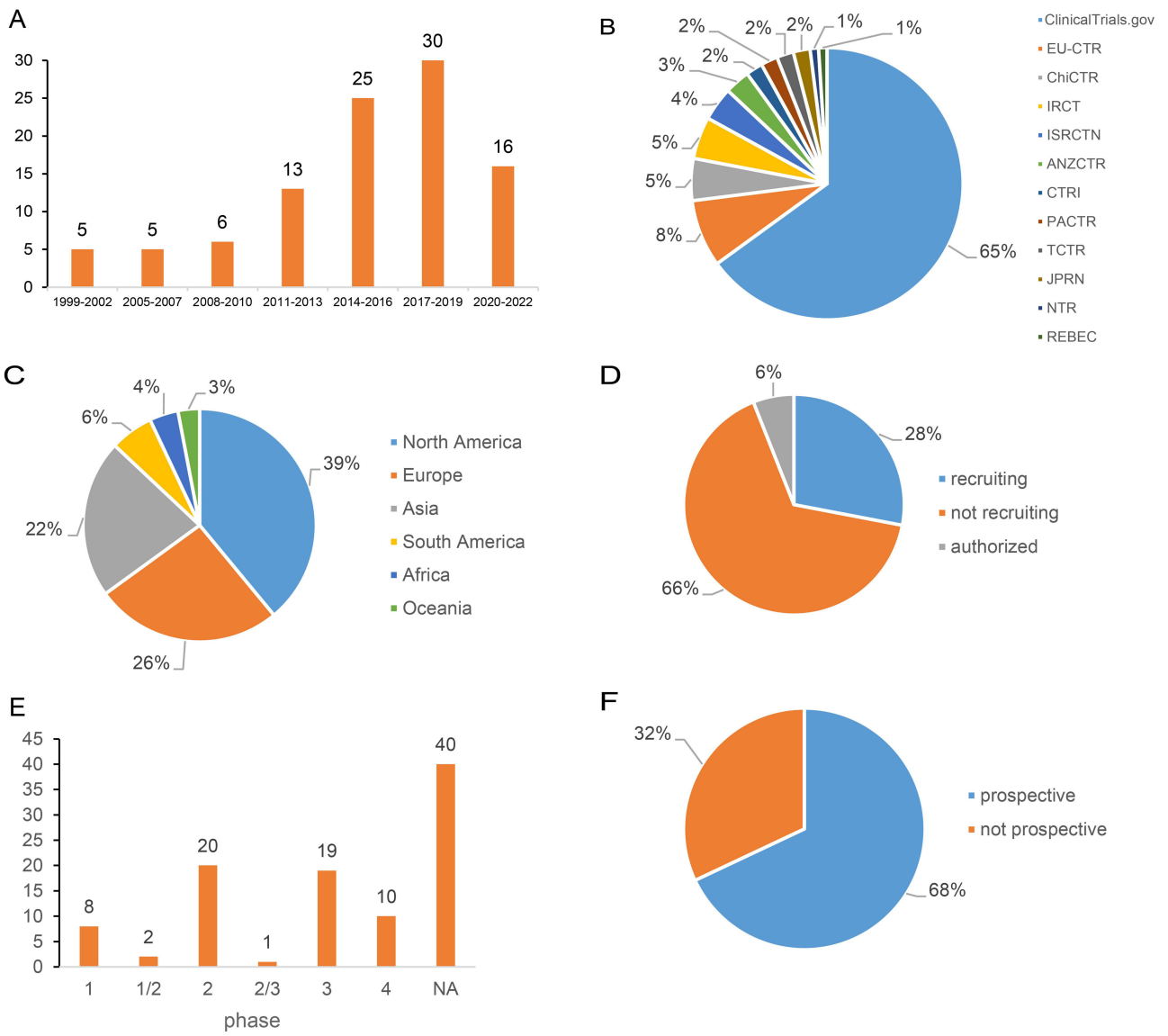

Figure 2 General information of anthracycline-related cardiotoxicity interventional trials. (**A**) registration years; (**B**) source register; (**C**) continent distribution; (**D**) recruitment status; (**E**) phase; (**F**) prospective.

Abbreviations: EU-CTR, EU Clinical Trials Register; ChiCTR, Chinese Clinical Trial Registry; IRCT, Iranian Registry of Clinical Trials; ISRCTN, International Standards of Reporting Clinical Trials; ANZCTR, Australia and New Zealand Trial Register; CTRI, Clinical Trial Registry of India; JPRN, Japan Primary Registries Network; PACTR, Pan African Clinical Trial Registry; TCTR, Thai Clinical Trials Register; NTR, Netherland National Trial Register; REBEC, Brazilian Clinical Trials Registry; NA, not applicable.

As shown in Figure 2B, the included trials were sourced from 12 different registries, with the vast majority registered in ClinicalTrial.gov. Geographically, the trials were dispersed across three major continents: North America, Europe and Asia (Figure 2C). The United States ranked first with 32 clinical trials. Among 26 individual countries, China (9 studies) and Italy (7 studies) were the most active in Asia and Europe, respectively. The majority (66.0%) were not in the recruitment phase (Figure 2D), suggesting progress toward completion or post-recruitment stages. Among the remaining 60 studies in the phase category, half (30.0%) were in early stages (phase 1, 2 and 1/2), while the other half (30.0%) were in late stages (phase 3 and 4) (Figure 2E). Most trials (68.0%) were registered prospectively (Figure 2F), underscoring the growing adherence to international standards for timely trial registration.

https://doi.org/10.2147/OAJCT.S501501

Intervention Strategies

To investigate effective interventions for AIC, clinical trials were classified into five main categories, including pharmacological agents, motoring strategies, exercise and lifestyle modifications and innovative therapies, as illustrated in Figure 3.

The most common interventions were the use of cardioprotective agents, representing 62.0% of trials. As depicted in Figure 4, these drugs included neurohormonal antagonists (n = 12), such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and combined angiotensin receptor and neprilysin inhibitor (ARNI, sacubitril/valsartan), β blockers (n = 9), dexrazoxane (n = 8) and combined therapies (n = 8). Traditional interventions like Chinese herbal medicine (7 trials) and statins (4 trials) were also explored. Among the combined therapies, six trials

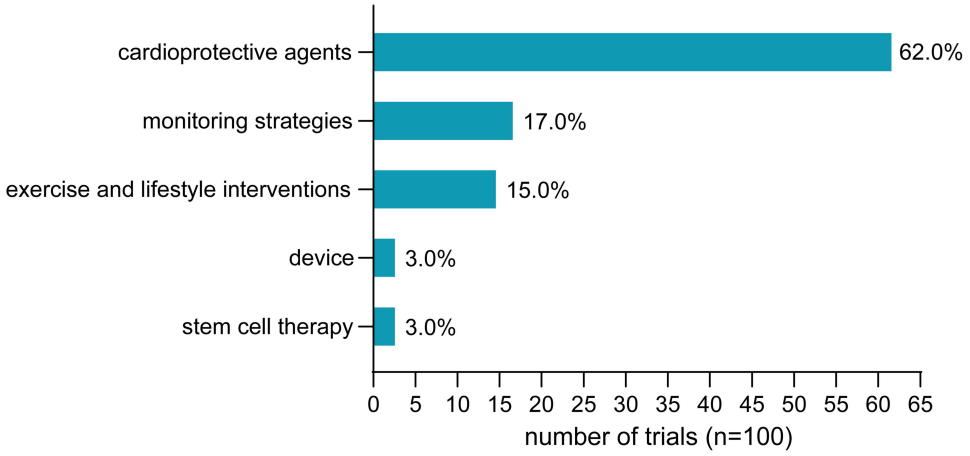

Figure 3 Five classes of interventions for anthracycline-induced cardiotoxicity (n=100).

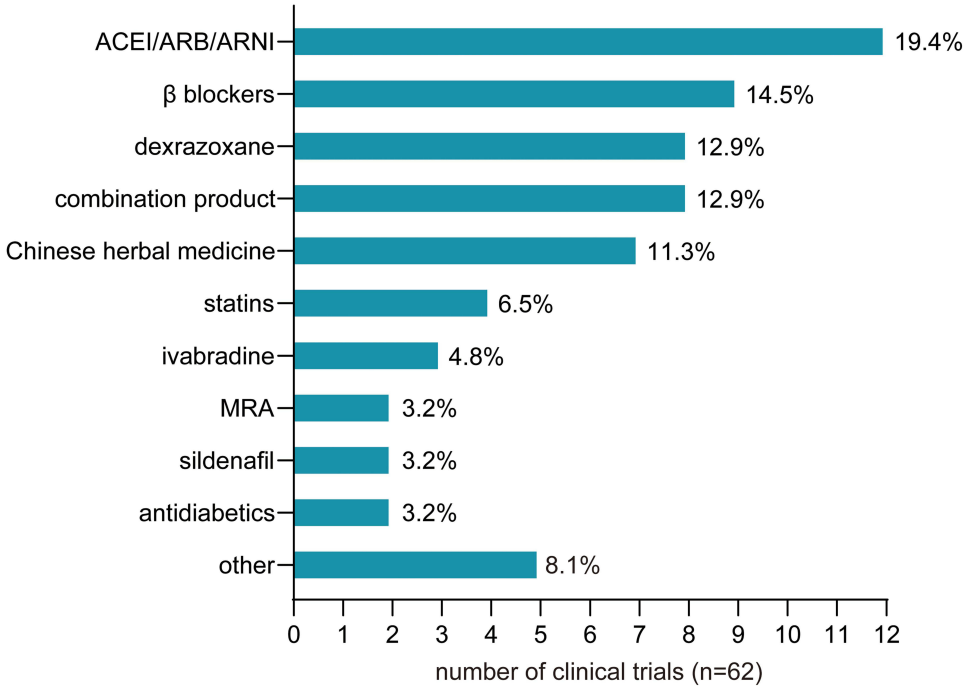

Figure 4 Type of drugs used in anthracycline-induced cardiotoxicity clinical trials (n=62).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor and neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

https://doi.org/10.2147/OAJCT.S501501

specifically assessed the potential synergistic effects of ACEI/ARB and β blockers, while others evaluated antidiabetics like metformin and empagliflozin (3 trials). Other agents, including ivabradine, mineralocorticoid receptor antagonist (MRA) and sildenafil, demonstrated promise in mitigating the cardiotoxic risks with anthracyclines. Other agents such as L-carnitine, α-calcitriol/vitamin D and coenzyme Q10 were also involved.

Seventeen trials (17.0%) employed various monitoring techniques for the early detection of AIC. These included imaging modalities such as MRI, CT, positron emission tomography/CT (PET/CT), along with echocardiography. Moreover, troponins and novel cardiac biomarkers such as microRNA were also frequently utilized.

Fifteen trials (15.0%) investigated the impact of exercise and lifestyle modifications. These interventions included structured exercise programs (13.0%) and dietary changes (2.0%), highlighting the potential role of lifestyle changes in mitigating AIC. A smaller proportion of trials (6.0%) explored novel therapies, including stem cell therapy (3.0%) and device (3.0%).

Trials Design

The clinical trial design characteristics for each intervention category are described in Table 1. Overall, the majority were randomized (82.0%, n = 82), with primary objectives focused on prevention (41.0%, n = 41) and treatment (39.0%, n = 39). Most trials targeted adult participants (89.0%, n = 89), and sample sizes varied widely. Thirty-six trials (36.0%) included fewer than 50 participants, and only 3.0% (n = 3) involved more than 500 participants.

Cardioprotective agent trials exhibited a balance focus on prevention (43.5%) and treatment (51.6%), reflecting their utility in addressing AIC. This category also featured the largest trial by sample size (1018 participants). While most trials targeted adults, a small proportion (4.8%, n = 3) included pediatric participants. Notably, 91.9% were randomized, indicating robust trial designs.

Monitoring strategies had the lowest randomization rate (35.3%) and generally smaller sample sizes. Nearly half (41.2%, n = 7) enrolled fewer than 50 participants, suggesting exploratory research designs focused on early detection methods.

Table 1 Design Features of Anthracycline-Related Cardiotoxicity Trials

	Cardioprotective Agents (n=62)	**Monitoring Strategies (n=17)**	**Exercise and Lifestyle Interventions (n=15)**	**Device (n=3)**	**Stem Cell Therapy (n=3)**	**Total (n=100)**
Sex						
Female	29 (46.8%)	5 (29.4%)	9 (60.0%)	0	0	43 (43.0%)
Both	33 (53.2%)	12 (70.6%)	6 (40.0%)	3 (100.0%)	3 (100.0%)	57 (57.0%)
Randomization						
Yes	57 (91.9%)	6 (35.3%)	13 (86.7%)	3 (100.0%)	3 (100.0%)	82 (82.0%)
No	5 (8.1%)	11 (64.7%)	2 (13.3%)	0	0	18 (18.0%)
Purpose						
Prevention	27 (43.5%)	4 (23.5%)	8 (53.3%)	2 (66.7%)	0	41 (41.0%)
Diagnosis	0	11 (64.7%)	0	0	0	11 (11.0%)
Treatment	32 (51.7%)	1 (5.9%)	3 (20.0%)	0	3 (100.0%)	39 (39.0%)
Supportive care	3 (4.8%)	1 (5.9%)	4 (26.7%)	0	0	8 (8.0%)
Device feasibility	0	0	0	1 (33.3%)	0	1 (1.0%)

(*Continued*)

Table 1 (Continued).

	Cardioprotective Agents (n=62)	Monitoring Strategies (n=17)	Exercise and Lifestyle Interventions (n=15)	Device (n=3)	Stem Cell Therapy (n=3)	Total (n=100)
Participant						
Children only	3 (4.8%)	0	0	1 (33.3%)	0	4 (4.0%)
Adults only	53 (85.5%)	17 (100.0%)	15 (100.0%)	1 (33.3%)	3 (100.0%)	89 (89.0%)
Both	6 (9.7%)	0	0	1 (33.3%)	0	7 (7.0%)
With older adults	48 (77.4%)	17 (100.0%)	13 (86.7%)	1 (33.3%)	3 (100.0%)	82 (82.0%)
Target size						
Range	8–1018	2–597	1–122	30–608	45–72	
1–50	18 (29.0%)	7 (41.2%)	8 (53.3%)	1 (33.3%)	2 (66.7%)	36 (36.0%)
51–100	16 (25.8%)	4 (23.5%)	5 (33.3%)	1 (33.3%)	1 (33.3%)	27 (27.0%)
101–150	8 (12.9%)	1 (5.9%)	2 (13.3%)	0	0	11 (11.0%)
151–200	6 (9.7%)	0	0	0	0	6 (6.0%)
201–500	13 (21.0%)	4 (23.5%)	0	0	0	17 (17.0%)
>500	1 (1.6%)	1 (5.9%)	0	1 (33.3%)	0	3 (3.0%)

Exercise and lifestyle intervention trials prioritized prevention (53.3%, n = 8) and supportive care (26.7%, n = 4). They were generally small-scale, with over half (53.3%) involving fewer than 50 participants.

Device-related trials demonstrated significant variability in sample sizes. Stem cell therapy trials featured modest sample sizes, ranging from 45 to 72 participants. Both of the two categories were randomized (100.0%), reflecting a structured approach to assess novel technologies.

Publications Corresponding to Intervention Strategies

In this section, we focused on the publications arising from the clinical trials. These publications played a critical role in assessing the effectiveness of different interventions and the quality of the clinical evidence available for AIC. Thirty-five trials resulted in the publication of 44 articles, accounting for 35% of all trials. Notably, five trials generated two or more publications. The publication dates ranged from 2009 to 2024, reflecting the evolving research landscape over the years. As illustrated in Figure 5, majority of studies focused on pharmacological and monitoring strategies. Exercise and advanced therapeutic interventions represented more specialized and emerging areas of investigation.

Table 2 consolidates the findings from the literature regarding different interventions. Cardioprotective drugs revealed varying levels of efficacy. Combined drug therapies, which typically involved combinations of ACEI/ARB and β blockers, showed promising outcomes in mitigating cardiotoxicity, contributing to a moderate level of effectiveness. Dexrazoxane consistently showed cardioprotection, particularly in pediatric and high-risk populations. Carvedilol demonstrated 100% effectiveness in preventing cardiotoxicity and left ventricular dysfunction across the two studies. Enalapril, vitamin D and salidroside each showed 100% positive results in preventing cardiotoxicity, although these findings were based on single trials. In contrast, atorvastatin, sildenafil and PC-SOD had limited or no cardioprotective effects.

Monitoring strategies showed high efficacy. Imaging techniques like CMR and global longitudinal strain (GLS)-guided-echocardiography were successful in early detection. Novel biomarkers like microRNA and cfDNA showed great potential to detect AIC. The efficacy of cardiac troponin appeared to be influenced by detection standards, as variations in

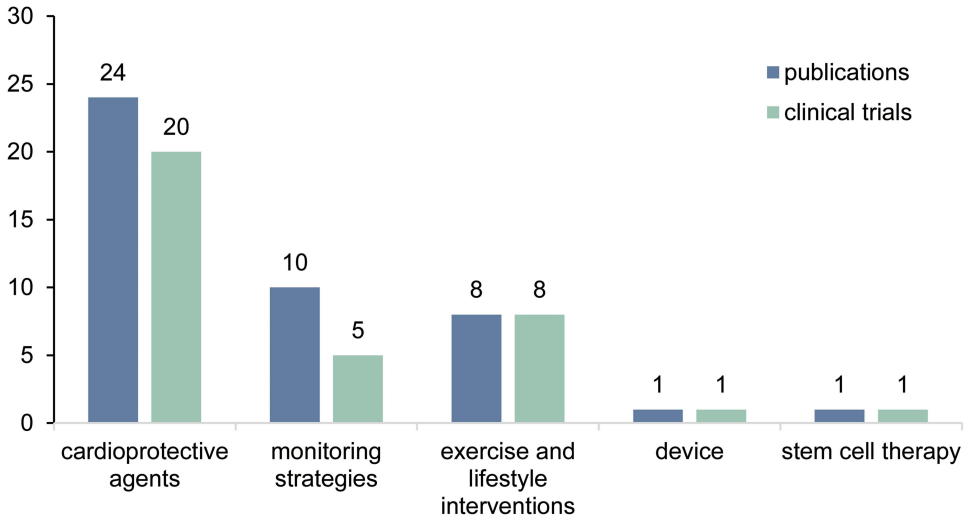

Figure 5 Distribution of clinical trials (n=35) and corresponding published articles (n=44).

criteria may affect the outcomes. These methods highlighted the value of combining imaging and biomarkers for improved detection of cardiotoxicity.

All studies on exercise-based strategies were consistently effective. Exercise interventions, including moderate and vigorous intensity training, improved cardiorespiratory fitness, cardiac reserve, and other heart failure-related parameters in cancer patients.

On the other hand, device therapy, such as remote ischemic conditioning, and allogeneic mesenchymal cell therapy, still in early stage of research, did not demonstrate significant cardioprotective effects.

Table 2 Summary of Cardioprotective Drug Trials for Anthracycline-Induced Cardiotoxicity

Interventions	Articles	Key Findings	Positive Rates (%, Positive Results/Article Numbers)
Cardioprotective agents (n=24)			
Carvedilol[15,16]	2	Offered protection as an early primary intervention	100% (2/2)
Enalapril[17]	1	Prevented left ventricular dysfunction, especially administered after the first rise in troponin levels.	100% (1/1)
Combined drug therapy[18–23]	6	Mixed results: early beneficial effects on cardiotoxicity in bisoprolol + ramipril, not in carvedilol + candesartan, candesartan + metoprolol had mixed results	75% (4/6)
Dexrazoxane[24–27]	4	Consistent cardioprotection, especially in pediatric and high-risk populations	75% (3/4)
Atorvastatin[28–31]	4	Generally ineffective in preventing LVEF decline	25% (1/4)
Sildenafil[32,33]	2	No cardioprotective benefits	0% (0/2)
MRA[34,35]	2	Spironolactone protected against myocardial injury, while eplerenone not	50% (1/2)
Vitamin D[36]	1	Showed cardioprotection against AIC	100% (1/1)

(*Continued*)

Table 2 (Continued).

Interventions	Articles	Key Findings	Positive Rates (%, Positive Results/Article Numbers)
Salidroside[37]	1	Prevented early LV systolic dysfunction	100% (1/1)
PC-SOD[38]	1	Failed to show cardioprotective effects	0% (0/1)
Monitoring strategies (n=10)			
cTn[39]	1	Incidence of asymptomatic cardiotoxicity varied based on biomarker criteria	100% (1/1)
CMR[40,41]	2	CMR detected AIC in low-risk patients	100% (2/2)
Echocardiography[42–45]	4	Global longitudinal strain (GLS) identified early myocardial dysfunction, good correlation with EF, and better detection with 3 apical views	100% (4/4)
Biomarker (microRNA[46,47] or cfDNA[48])	3	microRNA or cfDNA might be a potential biomarker for AIC	100% (3/3)
Exercise and lifestyle interventions (n=8)			
Exercise[49–56]	8	Exercise improved cardiorespiratory fitness, cardiac reserve, and heart failure-related parameters	100% (8/8)
Device (n=1)			
Remote Ischemic conditioning[57]	1	No cardioprotective effects were observed in pediatric patients	0% (0/1)
Stem cell therapy (n=1)			
Allogeneic mesenchymal cell therapy[58]	1	Cell therapy was safe and feasible but did not demonstrate efficacy in cardioprotection	0% (0/1)

Abbreviations: MRA, mineralocorticoid receptor antagonist; cTn, cardiac troponin; CMR, cardiac magnetic resonance.

Discussion

This study revealed critical insights into potential approaches concerning AIC through an analysis of interventional trials. A majority of trials were conducted in the United States, China and Italy, reflecting significant geographical disparities. A diverse range of intervention strategies was explored, highlighting the complexity of AIC management. Despite only 35% of the trials resulted in publications, promising outcomes were observed for cardioprotective agents, exercise interventions and monitoring strategies in reducing the incidence and severity of AIC. These findings underscored the growing potential for improving AIC outcomes through targeted and evidence-based approaches.

Current Status of Interventional Clinical Trials on AIC

AIC remains a major concern in cancer treatment, but the number of interventional clinical trials is still limited. It may be attributed to several reasons. First, AIC manifests variably as both acute or chronic heart dysfunction, complicating trial design and outcome assessment.[59] Second, AIC may result from multiple factors, including pre-existing cardiovascular diseases and aging, further complicating the identification of clear causal relationships. Third, advancements such as liposomal anthracyclines and reduced-dose regimens have potentially decreased the need for large-scale trials, particularly in countries with access to more advanced treatment options. Geographical disparity in clinical trials is another important consideration. These regional differences may influence the findings and generalizability of the results, as healthcare infrastructure, cancer treatment practices, and patient demographics vary widely. Additionally, cultural factors and differences in healthcare access may affect the design and outcomes of clinical trials.[60,61]

Major Findings and Contributions to Current Understanding

Our study contributed to the growing body of knowledge on AIC management by identifying effective interventions and highlighting areas requiring further research.

The significant role of pharmacological interventions like dexrazoxane, ACEI/ARB combination with β blockers, emerged as key players, underscoring the importance of early and proactive strategies to prevent and manage AIC. Dexrazoxane, as evidenced by our findings, continues to be promising for primary prevention of AIC, without compromising antineoplastic efficacy, especially in high-risk populations such as pediatrics or those receiving high cumulative anthracycline doses.[62,63] However, our data indicated that more research is needed to define its role in secondary prevention for adults with pre-existing cardiovascular issues. The trials examining ACEI/ARB with β blockers yielded mixed results. While studies such as PRADA and CECCY showed no significant improvements in left ventricular ejection fraction (LVEF), evidence suggested that these agents could be beneficial, particularly when combined.[15,18] Although these drugs might not directly counteract the immediate cardiotoxic effects of anthracyclines, they played a crucial role in preventing long-term myocardial remodeling and dysfunction, reducing the risk of chronic heart failure.[64] The clinical implication here is that ACEI/ARB combination with β blockers might be more effective as supportive treatments during and after chemotherapy, especially for patients with pre-existing heart conditions or other cardiovascular risk factors.

Emerging therapies such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors and ARNI represent new frontiers in AIC management. Our findings pointed to their potential in offering more tailored therapeutic options. SGLT-2 inhibitors, already effective in other forms of heart failure, offer dual benefits for metabolic and cardiac health.[65] Similarly, ARNI, with its combination of neurohormonal blockade and vasodilation, is gaining traction in mitigating the vascular and myocardial damage induced by anthracyclines.[66]

In addition to pharmacological interventions, early detection and monitoring strategies are critical to reduce AIC incidence. Techniques such as GLS-guided echocardiography and CMR have proven valuable in detecting subclinical cardiac dysfunction, preceding LVEF changes. A 10–15% decline in GLS has been recognized as a predictive indicator for subsequent LVEF decrease, providing clinicians with an early warning system for cardiotoxicity.[67] Blood biomarkers such as troponin-I and brain natriuretic peptide (BNP) are commonly used to detect cardiac injury. Our analysis showed that troponin-I may not always be sensitive enough to detect early or mild cases of AIC. On the other hand, emerging blood markers such as cfDNA and microRNA, showed greater sensitivity and specificity in both acute and chronic AIC scenarios. Our findings suggested that these markers could complement traditional biomarkers and can be combined with imaging techniques to create a more robust framework for early detection of AIC.[68,69]

Finally, exercise interventions demonstrated significant potential in AIC prevention. Both aerobic exercise and resistance training showed beneficial effects on cardiovascular outcomes in patients undergoing anthracycline treatment.[70,71] Exercise as a feasible and safe modality has been encouraged to implement cardiac rehabilitation.[72] Exercise not only mitigated cardiotoxicity but also improved overall cardiovascular fitness and patient outcomes. These findings support the integration of exercise programs as part of a holistic cancer care strategy.

Practical Applications of the Findings

Our findings suggested several key ways to integrate interventional strategies into clinical practice to prevent and manage AIC. Early use of cardioprotective agents, such as dexrazoxane, is critical for high-risk populations. Secondary prevention strategies, including ACEI/ARB combination with β blockers, can mitigate long-term cardiotoxic effects and reduce heart failure risk. Emerging therapies like SGLT-2 inhibitors and ARNI hold substantial promise and may provide tailored options for patients with specific risk profiles. Furthermore, the adoption of advanced imaging techniques and biomarkers can enhance early detection, enabling clinicians to intervene before irreversible damage occurs. Finally, incorporating exercise interventions into cancer treatment plans has the potential to improve both cardiovascular and overall patient outcomes. These strategies, when integrated into clinical practice, could reduce the burden of AIC and improve long-term survival and quality of life for cancer patients.

Limitations

While this study offered valuable insights into the current landscape of interventional strategies for AIC, several limitations should be considered. First, limited published trials: Only 35% of the trials were published, which might affect the generalizability of the results. Second, small sample sizes and short follow-up: Many trials had small sample sizes and short follow-up periods, which might not capture long-term outcomes or subtle effects of interventions. Third, variability in methodology: Considerable heterogeneity in intervention protocols and outcome measures made direct comparisons challenging. Last, new interventions with limited data: Novel treatments like device and stem cell therapy showed feasible, but data on their efficacy remain scarce.

Conclusion

In conclusion, this study highlighted the potential of cardioprotective agents, monitoring strategies, and exercise interventions in preventing and managing AIC. Our findings suggested that early intervention with drugs like dexrazoxane, ACEI/ARB combination with β blockers, coupled with dynamic monitoring techniques like GLS, CMR and novel biomarkers, could significantly reduce the risk of heart damage. Furthermore, exercise interventions showed promise in improving cardiovascular health. These findings contributed to the growing understanding of AIC and emphasized the importance of integrating these strategies into clinical practice. Future research with larger sample size and long-term follow-up are essential to refine these interventions and optimize their application.

Abbreviations

AIC, anthracycline-induced cardiotoxicity; ICTRP, International Clinical Trial Registration Platform; WHO, World Health Organization; CT, computed tomography; EU-CTR, EU Clinical Trials Register; ChiCTR, Chinese Clinical Trial Registry; IRCT, Iranian Registry of Clinical Trials; ISRCTN, International Standards of Reporting Clinical Trials; ANZCTR, Australia and New Zealand Trial Register; CTRI, Clinical Trial Registry of India; JPRN, Japan Primary Registries Network; PACTR, Pan African Clinical Trial Registry; TCTR, Thai Clinical Trials Register; NTR, Netherland National Trial Register; REBEC, Brazilian Clinical Trials Registry; NA, not applicable; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor and neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; CMR, cardiac magnetic resonance; PET/CT, positron emission tomography/computed tomography; SGLT-2, sodium-glucose cotransporter-2; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; BNP, brain natriuretic peptide.

Data Sharing Statement

Publicly available database was analyzed in this study. All data were available.

Acknowledgments

This paper has been uploaded to SSRN as a preprint: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4915063.

Funding

This work was supported by National Natural Science Foundation of China (No. 82070519), Beijing Municipal Science and Technology Project (No. Z161100000116071) and Peking University People's Hospital Scientific Research Development Funds (RDJP2022-58).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Jasra S, Anampa J. Anthracycline use for early-stage breast cancer in the modern era: a review. *Curr Treat Options Oncol*. 2018;19(6):30. doi:10.1007/s11864-018-0547-8

2. Sohail M, Sun Z, Li Y, Gu X, Xu H. Research progress in strategies to improve the efficacy and safety of doxorubicin for cancer chemotherapy. *Expert Rev Anticancer Ther*. 2021;21(12):1385–1398. doi:10.1080/14737140.2021.1991316
3. Tripaydonis A, Conyers R, Elliott DA. Pediatric anthracycline-induced cardiotoxicity: mechanisms, pharmacogenomics, and pluripotent stem-cell modeling. *Clin Pharmacol Ther*. 2019;105(3):614–624. doi:10.1002/cpt.1311
4. Groarke JD, Nohria A. Anthracycline cardiotoxicity: a new paradigm for an old classic. *Circulation*. 2015;131(22):1946–1949. doi:10.1161/CIRCULATIONAHA.115.016704
5. Sala V, Della SA, Hirsch E, Ghigo A. Signaling pathways underlying anthracycline cardiotoxicity. *Antioxid Redox Signal*. 2020;32(15):1098–1114. doi:10.1089/ars.2020.8019
6. Narezkina A, Narayan HK, Zemljic-Harpf AE. Molecular mechanisms of anthracycline cardiovascular toxicity. *Clin Sci*. 2021;135(10):1311–1332. doi:10.1042/CS20200301
7. Narezkina A, Nasim K. Anthracycline cardiotoxicity. *Circ Heart Fail*. 2019;12(3):e005910. doi:10.1161/CIRCHEARTFAILURE.119.005910
8. Papageorgiou C, Andrikopoulou A, Dimopoulos MA, Zagouri F. Cardiovascular toxicity of breast cancer treatment: an update. *Cancer Chemother Pharmacol*. 2021;88(1):15–24. doi:10.1007/s00280-021-04254-w
9. Pourier MS, Dull MM, Weijers G, et al. Left ventricular dyssynchrony in long-term childhood cancer survivors treated with anthracyclines: a retrospective cross-sectional study. *Int J Cardiovasc Imaging*. 2021;37(12):3469–3475. doi:10.1007/s10554-021-02347-4
10. Bottinor W, Chow EJ. Mitigating, monitoring, and managing long-term chemotherapy- and radiation-induced cardiac toxicity. *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):251–258. doi:10.1182/hematology.2022000342
11. Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U. Doxorubicin-induced cardiotoxicity: an update on the molecular mechanism and novel therapeutic strategies for effective management. *Biomed Pharmacother*. 2021;139:111708. doi:10.1016/j.biopha.2021.111708
12. Juneja A, Gupta J, Yadav N, et al. An overview of primary registries of WHO's international clinical trial registry platform. *AYU*. 2019;40(3):141–146. doi:10.4103/ayu.AYU_62_20
13. Namiot ED, Smirnovová D, Sokolov AV, Chubarev VN, Tarasov VV, Schiöth HB. The international clinical trials registry platform (ICTRP): data integrity and the trends in clinical trials, diseases, and drugs. *Front Pharmacol*. 2023;14:1228148. doi:10.3389/fphar.2023.1228148
14. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline chemotherapy and cardiotoxicity. *Cardiovasc Drugs Ther*. 2017;31(1):63–75. doi:10.1007/s10557-016-6711-0
15. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MRJ, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY trial. *J Am Coll Cardiol*. 2018;71(20):2281–2290. doi:10.1016/j.jacc.2018.02.049
16. Wanderley MRDB, Ávila MS, Fernandes-Silva MM, et al. Plasma biomarkers reflecting high oxidative stress in the prediction of myocardial injury due to anthracycline chemotherapy and the effect of carvedilol: insights from the CECCY trial. *Oncotarget*. 2022;13:214–223. doi:10.18632/oncotarget.28182
17. Cardinale D, Ciceri F, Latini R, et al. Anthracycline-induced cardiotoxicity: a multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial. *Eur J Cancer*. 2018;94:126–137. doi:10.1016/j.ejca.2018.02.005
18. Heck SL, Mecinaj A, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): extended follow-up of a 2×2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Circulation*. 2021;143(25):2431–2440. doi:10.1161/CIRCULATIONAHA.121.054698
19. Henriksen PA, Hall P, MacPherson IR, et al. Multicenter, prospective, randomized controlled trial of high-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta-blocker therapy to prevent anthracycline cardiotoxicity: the cardiac CARE trial. *Circulation*. 2023;148(21):1680–1690. doi:10.1161/CIRCULATIONAHA.123.064274
20. Heck SL, Gulati G, Hoffmann P, et al. Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial. *Eur Heart J Cardiovasc Imaging*. 2018;19(5):544–552. doi:10.1093/ehjci/jex159
21. Gulati G, Heck SL, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J*. 2016;37(21):1671–1680. doi:10.1093/eurheartj/ehw022
22. Gulati G, Heck SL, Røsjø H, et al. Neurohormonal blockade and circulating cardiovascular biomarkers during anthracycline therapy in breast cancer patients: results from the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) study. *J Am Heart Assoc*. 2017;6(11):e006513. doi:10.1161/JAHA.117.006513
23. Livi L, Barletta G, Martella F, et al. Cardioprotective strategy for patients with nonmetastatic breast cancer who are receiving an anthracycline-based chemotherapy: a randomized clinical trial. *JAMA Oncol*. 2021;7(10):1544–1549. doi:10.1001/jamaoncol.2021.3395
24. Kopp LM, Womer RB, Schwartz CL, et al. Effects of dexrazoxane on doxorubicin-related cardiotoxicity and second malignant neoplasms in children with osteosarcoma: a report from the Children's Oncology Group. *CardioOncology*. 2019;5:15. doi:10.1186/s40959-019-0050-9
25. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood*. 2009;114(10):2051–2059. doi:10.1182/blood-2008-10-184143
26. Chow EJ, Asselin BL, Schwartz CL, et al. Late mortality after dexrazoxane treatment: a report from the Children's Oncology Group. *J Clin Oncol*. 2015;33(24):2639–2645. doi:10.1200/JCO.2014.59.4473
27. Sun F, Qi X, Geng C, Li X. Dexrazoxane protects breast cancer patients with diabetes from chemotherapy-induced cardiotoxicity. *Am J Med Sci*. 2015;349(5):406–412. doi:10.1097/MAJ.0000000000000432
28. Nemec R, Scherrer-Crosbie M, Abramson JS, et al. Effect of atorvastatin versus placebo on efficacy in patients with diffuse large B-cell lymphoma receiving R-CHOP. *Leuk Lymphoma*. 2024;65(6):783–788. doi:10.1080/10428194.2024.2317343
29. Neilan TG, Quinaglia T, Onoue T, et al. Atorvastatin for anthracycline-associated cardiac dysfunction: the STOP-CA randomized clinical trial. *JAMA*. 2023;330(6):528–536. doi:10.1001/jama.2023.11887
30. Hundley WG, D'Agostino RJ, Crotts T, et al. Statins and left ventricular ejection fraction following doxorubicin treatment. *NEJM Evid*. 2022;1(9). doi:10.1056/evidoa2200097
31. Thavendiranathan P, Houbois C, Marwick TH, et al. Statins to prevent early cardiac dysfunction in cancer patients at increased cardiotoxicity risk receiving anthracyclines. *Eur Heart J Cardiovasc Pharmacother*. 2023;9(6):515–525. doi:10.1093/ehjcvp/pvad031
32. Attar A, Heydari M, Abtahi F, et al. Sildenafil for primary prevention of anthracycline-induced cardiac toxicity: a phase I/II randomized clinical trial, SILDAT-TAHA6 trial. *Cardiol Res Pract*. 2022;2022:5681510. doi:10.1155/2022/5681510

33. Poklepovic A, Qu Y, Dickinson M, et al. Randomized study of doxorubicin-based chemotherapy regimens, with and without sildenafil, with analysis of intermediate cardiac markers. *Cardio-Oncology*. 2018;4:7. doi:10.1186/s40959-018-0033-2
34. Akpek M, Ozdogru I, Sahin O, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. *Eur J Heart Fail*. 2015;17 (1):81–89. doi:10.1002/ejhf.196
35. Davis MK, Villa D, Tsang TSM, Starovoytov A, Gelmon K, Virani SA. Effect of eplerenone on diastolic function in women receiving anthracycline-based chemotherapy for breast cancer. *JACC CardioOncol*. 2019;1(2):295–298. doi:10.1016/j.jaccao.2019.10.001
36. El-Bassiouny NA, Helmy MW, Hassan M, Khedr GA. The cardioprotective effect of vitamin D in breast cancer patients receiving adjuvant doxorubicin based chemotherapy. *Clin Breast Cancer*. 2022;22(4):359–366. doi:10.1016/j.clbc.2022.01.008
37. Zhang H, Shen WS, Gao CH, Deng LC, Shen D. Protective effects of salidroside on epirubicin-induced early left ventricular regional systolic dysfunction in patients with breast cancer. *Drugs R D*. 2012;12(2):101–106. doi:10.2165/11632530-000000000-00000
38. Broeyer FJF, Osanto S, Suzuki J, et al. Evaluation of lecithinized human recombinant super oxide dismutase as cardioprotectant in anthracycline-treated breast cancer patients. *Br J Clin Pharmacol*. 2014;78(5):950–960. doi:10.1111/bcp.12429
39. Mecinaj A, Gulati G, Ree AH, et al. Impact of the ESC cardio-oncology guidelines biomarker criteria on incidence of cancer therapy-related cardiac dysfunction. *JACC CardioOncol*. 2024;6(1):83–95. doi:10.1016/j.jaccao.2023.10.008
40. Ferreira DST, Quinaglia ACST, Osorio CF, et al. Anthracycline therapy is associated with cardiomyocyte atrophy and preclinical manifestations of heart disease. *JACC Cardiovasc Imaging*. 2018;11(8):1045–1055. doi:10.1016/j.jcmg.2018.05.012
41. Voß F, Nienhaus F, Pietrucha S, et al. Anthracycline therapy induces an early decline of cardiac contractility in low-risk patients with breast cancer. *Cardio-Oncology*. 2024;10(1):43. doi:10.1186/s40959-024-00244-y
42. Narayan HK, Wei W, Feng Z, et al. Cardiac mechanics and dysfunction with anthracyclines in the community: results from the PREDICT study. *Open Heart*. 2017;4(1):e000524. doi:10.1136/openhrt-2016-000524
43. Negishi T, Thavendiranathan P, Penicka M, et al. Cardioprotection using strain-guided management of potentially cardiotoxic cancer therapy: 3-year results of the SUCCOUR trial. *JACC Cardiovasc Imaging*. 2023;16(3):269–278. doi:10.1016/j.jcmg.2022.10.010
44. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol*. 2021;77 (4):392–401. doi:10.1016/j.jacc.2020.11.020
45. Thavendiranathan P, Negishi T, Coté M, et al. Single versus standard multiview assessment of global longitudinal strain for the diagnosis of cardiotoxicity during cancer therapy. *JACC Cardiovasc Imaging*. 2018;11(8):1109–1118. doi:10.1016/j.jcmg.2018.03.003
46. Rigaud VO, Ferreira LR, Ayub-Ferreira SM, et al. Circulating miR-1 as a potential biomarker of doxorubicin-induced cardiotoxicity in breast cancer patients. *Oncotarget*. 2017;8(4):6994–7002. doi:10.18632/oncotarget.14355
47. Gioffré S, Chiesa M, Cardinale DM, et al. Circulating microRNAs as potential predictors of anthracycline-induced troponin elevation in breast cancer patients: diverging effects of doxorubicin and epirubicin. *J Clin Med*. 2020;9(5):1418. doi:10.3390/jcm9051418
48. Yu AF, Moore ZR, Moskowitz CS, et al. Association of circulating cardiomyocyte cell-free DNA with cancer therapy-related cardiac dysfunction in patients undergoing treatment for ERBB2-positive breast cancer. *JAMA Cardiol*. 2023;8(7):697–702. doi:10.1001/jamacardio.2023.1229
49. Kerrigan DJ, Reddy M, Walker EM, et al. Cardiac rehabilitation improves fitness in patients with subclinical markers of cardiotoxicity while receiving chemotherapy: a randomized controlled study. *J Cardiopulm Rehabil Prev*. 2023;43(2):129–134. doi:10.1097/HCR.0000000000000719
50. Foulkes SJ, Howden EJ, Haykowsky MJ, et al. Exercise for the prevention of anthracycline-induced functional disability and cardiac dysfunction: the BREXIT study. *Circulation*. 2023;147(7):532–545. doi:10.1161/CIRCULATIONAHA.122.062814
51. Schneider C, Ryffel C, Stütz L, et al. Supervised exercise training in patients with cancer during anthracycline-based chemotherapy to mitigate cardiotoxicity: a randomized-controlled-trial. *Front Cardiovasc Med*. 2023;10:1283153. doi:10.3389/fcvm.2023.1283153
52. Díaz-Balboa E, González-Salvado V, Rodríguez-Romero B, et al. Thirty-second sit-to-stand test as an alternative for estimating peak oxygen uptake and 6-min walking distance in women with breast cancer: a cross-sectional study. *Support Care Cancer*. 2022;30(10):8251–8260. doi:10.1007/s00520-022-07268-z
53. Chung W, Yang H, Hsu Y, et al. Real-time exercise reduces impaired cardiac function in breast cancer patients undergoing chemotherapy: a randomized controlled trial. *Ann Phys Rehabil Med*. 2022;65(2):101485. doi:10.1016/j.rehab.2021.101485
54. Foulkes SJ, Howden EJ, Bigaran A, et al. Persistent impairment in cardiopulmonary fitness after breast cancer chemotherapy. *Med Sci Sports Exerc*. 2019;51(8):1573–1581. doi:10.1249/MSS.0000000000001970
55. Antunes P, Joaquim A, Sampaio F, et al. Effects of exercise training on cardiac toxicity markers in women with breast cancer undergoing chemotherapy with anthracyclines: a randomized controlled trial. *Eur J Prev Cardiol*. 2023;30(9):844–855. doi:10.1093/eurjpc/zwad063
56. Kirkham AA, Eves ND, Shave RE, et al. The effect of an aerobic exercise bout 24h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: a RCT. *Breast Cancer Res Treat*. 2018;167(3):719–729. doi:10.1007/s10549-017-4554-4
57. Cheung Y, Li VW, So EK, et al. Remote ischemic conditioning in pediatric cancer patients receiving anthracycline chemotherapy: a sham-controlled single-blind randomized trial. *JACC CardioOncol*. 2023;5(3):332–342. doi:10.1016/j.jaccao.2022.11.020
58. Bolli R, Perin EC, Willerson JT, et al. Allogeneic mesenchymal cell therapy in anthracycline-induced cardiomyopathy heart failure patients: the CCTRN SENECA trial. *JACC CardioOncol*. 2020;2(4):581–595. doi:10.1016/j.jaccao.2020.09.001
59. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. 2020;7:26. doi:10.3389/fcvm.2020.00026
60. Kerbage A, Loesch J, Hamza E, et al. Evaluating equity in clinical trial accessibility: an analysis of demographic, socioeconomic, and educational disparities in irritable bowel syndrome drug trials. *Am J Gastroenterol*. 2024;9(24):1–10.
61. Boland MR, Tubridy E, Solorzano SS, Simpkins F, Smith AJB, Ko EM. Geographic disparities in gynecologic oncology clinical trial availability in the US. *JAMA Netw Open*. 2024;7(11):e2447635. doi:10.1001/jamanetworkopen.2024.47635
62. de Baat EC, van Dalen EC, Mulder RL, et al. Primary cardioprotection with dexrazoxane in patients with childhood cancer who are expected to receive anthracyclines: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Child Adolesc Health*. 2022;6(12):885–894. doi:10.1016/S2352-4642(22)00239-5
63. Chow EJ, Aggarwal S, Doody DR, et al. Dexrazoxane and long-term heart function in survivors of childhood cancer. *J Clin Oncol*. 2023;41 (12):2248–2257. doi:10.1200/JCO.22.02423
64. Sobczuk P, Czerwińska M, Kleibert M, Cudnoch-Jędrzejewska A. Anthracycline-induced cardiotoxicity and renin-angiotensin-aldosterone system-from molecular mechanisms to therapeutic applications. *Heart Fail Rev*. 2022;27(1):295–319. doi:10.1007/s10741-020-09977-1

65. Vafa RG, Sabahizadeh A, Mofarrah R. Guarding the heart: how SGLT-2 inhibitors protect against chemotherapy-induced cardiotoxicity: SGLT-2 inhibitors and chemotherapy-induced cardiotoxicity. *Curr Probl Cardiol*. 2024;49(3):102350. doi:10.1016/j.cpcardiol.2023.102350
66. Sobiborowicz-Sadowska AM, Kamińska K, Cudnoch-Jędrzejewska A. Neprilysin inhibition in the prevention of anthracycline-induced cardiotoxicity. *Cancers*. 2023;15(1):312. doi:10.3390/cancers15010312
67. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. *JAMA Cardiol*. 2019;4(10):1007–1018. doi:10.1001/jamacardio.2019.2952
68. Ananthan K, Lyon AR. The role of biomarkers in cardio-oncology. *J Cardiovasc Transl Res*. 2020;13(3):431–450. doi:10.1007/s12265-020-10042-3
69. Habibian M, Lyon AR. Monitoring the heart during cancer therapy. *Eur Heart J Suppl*. 2019;21(Suppl M):44–49. doi:10.1093/eurheartj/suz230
70. Hayward R, Lien CY, Jensen BT, Hydock DS, Schneider CM. Exercise training mitigates anthracycline-induced chronic cardiotoxicity in a juvenile rat model. *Pediatr Blood Cancer*. 2012;59(1):149–154. doi:10.1002/pbc.23392
71. Wu X, Wang L, Wang K, et al. ADAR2 increases in exercised heart and protects against myocardial infarction and doxorubicin-induced cardiotoxicity. *Mol Ther*. 2022;30(1):400–414. doi:10.1016/j.ymthe.2021.07.004
72. Kang DW, Wilson RL, Christopher CN, et al. Exercise cardio-oncology: exercise as a potential therapeutic modality in the management of anthracycline-induced cardiotoxicity. *Front Cardiovasc Med*. 2021;8:805735. doi:10.3389/fcvm.2021.805735