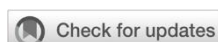


# Pharmacologic Strategies to Prevent Anthracycline-Related Cardiotoxicity

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## Abstract

Anthracycline-induced cardiotoxicity is a major complication of cancer therapy and a growing concern as long-term survival improves. Increasing cancer incidence, aging populations, and prevalent comorbidities further heighten vulnerability to cardiovascular injury. Standardized terminology such as cancer therapy-related cardiovascular toxicity and cancer therapy-related cardiac dysfunction, has been introduced to support clinical assessment. This narrative review aims to synthesize current evidence on pharmacologic strategies used to prevent anthracycline-related cardiotoxicity. Foundational therapies, including ACE inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, and mineralocorticoid receptor antagonists, have shown variable cardioprotective effects, with heterogeneous outcomes across clinical trials. Emerging approaches such as angiotensin-neprilysin inhibition, statins, and SGLT2 inhibitors demonstrate promising early results but remain limited by short follow-up periods and inconsistent findings. Additional options, including biologically active compounds and cardiometabolic-targeted therapies, currently lack sufficient clinical support. Dexrazoxane remains the only FDA-approved agent for anthracycline cardiotoxicity prevention. Overall, pharmacologic prevention plays a central role in mitigating anthracycline-induced cardiovascular injury, underscoring the need for further research to refine targeted strategies and improve long-term cardiovascular outcomes in cancer survivors.

**Keywords:** *anthracycline cardiotoxicity, cardio-oncology, pharmacologic prevention*

## Abstrak

Kardiotoksitas akibat antrasiklin merupakan salah satu komplikasi utama terapi kanker dan menjadi perhatian yang semakin besar seiring meningkatnya angka kesintasan jangka panjang. Peningkatan insidensi kanker, populasi yang menua, serta tingginya prevalensi komorbiditas semakin meningkatkan kerentanan terhadap cedera kardiovaskular. Terminologi yang terstandarisasi, seperti *cancer therapy-related cardiovascular toxicity* dan *cancer therapy-related cardiac dysfunction*, telah diperkenalkan untuk mendukung penilaian klinis. Tinjauan naratif ini bertujuan untuk merangkum bukti terkini mengenai strategi farmakologis yang digunakan untuk mencegah kardiotoksitas terkait antrasiklin. Terapi dasar, termasuk ACE inhibitor, angiotensin receptor blocker,  $\beta$ -blocker, dan antagonis reseptor mineralokortikoid, telah menunjukkan efek kardioprotektif yang bervariasi, dengan hasil yang heterogen pada berbagai uji klinis. Pendekatan yang lebih baru, seperti inhibisi angiotensin-neprilisin, statin, dan inhibitor SGLT2, menunjukkan hasil awal yang menjanjikan, tetapi bukti yang tersedia masih terbatas oleh masa tindak lanjut yang singkat dan temuan yang tidak konsisten. Pilihan lain, termasuk senyawa aktif biologis dan terapi yang menargetkan aspek kardiometabolik, saat ini masih belum memiliki dukungan klinis yang memadai. Dexrazoxane tetap menjadi satu-satunya agen yang disetujui FDA untuk pencegahan kardiotoksitas akibat antrasiklin. Secara keseluruhan, pencegahan farmakologis memiliki peran penting dalam mengurangi cedera kardiovaskular akibat antrasiklin, sekaligus menegaskan perlunya penelitian lebih lanjut untuk menyempurnakan strategi yang lebih terarah dan meningkatkan luaran kardiovaskular jangka panjang pada penyintas kanker.

**Kata kunci:** *kardio-onkologi, kardiotoksitas antrasiklin, pencegahan farmakologis.*

## Background

Major advances in oncology have markedly improved long-term survival, shifting clinical priorities toward preventing the cardiovascular consequences of cancer therapy.<sup>1</sup> Many anticancer agents, especially anthracyclines, are associated with substantial cardiotoxic potential, and in cancers such as early-stage breast cancer, survival now surpasses that of heart failure populations, underscoring the need for cardiovascular preservation during treatment.<sup>2,3</sup>

Because cancer and cardiovascular disease share multiple risk determinants, assessment of cardiovascular status before therapy initiation is increasingly emphasized in contemporary oncology practice.<sup>4</sup> This need is reinforced by rising cancer incidence, aging populations, and the high prevalence of comorbid conditions such as hypertension and diabetes, all of which elevate vulnerability to treatment-related injury.<sup>5</sup>

Real-world data further highlight the magnitude of this problem. In the CARDIOTOX-2020 registry, more than one-third of patients developed cardiotoxic manifestations during therapy.<sup>6</sup> Such injury may be acute, chronic, or delayed, ranging from subclinical biomarker elevation to overt dysfunction.<sup>7</sup> To standardize terminology and guide clinical decision-making, the 2022 European cardio-oncology consensus introduced the concepts of cancer therapy–related cardiovascular toxicity (CTR-CVT) and cancer therapy–related cardiac dysfunction (CTR-CD).<sup>8</sup>

Given the increasing prevalence of CTR-CVT/CD and the limited effectiveness of post-injury treatment, preventive pharmacologic strategies have become central to modern cardio-oncology. This review synthesizes current evidence on cardiovascular-protective therapies, with particular emphasis on preventing anthracycline-induced toxicity.

## Conceptual Framework for Cardiovascular Prevention in Cardio-Oncology

The primary objective of cardio-oncology is to optimize cancer outcomes while minimizing cardiovascular injury and preventing exacerbation of pre-existing disease. Multidisciplinary involvement is essential, as coordinated care facilitates personalized prevention strategies throughout the cancer trajectory.<sup>9</sup> A foundational concept in this field is permissive cardiotoxicity, which supports continuing effective

cancer therapy while implementing protective interventions rather than prematurely discontinuing treatment.<sup>10</sup> Even in patients with known cardiovascular disease, appropriate monitoring and individualized prevention can enable safe therapy continuation without precipitating major events.<sup>11</sup>

Baseline cardiovascular risk assessment is essential prior to anthracycline exposure and typically includes validated scoring systems such as HFA-ICOS, echocardiographic evaluation, and biomarker measurement.<sup>12</sup> Because anthracycline cardiotoxicity affects diverse myocardial and vascular cell types, risk cannot be estimated solely by cumulative dose. Thus, comprehensive prevention and early detection strategies have become integral components of cardio-oncology practice.<sup>13</sup>

Multiple professional societies recommend foundational cardiovascular-protective pharmacotherapies such as ACE inhibitors,  $\beta$ -blockers, angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA) as part of preventive pathways.<sup>8</sup> A meta-analysis of randomized trials highlights their potential, showing that spironolactone reduced LVEF decline and troponin release, enalapril significantly lowered BNP, and statins showed the greatest improvement in LVEF among the evaluated classes.<sup>14</sup>

## Foundational Cardioprotective Therapies: RAAS Inhibition and $\beta$ -Blockers

ACE inhibitors have long been used because of their antifibrotic and remodeling-preventive effects. However, evidence is mixed. For instance, the PROACT trial found that starting enalapril shortly before anthracycline therapy did not significantly reduce troponin elevation or prevent deterioration in LVEF or GLS, suggesting that monotherapy may be insufficient for robust prevention.<sup>15</sup> In the PRADA trial, candesartan preserved LVEF during anthracycline-based therapy, whereas metoprolol did not exhibit similar benefit.<sup>16</sup>

Combined RAAS inhibition and  $\beta$ -blockade has demonstrated more consistent cardioprotection in certain settings, likely because the two mechanisms act synergistically to mitigate remodeling, oxidative stress, and neurohormonal activation. For instance, the combination of enalapril and carvedilol prevented LVEF decline in patients undergoing therapy for hematologic malignancies.<sup>7</sup> Carvedilol may offer additional benefit through antioxidant effects and

modulation of  $\beta$ -arrestin signaling, thereby reducing mitochondrial injury and apoptotic pathways.<sup>17,18</sup>

Clinical trials, however, remain heterogeneous. The CECCY trial reported stabilization of diastolic function and lower troponin release with carvedilol but did not demonstrate significant prevention of early LVEF reduction.<sup>19</sup> Similarly, the PREVENT-HF study found that long-term carvedilol was safe in childhood cancer survivors but did not significantly improve structural cardiac parameters.<sup>20</sup>

## Emerging Pharmacologic Strategies

### Angiotensin-Neprilysin Inhibition

Interest in sacubitril/valsartan has increased due to its dual neurohormonal effects and the capacity to enhance endogenous natriuretic peptide signaling.<sup>21</sup> The SARAH trial provided early evidence supporting its cardioprotective potential, showing smaller declines in GLS and LVEF compared with placebo over six months in patients receiving anthracyclines. Nevertheless, short follow-up duration and the absence of hard outcomes such as survival limit broad implementation. Mild hypotension and electrolyte disturbances were more frequent in the treatment group.<sup>22</sup>

### Mineralocorticoid Receptor Antagonists

MRAs theoretically reduce fibrosis and oxidative stress, central pathways in anthracycline toxicity.<sup>23</sup> Small RCTs support these protective properties. One study showed that spironolactone attenuated LVEF decline and preserved diastolic function compared with placebo.<sup>24</sup> However, the ELEVATE trial found no significant benefit of eplerenone over six months.<sup>25</sup> Larger trials are needed before MRAs can be routinely recommended for prevention.

### Statins

Statins exert pleiotropic anti-inflammatory and antioxidant effects that may counteract anthracycline and trastuzumab-associated injury.<sup>26,27</sup> Evidence remains inconsistent across studies. A result study demonstrated meaningful reduction in LVEF decline among lymphoma patients treated with atorvastatin, whereas other studies did not observe similar benefits in more heterogeneous cancer populations.<sup>28-30</sup> Concerns regarding myalgia effect also affect real-world use.<sup>31</sup>

### Biologically Active Compounds

Natural compounds such as resveratrol, melatonin, curcumin, and spirulina demonstrate cardioprotective effects in preclinical models.<sup>32-35</sup> However,

clinical evidence remains sparse, inconsistent, and rarely designed to assess oncologic safety. These agents cannot be recommended outside research settings due to uncertainty in efficacy and possible interactions with cancer therapies.<sup>36</sup>

## Cardiometabolic Pathways as Therapeutic Targets

Decades of research have identified oxidative stress and ferroptosis as dominant pathways in anthracycline-induced injury, yet clinical translation remains challenging.<sup>37</sup> Dexrazoxane continues to be the only FDA-approved agent for preventing anthracycline cardiotoxicity, but concerns persist regarding its use in patients with reduced LVEF and its compatibility with modern chemotherapy regimens.<sup>38</sup> Increasing recognition of the roles of inflammation, metabolic dysfunction, endothelial injury, and impaired energetics has driven interest in therapies targeting cardiometabolic pathways.<sup>39</sup>

### SGLT2 Inhibitors

SGLT2 inhibitors have emerged as promising agents due to broad cardiovascular benefits across heart failure phenotypes.<sup>40</sup> Preclinical studies show that dapagliflozin and empagliflozin mitigate anthracycline-induced oxidative stress, inflammation, endothelial dysfunction, and structural injury, leading to improved strain parameters, biomarkers, and histopathologic profiles.<sup>41,42</sup> A large recent meta-analysis demonstrated significant reductions in heart failure hospitalization and incident heart failure among cancer patients receiving SGLT2 inhibitors, particularly those treated with anthracyclines.<sup>43</sup>

## Conclusions

Pharmacologic prevention of cancer therapy-related cardiovascular toxicity is essential in contemporary oncology, given the increasing number of long-term cancer survivors at risk for treatment-induced injury. Foundational therapies such as ACE inhibitors, angiotensin receptor blockers, and  $\beta$ -blockers provide partial cardioprotection but leave substantial residual risk. Emerging agents including angiotensin-neprilysin inhibitors, mineralocorticoid receptor antagonists, statins, cardiometabolic modulators, and SGLT2 inhibitors, offer promising additional benefit, although the evidence remains heterogeneous and often preliminary. These preventive strategies are particularly relevant for mitigating anthracycline-induced cardiotoxicity, which remains the most clinically significant and extensively studied form of chemotherapy-

related cardiovascular injury. Future work should prioritize mechanistically targeted therapies, standardized definitions of cardiotoxicity, and integrated cardio-oncology pathways to enable personalized prevention and improve long-term cardiovascular outcomes in cancer survivors.

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## Conflict of Interests

The authors declare no conflict of interest in this review.

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