

# Stem cell-derived exosomes in the treatment of chemotherapy-induced cardiotoxicity: A systematic review of *in vivo* and *in vitro* studies

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## ABSTRACT

**Introduction:** Chemotherapy-induced cardiotoxicity (CIC) is a significant challenge in cancer treatment, with limited therapeutic options available for preventing cardiac damage. This systematic review aimed to summarize the therapeutic efficacy of stem cell-derived exosomes in CIC.

**Methods:** PubMed/MEDLINE, Scopus, and Web of Science databases were systematically searched up to April 2024, to identify relevant *in vivo* and *in vitro* studies. Two reviewers independently screened and extracted data using a pilot-tested form. The quality of the included studies was evaluated using the SYRCLE risk of bias tool for animal studies and the QUIN (QUality IN vitro) Assessment Tool. Due to heterogeneity in models, exosome sources, isolation methods, dosing, routes, timing, and outcomes, we conducted a narrative synthesis without meta-analysis. **Results:** Among the 107 citations obtained from the databases, 27 were included. Exosome treatment improved cardiac function parameters, including left ventricular ejection fraction (LVEF), fractional shortening (FS), and stroke volume (SV). Exosomes were associated with favorable changes in cardiac biomarker levels, including significant reductions in troponin, creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH). Exosomes also reduced inflammation and oxidative stress markers, and ameliorated histopathological changes in cardiac tissues. They were associated with a reduction in apoptotic markers and enhanced cell survival. In addition, exosomes improved angiogenesis in daunorubicin-induced cardiac models. The available evidence suggests the beneficial effects of stem cell-derived exosomes for CIC treatment and prevention. **Conclusions:** Stem cell-derived exosomes demonstrate promising therapeutic effects in mitigating chemotherapy-induced cardiotoxicity by enhancing cardiac function, reducing inflammation and oxidative stress, and limiting apoptosis. These findings support the potential clinical application of exosomes as a novel, cell-free strategy for cardioprotection in cancer patients undergoing chemotherapy. Further clinical trials are warranted to confirm their efficacy and safety.

**Key words:** Exosome, Cardio-oncology, Cardiotoxicity, Chemotherapy

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## INTRODUCTION

In recent years, novel anti-cancer medications have remarkably improved survival rates of patients with malignancies. However, alongside these benefits, there has been a notable increase in morbidity and mortality among cancer patients due to adverse effects<sup>1</sup>. The most significant chemotherapy-induced adverse effect is cardiotoxicity, which can lead to impaired cardiac function, increased morbidity and mortality, and reduced quality of life<sup>1,2</sup>. Cardiotoxicity from anti-cancer drugs may cause serious complications, including myocardial infarction, arrhythmia, and hypertrophy. These complications can limit the future use of such medications<sup>3,4</sup>. Accordingly, anthracyclines, a primary class of chemotherapeutic agents, have been associated with an increased prevalence of chemotherapy-induced car-

diac dysfunction of up to 57% in Western countries<sup>5</sup>. Cardiac dysfunction may manifest years after chemotherapy, ranging from asymptomatic changes and subclinical disease to heart failure or death<sup>1,6,7</sup>.

Given the widespread use of chemotherapy medications, particularly anthracyclines, numerous pharmacological agents have been investigated for their protective effects against chemotherapy-induced cardiotoxicity (CIC)<sup>8</sup>. Similarly, mesenchymal stem cells (MSCs) have been proposed as a means to attenuate cardiotoxicity due to their key functions, including self-renewal and multilineage differentiation potential, pluripotency, and the ability to develop into different cell types<sup>9</sup>.

Recent studies have shown that the therapeutic effects of MSCs are attributed to extracellular vesicles (EVs) derived from these cells<sup>10,11</sup>. Exosomes are

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small EVs (30–100 nm) released by various cell types. They carry proteins, lipids, growth factors, and miRNAs, enabling cell-to-cell communication<sup>12,13</sup>. They engage target cells via various mechanisms, including promotion of cell proliferation, suppression of apoptosis, attenuation of oxidative stress in recipient cells, regulation of immune responses, and improvement in oxygen delivery<sup>11</sup>. Exosomes may serve as an alternative to MSC-based therapies due to their biocompatibility, low immunogenicity, and reduced risk of embolism. They circumvent many drawbacks of cell-based treatments and hold promise for cardiac repair<sup>14,15</sup>.

With increasing cancer patient survival, more attention is needed for chemotherapy side effects, particularly cardiotoxicity, and the discovery of more effective treatment methods to ameliorate the cardiotoxic effects of these medications remains a significant challenge. To the best of our knowledge, no prior systematic review has comprehensively evaluated the therapeutic effects of stem cell-derived exosomes in models of chemotherapy-induced cardiotoxicity. This review aims to fill that gap by synthesizing preclinical evidence from both *in vitro* and *in vivo* studies. Therefore, in this systematic review, we aim to summarize the potential of exosomes in the treatment of CIC.

## METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>16</sup> (see Table S1). It was not registered.

### Search Strategy

A systematic literature search was conducted using three electronic databases from their inception to April 8, 2024, namely PubMed/MEDLINE, Scopus, and Web of Science. Manual searches for additional studies were also performed using Google and Google Scholar, and the reference lists of included reviews were screened. The search query shown in Table S2 was used for the systematic search. There were no restrictions on study location or publication date.

### Eligibility Criteria

Two reviewers (R. A. B. and B. D.) screened the literature according to predetermined inclusion criteria for eligible articles. Inclusion comprised non-duplicate, English-language, *in vivo*, or *in vitro* articles evaluating the therapeutic effect of stem cell-derived exosomes on chemotherapy drug-induced

cardiotoxicity. We excluded non-English articles, duplicate reports, irrelevant studies, and those reporting only prophylactic effects without investigating therapeutic effects.

### Study Selection and Data Extraction

Two reviewers (H. S. and Z. G.) independently screened titles and abstracts for duplication and selected potentially relevant articles. All full-text articles were independently reviewed to determine inclusion. EndNote software version 21 was used to remove duplicates from screened records. When data were missing, additional information was requested from the authors.

The following data were extracted from eligible articles using a predesigned Microsoft Excel form: general study parameters (first author, year of publication, and study design), animal model (animal species, animal model, animal sex, and age), experimental sample characteristics, stem cell type and source (isolation method for exosomes, dosage, route, and timing of exosome administration, and particle size), targeted non-coding RNA, and outcomes of interest. Any disagreements in the screening process or data extraction were resolved by discussion and consultation with a third reviewer (M. R. R.).

### Outcomes of Interest

All outcomes were continuous; we extracted study-level group means ( $\pm$ SD/SEM) and mean differences (or change-from-baseline, when reported).<sup>1</sup> Cardiac function: LVEF/LVFS, stroke volume;<sup>2</sup> Biomarkers: troponin, CK-MB, LDH, NT-proBNP;<sup>3</sup> Inflammation, oxidative stress: cytokines, ROS, MDA, antioxidant enzymes;<sup>4</sup> Histology, fibrosis: injury, fibrosis scores or % fibrotic area;<sup>5</sup> Cell death: TUNEL %, caspase activity, Bax/Bcl-2;<sup>6</sup> Angiogenesis: capillary density, marker expression;<sup>7</sup> Mitochondrial function: ATP, fusion/fission, biogenesis proteins. Because measures, units, and time points varied across studies, we did not pool effects; results are presented as study-level contrasts and direction-of-effect summaries.

### Quality Assessment of Included Studies

Two reviewers (R. A. B. and B. D.) independently assessed the risk of bias and quality of included studies using the SYRCLE risk of bias tool<sup>17</sup>. It assesses the risk of bias in ten domains, including selection bias (sequence generation, baseline characteristics, and allocation concealment), performance bias (random blinding and housing, and blinding), detection

bias (random outcome assessment and blinding), other biases<sup>17</sup>. Responses to these domains were “yes” (low risk of bias), “no” (high risk), or “?” (unclear). For in vitro studies, risk of bias was evaluated with the QUIN (Quality Assessment Checklist) tool, which includes 12 criteria scored as adequate (2 points), inadequate (1 point), or not specified (0 points; not applicable criteria excluded). Studies were classified as having low risk of bias (>70%), medium risk (50%–70%), or high risk (<50%)<sup>18</sup>.

### Synthesis Methods

Narrative synthesis was performed due to heterogeneity in models, agents, and exosome preparations. Studies were grouped by prespecified outcome domains (function, biomarkers, inflammation, oxidative stress, histopathology, fibrosis, cell death, angiogenesis, mitochondrial function), tabulated with model, intervention details, and summarized by direction of effect. We extracted all measures and time points but prioritized canonical indicators and the latest post-intervention readouts for each summary. Risk of bias (SYRCLE/QUIN) informed interpretation; no meta-analysis or formal assessments of reporting bias or certainty were performed.

## RESULTS

### Search results

Database searches yielded 107 articles. After removing duplicates, 80 citations were screened, and 54 underwent full-text review. Of these, 27 published papers were deemed relevant and included<sup>19–45</sup>. A PRISMA flowchart of the study selection process is presented in Figure 1.

### Study characteristics

The included studies comprised 14 performed in both in vitro and in vivo settings, 8 performed solely in vivo, and 5 performed solely in vitro. Among them, 15 focused on male subjects, whereas 3 examined female subjects exclusively, and 1 included both male and female subjects. Publication years ranged from 2015 to 2024.

For animal species, 13 studies used mice, including 8 using C57BL/6 mice, 2 using CI-1 mice, and 1 using nude mice. Additionally, 7 studies used rats, with 4 using Wistar rats, and 3 using Sprague-Dawley rats. Notably, one study used fertilized chicken eggs for chorioallantoic membrane assays. Among the studies with in vitro components, samples included various cell types, such as rat embryonic cardiomyocyte

cells (H9c2), neonatal rat cardiac myocytes (NR-CMs), neonatal mouse cardiac myocytes, primary mouse cardiomyocytes, human AC16 cells, human cardiac microvascular endothelial cells, NR8383 rat macrophage cells, patient-specific induced pluripotent stem cell-derived cardiomyocytes (iCMs), and human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) from full-term cesarean deliveries; plus mouse ventricular myocytes from C57BL/6 mice, and human induced pluripotent stem cell-derived cardiomyocytes. The characteristics of the included studies are presented in Table 1.

### Risk of bias and quality of the studies

Quality assessment results are presented in Tables S3–S4. Among the 20 in vivo studies, 9 (45%) reported random allocation sequence generation, and 11 (55%) lacked clear reporting on random sequence generation. All studies accounted for baseline differences in participant characteristics. Performance blinding was reported in 4 studies (20%), was unclear in 11 (55%) due to insufficient reporting, and was absent in 5 (25%). Random animal housing was reported in 5 studies (25%); the remainder lacked sufficient information on this. Random outcome assessment was reported in 5 (25%) studies; 15 (75%) lacked sufficient data on random outcome assessment. Detection blinding was reported in 3 studies (15%). Risks of other sources of bias and reporting bias were low across all studies. Additionally, 19 studies showed low risk of attrition bias. For in vitro studies, the QUIN tool was used. All 19 in vitro studies clearly stated their aims and objectives and provided detailed descriptions of methods. Moreover, all adequately described methods for outcome measurement, statistical analysis, and data presentation. However, none reported sample size calculations, interventions, randomization, or outcome assessor blinding. Reporting of control group details and sampling techniques was inadequate in 5 (25%) and 2 (10%) studies, respectively.

### Exosome Administration

Exosomes were isolated from various cell types, including bone marrow and umbilical cord mesenchymal stem cells (MSCs) from rats, mice, and humans; fourth-generation adipose-derived mesenchymal stem cells from C57 mice (ADSCs); human trophoblast stem cells (TSCs); human iPSC-derived cardiac progenitor cells (EV-CPCs); serum extracellular vesicles (EVs) derived from saline-treated rats (SAL-EVs); and serum EVs derived from doxorubicin-treated rats 1 month after saline or doxorubicin

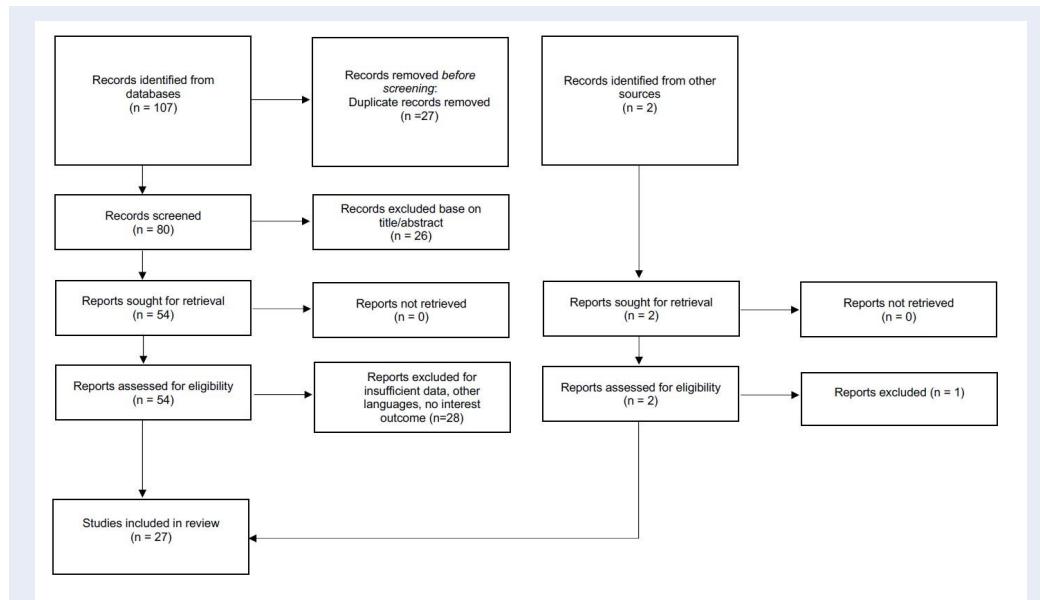


Figure 1: The flowchart of study selection

treatment; allogeneic embryonic stem cells from the CGR8 mouse ES cell line (ESCs); allogeneic mouse embryonic fibroblasts (MEFs); and human cardiac stem cells (hCSCs). Most studies employed ultracentrifugation or tangential flow filtration for exosome isolation. Size exclusion chromatography was used in four studies, and exosome extraction reagents were used in seven studies. Particle size was reported in 23 studies and ranged from 30 to 450 nm. Administration was primarily via the intravenous route; however, alternative methods of administration, such as intraperitoneal injection, intramyocardial injection, and intraventricular injection, were also used. The characteristics of the stem cell-derived exosomes and their treatment strategies are shown in Table 2.

### Cardiac Function

Eighteen studies reported data on cardiac function. Mice treated with exosomes exhibited higher left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), and stroke volume (SV) compared to the doxorubicin-induced heart failure group, although these values remained lower than those in the control group<sup>24,27,30,31,36,39-42,44,45</sup>. A study in C57BL/6 mice reported that the exosome-treated group exhibited a higher LVEF and LVFS; however, no significant differences were observed in left ventricular systolic and diastolic diameters<sup>25</sup>. In contrast, Ebrahim et al. reported that

exosome administration before or after doxorubicin treatment was significantly associated with lower systolic and diastolic left ventricular diameters. Moreover, preventive (pre-treatment) administration of exosomes resulted in better results than post-treatment (curative) administration<sup>31</sup>. A cyclophosphamide-based study reported similar findings: exosomes decreased LV diameters and increased LVEF<sup>23</sup>. A study by Lee et al. also corroborated a decrease in left ventricular end-systolic diameter/volume (LVESD/V), left ventricular end-diastolic diameter/volume (LVEDD/V), and increases in fractional shortening (FS) and ejection fraction (EF) after exosome administration<sup>36</sup>. However, two studies found that exosomes did not significantly affect cardiac function parameters, such as LVEF, LVFS, basal circumferential strain, basal endocardial circumferential strain, basal epicardial circumferential strain, and global longitudinal strain<sup>26,33</sup>.

### Cardiac biomarkers

Eight studies reported changes in cardiac enzyme levels. A study by Imam et al.<sup>20</sup> on Wistar albino rats reported that exosomes decreased troponin I, creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH). Consistent with these results, another study on Sprague-Dawley rats treated with cyclophosphamide reported that combination treatment with exosomes decreased LDH, troponin, and

**Table 1: Summary of characteristic for included studies**

First author	Year	Study Design	Gender	Animal species	Animal model	Age (weeks)	Experimental sample	Stem cell type and source
Zhang et al.	2024	in vivo and in vitro	-	Fertilized eggs of chicken	Chicken Chorioallantoic Membrane	NR	Human cardiac microvascular endothelial cell	MSCs xenogenic in vivo/allogenic in vitro
Imam et al.	2024	in vivo	M	Rat	Wistar	NR	-	Bone marrow-derived MSCs from Fora and tibiae of Wistar albino rats/allogenic
Ali et al.	2024	in vitro	-	-	-	-	Rat embryonic cardiomyocyte cells (H9c2)	C57BL/6 mouse bone MSCs xenogenic
Zeng et al.	2023	in vitro	-	-	-	-	Embryonic cardiomyocyte cells (H9c2)	Rat Bone marrow stromal cells -allogenic
Xiong et al.	2023	In vivo	M	Rat	Specific pathogen-free Sprague Dawley	6	-	Adipose-derived mesenchymal stem cell-xenogenic
Wang et al.	2023	in vivo	M	Rat	Wistar	NR	-	Fourth-geneRation adipose-derived mesenchymal stem from C57 mice xenogenic
Duan et al.	2023	in vivo and in vitro	M	Mice	C57BL/6	8	H9c2 cardiac myoblast cells	Human trophoblast stem cells xenogenic
Desgres et al.	2023	in vivo	M	Mice	BALB/c	9 -12	-	Cardiac progenitor cells differentiated from human induced pluripotent stem cells - xenogenic
Desgres et al.	2023	in vivo	F	Rat	Wistar	8	-	Human iPSC-derived CPC-xenogenic
Yu et al.	2022	in vivo and in vitro	M	Mice	Wild-type (WT) C57BL/6	8	Neonatal Rat cardiac myocytes (NRCMs): Normoxic and Hypoxic MSCs	Human umbilical cord mesenchymal stem cells from healthy adults-xenogenic
Tian et al.	2022	in vivo and in vitro	M	Mice	C57BL/6	10	Neonatal cardiomyocytes of Kunming mice at 1-3 days postnatally	Bone marrow MSCs
Huang et al.	2022	in vivo and in vitro	M	Mice	CD1	4-6	Primary mouse cardiomyocytes	human placenta-derived MSCs xenogenic
Fan et al.	2022	in vivo	NR	nude Mice	NR	NR	-	Bone marrow MSCs from Fur and tibia of three-week-old Rats- xenogenic

Ebrahim et al.	2022	in vivo	M	Rat	Wistar	8	-	Rat-adipose-derived MSCs allogenic
Zhong et al.	2021	in vitro	-	-	-	-	Human AC16	human umbilical cord MSCs allogenic
O'Brien et al.	2021	in vitro	-	-	-	-	Patient-specific induced pluripotent stem cell-derived cardiomyocytes (iCMs)	bone marrow derived MSCs from a young, healthy female-allogeneic
Li et al.	2021	In vitro	-	-	-	-	Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) from full-term cesarean section deliveries	human placental MSCs from full-term cesarean section deliveries-allogenic
Lei et al.	2021	in vivo and in vitro	F	Rat	Sprague Dawley	NR	H9c2	The third generation of bone marrow MSCs from femur and tibia of female adult Sprague Dawley rats-allogenic
Lee et al.	2021	in vivo and in vitro	M	Mice	C57BL/6	6	Rat neonatal H9c2 cardiac myoblast cell line	murine embryonic MSCs- allogenic in vivo-xenogenic in vitro
Zhuang et al.	2020	in vivo and in vitro	M	Mice	C57/Bl6	8	Mouse ventricular myocytes from C57BL/6 mice	Bone marrow-derived MSCs from the femur and tibia of mice pretreated with macrophage migration inhibitory factor-allogenic
Xia et al.	2020	in vitro	-	-	-	-	Human-induced pluripotent stem cell-derived cardiomyocytes	Human adipose-derived MSCs some exosomes pretreated with hypoxia-allogenic
Ni et al.	2020	in vivo and in vitro	M	Mice	C57/Bl6	8	Primary cardiomyocytes from neonatal mice (post 1-2 days)	Human trophoblast stem cells (HTR8-Svneo/TSCs)-xenogenic
Ni et al.	2020	in vivo and in vitro	M	Mice	C57/Bl6	8-10	The human cardiomyocyte cell line AC16	Human trophoblast stem cells (HTR8-Svneo/TSCs)-xenogenic in vivo, allogenic in vitro
Milano et al.	2020	in vivo and in vitro	F	Rat	Sprague Dawley	NR	Primary cardiomyocytes from Wistar neonatal rat at p1-3	Human cardiac-resident mesenchymal progenitor cells from right cardiac atrial appendage tissue specimens obtained from 21 patients
Singla et al.	2019	in vivo	M/F	Mice	C57BL/6J JAX: 000664	10	-	Embryonic stem cells from CGR8 -allogenic
Dargani et al.	2019	in vitro	-	-	-	-	H9c2 cardiomyoblast	Mouse embryonic stem cell line, Mouse embryonic fibroblasts cell line-xenogenic

Sun et al.	2018	in vivo and in vitro	M	Mice	C57BL/6j	8-10	Cardiac myocytes from 1-3-day-old C57BL/6j mice	MSCs from the conditioned media of murine-allogenic
Vandergriff et al.	2015	in vivo and in vitro	M	Mice	CD-1	6-8	Neonatal rat cardiomyocytes (NRCMs)	Human cardiac stem cells-xenogeneic

M, male; F, female; NR, not reported; MSC, mesenchymal stem cells.

**Table 2: Summary of treatment and stem cell-derived exosome parameters**

First author	Year	Particle nm	Isolation method	Route	Timing	Dosage	Type of drug
Zhang et al.	2024	NR	NR	NR	NR	150 µg/egg	Doxorubicin
Imam et al.	2024	Mean 50 nm	Ultracentrifugation	Intraperitoneal	Single injection	800 µg protein concentration, suspended in 1 mL PBS	Doxorubicin
Ali et al.	2024	less than 200 nm	Exoquick-TC exosome precipitation solution and then centrifugation	NR	24 hours after Dox	10 µg of MSC-exosome	Doxorubicin
Zeng et al.	2023	50 to 200 nm	Ultracentrifugation	NR	NR	NR	Doxorubicin
Xiong et al.	2023	80-200 nm	Ultracentrifugation	Intraperitoneal injection	2 times: 1 week before CYP and 1 week later	$3 \times 10^{10}$ AdMSCs-Exos (in 0.1 mL PBS)	Cyclophosphamide
Wang et al.	2023	NR	Exo extraction reagent and centrifugation	Injection via the tail vein	Once every 2 days for two consecutive times	100 µL of exosomes suspension at a concentration of 0.2 mg/mL	Doxorubicin
Duan et al.	2023	Mean 113 nm	Ultracentrifugation	Intracardiac injection for in vivo	In vitro: 24 h	25 µl of PBS containing 50 µg exosomes for in vivo 20 µg of exosomes for in vitro	Doxorubicin
Desgres et al.	2023	50 nm to 450 nm	Ultracentrifugation	Intravenous injection	Three times over 2 weeks	A total dose of 30E+9 particles	Doxorubicin
Desgres et al.	2023	Tangential flow filtration	Intravenous injection	3 equal injections one every 2 days	NR	A total dose of 100E+9/injection	Doxorubicin
Yu et al.							
Tian et al.	2022	100-150 nm	Ultracentrifugation	Injection via tail vein	Day 1, 2, 3, 5, 6, and 7	200ug/100ul PBS	Doxorubicin

Huang et al.	2022	100 nm	Differential ultracentrifugation	Injection via the tail vein	Day 8, 11, and 14	50µg	Doxorubicin
Fan et al.	2022	NR	MSCs and lung tissue-derived cell type (MRC5)-EVs: ultracentrifugation Peripheral blood-derived EVs: Total Exosome Isolation	Injected via the tail vein	NR	200 µmol/L	Doxorubicin
Ebrahim et al.	2022	Mode 108 nm	Exosome extraction kit (exosome extraction reagent and then centrifugation)	Intravenous injection	4 h before injection	500 µL of PBS containing 20 µg combination of exosomes	Doxorubicin
Zhong et al.							
O'Brien et al.	2022	40-120 nm	Ultracentrifugation	Intraperitoneal injection	Protective group: 1 dose of exosomes 1w before the induction of cardiotoxicity. Curative group: Six weeks after the final injection.	each dose $3 \times 10^{10}$ exosome, re-suspended in 0.1 mL PBS	Doxorubicin and trastuzumab
Li et al.	2021	30-100 nm	Ultracentrifugation	NR	NR	MSC with the dosage of 0 µg/ml, 50 µg/ml, 100 µg/ml, and 200 µg/ml	Doxorubicin
Lei et al.	2021	large extracellular vesicles (L-EVs): mean 428 nm (350-800 nm) small extracellular vesicles (S-EVs): mean 92 nm (58-122 nm)	Centrifugation for EV>200 nm → proprietary size-based filtration platform (Exosome Total Isolation Chip - exosome TIC)	NR	24 h after injection	NR	Doxorubicin
Lee et al.	2021	100-200 nm	Differential centrifugation	NR	NR	NR	Doxorubicin
Zhuang et al.	2021	30 to 100 nm/ mean 90nm	Centrifugation	Injection via the tail vein	Days 5 and 11	$3 \times 10^{10}$ particles each dose resuspended in 0.1 mL of PBS	Doxorubicin

Xia et al.	2021	Approximately 135 nm	Ultrafiltration	Intravenous injection	At 1 day before injection (15 mg/kg, i.p.), and then every other day for 14 days	in vivo: $4 \times 10^{10}$ in vitro: MSC at a concentration of $3 \times 10^9$	Doxorubicin
Ni et al.	2020	50–100 nm	Exosome quick extraction solution	Intraperitoneal injection	alternative days between treatments (Tuesday, Thursday, and Saturday)	400 $\mu$ L/injection with 50 $\mu$ g concentration of exosome	Doxorubicin
Ni et al.	2020	50–100 nm	Exosome quick extraction solution	NR	NR	NR	Doxorubicin
Milano et al.	2020	Mean 101 nm	Differential ultracentrifugation	Intramyocardial injection	One dose	25 $\mu$ L of PBS containing 50 $\mu$ g exosome	Doxorubicin
Singla et al.	2020	50–150 nm	Ultracentrifugation	Injected into the left ventricle myocardium	At multiple points	100 $\mu$ L per mouse; 1 $\mu$ g/ $\mu$ L	Doxorubicin
Dargani et al.	2020	Predominantly <150 nm	Ultracentrifugation	Injection via tail vein	Three doses on Days 5, 11, and 19.	$3 \times 10^{10}$ particles each dose re-suspended in 0.1 mL PBS	Doxorubicin and trastuzumab
Sun et al.	2019	NR	Exoquick TC exosome isolation kit and the centrifugation	Intraperitoneal injection	Alternative days of a week between Dox treatments (Tuesday, Thursday, and Saturday)	400 $\mu$ L/injection with 50 $\mu$ g concentration of exosome	Doxorubicin
Vandergriff et al.	2019	NR	Exoquick-TC exosome precipitation solution and then centrifugation	NR	48h after injection	10 $\mu$ g/24h	Doxorubicin

NR, not reported; MSC, mesenchymal stem cells; PBS, phosphate buffered saline; EV, extracellular vesicle

CK-MB levels<sup>23</sup>. Another study on Sprague-Dawley rats/H9c2 cells reported that exosomes decreased the levels of troponin, CK-MB, and LDH compared to those in doxorubicin-treated rats<sup>35</sup>. Ebrahimi et al. evaluated the effects of exosomes in eight-week-old albino rats, comparing three groups: the protective group (that received one dose of exosomes one week before the induction of cardiotoxicity, plus two doses thereafter following trastuzumab administration), the curative group (that received only two doses of exosomes as treatment after cardiotoxicity induction with trastuzumab), and the doxorubicin+trastuzumab control group. The results indicated that both the protective and curative approaches decreased the levels of troponin, LDH, and CK-MB compared to the doxorubicin+trastuzumab control group. Moreover, rats in the curative group had higher levels of these cardiac enzymes, suggesting greater efficacy from exosome administration before chemotherapy<sup>31</sup>. Other studies reported that exosomes decreased HF-related cardiac biomarkers, such as atrial natriuretic peptide (ANP), N-terminal pro-BNP (NT-proBNP),  $\beta$ -cardiac myosin heavy chain ( $\beta$ -MHC), and collagen I<sup>39,40</sup>. Furthermore, a study comparing exosomes with tetrahedral DNA nanostructure (TDN) alone when added to doxorubicin to a combination of exosome-TDN plus cardiomyopathic peptide reported that the latter approach resulted in lower NT-proBNP and troponin levels<sup>30</sup>.

### Inflammation and oxidative stress

Seventeen studies have examined the effects of exosomes on inflammation and/or oxidative stress. Seven studies reported a significant decrease in ROS following exosome treatment<sup>22,25,28,32,33,41,44</sup>. Imam et al. reported that exosomes reduced IL-6 and MDA, while increasing IL-10, GSH, catalase, and the percentage area of Nrf2-positive staining in immunohistochemical analyses<sup>20</sup>. Tian et al.<sup>28</sup>, Ni et al.<sup>39</sup>, and Dargani et al.<sup>43</sup> reported a significant decrease in IL-6 and IL-1 $\beta$  levels after exosome administration. Lei et al.<sup>35</sup> found that exosomal miR-96 reduced TNF- $\alpha$ , IL-6, and IL-1 $\beta$  levels by inhibiting the Rac/nuclear factor  $\kappa$ B pathway. Sun et al. reported that exosomes decreased the mRNA expression of IL-1, IL-6, and TNF- $\alpha$  and reduced the number of pro-inflammatory macrophages through the JAK2-STAT6 pathway<sup>44</sup>. A significant reduction in CD68+, CD11b+, and CD80+ cells and an increase in CD206+ cells were observed in previous studies<sup>30,41,42,44</sup>. Zhong et al.<sup>32</sup> and Yu et al.<sup>27</sup> reported a reduction in MDA levels and an increase in

GSH levels following exosome therapy. Ebrahimi et al. reported a greater reduction in iNOS and MDA levels in the protective group than in the curative group<sup>31</sup>. Moreover, higher SOD activity was observed in exosome-treated groups<sup>20,31,32,35</sup>.

### Histopathological Changes

Histopathological changes were observed in 12 studies. Exosome treatment ameliorated doxorubicin-induced disturbed cardiac architecture, extensive hyalinization, interstitial edema, multifocal leukocytic cell infiltration, fibroblast invasion, and blood vessel congestion<sup>20,29,30,40,45</sup>. Exosomes reduced swelling, necrosis, and disarrangement of cardiomyocytes<sup>24</sup>. In comparison to the control, heart tissue from the doxorubicin group exhibited enlarged chambers and thinner ventricular walls, which were ameliorated in the doxorubicin + exosome group<sup>25</sup>. Exosomes ameliorated retrogressive changes, congestion, increased myocyte cross-sectional area and collagen accumulation, and resultant fibrosis in cardiac tissues<sup>23</sup>. Exosomes reduced Collagen-1 and MMP-9 mRNA levels, as well as perivascular and interstitial collagen deposition<sup>20,31,35</sup>.

Groups treated with exosomes exhibited reduced intracytoplasmic vacuolization and preserved normal structure and morphology of the myocardium<sup>31</sup>. Lei et al. reported that exosomes attenuated doxorubicin-induced loss of cardiac muscle fibers, myocardial vacuole degeneration, and inflammatory infiltration<sup>35</sup>. Histological staining of the heart at week 4 revealed that the exosome treatment group had greater myocardial thickness and smaller cardiac chamber diameter compared to the doxorubicin group<sup>44</sup>. Furthermore, exosome treatment was associated with a reduction in myofibril loss and cardiac hypertrophy<sup>42</sup>.

### Apoptosis

The outcomes regarding cell survival and apoptosis were reported in 16 studies. Overexpression of Bcl-2 and downregulation of Bax following treatment with exosomes were reported in seven<sup>23,24,30,31,36,39,40</sup> and three studies, respectively<sup>24,31,34</sup>. In addition, one study showed that exosomes decreased the Bax/Bcl-2 ratio<sup>44</sup>. Exosomes also inhibited the activity of caspases, including caspase-1, -3, and -9<sup>20,23,24,30,34,39,40</sup>, as well as the number of dUTP nick end labeling (TUNEL)-positive apoptotic cells<sup>36,44,45</sup>. Imam et al. and Sun et al. reported a reduction in Annexin V staining levels after treatment with exosomes<sup>20,44</sup>. Moreover, a reduction in p53 expression has been reported in those

studies<sup>20,24</sup>. Overall, exosomes significantly inhibit apoptosis and promote cell survival.

### Angiogenesis

Zhang et al. evaluated the pro-angiogenic efficacy of exosomes using models of daunorubicin-damaged cardiac microvascular endothelial cells and the chicken chorioallantoic membrane (CAM) model of Chicken Chorioallantoic Membrane blood vessels. Their results suggested that administration of 150 µg/egg of exosomes significantly enhanced angiogenesis in the chicken CAM (an *in vivo* daunorubicin-damaged model)<sup>19</sup>. A summary of the outcomes of the included studies is shown in Table 3.

## DISCUSSION

Currently, there is no specific treatment that offers cardioprotection against CIC. This systematic review evaluated the therapeutic effects of stem cell-derived exosomes in both *in vitro* and *in vivo* models of CIC. Our results suggest that exosome transplantation can improve cardiac function, reduce fibrosis, and ameliorate elevated inflammation, cardiac markers, and apoptosis induced by chemotherapy drugs.

However, the exact mechanisms of CIC remain unclear. Previous studies have identified that the generation of reactive oxygen species (ROS) and the promotion of several inflammation-dependent pathways represent plausible mechanisms of action for these agents<sup>46,47</sup>. ROS generation may disrupt mitochondrial function, leading to apoptosis<sup>48</sup>. The results of this review demonstrated that exosomes reduced ROS production, expression of inducible nitric oxide synthase (iNOS), lipid peroxidation, and inflammatory markers such as IL-1 $\beta$ , IL-1, IL-6, and IL-18. Furthermore, exosomes inhibit apoptosis by downregulating caspase-3, caspase-1, and p53; upregulating the Bcl-2 protein; and promoting mitochondrial fusion.

Chemotherapy agents may inhibit matrix metalloprotease-1 (MMP-1) in cancer tissues, which reduces the mobility of tumor cells<sup>49</sup>. However, this mechanism of action results in the upregulation of other MMPs<sup>50</sup>. The activation of other MMPs can promote collagen deposition in cardiomyocytes and activate transforming growth factor beta (TGF- $\beta$ ) signaling, leading to cardiac fibrosis<sup>51,52</sup>. This review demonstrates that exosomes possess the therapeutic potential to counteract dysregulated MMPs and the TGF- $\beta$  pathway, which could prove instrumental in safeguarding cardiac

function and preventing the progression of cardiac fibrosis induced by chemotherapeutic agents.

Several signaling pathways mediate the cardioprotective effects of stem cell-derived exosomes, as summarized in our tables. These include Rac1/NF- $\kappa$ B, PI3K-AKT-Foxo1, and JAK2-STAT6. Although these pathways differ in their upstream triggers and downstream targets, they converge on key cellular processes, including inflammation suppression, oxidative stress reduction, and apoptosis inhibition. Rac1/NF- $\kappa$ B signaling, for example, reduces oxidative stress, inflammation, and fibrosis, thereby improving cardiac function. The PI3K-AKT-Foxo1 pathway primarily contributes to oxidative stress reduction. The JAK2-STAT6 pathway promotes polarization of macrophages from pro-inflammatory to anti-inflammatory phenotypes, resulting in decreased cardiac inflammation, fewer circulating macrophages, reduced cytokine production, and improved cardiac function and cardiomyocyte survival.

Cardiac biomarkers may be elevated despite normal cardiac echocardiography findings in the first stage of cardiotoxicity<sup>53,54</sup>. Recent studies have shown that cardiac biomarkers are valid predictors of CIC. Cardinale et al. demonstrated that an increase in troponin I levels within 72 hours after high-dose chemotherapy predicts declines in LVEF<sup>55</sup>. Rüger et al. reported that NT-proBNP levels measured 6 weeks after chemotherapy initiation were associated with cardiotoxicity in patients with early-stage breast cancer<sup>56</sup>. Our study found that administration of stem cell-derived exosomes was associated with a significant decrease in cardiac biomarkers, including troponin, NT-proBNP, CK-MB, and ANP. The significant decrease in these cardiac biomarkers following exosome treatment suggests not only a therapeutic effect but also the potential for preventing the onset of LVEF reduction and subsequent functional decline in cardiotoxicity among patients receiving chemotherapeutic drugs.

Although exosomes have shown significant therapeutic effects in preclinical studies, several challenges must be addressed to enable future clinical application. Challenges include the standardization of isolation and purification methods for exosomes, identification of optimal dosing regimens, elucidation of the mechanisms of action underlying their therapeutic effects, and assessment of long-term safety and efficacy in clinical trials. A few ongoing clinical trials are investigating the role of exosomes in cardiovascular diseases, such as

**Table 3: Summary of key outcomes**

First author	In vivo outcomes	In vitro outcomes
Zhang et al.	Exosomes by the miR-185-5p-PARP9-STAT1/pSTAT1 pathway, significantly improve angiogenesis.	Exosomes by the miR-185-5p-PARP9-STAT1/pSTAT1 pathway, significantly improve migration, proliferation, and angiogenesis.
Imam et al.	Exosomes reduced cardiac tissue levels of Troponin I, CK-MB, and LDH. Besides, reduced the inflammatory biochemical markers, adverse histopathological changes, improved myocardial apoptosis by decrease in both genes' expression, act as an antioxidant, and anti-fibrotic. The exosomes significantly modulated biochemical cardiac tissue levels of oxidative stress markers (GSH, Catalase, GPX, MDA, SOD, Nitric oxide), and restored the number of telocytes in cardiac tissue.	
Ali et al.		Exosomes increased cell viability, reduced the HMGB1/TLR4 axis, inflammasome formation (NLRP3), pyroptotic markers (Caspase-1, IL-1 $\beta$ , and IL-18), and pyroptotic.
Zeng et al.		Exosomes reduced pyroptosis, and mitochondrial damage. Exosomes suppressed GSDMD transcription via the PI3K-AKT-Foxo1 axis and improved oxidative stress.
Xiong et al.	Exosome reduced CYP-induced enhancement in heart weight and heart/body weight ratio, cardiac injury, oxidative stress levels, autophagy, and apoptosis.	
Wang et al.	The LVEF, LVFS, and SV of rats in the exosome group were higher than those in the control group. Exosomes improved heart, decreased apoptosis, increased ATP levels, and suppressed Bax, caspase-3 and p53 protein expression.	
Duan et al.	Exosomes treatment improved EF and FS. Exosomes group had better cardiac function, lower myocardial fibrosis, lower cardiomyocyte mitochondrial fragmentation).	Exosomes reduced ROS, and apoptosis. Exosomes reduce enhanced mitochondrial fusion via increased Mfn2 expression.
Desgres et al.	Exosomes improved early survival and heart contractility	
Desgres et al.	Exosomes significantly protect against chemotherapeutic effects on survival, cardiac function and fibrosis, and reduce ferroptosis-related measures.	Exosomes significantly protect against Dox-induced effect on cell viability and reduced ferroptosis-related measures.
Yu et al.	Exosomes improved survival rate and reduced fibrosis and inflammation-related mRNAs.	Exosomes improved cell viability and reduced cellular inflammation and oxidative stress.
Tian et al.		Exosomes reduced ER stress-induced apoptosis through miR-181a-5p.

Huang et al.	Exosomes improved cell viability, reduced inflammatory markers and polarized M0 or M1 macrophages to the M2 phenotype. Exosomes reduced damage to heart tissue. decreased cardiac biomarkers, polarized M0 or M1 macrophages to the M2 phenotype, and improved cardiac function	
Fan et al.	Exosomes reduce the effect of Dox on cardiac function, serum cardiotoxicity indices, cardiac tissue injury, cardiac oxidative stress, DNA Damage, apoptosis, and fibrosis in cardiac tissues It also improved cardiac Ca <sup>2+</sup> homeostasis.	
Ebrahim et al.		Exosomes significantly reduced oxidative stress levels at the concentrations of 50 µg/ml, 100 µg/ml, and 200 µg/ml. Exosome treatment significantly inhibited Dox-induced apoptosis oxidative stress, LDH, and decreased levels of SOD and NOX4 and NOX2 expression.
Zhong et al.		Exosomes improved iCM viability and attenuated apoptosis, improved contractility, oxidative stress, ATP production, and mitochondrial biogenesis. Exosomes were found to be enriched in mitochondria, which were shown to be taken up by iCMs. Inhibiting mitochondrial function with 1-methyl-4-phenylpyridinium reduce these effects. MSC-treated patient demonstrated improved myocardial function and remodeling.
O'Brien et al.	Exosomes reduced cardiac enzymes, oxidadive stress, fibrosis, inflammatory responses, and protect the cardiac function.	miR-96, derived from exosomes, can inhibit the Rac1/NF-κB signaling pathway, protecting H9c2 cardiomyocytes from Dox-induced toxicity. It can reduce oxidative stress, inflammation, and fibrosis and enhancing cardiac function. miR-96 overexpression inhibited inflammatory responses induced by Dox-induced myocardial toxicity.
Li et al.	Exosomes improved cardiac function and play anti-apoptotic role by upregulating Bcl-2 expression.	Exosomes restore the survivin expression reduced by DOX via Akt activation. Exosomes activate Akt, which activates Sp1 while suppressing p53 activation, resulting in increased survivin expression in Dox-treated cardiomyocytes.
Lei et al.		Exosomes reduced cell apoptosis than Dox by the upregulation of hsa-miR-11401.
Lee et al.	Exosomes significantly increased expression of ejuvenation-related genes, lower senescence-related genes, and improved cardiac function. Exosomes reduced the percentage of cells in the G0/G1 phase, p27 and p16, and SA-β-gal-positive cells. They also elevated telomere length and activity.	Exosomes group had higher ejuvenation-related genes, lower Senescence-related genes, and lower apoptosis.

Zhuang et al.		Exosomes significantly improved rejuvenation in cardiomyocytes. Exosomes specifically transported the lncRNA-MALAT1, which inhibited miR-92a-3p, activating ATG4a and enhancing mitochondrial metabolism while additionally contributing to rejuvenation.
Xia et al.	Exosomes reduced the effect of Dox on cardiac function, fibrosis, apoptosis, and inflammation.	Exosomes group had lower cell apoptosis, C-caspase 3 expression and higher Bcl-2 expression.
Ni et al.	Exosomes significantly protect cardiac function and reduce inflammation and heart failure markers in Dox-induced dilated cardiomyopathy.	Exosomes downregulated YAP signaling and result in significant reduction in apoptosis and fibrosis and protect against Dox-induced pathological changes.
Ni et al.	Exosomes improved cardiac function, oxidative stress, and fibrosis.	Exosomes suppressed oxidative stress in myocytes ( $p < 0.05$ )
Milano et al.	Exosomes reduced the effect of Dox increased expression of inflammatory markers, pyroptotic markers, cell signaling proteins, heart function, fibrosis, and histopathological changes. Exosomes decreased pro-inflammatory M1 macrophages, and TNF- $\alpha$ cytokine) and increase M2 macrophages and anti-inflammatory cytokine, IL-10. Exosomes improved LVIDd, LVIDs, LVEDV, LVESV, FS, and LVEF. Exosomes treatment decreased both vascular and interstitial fibrosis as well as extracellular pro-fibrotic protein MMP-9 in the Dox-induced cardiomyopathy heart.	Exosomes improved cell death and expression of miR-146a-5p target genes.
Singla et al.		Exosomes decreased the expression of inflammasome, pyroptosis, and proinflammatory cytokines and increased anti-inflammatory cytokines.
Dargani et al.	Exosomes improved cardiac function reduced cardiomyocytes apoptosis, cardiac inflammation cytokines production, circulating macrophages amount, and promoting the conversion of macrophages from pro-inflammatory to anti-inflammatory through JAK2-STAT6 pathway.	Exosomes group had higher anti-inflammatory cytokines IL-4, IL-9, and IL-13 and lower proinflammatory cytokines Fas ligand, Fractalkine, granulocyte colony-stimulating factor (GCSF), IL-12, leptin, stromal cell-derived factor 1 (SDF1 $\alpha$ ), TNF- $\alpha$ , and TNF receptor 1. Cardiomyocytes apoptosis is reduced by exosomes showed by significant reduction in TUNEL ratio.
Sun et al.	Exosomes improved cardiac, decreased apoptosis and fibrosis with no adverse immune reaction.	Exosomes reduced apoptosis and fibrosis.

CK-MB, creatine kinase-MB; LDH, lactate dehydrogenase; IL, interleukin; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; DOX, doxorubicin; ROS, reactive oxygen stress; TNF, tumor necrosis factor; SOD, superoxide dismutase; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling.

atrial fibrillation (NCT03478410) and aortic dissection (NCT04356300). This comprehensive review of the *in vivo* and *in vitro* outcomes of exosomes for the prevention and treatment of CIC highlights the potential therapeutic effects of stem cell-derived exosomes. Well-designed controlled clinical trials are warranted to validate the safety and efficacy of exosome treatment for CIC.

To our knowledge, based on a thorough literature search, this is the first systematic review to specifically examine the cardioprotective mechanisms of stem cell-derived exosomes in the context of chemotherapy-induced cardiotoxicity. By integrating findings across diverse models and exosome sources, our review provides a foundational framework for future translational and clinical research.

This review has several limitations. Considerable heterogeneity existed in the stem cell source, route (of administration), timing (of administration), sample types, animal model, and exosome dosage among the included studies. These methodological variations likely influenced the results of the included studies. Although the heterogeneity in study design prevented a quantitative synthesis, it also complicated the qualitative interpretation of the results. These differences could influence therapeutic outcomes and limit the generalizability of the findings. For instance, studies using human-derived exosomes or specific purification methods may exhibit stronger anti-inflammatory effects, whereas others may differ in their effects on cardiac function. This variability underscores the need for standardized protocols in future research to enable clearer comparisons and more robust conclusions. Notably, Table 2 highlights a wide range of dosing strategies, with some studies reporting absolute quantities (e.g.,  $\mu$ g of protein or total volume) rather than standardized metrics such as particles/kg or protein content/kg. This lack of uniformity hinders cross-study comparisons and dose-response assessments. Therefore, future research should prioritize the development and adoption of standardized protocols for exosome characterization and dosing, which would enable clearer comparisons and facilitate clinical translation.

Moreover, the majority of the studies included in this review used doxorubicin to induce cardiotoxicity; thus, the effects of exosomes on cardiotoxicity induced by other chemotherapeutic agents remain unclear. Finally, the follow-up durations in these preclinical studies were relatively short. Further research is necessary to assess the applicability of these findings to clinical settings.

## CONCLUSION

In conclusion, stem cell-derived exosomes were associated with a trend toward higher LVEF and LVFS, and a reduction in levels of troponin and NT-proBNP, in models of CIC. These exosomes were also associated with reductions in oxidative stress, levels of inflammatory markers, and rates of apoptosis. Larger, randomized controlled trials are warranted to confirm these results. Notably, the current evidence is strongest for anthracycline-induced cardiotoxicity, particularly doxorubicin-induced cardiotoxicity, while the efficacy of exosomes to mitigate cardiotoxicity induced by other chemotherapeutic agents such as trastuzumab and cyclophosphamide remains less established and warrants further investigation.

## ABBREVIATIONS

**ANP:** Atrial natriuretic peptide; **APC:** Antigen-presenting cell; **Bcl-2:** B-cell lymphoma 2; **B-MHC:** Beta-myosin heavy chain; **CK-MB:** Creatine kinase-MB; **CIC:** Chemotherapy-induced cardiotoxicity; **Dox:** Doxorubicin; **EF:** Ejection fraction; **ESC:** Embryonic stem cells; **EV:** Extracellular vesicle; **FS:** Fractional shortening; **GSH:** Glutathione; **H9c2:** Rat embryonic cardiomyocyte cell line; **IL:** Interleukin; **iCMs:** Induced pluripotent stem cell-derived cardiomyocytes; **iNOS:** Inducible nitric oxide synthase; **LDH:** Lactate dehydrogenase; **L-EV:** Large extracellular vesicle; **LVEDD:** Left ventricular end-diastolic diameter; **LVEF:** Left ventricular ejection fraction; **LVESD:** Left ventricular end-systolic diameter; **LVFS:** Left ventricular fractional shortening; **MDA:** Malondialdehyde; **miR:** MicroRNA; **miRNA:** MicroRNA; **MSC:** Mesenchymal stem cell; **NF- $\kappa$ B:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **NOX:** NADPH oxidase; **NT-proBNP:** N-terminal pro-brain natriuretic peptide; **PBS:** Phosphate-buffered saline; **ROS:** Reactive oxygen species; **SOD:** Superoxide dismutase; **SV:** Stroke volume; **SYRCLE:** Systematic Review Centre for Laboratory animal Experimentation; **TDN:** Tetrahedral DNA nanostructure; **TGF- $\beta$ :** Transforming growth factor beta; **TNF- $\alpha$ :** Tumor necrosis factor alpha; **TUNEL:** Terminal deoxynucleotidyl transferase dUTP nick end labeling

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## AUTHORS' CONTRIBUTIONS

[M.R.R.]: Conceptualization, Methodology, Supervision, Writing—review & editing, [G.G.D.]:

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## ETHICS APPROVAL

Ethical approval was not applicable to this systematic review.

## CONSENT TO PARTICIPATE

Not applicable

## CONSENT FOR PUBLISH

Not applicable

## AVAILABILITY OF DATA AND MATERIAL (DATA TRANSPARENCY)

All data generated or analyzed during this study are included in this published article.

## DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative AI (a type of artificial intelligence technology that can produce various types of content including text, imagery, audio and synthetic data).

## COMPETING INTERESTS

The authors declare no competing interests.

## REFERENCES

- Kourek C, Touloupaki M, Rempakos A, Loritis K, Tsougkos E, Paraskevaidis I, et al. Cardioprotective strategies from cardiotoxicity in cancer patients: a comprehensive review. *J Cardiovasc Dev Dis.* 2022 Aug;9(8):259. PMID: 36005423. Available from: [10.3390/jcdd9080259](https://doi.org/10.3390/jcdd9080259).
- Trapani D, Zagami P, Nicolò E, Pravettoni G, Curgiliano G. Management of cardiac toxicity induced by chemotherapy. *J Clin Med.* 2020 Sep;9(9):2885. PMID: 32906611. Available from: [10.3390/jcm9092885](https://doi.org/10.3390/jcm9092885).
- Ma W, Wei S, Zhang B, Li W. Molecular mechanisms of cardiomyocyte death in drug-induced cardiotoxicity. *Front Cell Dev Biol.* 2020 Jun;8:434. PMID: 32582710. Available from: [10.3389/fcell.2020.00434](https://doi.org/10.3389/fcell.2020.00434).
- Renu K, Abilash VG, Tirupathi Pichiah PB, Arunachalam S. Molecular mechanism of doxorubicin-induced cardiomyopathy - An update. *Eur J Pharmacol.* 2018 Jan;818:241–253. PMID: 29074412. Available from: [10.1016/j.ejphar.2017.10.043](https://doi.org/10.1016/j.ejphar.2017.10.043).
- Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Calderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J.* 2016 Sep;37(36):2768–2801. PMID: 27567406. Available from: [10.1093/eurheartj/ehw211](https://doi.org/10.1093/eurheartj/ehw211).
- Jacobse JN, Steggink LC, Sonke GS, Schaapveld M, Hummel YM, Steenbruggen TG, et al. Myocardial dysfunction in long-term breast cancer survivors treated at ages 40–50 years. *Eur J Heart Fail.* 2020 Feb;22(2):338–346. PMID: 31696625. Available from: [10.1002/ejhf.1610](https://doi.org/10.1002/ejhf.1610).
- Mir A, Badi Y, Bugazia S, Nourelden AZ, Fathallah AH, Ragab KM, et al. Efficacy and safety of cardioprotective drugs in chemotherapy-induced cardiotoxicity: an updated systematic review & network meta-analysis. *Cardiooncology.* 2023 Feb;9(1):10. PMID: 36804940. Available from: [10.1186/s40959-023-00159-0](https://doi.org/10.1186/s40959-023-00159-0).
- Lei B, Wu X, Xia K, Sun H, Wang J. Exosomal Micro-RNA-96 Derived From Bone Marrow Mesenchymal Stem Cells Inhibits Doxorubicin-Induced Myocardial Toxicity by Inhibiting the Rac1/Nuclear Factor-κB Signaling Pathway. *J Am Heart Assoc.* 2021 Sep;10(17):e020589. PMID: 34459233. Available from: [10.1161/JAH.120.020589](https://doi.org/10.1161/JAH.120.020589).
- Wei X, Yang X, Han ZP, Qu FF, Shao L, Shi YF. Mesenchymal stem cells: a new trend for cell therapy. *Acta Pharmacol Sin.* 2013 Jun;34(6):747–754. PMID: 23736003. Available from: [10.1038/aps.2013.50](https://doi.org/10.1038/aps.2013.50).
- Bodart-Santos V, de Carvalho LR, de Godoy MA, Batista AF, Saraiva LM, Lima LG, et al. Extracellular vesicles derived from human Wharton's jelly mesenchymal stem cells protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers. *Stem Cell Res Ther.* 2019 Nov;10(1):332. PMID: 31747944. Available from: [10.1186/s13287-019-1432-5](https://doi.org/10.1186/s13287-019-1432-5).
- Fujii S, Miura Y, Fujishiro A, Shindo T, Shimazu Y, Hirai H, et al. Graft-Versus-Host Disease Amelioration by Human Bone Marrow Mesenchymal Stromal/Stem Cell-Derived Extracellular Vesicles Is Associated with Peripheral Preservation of Naive T Cell Populations. *Stem Cells.* 2018 Mar;36(3):434–445. PMID: 29239062. Available from: [10.1002/stem.2759](https://doi.org/10.1002/stem.2759).
- Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. *Cell Biosci.* 2019 Feb;9(1):19. PMID: 30815248. Available from: [10.1186/s13578-019-0282-2](https://doi.org/10.1186/s13578-019-0282-2).
- Jadli AS, Parasor A, Gomes KP, Shandilya R, Patel VB. Exosomes in cardiovascular diseases: pathological potential of nano-messenger. *Front Cardiovasc Med.* 2021 Nov;8:767488. PMID: 34869682. Available from: [10.3389/fcvm.2021.767488](https://doi.org/10.3389/fcvm.2021.767488).
- Tian C, Yang Y, Li B, Liu M, He X, Zhao L, et al. Doxorubicin-Induced cardiotoxicity may be alleviated by bone marrow mesenchymal stem cell-derived exosomal lncRNA via inhibiting inflammation. *J Inflamm Res.* 2022 Aug;15:4467–4486. PMID: 35966005. Available from: [10.2147/JIR.S358471](https://doi.org/10.2147/JIR.S358471).
- Mentkowski KJ, Snitzer JD, Rusnak S, Lang JK. Therapeutic Potential of Engineered Extracellular Vesicles. *AAPS J.* 2018 Mar;20(3):50. PMID: 29546642. Available from: [10.1208/s12248-018-0211-z](https://doi.org/10.1208/s12248-018-0211-z).
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021 Mar;372:n71. PMID: 33782057. Available from: [10.1136/bmj.n71](https://doi.org/10.1136/bmj.n71).
- Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol.* 2014 Mar;14(1):43.

PMID: 24667063. Available from: [10.1186/1471-2288-14-43](https://doi.org/10.1186/1471-2288-14-43).

18. Sheth VH, Shah NP, Jain R, Bhanushali N, Bhatnagar V. Development and validation of a risk-of-bias tool for assessing in vitro studies conducted in dentistry: the QUIN. *J Prosthet Dent.* 2022; PMID: 35752496.
19. Zhang S, Li D, Liu L, Shi Q, Ju X. Extracellular vesicles derived from HuMSCs alleviate daunorubicin-induced cardiac microvascular injury via miR-186-5p/PARP9/STAT1 signal pathway. *Regen Ther.* 2024 Feb;25:320-330. PMID: 38327716. Available from: [10.1016/j.reth.2024.01.011](https://doi.org/10.1016/j.reth.2024.01.011).
20. Imam RA, Aboulhoda BE, Amer MM, Hassan FE, Alghamdi MA, Abdel-Hamed MR. Role of mesenchymal stem cells-derived exosomes on inflammation, apoptosis, fibrosis and telocyte modulation in doxorubicin-induced cardiotoxicity: A closer look at the structural level. *Microsc Res Tech.* 2024 Jul;87(7):1598-1614. PMID: 38441397. Available from: [10.1002/jemt.25444](https://doi.org/10.1002/jemt.25444).
21. Ali SA, Singla DK. Mesenchymal Stem Cell-Derived Exosomes Ameliorate Doxorubicin-Induced Cardiotoxicity. *Pharmaceuticals (Basel).* 2024 Jan;17(1):93. PMID: 38256928. Available from: [10.3390/ph17010093](https://doi.org/10.3390/ph17010093).
22. Zeng H, Yang Y, Tou F, Zhan Y, Liu S, Zou P, et al. Bone marrow stromal cell-derived exosomes improve oxidative stress and pyroptosis in doxorubicin-induced myocardial injury in vitro by regulating the transcription of GSDMD through the PI3K-AKT-Foxo1 pathway. *Immunol Inflamm Dis.* 2023 Mar;11(3):e810. PMID: 36988259. Available from: [10.1002/iid3.810](https://doi.org/10.1002/iid3.810).
23. Xiong J, Ding B, Zhu W, Xu L, Yu S. Exosomes from Adipose-Derived Mesenchymal Stem Cells Protect Against Cyclophosphamide-Induced Cardiotoxicity in Rats. *Int Heart J.* 2023;64(5):935-944. PMID: 37778997. Available from: [10.1536/ihj.23-201](https://doi.org/10.1536/ihj.23-201).
24. Wang L, Zhang JJ, Wang SS, Li L. Mechanism of adipose-derived mesenchymal stem cell exosomes in the treatment of heart failure. *World J Stem Cells.* 2023 Sep;15(9):897-907. PMID: 37900939. Available from: [10.4242/wjsc.v15.i9.897](https://doi.org/10.4242/wjsc.v15.i9.897).
25. Duan J, Liu X, Shen S, Tan X, Wang Y, Wang L, et al. Trophoblast Stem-Cell-Derived Exosomes Alleviate Cardiotoxicity of Doxorubicin via Improving Mfn2-Mediated Mitochondrial Fusion. *Cardiovasc Toxicol.* 2023 Jan;23(1):23-31. PMID: 36609664. Available from: [10.1007/s12012-022-09774-2](https://doi.org/10.1007/s12012-022-09774-2).
26. Desgres M, Lima Correa B, Petrusca L, Autret G, Pezzana C, Marigny C, et al. Therapeutic potential of extracellular vesicles derived from cardiac progenitor cells in rodent models of chemotherapy-induced cardiomyopathy. *Front Cardiovasc Med.* 2023 Jul;10:1206279. PMID: 37485274. Available from: [10.3389/fcvm.2023.1206279](https://doi.org/10.3389/fcvm.2023.1206279).
27. Yu Y, Wu T, Lu Y, Zhao W, Zhang J, Chen Q, et al. Exosomal thioredoxin-1 from hypoxic human umbilical cord mesenchymal stem cells inhibits ferroptosis in doxorubicin-induced cardiotoxicity via mTORC1 signaling. *Free Radic Biol Med.* 2022 Nov;193(Pr 1):108-121. PMID: 36241072. Available from: [10.1016/j.freeradbiomed.2022.10.268](https://doi.org/10.1016/j.freeradbiomed.2022.10.268).
28. Tian C, Yang Y, Li B, Liu M, He X, Zhao L, et al. Doxorubicin-Induced cardiotoxicity may be alleviated by bone marrow mesenchymal stem cell-derived exosomal lncRNA via inhibiting inflammation. *J Inflamm Res.* 2022 Aug;15:4467-4486. PMID: 3596005. Available from: [10.2147/JIR.S358471](https://doi.org/10.2147/JIR.S358471).
29. Huang A, Liu Y, Qi X, Chen S, Huang H, Zhang J, et al. Intravenously transplanted mesenchymal stromal cells: a new endocrine reservoir for cardioprotection. *Stem Cell Res Ther.* 2022 Jun;13(1):253. PMID: 35715868. Available from: [10.1186/s13287-022-02922-z](https://doi.org/10.1186/s13287-022-02922-z).
30. Fan M, Li H, Shen D, Wang Z, Liu H, Zhu D, et al. Decoy Exosomes Offer Protection Against Chemotherapy-Induced Toxicity. *Adv Sci (Weinh).* 2022 Nov;9(32):e2203505. PMID: 36058003. Available from: [10.1002/advs.202203505](https://doi.org/10.1002/advs.202203505).
31. Ebrahim N, Al Sahati HA, Mostafa O, Hassouna A, Abdusamea S, Abd El Aziz M, et al. Prophylactic Evidence of MSCs-Derived Exosomes in Doxorubicin/Trastuzumab-Induced Cardiotoxicity: Beyond Mechanistic Target of NRG-1/Erb Signaling Pathway. *Int J Mol Sci.* 2022 May;23(11):5967. PMID: 35682646. Available from: [10.3390/ijms23115967](https://doi.org/10.3390/ijms23115967).
32. Zhong Z, Tian Y, Luo X, Zou J, Wu L, Tian J. Extracellular Vesicles Derived From Human Umbilical Cord Mesenchymal Stem Cells Protect Against DOX-Induced Heart Failure Through the miR-100-5p/NOX4 Pathway. *Front Bioeng Biotechnol.* 2021 Aug;9:703241. PMID: 34513812. Available from: [10.3389/fbioe.2021.703241](https://doi.org/10.3389/fbioe.2021.703241).
33. O'Brien CG, Ozen MO, Ikeda G, Vaskova E, Jung JH, Bayardo N, et al. Mitochondria-Rich Extracellular Vesicles Rescue Patient-Specific Cardiomyocytes From Doxorubicin Injury: Insights Into the SENECA Trial. *JACC Cardiooncol.* 2021 Jul;3(3):428-440. PMID: 34604804. Available from: [10.1016/j.jacc.2021.05.006](https://doi.org/10.1016/j.jacc.2021.05.006).
34. Li H, Huang H, Chen X, Chen S, Yu L, Wang C, et al. The delivery of hsa-miR-1101 by extracellular vesicles can relieve doxorubicin-induced mesenchymal stem cell apoptosis. *Stem Cell Res Ther.* 2021 Jan;12(1):77. PMID: 33482923. Available from: [10.1186/s13287-021-02156-5](https://doi.org/10.1186/s13287-021-02156-5).
35. Lei B, Wu X, Xia K, Sun H, Wang J. Exosomal Micro-RNA-96 Derived From Bone Marrow Mesenchymal Stem Cells Inhibits Doxorubicin-Induced Myocardial Toxicity by Inhibiting the Rac1/Nuclear Factor- $\kappa$ B Signaling Pathway. *J Am Heart Assoc.* 2021 Sep;10(17):e020589. PMID: 34459233. Available from: [10.1161/JAHA.120.020589](https://doi.org/10.1161/JAHA.120.020589).
36. Lee JY, Chung J, Byun Y, Kim KH, An SH, Kwon K. Mesenchymal Stem Cell-Derived Small Extracellular Vesicles Protect Cardiomyocytes from Doxorubicin-Induced Cardiomyopathy by Upregulating Survivin Expression via the miR-199a-3p-Akt-Sp1/p53 Signaling Pathway. *Int J Mol Sci.* 2021;22(13):7102. Available from: [10.3390/ijms22137102](https://doi.org/10.3390/ijms22137102).
37. Zhuang L, Xia W, Chen D, Ye Y, Hu T, Li S, et al. Exosomal LncRNA-NEAT1 derived from MIF-treated mesenchymal stem cells protected against doxorubicin-induced cardiac senescence through sponging miR-221-3p. *J Nanobiotechnology.* 2020 Oct;18(1):157. PMID: 33129330. Available from: [10.1186/s12951-020-00716-0](https://doi.org/10.1186/s12951-020-00716-0).
38. Xia W, Chen H, Xie C, Hou M. Long-noncoding RNA MALAT1 sponges microRNA-92a-3p to inhibit doxorubicin-induced cardiac senescence by targeting ATG4a. *Aging (Albany NY).* 2020 May;12(9):8241-8260. PMID: 32384281. Available from: [10.18632/aging.103136](https://doi.org/10.18632/aging.103136).
39. Ni J, Liu Y, Kang L, Wang L, Han Z, Wang K, et al. Human trophoblast-derived exosomes attenuate doxorubicin-induced cardiac injury by regulating miR-200b and downstream Zeb1. *J Nanobiotechnology.* 2020 Nov;18(1):171. PMID: 33218341. Available from: [10.1186/s12951-020-00733-z](https://doi.org/10.1186/s12951-020-00733-z).
40. Ni J, Liu Y, Wang K, Wu M, Kang L, Sha D, et al. Trophoblast Stem-Cell-Derived Exosomes Improve Doxorubicin-Induced Dilated Cardiomyopathy by Modulating the let-7i/YAP Pathway. *Mol Ther Nucleic Acids.* 2020 Oct;22:948-956. PMID: 33294288. Available from: [10.1016/j.omtn.2020.10.014](https://doi.org/10.1016/j.omtn.2020.10.014).
41. Milano G, Biemmi V, Lazzarini E, Balbi C, Ciullo A, Bolis S, et al. Intravenous administration of cardiac progenitor cell-derived exosomes protects against doxorubicin/trastuzumab-induced cardiac toxicity. *Cardiovasc Res.* 2020 Feb;116(2):383-392. PMID: 31098627.
42. Singla DK, Johnson TA, Tavakoli Dargani Z. Exosome Treatment Enhances Anti-Inflammatory M2 Macrophages and Reduces Inflammation-Induced Pyroptosis in Doxorubicin-Induced Cardiomyopathy. *Cells.* 2019 Oct;8(10):1224. PMID: 31600901. Available from: [10.3390/cells8101224](https://doi.org/10.3390/cells8101224).
43. Tavakoli Dargani Z, Singla DK. Embryonic stem cell-derived exosomes inhibit doxorubicin-induced TLR4-NLRP3-mediated cell death-pyroptosis. *Am J Physiol Heart Circ Physiol.* 2019 Aug;317(2):H460-H471. PMID: 31172809. Available from: [10.1152/ajpheart.00056.2019](https://doi.org/10.1152/ajpheart.00056.2019).
44. Sun X, Shan A, Wei Z, Xu B. Intravenous mesenchymal stem cell-derived exosomes ameliorate myocardial inflammation in the dilated cardiomyopathy. *Biochem Biophys Res Commun.*

2018 Sep;503(4):2611–2618. PMID: 30126637. Available from: [10.1016/j.bbrc.2018.08.012](https://doi.org/10.1016/j.bbrc.2018.08.012).

45. Vandergriff AC, de Andrade JBM, Tang JN, Hensley MT, Piedrahita JA, Caranasos TG, et al. Intravenous Cardiac Stem Cell-Derived Exosomes Ameliorate Cardiac Dysfunction in Doxorubicin Induced Dilated Cardiomyopathy. *Stem Cells International*. 2015;2015. Available from: [10.1155/2015/960926](https://doi.org/10.1155/2015/960926).

46. Abdul-Rahman T, Dunham A, Huang H, Bukhari SM, Mehta A, Awuah WA, et al. Chemotherapy Induced Cardiotoxicity: A State of the Art Review on General Mechanisms, Prevention, Treatment and Recent Advances in Novel Therapeutics. *Curr Probl Cardiol*. 2023 Apr;48(4):101591. PMID: 36621516. Available from: [10.1016/j.cpcardiol.2023.101591](https://doi.org/10.1016/j.cpcardiol.2023.101591).

47. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc*. 2014 Apr;3(2):e000665. PMID: 24755151. Available from: [10.1161/JAHA.113.000665](https://doi.org/10.1161/JAHA.113.000665).

48. Nagy A, Börzsei D, Hoffmann A, Török S, Veszelka M, Almási N, et al. A Comprehensive Overview on Chemotherapy-Induced Cardiotoxicity: Insights into the Underlying Inflammatory and Oxidative Mechanisms. *Cardiovascular Drugs and Therapy*. 2024;.

49. Wang QM, Lv L, Tang Y, Zhang L, Wang LF. MMP-1 is overexpressed in triple-negative breast cancer tissues and the knockdown of MMP-1 expression inhibits tumor cell malignant behaviors in vitro. *Oncol Lett*. 2019 Feb;17(2):1732–1740. PMID: 30675232.

50. Spallarossa P, Altieri P, Garibaldi S, Ghigliotti G, Barisione C, Manca V, et al. Matrix metalloproteinase-2 and -9 are induced differently by doxorubicin in H9c2 cells: the role of MAP kinases and NAD(P)H oxidase. *Cardiovasc Res*. 2006 Feb;69(3):736–745. PMID: 16213474. Available from: [10.1016/j.cardiores.2005.08.009](https://doi.org/10.1016/j.cardiores.2005.08.009).

51. 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 Jul;139:111708. PMID: 34243633. Available from: [10.1016/j.bioph.2021.111708](https://doi.org/10.1016/j.bioph.2021.111708).

52. Goraksha-Hicks P, Rathmell JC. TGF- $\beta$ : a new role for an old AktTOR. *Dev Cell*. 2009 Jul;17(1):6–8. PMID: 19619487. Available from: [10.1016/j.devcel.2009.07.004](https://doi.org/10.1016/j.devcel.2009.07.004).

53. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement. *Eur J Heart Fail*. 2020 Sep;22(9):1504–1524. PMID: 32621569. Available from: [10.1002/ejhf.1957](https://doi.org/10.1002/ejhf.1957).

54. Pareek N, Cevallos J, Moliner P, Shah M, Tan LL, Chambers V, et al. Activity and outcomes of a cardio-oncology service in the United Kingdom—a five-year experience. *Eur J Heart Fail*. 2018 Dec;20(12):1721–1731. PMID: 30191649. Available from: [10.1002/ejhf.1292](https://doi.org/10.1002/ejhf.1292).

55. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000 Aug;36(2):517–522. PMID: 10933366. Available from: [10.1016/S0735-1097\(00\)00748-8](https://doi.org/10.1016/S0735-1097(00)00748-8).

56. Rüger AM, Schneeweiss A, Seiler S, Tesch H, van Mackelenbergh M, Marmé F, et al. Cardiotoxicity and Cardiovascular Biomarkers in Patients With Breast Cancer: Data From the GeparOcto-GBG 84 Trial. *J Am Heart Assoc*. 2020 Dec;9(23):e018143. PMID: 33191846. Available from: [10.1161/JAHA.120.018143](https://doi.org/10.1161/JAHA.120.018143).