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CARDIO-ONCOLOGY

Cardioprotection strategies for anthracycline cardiotoxicity

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Abstract
Thanks to the fantastic progress in cancer therapy options, there is a growing population of cancer survivors. This success has resulted in a need to focus much effort into improving the quality of life of this population. Cancer and cardiovascular disease share many common risk factors and have an interplay between them, with one condition mechanistically affecting the other and vice versa. Furthermore, widely prescribed cancer therapies have known toxic effects in the cardiovascular system. Anthracyclines are the paradigm of efficacious cancer therapy widely prescribed with a strong cardiotoxic potential. While some cancer therapies cardiovascular toxicities are transient, others are irreversible. There is a growing need to develop cardioprotective therapies that, when used in conjunction with cancer therapies, can prevent cardiovascular toxicity and thus improve long-term quality of life in survivors. The field has three main challenges: (i) identification of the ultimate mechanisms leading to cardiotoxicity to (ii) identify specific therapeutic targets, and (iii) more sensible diagnostic tools to early identify these conditions. In this review we will focus on the cardioprotective strategies tested and under investigation. We will focus this article into anthracycline cardiotoxicity since it is still the agent most widely prescribed, the one with higher toxic effects on the heart, and the most widely studied.

Keywords Cardio-oncology · Cardiotoxicity · Cardioprotection · Anthracyclines

Introduction

The great development of cancer therapies has resulted in a significant increase in life expectancy for most cancer types. The population of cancer survivors is growing and this has resulted in a new clinical and research challenge: improve quality of life in cancer survivors. Cancer patients (and cancer survivors) are at increased risk for cardiovascular disease. While there is a known interaction between oncologic processes and cardiovascular disease, a big contributor to this increased cardiovascular risk is the known cardiovascular side effects of effective cancer therapies. The more paradigmatic case is anthracyclines that more than 50 years after its discovery and clinical use initiation, remains a fundamental treatment for different types of cancer both as a curative regimen and as adjuvant chemotherapy (lymphomas, leukemias, sarcomas and breast cancer). Although their use still remains essential to increase cancer survival, and despite changes in current regimens (use of lower doses and early evaluation of underlying heart disease), they remain a cause of morbidity and mortality in cancer survivors. While most side effects of anthracyclines are transient and recover after finishing treatment, some can be irreversible, resulting in an important burden to cancer survivors. Among the latter, myocardial damage is the most feared one since it can be associated with cardiac dysfunction and heart failure (HF) [66]. Anthracycline cardiotoxicity (AC) is known for many decades but it is not until recently that the development of cardiac imaging [28, 63], biomarkers and, more importantly, the creation of cardio-oncology units that more attention has been paid to the early diagnosis of this side effect and to the identification of strategies that can prevent it. Newer interventions increasingly used, are increasingly acknowledged to be associated with toxicity in any part of the cardiovascular system. Among them, besides anthracyclines, trastuzumab

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and other HER2 receptor blockers, tyrosine kinase inhibitors (TKIs), alkylating agents, antimetabolites, angiogenesis inhibitors and immune checkpoints inhibitors (ICIs) have been shown to have a potential cardiovascular toxicity potential. Given the different agents involved in cardiac injury and different cancer types, the European Society of Cardiology (ESC) cardio-oncology guidelines currently suggest the use of the term cancer therapy-related cardiac dysfunction (CTRCD) [66].

Translational research is a critical discipline to cope with this relatively new cardiovascular condition, since it is imperative to know the mechanisms leading to cardiovascular toxicity (different for each anticancer treatment) to be able to identify therapeutic targets. The generation of relevant animal models is also of outmost importance to have a preclinical validation of these cardioprotective candidates before they are tested in patients [14].

In this document, we will focus on mainly on the mechanism leading to cardiac toxicity of anthracyclines, still the most widely prescribed cancer therapy, and present potential cardioprotective strategies proposed to prevent this condition. We will also mention the potential myocardial toxicity associated with other cancer therapies, such as immunotherapy and radiotherapy. We also present an updated landscape of the ongoing clinical trials in the field.

Scope of the problem: epidemiology of anthracycline cardiotoxicity (AC)

The risk of AC is greatly associated with the total cumulative dose received. Other factors such as extreme age (pediatric and older populations), concomitant or previous thoracic radiotherapy, presence of cardiovascular risk factors or underlying cardiac disease also increase the risk for AC also contribute to an increased risk [66].

AC represents a continuum of severity, ranging from overt HF to asymptomatic changes in cardiac function/structure or elevation in cardiac biomarkers. The actual incidence of AC is difficult to determine since it significantly varies according to the cardiotoxicity criteria used.

Classical studies determined the incidence of AC according to clinical criteria (mainly clinical HF). In these old studies, the reported incidence of AC (clinical HF) was ≈5% at a cumulative dose of 400 mg/m^2, and up to ≈50% at a cumulative dose ≥ 700 mg/m^2 [79, 106]. These studies were the basis for limiting the total lifetime cumulative dose of anthracyclines.

The introduction of imaging to follow-up patients undergoing anthracycline-based cancer treatment has provided a different landscape, with asymptomatic cardiotoxicity being considered [50]. Again, the different criteria used to determine the presence of asymptomatic AC has a great impact on the reported incidence. In a cohort of 2625 patients treated with anthracyclines, with a mean follow-up of 5.2 years, AC was defined as reduction in left ventricular ejection fraction (LVEF) > 10 absolute points from baseline to a final LVEF < 50%, and the incidence estimated in 9% [17]. Conversely, in the CARDIOTOX registry in 865 patients [65], the incidence of AC was much higher (37.5%). In the latter, AC was categorized as mild, moderate and severe. The apparently high incidence of AC was mainly because of the permissive criteria used in the mild category: normal LVEF (> 50%) but elevation in cardiac biomarkers or any abnormal echocardiogram parameter (LV or left atrial volume, decrease in 10% LVEF points to a value < 53%, abnormal LV filling, or abnormal LV global longitudinal strain (GLS)). Whether mild AC according to these criteria has any clinical impact in the long term is not clearly determined. In the same CARDIOTOX registry, more severe forms of AC, including overt LV systolic dysfunction (LVEF < 40%) or meet of ESC HF clinical criteria were estimated in < 2.5%.

Pathophysiological mechanisms of anthracycline cardiotoxicity

In cancer cells, anthracyclines induce cell death by targeting these highly replicative cells. In other organs, anthracyclines eliminate severely damaged cells, allowing the replication of healthier surviving cells to restore organ function. For instance, this occurs with the severe but transient effects of anthracyclines on the gastrointestinal system. However, in non-replicating cells like cardiomyocytes, damaged cells cannot be replaced by neighboring cells, leading to permanent organ injury. Therefore, it is crucial to deepen our understanding of the mechanisms by which anthracyclines cause myocardial injury, enabling the development of targeted therapies.

Cytotoxic mechanisms (on-target effect in cancer cells)

Anthracyclines, with doxorubicin as a paradigmatic example, exert their cytotoxic effects through multiple mechanisms. Specifically, doxorubicin inhibits Topoisomerase IIb (TOP2B), an essential enzyme involved in DNA replication and repair [75, 115]. Inhibition of TOP2B by doxorubicin leads to the accumulation of DNA double-strand breaks and ultimately contributes to cell death [34, 61, 122]. To repair this DNA damage, cells activate a fine-tuned signaling cascade to ensure genomic and proteomic homeostasis, collectively known as the DNA Damage Response (DDR). DDR is driven by multiple pathways including the recruitment of ATM and ATR proteins activating p53 which can initiate an apoptosis cascade [60]. Doxorubicin not only interferes in

the nuclear DNA but also can induce mutations and defects in mitochondrial DNA (mtDNA). Disruption of mitochondrial function is known to be a crucial factor in AC [12]. For example, doxorubicin binds to cardiolipin, a crucial lipid in inner mitochondria membrane, impairing oxidative phosphorylation [93, 118].

Mitochondrial damage mechanisms in non-replicating cells (e.g., cardiomyocytes):

Mitochondria in cardiomyocytes are not generated de novo but are derived from pre-existing mitochondria through the processes of fusion/fission. These dynamic processes maintain mitochondrial function and integrity, allowing the organelles to divide, repair, and adapt to the cell's energy demands and stress conditions. This reliance on pre-existing mitochondria is crucial for maintaining the high energy demands of cardiomyocytes, which require a constant and stable population of functional mitochondria to support continuous cardiac function. Therefore, irreversible injury to mitochondria in cardiomyocytes has a significant impact on cardiac function. Doxorubicin leads to several damage in mitochondrial bioenergetics through the disruption of sirtuins (e.g., SIRT1, SIRT3), which catalyze the deacetylation of histone and non-histone lysine residues [3, 39]. Doxorubicin reduction by NADPH-oxidoreductases in cardiac mitochondria also generates unstable metabolites producing ROS, which affect the activity of mitochondrial enzyme complexes and lead to DNA, protein and lipid damage, and subsequent cardiomyocyte death. Doxorubicin also induces excessive lipid peroxidation in mitochondria, leading to mitochondria-dependent ferroptosis [108]. Doxorubicin and its metabolites (e.g., doxorubicinol) form compounds with iron and interfere with its transporting/binding, therefore disrupting the overall cellular iron homeostasis. These effects boost intracellular ROS generation, which generates toxic mediators that can destroy cellular components activating mitochondria-initiated cell death [42, 82, 101]. In order to restore mitochondrial homeostasis after doxorubicin insult, cells can activate quality control machinery, autophagy and mitophagy (i.e., mitochondrial autophagy), in an attempt to eliminate dysfunctional mitochondria and cellular structures [56]. In fact, doxorubicin initially stimulates autophagy that gets interrupted afterward leading to accumulation of undegraded autophagosomes and autolysosomes, which contribute to ROS generation and cardiotoxicity [2, 8, 42, 95].

The effects of doxorubicin mitochondrial toxicity specially compromise cardiomyocyte metabolism since the energy in the cardiac tissue is mainly derived from the mitochondrial oxidative phosphorylation. By affecting mitochondrial structure and function, anthracyclines disrupt normal cardiomyocyte metabolism. In fact, metabolic reprogramming induced by anthracyclines precede and contribute to cardiac dysfunction [22].

Damage to contractile apparatus by anthracyclines:

Doxorubicin induces Ca^{2+} homeostasis dysregulation in cardiomyocytes, contributing to the development of cardiac contractile dysfunction [103]. The increase in Ca^{2+} activate calpains (calcium-dependent proteases), which are intimately implicated in the destruction of cardiac muscle proteins, resulting in myofibrillar deterioration including the degradation of titin protein [59, 95]. Other mechanism associated with doxorubicin cardiotoxicity is epigenetic modifications including DNA methylation (downregulation of DNA methyltransferase 1 (DNMT1) and global hypomethylation) [24], post-translational histone modifications (e.g., histone deacetylase 6 (HDAC6) overexpression) [104], and regulation of microRNAs (miRNAs), which could increase the susceptibility of the cardiomyocyte to subsequent metabolic disturbances [58, 61, 110]. These effects on cardiomyocyte fibers results in cardiac atrophy, characteristic of early stages of AC [22].

Anthracycline myocardial damage in non-cardiomyocyte cell compartments:

The heart is a complex multicellular organ where doxorubicin toxicity is also extended to other cell type populations such as endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) contributing to vascular dysregulation [29]. The resulting cardiovascular toxicity have been recognized to have persistent and long-term implications which affect cardiac blood flow to surrounding organs and alter the paracrine signaling between the heart and endothelium among others [89]. A pro-inflammatory response has also been reported in the context of doxorubicin cardiotoxicity. This immune response is illustrated by the secretion of chemokines and cytokines. For instance, different cytokines (IFN-γ, CCL27 and MIF) were found elevated in patients undergoing doxorubicin treatment [60]. Furthermore, increased plasma levels of myeloperoxidase (MPO) were recently reported [88]. MPO catalyzes the formation of ROS and is mainly expressed in neutrophils [6], whose infiltration and release of activation byproducts (neutrophil elastase or neutrophil extracellular traps, NETs) were key components exacerbating cardiotoxicity in animal models [11, 100, 124]. Therefore, MPO constitutes a promising biomarker predicting doxorubicin-induced cardiotoxicity [88].

Together, all these multifactorial cytotoxic effects contribute to the initiation and progression of AC.

Diagnosis of anthracycline cardiotoxicity and its implications for clinical trials endpoint selection

AC refers to any injury induced by anthracyclines to the myocardium, and can vary from minor reversible injury not affecting cardiac function to severe irreversible damage associated with overt heart failure. Since the definition of AC covers the entire spectrum [66], the incidence of AC in modern registries is alarmingly high (> 30%) [65]. However, the clinical relevance of each form of AC is very disparate. Asymptomatic minor to moderate transient elevation of cardiac injury biomarkers (mainly troponins) without cardiac functional impairment, while not ideal, does not seem to carry any impact on patient's prognosis. In fact, very recently the concept of "*permissive cardiotoxicity*" has emerged [94]. Permissive cardiotoxicity refers to certain degree of cardiac injury that is acceptable within the benefits afforded by maintaining the anticancer therapy. On the contrary, permanent cardiac structural and functional impairment can carry important clinical implications for the quality of life of cancer survivors. Within the context of the present review, focused on cardioprotective strategies, the latter form of AC is the one that ideally should be prevented by a given intervention. This is relevant since several clinical trials in the field use cardiac injury biomarkers as main outcome measure (see Tables 1 and 2). Therefore, within the context of cardioprotection against AC, outcome measures should include cardiac structural of functional impairment (Figs. 1, 2 and 3).

The best validated functional impairment outcome is systolic function (LVEF). Permanent deterioration in LVEF is very well established as a sign of worse long-term clinical outcome, regardless the etiology [48]. In recent years, myocardial deformation (strain), evaluated by echocardiography or cardiac magnetic resonance (CMR), has emerged as a clinically relevant surrogate outcome [66]. Both deterioration in LVEF and LV GLS are included in the current definition of AC by clinical practice guidelines [66]. Other CMR parameters associated with AC include alterations (prolongation) in T1 [84] or T2 [28, 76] relaxation times, or altered cardiac perfusion [29]. As presented above, AC is characterized by very early changes in cardiac metabolism [22]. MR spectroscopy can quantify myocardial energetics non-invasively and is thus a technique with great potential for very early diagnosis of AC [69, 86]. Another technique able to track cardiac metabolism is positron emission tomography (PET) [77]. 18-FDG PET can determine glucose uptake to the myocardium. As discussed above, loss of metabolic flexibility with a bias toward anaerobic glycolysis is a hallmark of early stages of AC [22]. Several studies in animal models and humans have shown that increase in myocardial uptake of 18FDG on PET occurs in subjects with subsequent development of AC (reviewed elsewhere [9]). Changes in cardiac fibers orientation can be measured by CMR diffusion tensor imaging (DTI). A recent study in mice showed that typical features of AC (reduced LVEF, impaired GLS, and cardiac atrophy) were associated with changes in LV geometric shape on ex-vivo DTI CMR [63]. The main limitation at the moment to apply DTI is that studies require a very long tome of acquisition. In fact, time of acquisition is one of the main limitations of CMR precluding its universal acceptance. This is especially relevant for the vulnerable patient population, like those with cancer. In this regard, ultrafast CMR protocols are being developed with different approaches. Among those, ESSOS is a new sequence able to acquire a complete cardiac anatomy and function evaluation in 20 s [35]. In this revolutionary clinical study, whole heart late gadolinium enhancement was obtained with another 20 s sequence, making a very complete study in less than 1 min [35]. ESSOS CMR methodology is being tested in the ongoing RESILIENCE clinical trial undertaken in cancer patients at high-risk of AC [83]. The same trial is also testing other CMR sequences in the context of AC, such as T2 relaxation time prolongation [28], quantitative perfusion [99], and fast-strain encoded magnetic resonance (fast-SENC [57]). For additional information on the comprehensive imaging protocol in RESILIENCE trial, we refer to the design paper publication [83]. Besides ultrafast (whole heart in a single breath hold) cine and delayed gadolinium enhancement, single breath-hold T1 mapping is also feasible today [25]. Therefore, it is possible that in the close future, all these CMR sequences deeply characterizing the myocardium of patients at risk for AC can be performed very fast allowing vulnerable cancer patients to tolerate the exams.

Cardioprotective strategies to prevent/reverse anthracycline cardiotoxicity

In the literature there is a massive number of publications reporting different cardioprotective strategies in different models of AC. In this section of evolving strategies, we will focus on the most recent advances in light of the newest AC mechanistic insights [22, 98] related with mitochondrial dynamics and cardiac metabolism (two main mechanisms of AC as presented above).

Mitochondrial quality control: remote ischemic conditioning

Mitochondria are dynamic organelles with a primary (albeit not unique) function of generating ATP. Mitochondrial

Table 1 Completed clinical trials testing cardioprotective strategies to prevent anthracycline cardiotoxicity

NCT No	References	Study name	Primary endpoint	Intervention	Cancer treatment	Sample size	Design and follow-up	Cancer type	Outcome
NCT02943590	[87]	STOP-CA (Statins TO Prevent the Cardiotoxicity From Anthracyclines)	Drop LVEF of > 10% from baseline to a final value of < 55%. CMR	Atorvastatin 40 mg/d or placebo	Anthracycline	300	RCT/12 months	NHL and HL	No difference in LVEF
NCT01988571	[47]	Preventing Anthracycline Cardiovascular Toxicity With Statins (PREVENT)	Difference LVEF between groups. CMR	Atorvastatin 40 mg/d or placebo	Anthracycline	279	RCT/24 months	Breast cancer or lymphoma	No difference in LVEF
NCT03186404	[111]	Statins for the Primary Prevention of Heart Failure in Patients Receiving Anthracycline Pilot Study (SPARE-HF)	Difference LVEF between groups	Atorvastatin 40 mg/d or placebo	Anthracycline	112	RCT/ Within 4 weeks of cancer therapy completion	Breast cancer, lymphomas, leukemia or sarcoma	No difference in LVEF
NCT01968200	[16, 80]	Prevention of Anthracycline-induced Cardiotoxicity ICOS-ONE	Incidence of troponin elevation between-group. TTE: LVEF of ≥ 10% to a value < 50%	Preventive treatment enalapril 10 mg b.i.d. vs troponin-triggered treatment	Anthracycline	273	Randomized Open-label Multicenter/ 3 years	First diagnosis of cancer and indication for first-line therapy with anthracyclines	No difference in incidence of troponin elevation. No difference in LVEF. No new cases of incident AC at 3-y follow-up
NCT00292526	[18]	Prevention of Chemotherapy-induced Cardiotoxicity in High-risk Patients	Incidence of chemotherapy-induced cardiotoxicity, 12-month period	Enalapril 20 mg q.d. vs control	Anthracycline	114	RCT/12 months	Various (Breast cancer, acute myeloid leukemia, relapsed or refractory poor-prognosis HL, high-grade NHL, myeloma, and Ewing's sarcoma)	No drop in LVEF, MACE lower incidence
NCT02236806	[62]	Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab (SAFE)	Change in LVEF by TTE 2D and 3D. change in GLS	Bisoprolol 5 mg q.d. vs ramipril 5 mg q.d. vs bisoprolol 5 mg q.d. plus ramipril 5 mg q.d. vs placebo	Neoadjuvant and/or adjuvant anthracyclines with or without anti-HER2 therapy	262	RCT/24 months	Breast cancer	Bisoprolol, ramipril, and bisoprolol plus ramipril attenuated the reduction in LVEF. Bisoprolol and ramipril prevented worsening in peak GLS

Table 1 (continued)

NCT No	References	Study name	Primary endpoint	Intervention	Cancer treatment	Sample size	Design and follow-up	Cancer type	Outcome
NCT01434134	[37, 41]	Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy	Change in LVEF by CMR	Metoprolol 100 mg q.d. plus Candesartan 32 mg q.d. metoprolol 100 mg q.d. plus placebo vs Candesartan 32 mg q.d. plus placebo vs placebo plus placebo	Adjuvant chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide	130	RCT/72 weeks	Breast cancer	Candesartan attenuated the reduction in LVEF. follow-up: no difference in change in LVEF from baseline to extended follow-up
NCT01724450	[7]	Carvedilol Effect in Preventing Chemotherapy—Induced Cardiotoxicity (CECCY)	Drop LVEF of > 10% from baseline by TTE	Carvedilol 50 mg q.d or placebo	Anthracycline, cyclophosphamide, and taxane	200	RCT/6 months	Breast cancer	No difference in LVEF
NCT01110824	[13]	Prevention of Left Ventricular Dysfunction During Chemotherapy (OVERCOME)	Change in LVEF by CMR	Enalapril 5 and 10 mg b.i.d. plus carvedilol 12.5 mg and 25 mg b.i.d. vs control	Hematopoietic stem cell transplantation (HSCT)	90	RCT/6 months	Hematological	No drop LVEF; lower incidence of death and HF
NCT02053974	[4]	Spironolactone Against Anthracycline-induced Cardiomyopathy	Drop in LVEF by TTE	Spironolactone 25 mg q.d. vs placebo	Anthracycline	83	RCT/6 months	Breast cancer	No drop LVEF; no impairment in diastolic function
NCT03166813	[19]	Remote Ischemic Preconditioning in Childhood Cancer	Change in biomarkers from baseline to 3 month	RIC vs Sham	Anthracycline	68	RCT/3 months	Childhood cancer	No differences in biomarkers levels or LV tissue Doppler and strain parameters between groups
NCT02471885	[74]	Effect of Remote Ischemic Conditioning in Oncology Patients (ERIC-ONC)	High-sensitivity troponin T AUC before and after each chemotherapy cycle and at 1-, 3-, 6-, and 12-month follow-up	RIC vs Sham	Anthracycline	128	RCT/12 months	Cancer diagnosis	No difference in biomarker between groups; nor any differences in cardiac function

fitness is essential for a normal cardiomyocyte function. In order to cope with different conditions and stressors, mitochondria undergo several processes, ranging from biogenesis (expansion of mitochondrial mass) to fusion/fission (mitochondrial dynamics) and mitophagy (selective elimination of damaged mitochondrial). Several therapies targeting these mitochondrial processes have been tested at the experimental level (reviewed elsewhere [90]). Here we will focus in mitochondrial quality control (mitophagy) since some interventions are currently being tested at the clinical level.

Quality control is a processes where damaged structures are selectively eliminated to improve cellular fitness. Autophagy, and a more selective mitophagy, are quality control processes that have been shown beneficial in several cardiac conditions such as ischemia/reperfusion [114]. Since doxorubicin cumulative exposure is associated with a progressive damage in different cellular compartments (mainly mitochondria), enhanced quality control appears as a very promising strategy to limit AC [117].

Ischemic conditioning is an intervention where repetitive brief episodes of blood flow interruption followed by reperfusion render the tissue more resistant to injuries [43]. When ischemic conditioning is undertaken before the actual injury (ischemic preconditioning), it has the strongest protective effects. Ischemic conditioning performed immediately after the injury event (postconditioning), has also been shown to provide (weaker) protection. As originally described, ischemic conditioning can be done in the same organ/tissue that lately will suffer the injury (local conditioning) or can be applied in a different organ at a distance (remote ischemic conditioning, RIC [10]). RIC has the advantage of can be applied in accessible organs (e.g., the arm by intermittent inflation of blood pressure cuffs) to render protection to less accessible organs (e g,heart or brain). At the experimental and clinical levels, RIC has been applied mostly in the context of ischemia/reperfusion injury (i.e., myocardial infarction). While at the experimental level RIC´s cardioprotection is very consistent, clinical trials have been more heterogeneous, with some showing protection and others not. Due to the unpredictable nature of myocardial infarction onset in patients, RIC can only be applied after the ischemic injury has been in place for a significant time. Among others, this is one of the reasons why its cardioprotection in this setting is not consistent. In other cardiac conditions where the onset of injury is predictable (e.g., cardiac injury secondary to global ischemia during cardiac surgery), RIC has been shown to be associated with cardioprotection and long-term clinical benefits [97, 113]. In this sense, injection of doxorubicin is a programmed intervention and thus ideally suited for implementing RIC before [44].

In the context of ischemia/reperfusion injury, ischemic conditioning has been shown to exert cardioprotection by mechanism involving mitochondrial quality control [32, 54, 123]. Cell culture [78], isolated perfused rat hearts [102], and murine in vivo studies [33, 40] have suggested that ischemic conditioning protects the heart against AC. A recent study in a translatable pig model of AC have shown that RIC applied before each of the injections of doxorubicin was associated with a strong protection against AC [30]. This large animal study set the basis for testing RIC in patients receiving anthracyclines to prevent the development of cardiotoxicity. Two small trials have reported a neutral effect of RIC in terms of cardiac function in patients undergoing anthracycline-based chemotherapy [19, 73]. However, these trials enrolled patients at very low risk for AC and thus the chances to observed cardioprotection being very small [49].

In one of these small trials, there were more cancer deaths in the group of patients undergoing RIC [73]. However, patients allocated to RIC were more frequently included at cancer relapse (i.e., not first cancer diagnosis) and had at baseline significantly higher prevalence of metastatic disease. This imbalance (poorer cancer prognosis at baseline) likely accounted for more cancer deaths in the RIC group in this trial, albeit this possibility needs to be surveilled in prospective studies [55]. The large ongoing RESILIENCE trial in lymphoma patients at high risk for AC will determine whether this strategy is beneficial in this context [83].

More sophisticated mitochondrial-targeted therapies are being tested at the experimental level. Among them, mitochondrial transplantation arises as a revolutionary intervention that could not only prevent the development of AC but treat this condition even at advanced stages [51]. The rationale for this promising therapy is that once mitochondria are irreversibly bound to doxorubicin, no new mitochondria can be generated. Transplantation of fresh healthy mitochondrial can replenish its population within cardiomyocytes and eventually improve energetics and cardiac function. To date, only few in-vitro studies [72, 105] studies and one in vivo study in rats [71] have tested this revolutionary intervention. Before this strategy can be translated to the clinics, the results of ongoing large animal experiments are awaited.

Cardiac metabolism: strategies to maintain metabolic flexibility

The heart is an omnivore organ able to consume any type of fuel for energy production. Among all fuels, the preferred metabolic substrate in homeostatic conditions are fatty acids since they are the most efficient for mitochondrial energy production [64, 96]. As discussed above, AC is characterized by a cardiomyocyte loss of metabolic flexibility (i.e., capacity to use different fuels for energy production) and a metabolic switch characterized by a reduction in the fatty acid metabolism [22]. This metabolic switch is also present in other cardiac conditions, such as HF. There are several

Table 2 Ongoing clinical trials testing cardioprotective strategies to prevent anthracycline cardiotoxicity

NCT No	Study	Primary endpoint	Intervention	Cancer treatment	Sample size	Start date	Design and follow-up	Cancer type
NCT05223413	REmote iSchemic condItioning in Lymphoma PatIents REceiving ANthraCyclinEs (RESILIENCE)	Change in LVEF assessed by serial cardiac magnetic resonance (CMR) studies	RIC vs Sham	Anthracyclines	608	Jan. 2022	RCT/42 months	Lymphoma
NCT05792293	Role of Statin Therapy in Prevention of Anthracycline-Induced Cardiotoxicity	Drop LVEF of > 10% from baseline to a final value of < 53%. TTE 3D	Atorvastatin 40 mg q.d. vs placebo	Anthracyclines (doxorubicin)	110	June 2021	RCT/6 months	Breast cancer
NCT02096588	Detection and Prevention of Anthracycline-Related Cardiac Toxicity With Concurrent Simvastatin	Change in Echocardiographic Global Longitudinal Strain (GLS)	Simvastatin 40 mg q.d. vs placebo	Anthracyclines (doxorubicin)/ cyclophosphamide	34	May 2014	RCT/15 week	Breast cancer
NCT03265574	PROACT: Can we Prevent Chemotherapy-related Heart Damage in Patients With Breast Cancer and Lymphoma?	Cardiac troponin T release during anthracycline treatment (1 months after last dose of anthracycline)	Enalapril (titrated to a maximum tolerated dose) vs usual care	Anthracyclines (epirubicin)	111	Oct. 2017-Aug. 2023	RCT/1 months	Breast cancer/NHL
NCT05465031	Sacubitril/Valsartan in PriMAry preventIoN of the Cardiotoxicity of Systematic breaST canceR trEAtMent (MAINSTREAM)	Drop LVEF ≥ 5%. At 12 months CMR	Sacubitril-valsartan 97/103 mg b.i.d. vs placebo	Anthracyclines and/ or anti-human epidermal growth factor receptor 2	480	Feb. 2023	RCT/24 months	Breast cancer
NCT04939883	Effects of Carvedilol on Cardiotoxicity in Cancer Patients Submitted to Anthracycline Therapy (CardioTox)	Drop in LVEF > 10% from baseline to value < 50%. Cardiac events	Carvedilol 25 mg b.i.d. vs Placebo	Anthracyclines	1018	Aug. 2023	RCT/12 months	Cancer and anthracyclines indication
NCT03760588	Prevention of Cardiac Dysfunction During Breast Cancer Therapy (PRADAII)	Change in LVEF assessed by CMR from baseline to 18 months	Sacubitril-valsartan 97/103 mg b.i.d. vs placebo	Anthracyclines with/ without trastuzumab/pertuzumab	214	Jan. 2019	RCT/18 months	Breast cancer

Table 2 (continued)

NCT No	Study	Primary endpoint	Intervention	Cancer treatment	Sample size	Start date	Design and follow-up	Cancer type
NCT02717507	Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors	LV posterior wall thickness, LV systolic and diastolic function, and afterload; natriuretic peptides, troponins, and galectin-3	Carvedilol low-dose vs placebo	Anthracyclines	182	Apr. 2016	RCT/24 months	Childhood cancer survivors
NCT06005259	Effect of Spironolactone in the Prevention of Anthracycline-induced Cardiotoxicity (SPIROTOX)	Drop in LVEF > 10% from baseline to value < 50% or TTE. Change in GLS > 15% or increase in cardiac biomarkers	Spironolactone 5 mg q.d. vs placebo	Anthracyclines	264	Oct. 2023	RCT/12 months	Cancer and anthracyclines indication
NCT03650205	Ivabradine to Prevent Anthracycline-induced Cardiotoxicity (IPAC)	Reduction in GLS of ≥ 10% from baseline to 12 months	Ivabradine 5 mg b.i.d. vs placebo	Anthracyclines	160	Jan. 2019-Dec. 2021	RCT/12 months	Cancer and anthracyclines indication
NCT04030546	Ivabradine to Prevent Anthracycline-induced Cardiotoxicity (IPAC)	Change in GLS at 1, 3, and 6 months of ≥ 3%	Ivabradine 5 mg b.i.d. vs usual care	Anthracyclines	128	June 2019-Dec. 2020	RCT/6 months	Cancer and anthracyclines indication
NCT05271162	Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines	Drop in LVEF. TTE, CMR baseline to 24 months	Empagliflozin 10 mg q.d. vs placebo	Anthracyclines	220	Sept. 2023	RCT/24 months	Cancer and anthracyclines indication
NCT06220032	Prevention of Anthracycline-Induced Cardiac Dysfunction With Dexrazoxane in Patients With Diffuse Large-B Cell Lymphoma (HO170DLBCL)	The incidence of AC (measured by ETT 2D) within 12 months after registration., 12 months after LPI	Dexrazoxane 500 mg/m^2 (iv) prior doxorubicin infusion vs current standard of care	Anthracyclines (R-CHOP)	324	May 2024	RCT/12 months	Lymphoma

Table 2 (continued)

NCT No	Study	Primary endpoint	Intervention	Cancer treatment	Sample size	Start date	Design and follow-up	Cancer type
NCT03934905	Protective Effects of the Nutritional Supplement Sulforaphane on Doxorubicin-Associated Cardiac Dysfunction	Change in cardiac function by 2D echocardiography from baseline to 12 months	Sulforaphane (2–8 caplets q.d based on weight) vs placebo	Anthracyclines (Doxorubicin)	70	June 2022	RCT/12 months	Breast cancer
NCT04023110	Risk-Guided Cardioprotection With Carvedilol in Breast Cancer Patients Treated With Doxorubicin and/or Trastuzumab	Change in LVEF from baseline to 24 monthsassessed by echocardiography, treatment adherence, adverse events	Risk-guided cardioprotective treatment with carvedilol 25 mg b.i.d. vs usual care	Anthracyclines, trastuzumab, or the combination	110	Aug. 2019-Dec. 2024	RCT/12 months	Breast cancer
NCT02571894	The Cardio-Oncology Breast Cancer Study (COBC)	Event-free survival at 1 y after the completion of chemotherapy	Subclinical cardiotoxicity surveillance and treatment vs standard care	Neoadjuvant or adjuvant chemotherapy, with or without trastuzumab	320	July 2014-Feb. 2020	RCT/ 10 years	Breast cancer

drugs approved for other conditions that and prevent a metabolic switch by biasing cardiomyocyte metabolism toward fatty-acids oxidation. Among them, peroxisome proliferator-activator receptors alpha (PPARα) appears as a very promising strategy for AC. PPARs are ligand-activated transcription factors of nuclear factors involved (among other processes) in the regulation of fatty acid metabolism, storage and usage by the cell [81]. PPARs activation exerts cardioprotective effect in animals' models of ischemia/reperfusion injury through a mechanism involved cardiac metabolism. Glitazones are PPAR-α and γ agonists and are commonly used for patients with hyperlipidemia and hyperglycemia, improving insulin sensitivity. Glitazones have been tested in small animal models of AC with overall positive results [5, 27, 92]. While this metabolic intervention seems very well suited for being tested in patients, its paradoxical deterioration of congestion in patients with HF warrants attention [52]. It might be the case that glitazones are well suited as a preventive strategy against AC but not that beneficial once overt HF is present.

As expanded below, non-pharmacologic interventions (e.g., nutritional therapies) that can modulate cardiac metabolism toward fatty acid consumption hold promise as alternative strategies to prevent AC. In this sense, high fat diet has been shown to improve cardiac function in animal models of HF secondary to mitochondrial pathology [116]. In HF patients, the administration of systemic lipids has been shown to improve cardiac energetics and function [119].

Other metabolic interventions with promise in the context of AC prevention include the use of Sodium-glucose Cotransporter-2 inhibitors (SGLT2i). This class of drugs has been very rapidly incorporated in the armamentarium for treating HF of different etiologies. Observational retrospective studies suggest that therapy with SGLT2i can be associated with a reduced incidence of AC [36]. While the suggested mechanism of action is the modification of cardiac substrate utilization (preventing a glycolysis-driven one), there is a lack of experimental mechanistic studies to support this important mechanism responsible for the cardioprotection. Once these mechanistic studies are published, its test in the clinical environment will be undertaken.

Exercise and dietary interventions

A healthy lifestyle, including physical activity and specific dietary approaches, is crucial in any cardiovascular prevention program. The context of AC, several studies have suggested the benefits of healthy habits in the prevention of this condition [67, 120].

Several studies have tested the effects of exercise during anthracycline-chemotherapy, but most of them are very small (sample size usually less than 30 patients). Is several small studies, aerobic plus resistance exercise while on

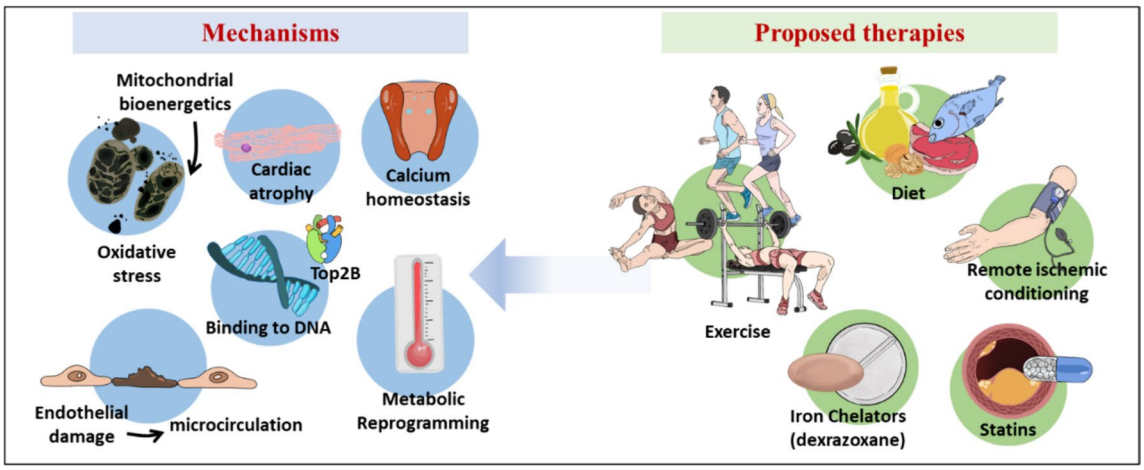

Fig. 1 Mechanisms and proposed therapies for anthracycline cardiotoxicity. This figure summarizes the complex interactions between the mechanisms of cardiotoxicity and the potential therapeutic interventions that could ameliorate these effects. Left Panel: Various mechanisms contributing to anthracycline cardiotoxicity are depicted. Right Panel: Proposed cardioprotective therapies than can target the mechanisms of anthracycline cardiotoxicity (AC)

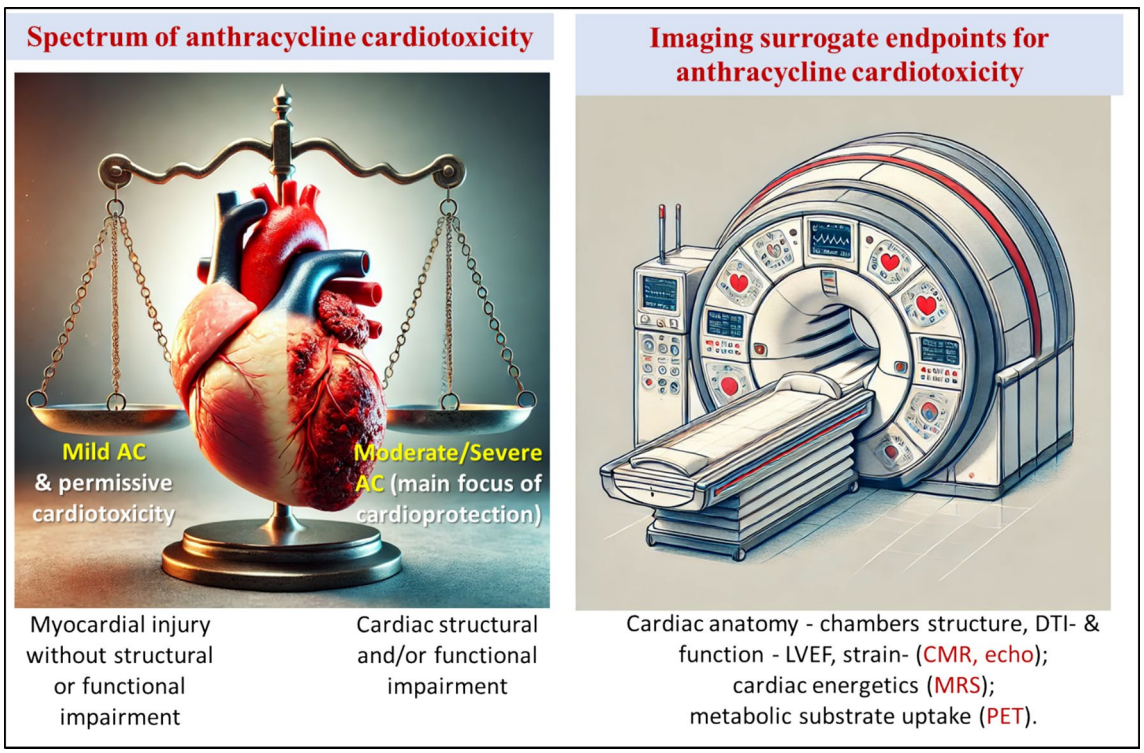

Fig. 2 Key concepts in the evaluation of anthracycline cardiotoxicity. Left Panel: The balance represents the spectrum of anthracycline cardiotoxicity (AC), ranging from mild and reversible injury, to moderate/severe irreversible damage. The left side of the balance, showing the healthy portion of the heart, symbolizes minor myocardial injury that does not lead to structural or functional impairment. This level of injury is often considered acceptable ("permissive cardiotoxicity") due to the benefits of ongoing cancer therapy. The right side of the balance, displaying the damaged portion of the heart, represents significant structural and/or functional impairment, which is the primary focus of cardioprotective strategies. Right Panel: The illustration depicts modern imaging techniques used to monitor AC. Imaging can evaluate cardiac anatomy, including chamber structure, function (such as LVEF and strain via CMR and echocardiography), cardiac energetics (MRS), and metabolic substrate uptake (PET). These imaging endpoints are crucial for assessing the extent of cardiotoxicity and guiding therapeutic decisions. Some parts of the illustrations have been created assisted by AI. Abbreviations: *AC* Anthracycline Cardiotoxicity, *LVF* Left Ventricular Ejection Fraction, *CMR* Cardiac magnetic resonance, *MRS* Magnetic Resonance Spectroscopy, *PET* Positron emission tomography, *DTI* Diffusion tensor imaging, *Echo* Echocardiography

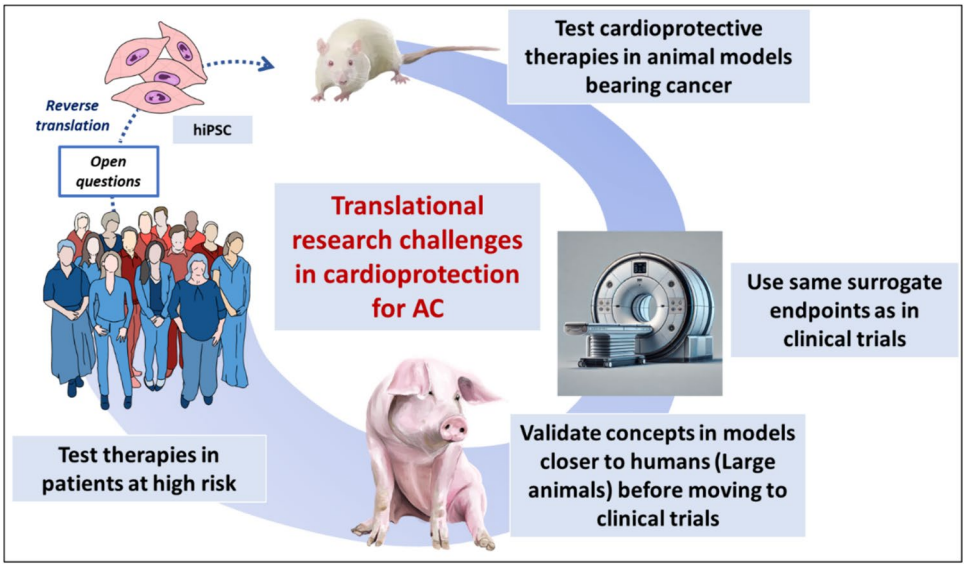

Fig. 3 Translational research challenges in the field of cardioprotection for anthracycline cardiotoxicity. The critical steps from preclinical models to clinical application are highlighted. Reverse translation is also emphasized, where open questions and findings from human studies or complex animal models can inform further research using Human-Induced Pluripotent Stem Cells (hiPSC) and other basic science models. This step helps refine and optimize cardioprotective strategies, creating a feedback loop that continuously improves understanding and treatment of AC. The magnetic resonance imaging equipment illustration has been created assisted by AI. Abbreviations: *AC* Anthracycline Cardiotoxicity, *hiPSC* Human-Induced Pluripotent Stem Cells

anthracycline-chemotherapy resulted in better echo-based LVEF [20], better cardiac output [53], or improved cardiopulmonary exercise [45]. In the largest trial in 104 breast cancer patients, aerobic plus resistance exercise resulted in better LVEF reserve [26]. These results are encouraging but the important limitations of the studies prevent a definite conclusion.

Dietary interventions are also the matter of recent interest. In a rat AC model, caloric restriction was associated with improved hemodynamics and also with reduced doxorubicin accumulation in hearts [38]. Conversely, in another mouse study, intermittent fasting was associated with exacerbated AC [91].

A recent small animal study has suggested that several dietary interventions (isocaloric diets enriched in fat or proteins) might be beneficial to prevent AC [22]. However, these have not been formally tested so far.

Overall, lifestyle interventions hold promise to help in the prevention of AC, but the evidence so far is not well established.

Unspecific HF interventions:

Since AC can evolve into HF, the most obvious therapeutic options to be tested are drugs with proven efficacy in the HF context. The obvious advantage of this strategy is that these interventions are proven to be safe and efficacious in other forms of HF. The drawback is that they are not mechanistically oriented, meaning that they exert their actions targeting pathways not necessarily involved in AC. Here we present the evidence regarding β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone antagonists.

A recent meta-analysis including 6 randomized clinical trials evaluated the potential benefit of the βblocker carvedilol to prevent AC [46]. Main results were that carvedilol did not prevent the deterioration of LVEF (as compared to placebo), but it was associated with less clinically overt cardiotoxicity events. The ACE inhibitor enalapril was tested in an open label fashion in a trial enrolling 114 patients who displayed elevation of cardiac biomarkers at the end of the chemotherapy including high-dose anthracyclines [18]. Thus, this study did not test its AC preventive capacity, but its clinical value to prevent further deterioration. The progressive deterioration of LVEF observed in control patients was not observed in those randomized to receive enalapril. Other trials have tested the cardioprotection exerted by the combination of β-blockers and ACE inhibitors. In the extended follow-up of the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial, 120 patients were randomized in a 2 × 2 manner to the ARB candesartan vs placebo and to the βblocker metoprolol vs placebo [41]. None of the agents was associated with a benefit in terms of improved LVEF. However, candesartan was associated with a modest reduction in LV end-diastolic volume and preserved GLS.

The OVERCOME trial investigated the preventive effects of the combination of enalapril and carvedilol in 90 patients with hematologic malignancies treated with anthracyclines [13]. After 6 months of follow-up, the intervention group showed no change in LVEF, whereas the controls experienced a significant decrease. Compared to controls, patients randomized to enalapril, and carvedilol had a lower incidence of death or HF. The small sample size precludes a definite conclusion on the cardioprotection of this combination of HF drugs to prevent AC.

The ARB telmisartan was tested against placebo in a small trial of 49 patients with various solid cancers receiving epirubicin [15]. At low cumulative anthracycline dose, LV strain deterioration (as measured by echocardiography) was not different between groups, but in patients receiving high cumulative dose of epirubicin, telmisartan was associated with better LV strain than placebo-treated patients. Circulating oxidative stress and inflammatory markers were reduced in patients randomized to telmisartan. Finally, the aldosterone antagonist spironolactone was tested against placebo in a trial of 83 breast cancer patients receiving anthracyclines. In this pilot trial, spironolactone was associated with less pronounced LVEF decline and preserved diastolic function, as well as with lower circulating levels of cardiac injury biomarkers [4].

In conclusion, most of these trials testing unspecific HF therapies are small and therefore inconclusive. Since these drugs are approved by other forms of HF, and despite the lack of robust benefit, the ESC cardio-oncology guidelines consider that the use of βblockers, ACE inhibitors or ARBs should also be considered for primary prevention of AC in high- and very high-risk patients receiving anthracyclines and/or anti-HER2 therapies, as well as those receiving targeted cancer therapies that may cause HF [66].

Statins

Statins are a unique class of lipid-lowering agents since several pleiotropic effects have been ascribed to them. Several studies have tested the benefits of statins to prevent AC, with some trials showing positive results (i.e., statins associated with cardioprotection) [1, 85], and some others with neutral results [112]. The two largest trials on the topic have been recently reported with apparent disparate results. In the PREVENT (Preventing Anthracycline Cardiovascular Toxicity with Statins) trial, 279 breast cancer and lymphoma patients receiving anthracycline therapy were randomized to atorvastatin 40 mg daily or placebo [47]. At 2 years follow-up, LVEF did not differ between groups. Conversely, in the STOP-CA trial that randomized 300 lymphoma patients were to atorvastatin 40 mg daily or placebo, the incidence of cardiotoxicity events (defined according to a pre-specified decline in LV systolic function) was significantly reduced in the active treatment group [87]. Several factors could explain these differing outcomes. It's possible that only patients receiving high doses of anthracyclines benefit from statin therapy, as seen in the STOP-CA trial [87] where the anthracycline dose was higher. In addition, variations in study size, dropout rates, and follow-up durations may have influenced the results. Differences in background treatments and the timing of outcome assessments could also play a role. In animal models, statins have shown to be cardioprotective against other forms of cancer therapy-related cardiotoxicity [23].

Similar to the unspecific therapies for HF, using the same rationale, the ESC Cardio-Oncology guidelines propose that the use of statins should be considered for patients at high risk for AC [66].

Iron chelators

As discussed above, doxorubicin alters intracellular iron homeostasis and trafficking, resulting in iron accumulation and its interaction with oxygen species [31]. The most compelling evidence involving iron in AC is that the iron chelator dexrazoxane was considered protective against clinical AC in old trials [107]. Dexrazoxane is the only FDA-approved drug for the prevention of AC. A Cochrane analysis and meta-analyses have corroborated dexrazoxane's cardioprotection against AC [21, 68]. In addition to its iron chelating capacities, dexrazoxane induces conformational changes in topoisomerase 2b. Consistent with this (old) data, the ESC Cardio-Oncology guidelines propose that dexrazoxane should be considered for patients at high risk for AC or who have already received significant doses of anthracycline [66].

Pegylated liposomal doxorubicin and Liposomal

Pegylated and non-pegylated liposomal doxorubicin are presentations whose tissue distribution does not compromise their anticancer efficacy. They are currently approved for metastatic breast cancer, advanced ovarian cancer, Kaposi's sarcoma and MM, as well as liposomal daunorubicin in patients with pre-existing CVD. In a meta-analysis, liposomal doxorubicin was shown to produce less cardiotoxic effects than conventional doxorubicin [121].

Table 1 summarizes the design, endpoints and main results of most of the clinical trials reported in the field and presented in this review paper.

Ongoing clinical trials testing cardioprotective strategies in anthracycline cardiotoxicity

The field of prevention AC is a very active one and several trials are ongoing testing many different cardioprotective strategies. Here we present some of these trials.

Table 2 summarizes the design of the most relevant ongoing trials in the field of AC.

A RCT testing Sacubitril-valsartan vs placebo (Sacubitril/Valsartan in PriMAry preventIoN of the Cardiotoxicity of Systematic breaST canceR trEAtMent [109] (MAINSTREAM)) NCT05465031 is currently active and will enroll 480 breast cancer patients receiving anthracyclines. This study will assess LVEF drop with MRI with a 12-month follow-up. Similarly, the PRADAII study (Prevention of Cardiac Dysfunction During Breast Cancer Therapy NCT03760588) will assess the change in LVEF by cardiovascular MRI, from randomization to end of blinded therapy (18 months), in a population of 214 patients with breast cancer receiving chemotherapy that includes anthracyclines.

PROACT trial (NCT03265574) testing Enalapril vs usual care, has enrolled 111 patients with breast cancer and NHL has been completed and is awaiting results [70].

As for beta-blockers, studies are underway with carvedilol. RCT to enroll 1018 to evaluate carvedilol vs placebo in adults with cancer receiving anthracyclines and to assess drop in LVEF > 10% from baseline to value < 50% and cardiac events (Effects of Carvedilol on Cardiotoxicity in Cancer Patients Submitted to Anthracycline Therapy/CardioTox) NCT04939883. And another study will assess Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors, recruiting 182 child cancer survivors and assessing LV systolic diastolic function and cardiac biomarkers NCT02717507.

Effect of Spironolactone in the Prevention of Anthracycline-induced Cardiotoxicity (SPIROTOX) NCT06005259 will recruit 264 patients with cancer and anthracycline indication, and evaluate AC by change in LVEF, GLS and cardiac biomarkers in spironolactone vs placebo groups, with a 12-month follow-up.

Trials to assess the possible cardioprotective effect of ivabradine vs placebo (160 patients) or ivabradine vs usual care (128 patients) are being conducted in cancer patients receiving anthracyclines (Ivabradine to Prevent Anthracycline-induced Cardiotoxicity /IPAC) NCT0365050205 and NCT04030546, assessing left ventricular dysfunction by GLS.

A trial of Dexrazoxane (Prevention of anthracycline-induced cardiac dysfunction with dexrazoxane in patients with diffuse large B-cell lymphoma), which will enroll 324 patients who will receive chemotherapy that includes anthracyclines (R-CHOP), will test the incidence of AC in this intervention vs standard care, with a follow-up of up to 12 months. NCT0622003.

An emerging therapy for heart failure will also be tested in the field of cardio-oncology, a sodium–glucose co-transporter (SGLT-2). Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines (EMPACT) NCT05271162. This RCT (Empagliflozin vs placebo) will include 220 patients with cancer and anthracyclines indication will assess changes in LVEF by CMR with a follow-up of up to 24 months.

The largest trial in cardio-oncology, RESILIENCE (REmote iSchemic condItioning in Lymphoma PatIents REceiving ANthraCyclinEs; NCT05223413), is currently underway in five European countries [83]. This trial funded by the European Commission, with the goal of recruiting a total of 608 lymphoma patients, is focused on those at increased risk of developing cardiotoxicity. Patients are randomized to weekly RIC vs Sham during the period of chemotherapy including anthracyclines and undergo a full MRI scan at baseline, mid-chemotherapy and 9 weeks after completion of chemotherapy treatment. Given the sample size and the fact that this is a population at higher risk of developing cardiotoxicity, the assessment of the efficacy of RIC in the RESILIENCE trial, while awaiting results, makes this intervention very promising for preventing anthracycline cardiotoxicity.

Future perspectives

AC is an unmet clinical challenge. Recent discoveries regarding the mechanisms responsible for AC are opening new preventive opportunities. While several animal studies have proposed different interventions, there is still no therapy in clinical practice that has been definitively associated with cardioprotection against AC.

The focus of cardioprotective therapies should be on preventing clinically relevant AC (i.e., AC associated with irreversible cardiac structural and functional impairment). The recent concept of permissive cardiotoxicity (not severe myocardial injury that can be tolerated within the significant benefits of anthracycline therapy) is gaining acceptance. Since several risk factors are known to be associated with AC, there is an opportunity to enroll patients at the highest risk. By doing so, the chances of identifying effective therapies will significantly increase. Outcome measures in experimental and clinical studies testing cardioprotective strategies should include both structural and functional evaluations of the heart. Non-invasive imaging plays a key role in this regard, with CMR being particularly important, as it can evaluate cardiac structure, function, composition, perfusion, and energetics in a single session.

One key aspect that remains unresolved is demonstrating that any cardioprotective therapy preventing AC does not negatively impact cancer outcomes. While there is no evidence of this in the literature, from a mechanistic perspective, it is plausible that any intervention protecting cardiomyocytes from anthracycline injury could also protect

cancer cells. Therefore, it is important that animal models testing cardioprotective strategies against AC are conducted in animals with cancer, and that clinical trials include a primary safety outcome of cancer progression during interventions [44].

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Data availability Data are available upon reasonable request to corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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