



Cancer Therapy-Related Cardiac Dysfunction (CTRCD): A Cardiologist's Perspective on Mechanisms, Detection, and Cardioprotective Strategies

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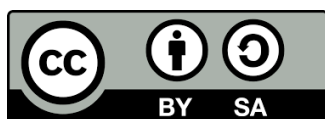
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Abstract

Advances in cancer treatment have improved survival but have also increased concerns regarding cancer therapy-related cardiac dysfunction (CTRCD), which may compromise cardiovascular health and continuity of oncologic treatment. This review aimed to synthesize the mechanisms, detection methods, and cardioprotective strategies associated with CTRCD from a cardiologist's perspective and to discuss their relevance to cancer care in Indonesia. A narrative review was conducted using clinical practice guidelines, consensus statements, randomized controlled trials, observational studies, and foundational mechanistic research. Evidence was synthesized thematically without quantitative pooling. The synthesis highlighted distinct and overlapping mechanisms associated with anthracyclines, human epidermal growth factor receptor 2 (HER2)-targeted therapies, and other anticancer treatments, supporting individualized cardiovascular risk assessment. Baseline cardiovascular risk stratification, cardiac biomarkers, and echocardiography incorporating global longitudinal strain (GLS) provide complementary information for detecting myocardial injury and left ventricular dysfunction. Evidence regarding cardioprotective strategies remains heterogeneous; established interventions require risk-based selection, while statins and emerging therapies have demonstrated potential benefits in selected populations, often based on imaging endpoints rather than definitive clinical outcomes. Multidisciplinary cardio-oncology assessment is essential when considering modification or interruption of anticancer therapy. In Indonesia, a collaborative care framework could facilitate standardized referral, cardiovascular surveillance, and clinical documentation while accounting for differences in resource availability. In conclusion, CTRCD management requires integrated, treatment-specific strategies for prevention and early detection, supported by coordinated cardiology–oncology care. Proposed clinical pathways should undergo prospective evaluation to establish their feasibility, effectiveness, and ability



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INTRODUCTION

Advances in systemic anticancer therapy have transformed many malignancies into chronic, survivable conditions, but this success has been accompanied by a growing burden of treatment-related cardiovascular disease. Global cancer incidence, already approaching 20 million new cases annually, is projected to exceed 35 million by 2050, and an increasing proportion of these patients will be exposed to one or more cardiotoxic agents during their

treatment course (Bray et al., 2024; Ferlay et al., 2024). Cancer therapy-related cardiac dysfunction (CTRCD)—encompassing asymptomatic declines in left ventricular function and overt heart failure—has therefore become a central concern not only for oncologists but also for cardiologists, who are increasingly integrated into oncology care pathways as members of dedicated cardio-oncology services (Lyon et al., 2022).

For the practicing cardiologist, CTRCD poses a distinctive clinical challenge. Unlike most causes of heart failure encountered in general cardiology practice, the cardiotoxic insult is often predictable, dose-related, and temporally associated with a defined treatment course, creating a genuine opportunity for anticipation and prevention rather than reactive treatment. At the same time, the imperative to preserve oncologic efficacy means that cardiologists cannot simply withhold or delay potentially life-saving anticancer therapy on the basis of modest cardiac risk; therapeutic decisions must instead be individualized, dynamic, and made jointly with the treating oncologist (Lyon et al., 2022; Sánchez et al., 2025). This narrative review approaches CTRCD from this clinical perspective, summarizing the mechanistic basis of cardiotoxicity across major drug classes, the tools available for risk stratification and surveillance, and the pharmacological and emerging strategies used to protect the heart while cancer therapy proceeds.

Recent clinical research has demonstrated that cardioprotection can preserve ventricular function in selected populations. In the STOP-CA randomized clinical trial, Neilan et al. (2023) enrolled 300 patients with lymphoma receiving anthracycline-based chemotherapy and compared atorvastatin with placebo. The primary endpoint, an absolute LVEF decline of at least 10 percentage points to below 55% over 12 months, occurred in 9% of participants receiving atorvastatin and 22% of those receiving placebo. However, incident heart failure did not differ significantly between the groups during the reported follow-up. These findings support the potential value of statin-based prevention in an appropriately selected population while illustrating the distinction between improvement in an imaging endpoint and a demonstrated reduction in clinical heart failure. This distinction is essential when translating trial results into clinical practice.

Evidence concerning neurohormonal blockade further demonstrates why preventive treatment requires critical appraisal. Extended follow-up of the PRADA trial showed no significant between-group differences in LVEF decline approximately two years after randomization among patients receiving candesartan, metoprolol, or their corresponding controls. Similarly, the Cardiac CARE trial investigated troponin-guided treatment with candesartan and carvedilol without demonstrating a clear preventive benefit for its primary ventricular function outcome. Together, these studies indicate that biological plausibility and early biomarker abnormalities do not automatically establish the effectiveness of a particular cardioprotective strategy. Differences in patient selection, baseline risk, treatment timing, and follow-up duration also complicate comparisons. Accordingly, a clinically useful synthesis must explain the conditions under which these findings apply rather than treating cardioprotection as universally effective.

Alongside these mixed findings, newer investigations have examined whether earlier recognition of subclinical dysfunction can improve the selection of interventions. The SUCCOUR-MRI trial investigated cardioprotection in patients who developed an isolated

relative reduction in global longitudinal strain (GLS) of greater than 12%, using cardiac magnetic resonance-derived LVEF to assess subsequent changes in cardiac function. More recently, Bonatto et al. (2025) randomized 114 patients with elevated troponin concentrations during anthracycline treatment in the SARAH trial. A GLS reduction of greater than 15% occurred in 7% of patients receiving sacubitril/valsartan and 25% of those receiving placebo, although hypotension was more frequent with active treatment. These investigations advance the discussion of surveillance-guided prevention, but their thresholds, study populations, and surrogate endpoints require careful interpretation. They also reinforce the need to distinguish promising emerging treatments from interventions supported by broader evidence on clinical outcomes.

Considered together, these studies reveal an evidence-to-practice gap involving the integration of mechanisms, risk assessment, surveillance findings, and cardioprotective treatment decisions. Individual trials address specific populations and interventions, whereas clinicians must manage patients receiving diverse treatment regimens and presenting with different comorbidities and evolving cardiovascular risk. For the present review, the gap therefore concerns how heterogeneous evidence can be organized into a coherent clinical framework, including its relevance to Indonesian practice. The manuscript's observations regarding local referral patterns should remain identified as clinical impressions rather than established national findings. The urgency of this synthesis arises from the need to recognize potentially actionable cardiac dysfunction while preserving appropriate cancer treatment, particularly when clinical decisions require close collaboration between cardiologists and oncologists.

To address this gap, the present narrative review aims to synthesize evidence on the mechanisms, detection, prevention, and management of CTRCD from a cardiologist's perspective. Its objectives are to explain treatment-specific pathways of cardiac injury, examine baseline risk stratification and multimodal surveillance, critically compare established and emerging cardioprotective strategies, and identify considerations for multidisciplinary implementation. The proposed contribution is an integrated clinical interpretation linking these components across pretreatment assessment, active cancer therapy, and survivorship. Its intended novelty lies in combining this synthesis with a practical framework for collaborative cardio-oncology care relevant to Indonesia. This contribution should be understood as a proposed organization of existing evidence and clinical reasoning, the feasibility and effectiveness of which require subsequent evaluation.

Through this approach, the review seeks to contribute both to clinical understanding and to the development of coordinated care pathways. For cardiologists, the anticipated benefit is a clearer interpretation of cardiovascular risk and surveillance abnormalities within the context of ongoing cancer treatment. For oncologists, it offers a shared basis for discussing cardiac findings and treatment continuity with cardiovascular specialists. For healthcare institutions, the proposed framework may inform locally adapted referral criteria, documentation practices, surveillance protocols, and professional training. It may also help define priorities for future Indonesian research, including prospective CTRCD registries and evaluations of care pathway implementation. Ultimately, the review aims to support cardiovascular protection as an integral

component of effective cancer care while explicitly acknowledging the limitations of the current evidence.

METHOD

This narrative review synthesized current evidence on cancer therapy-related cardiac dysfunction (CTRCD) from a cardiology perspective. Relevant literature was selected according to the main themes of the review, including cardiotoxicity mechanisms, cardiovascular risk assessment, surveillance and early detection, prevention and treatment, and emerging cardioprotective strategies. Priority was given to contemporary clinical guidelines, consensus statements, randomized clinical trials, observational studies, systematic reviews, and relevant mechanistic studies. Landmark studies were included when they provided foundational evidence applicable to current clinical practice. The selected evidence was synthesized narratively and organized thematically without quantitative pooling. Clinical implications were interpreted within the context of multidisciplinary cardio-oncology practice, with emphasis on the cardiologist's role in identifying and managing treatment-related cardiac injury while maintaining appropriate cancer therapy.

RESULTS AND DISCUSSION

Epidemiology and the Scale of the Problem

The incidence of CTRCD varies substantially according to the agent used, cumulative dose, combination regimens, and patient-specific factors such as age and baseline cardiovascular risk (Sánchez et al., 2025). Classic dose-response data with doxorubicin illustrate the point starkly: the incidence of clinical heart failure rose from approximately 5% at a cumulative dose of 400 mg/m² to 48% at 700 mg/m², and when asymptomatic reductions in left ventricular ejection fraction (LVEF) are included, cardiac events occur even at cumulative doses as low as 150 mg/m² (Sánchez et al., 2025). A large meta-analysis of more than 35,000 patients estimated a pooled incidence of chemotherapy-related cardiac dysfunction of approximately 63 per 1000 person-years, with the highest rates observed in breast cancer, followed by leukemia and lymphoma, and with markedly higher risk in patients aged 50 years or older (Sánchez et al., 2025). These figures underscore why cardiologists can no longer regard cardio-oncology as a niche subspecialty; CTRCD surveillance is now a routine component of care for a large fraction of cancer survivors.

Mechanisms of Cardiotoxicity: A Framework for the Cardiologist

Understanding the mechanistic basis of cardiotoxicity is not merely academic; it directly informs which patients need closer surveillance, which cardioprotective agents are biologically plausible, and which forms of cardiac injury are likely to be reversible.

Anthracyclines

Anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) remain the archetype of irreversible, dose-dependent cardiotoxicity. Their principal cardiotoxic mechanism involves inhibition of topoisomerase II β in cardiomyocytes, producing double-strand DNA breaks that trigger p53-mediated apoptosis (Contaldi et al., 2025; Zhang et al., 2012). This is compounded by disruption of intracellular iron handling, which drives mitochondrial iron accumulation and amplifies reactive oxygen species generation; suppression of mitochondrial respiratory chain

activity with consequent ATP depletion; endothelial injury with impaired vascular signalling; and dysregulated calcium handling secondary to sarcoplasmic reticulum dilation (Contaldi et al., 2025; Henriksen, 2018). The net effect is progressive, cumulative myocyte loss that is classically irreversible-a mechanistic reality that explains why anthracycline-induced left ventricular dysfunction responds less completely to standard heart failure therapy than most other cardiomyopathies, and why cumulative dose thresholds (a cumulative doxorubicin-equivalent dose of ≥ 250 mg/m² is generally considered high risk) remain central to risk stratification (Henriksen, 2018).

HER2-Targeted Therapy

Trastuzumab and related HER2-directed agents act through a fundamentally different mechanism. HER2 signalling through neuregulin-1 is cardioprotective, supporting cardiomyocyte survival, mitochondrial integrity, and sarcoplasmic reticulum calcium handling via the PI3K/AKT, MAPK, and eNOS pathways. Trastuzumab blocks this signalling, producing a form of cardiac dysfunction that, in contrast to anthracycline toxicity, generally lacks ultrastructural myocyte damage and is typically reversible with treatment interruption and heart failure therapy (Contaldi et al., 2025; Wakasa et al., 2025). Cardiotoxicity is more frequent and often more severe when trastuzumab is administered concurrently with, or shortly after, anthracyclines-a well-recognized "two-hit" phenomenon that has important implications for treatment sequencing and surveillance intensity (Sánchez et al., 2025).

Targeted and Immune-Based Therapies

Vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKIs) most commonly manifest as hypertension, related to reduced endothelial nitric oxide synthase activity and increased endothelin-1, but can also cause left ventricular dysfunction through mitochondrial injury and, with agents such as ponatinib, direct vascular and myocardial toxicity (Sánchez et al., 2025). Immune checkpoint inhibitors (ICIs) are associated with a distinct and important entity: immune-mediated myocarditis, which is uncommon but carries a mortality rate that has been reported as high as 50% in some series, driven by molecular mimicry between tumour and cardiac antigens (Palaskas et al., 2024). Newer modalities-proteasome inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and histone deacetylase inhibitors-add further mechanistic diversity, from impaired proteostasis and autophagy to cytokine-release-associated cardiac injury, and are increasingly encountered as cardio-oncology referrals grow in complexity (Contaldi et al., 2025; Palaskas et al., 2024).

Risk Assessment: A Practical Framework for Implementation

Risk assessment is the single step in the CTRCD pathway with the greatest leverage, because every subsequent decision-how often to image, whether to start a cardioprotective drug, and how aggressively to investigate a falling ejection fraction-depends on where the patient sits on the risk spectrum at the outset. In practice, however, risk assessment is often performed inconsistently: some patients are referred to cardiology only after a fall in LVEF has already occurred, at which point the opportunity for primary prevention has been lost. This section sets out a stepwise, reproducible approach that a cardiologist can apply in an outpatient cardio-oncology clinic or as part of a joint tumour board, and proposes an original algorithm (Figure 1) that operationalizes this process from the point of treatment planning through survivorship.

Step 1 - Baseline Cardiovascular Assessment

Every patient being considered for a potentially cardiotoxic regimen should undergo a structured baseline evaluation before the first cycle, ideally at the time treatment is planned rather than on the day of the first infusion. This should include: (i) a focused history covering prior cardiovascular disease, prior cardiotoxic chemotherapy or thoracic radiotherapy, and traditional risk factors (hypertension, diabetes, dyslipidaemia, obesity, smoking); (ii) physical examination and blood pressure measurement; (iii) a 12-lead electrocardiogram; (iv) baseline cardiac biomarkers, specifically high-sensitivity troponin and a natriuretic peptide (NT-proBNP or BNP); and (v) transthoracic echocardiography with both LVEF (three-dimensional where available) and GLS, since baseline GLS and lower-normal LVEF are themselves independent predictors of subsequent CTRCD (Herrmann et al., 2022; Lyon et al., 2022; Sánchez et al., 2025). This baseline dataset serves two purposes: it identifies patients with occult cardiovascular disease who may need cardiology optimization before chemotherapy begins, and it establishes the individual reference values against which all future surveillance is compared.

Step 2 - Formal Risk Stratification with the HFA-ICOS Score

The baseline data are then used to calculate the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk score, endorsed by the 2022 ESC cardio-oncology guidelines as the standard tool for pre-treatment risk stratification (Lyon et al., 2022). The score integrates four domains: (a) the cardiotoxic potential and planned cumulative dose of the specific regimen (for example, a planned cumulative doxorubicin-equivalent dose ≥ 250 mg/m², or a combination anthracycline-trastuzumab regimen); (b) prior cardiotoxic exposure, including previous anthracyclines, HER2-targeted therapy, or mediastinal/left chest radiotherapy; (c) cardiovascular history and risk factors, including prior heart failure, coronary disease, moderate-to-severe valve disease, hypertension, diabetes, and chronic kidney disease; and (d) baseline biomarker and imaging findings, such as an elevated troponin or NT-proBNP, borderline GLS, or low-normal LVEF (Herrmann et al., 2022; Lyon et al., 2022). Patients are classified into low, moderate, high, or very-high-risk categories, and this classification-not clinical impression alone-should determine the surveillance and prevention plan that follows.

Step 3 - Risk-Based Surveillance and On-Treatment Monitoring

Once the risk category is established, surveillance intensity should be tailored accordingly rather than applied uniformly to all patients. Low-risk patients generally require only their baseline assessment and a reassessment at the completion of treatment. Moderate-risk patients benefit from echocardiography, with or without biomarkers, approximately every three to four cycles (roughly every six to twelve months for prolonged regimens). High-risk patients should undergo echocardiography with GLS and biomarkers approximately every three months, with consideration of prophylactic ACE inhibitor/ARB and beta-blocker therapy. Very-high-risk patients warrant surveillance at every cycle, early initiation of cardioprotective therapy (with dexrazoxane considered for those continuing anthracyclines), and, ideally, a joint cardiology-oncology review before each cycle (Addison et al., 2023; Lyon et al., 2022; Sánchez et al., 2025). During treatment, a relative GLS decline greater than 15% from baseline, an absolute LVEF fall of 10 percentage points or more to a value below 50%, or a rising troponin trajectory should trigger a defined response: repeat imaging within three to four weeks,

initiation or intensification of neurohormonal blockade, and a multidisciplinary discussion about whether cancer therapy should continue unchanged, be modified, or be temporarily interrupted (Addison et al., 2023; Lyon et al., 2022; Sánchez et al., 2025). This entire pathway, from baseline assessment through survivorship, is summarized in the algorithm proposed in Figure 1.

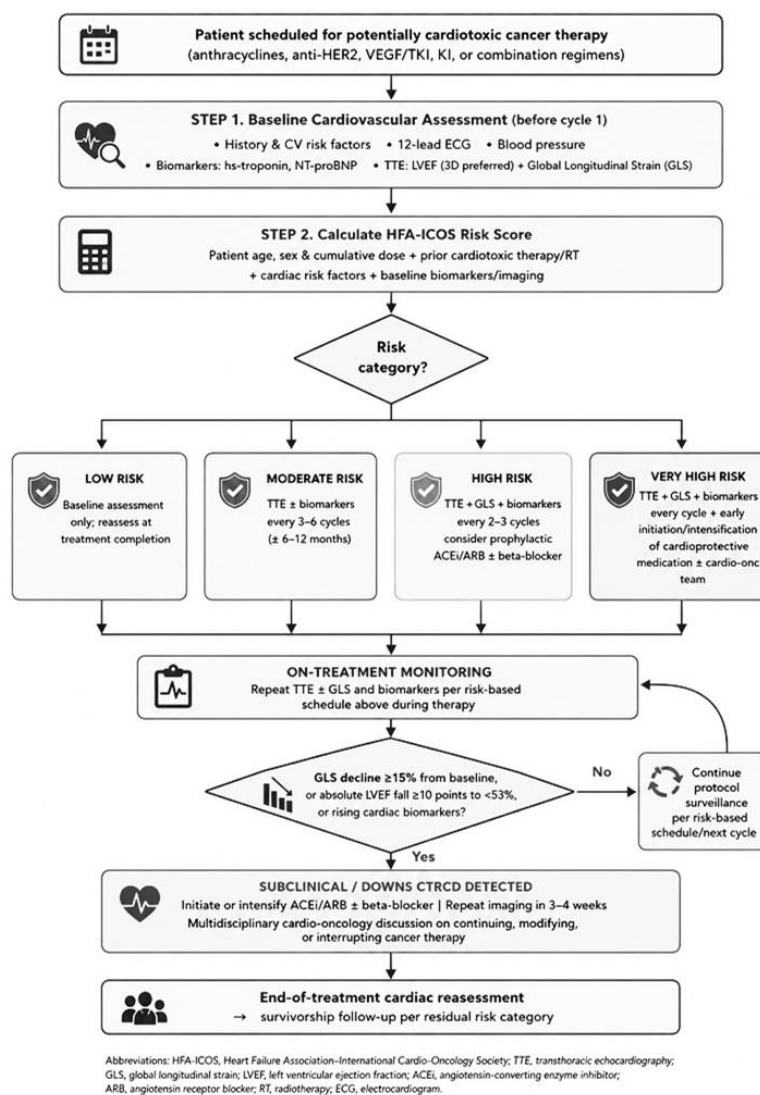


Figure 1. Algorithm for CTRCD risk assessment and risk-based surveillance, from baseline evaluation through on-treatment monitoring and survivorship follow-up.

It is worth emphasizing that this algorithm is deliberately structured as a closed loop rather than a linear pathway: patients who do not meet criteria for subclinical CTRCD return to their risk-based surveillance schedule and continue treatment, while those who do meet criteria enter a cardioprotection-and-reassessment cycle that itself feeds back into ongoing monitoring. This design reflects the reality that cardiotoxicity risk is dynamic-changing with cumulative dose, added agents, and evolving comorbidity-so risk assessment in cardio-oncology should be understood as a continuous process rather than a single, one-time triage step performed only before the first cycle (Herrmann et al., 2022; Lyon et al., 2022).

Detection and Monitoring

Cardiac Biomarkers

Cardiac troponin and natriuretic peptides (B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide) are the principal biomarkers used for early detection of CTRCD. Baseline and serial troponin measurement, particularly within 72 hours of anthracycline administration and again at approximately one month, can identify patients developing subclinical myocardial injury before any change in LVEF is apparent, and persistently elevated troponin has been associated with worse prognosis and incomplete recovery of LVEF (Cardinale et al., 2018; Sánchez et al., 2025). Natriuretic peptides add complementary information on haemodynamic stress, although universally accepted cut-offs in the oncology population remain elusive because levels are confounded by age, renal function, and comorbidity, so biomarker trends must always be interpreted within the individual patient's clinical trajectory (Cardinale et al., 2018; Herrmann et al., 2022).

Cardiovascular Imaging

Transthoracic echocardiography remains the first-line imaging modality because of its availability, safety, and reproducibility. Three-dimensional LVEF assessment is preferred where available, but the single most clinically useful addition for the cardiologist is global longitudinal strain (GLS), which detects subclinical systolic dysfunction before any measurable fall in LVEF; a relative GLS decline of more than 15% from baseline is now widely accepted as the threshold denoting subclinical cardiotoxicity (Addison et al., 2023; Lyon et al., 2022; Sánchez et al., 2025). Cardiac magnetic resonance (CMR) serves as the preferred second-line modality when echocardiographic windows are poor or when tissue characterization is required, offering T1/T2 mapping and late gadolinium enhancement that can distinguish oedema and inflammation (as in ICI-associated myocarditis) from established fibrosis (Addison et al., 2023). Cardiac computed tomography and multigated acquisition (MUGA) nuclear imaging are reserved for selected situations, such as coronary assessment or when echocardiography and CMR are unavailable or contraindicated (Addison et al., 2023).

Prevention and Management: The Pharmacological Arsenal

For patients at high or very high-risk undergoing anthracycline and/or anti-HER2 therapy, the 2022 ESC guidelines recommend consideration of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) together with beta-blockers, and statins are also recommended in this population (Lyon et al., 2022). The evidence base, however, is more nuanced than a single class recommendation suggests: while several randomized trials (including OVERCOME and the ICOS-ONE registry-based approach) demonstrated benefit of enalapril and carvedilol in preserving LVEF and reducing troponin elevation (Bosch et al., 2013; Cardinale et al., 2018), other adequately powered trials in low-to moderate-risk populations, such as CECCY and PRADA, failed to show a clear benefit of carvedilol or candesartan on hard cardiac endpoints (Gulati et al., 2016). This heterogeneity reinforces a central message for the practising cardiologist: neurohormonal blockade is most clearly justified in patients stratified as high risk, rather than applied indiscriminately to all patients receiving cardiotoxic therapy.

Dexrazoxane, an iron-chelating agent that reduces topoisomerase-anthracycline complex formation and intracellular free iron, remains the only agent specifically recommended for

high-risk patients requiring continued anthracycline therapy, and liposomal anthracycline formulations offer an alternative strategy to reduce cardiotoxicity while preserving oncologic efficacy (Lyon et al., 2022). More recently, the STOP-CA trial demonstrated that atorvastatin reduced the incidence of cardiac dysfunction in lymphoma patients receiving anthracyclines, providing one of the few positive randomized trials of a statin-based cardioprotective strategy in this setting (Gulati et al., 2016; Neilan et al., 2023).

Emerging Cardioprotective Agents

Three classes of heart failure therapy developed outside oncology are now being actively repurposed for CTRCD. Sacubitril/valsartan (an angiotensin receptor-neprilysin inhibitor) has shown encouraging results in the SARAH trial, in which treatment reduced the proportion of high-risk patients developing a clinically significant GLS decline at six months compared with placebo (Bonatto et al., 2025), with a larger confirmatory trial (MAINSTREAM) currently ongoing and yet to report primary outcome data (Tajstra et al., 2023). Sodium-glucose co-transporter 2 inhibitors (SGLT2i), such as empagliflozin and dapagliflozin, have generated some of the most compelling recent data: the EMPACARD-PILOT study reported a substantial reduction in CTRCD incidence with empagliflozin in high-risk breast cancer patients receiving anthracyclines, and a large retrospective analysis of over 95,000 patients found that SGLT2i use was associated with a lower risk of CTRCD across multiple cardiotoxic regimens (Bhatti et al., 2024). Current evidence is largely derived from observational studies together with early pilot randomized trials. Vericiguat, a soluble guanylate cyclase stimulator, has shown mechanistic promise in preclinical models of anthracycline cardiotoxicity-including improved cardiac remodelling and systolic function in a doxorubicin-induced cardiomyopathy rat model (Chen et al., 2025)-and in isolated case reports of refractory, late-onset anthracycline-induced heart failure, although controlled clinical data in cardio-oncology remain limited (Chen et al., 2025). Beyond pharmacotherapy, structured aerobic and resistance exercise programmes have consistently been associated with better preservation of LVEF and cardiorespiratory fitness during anthracycline-based treatment, and should be discussed with patients as a complementary, low-risk intervention (Kang et al., 2022). The guideline-recommended agents, emerging cardioprotective agents, and non-pharmacological strategy discussed above are summarized in Figure 2.

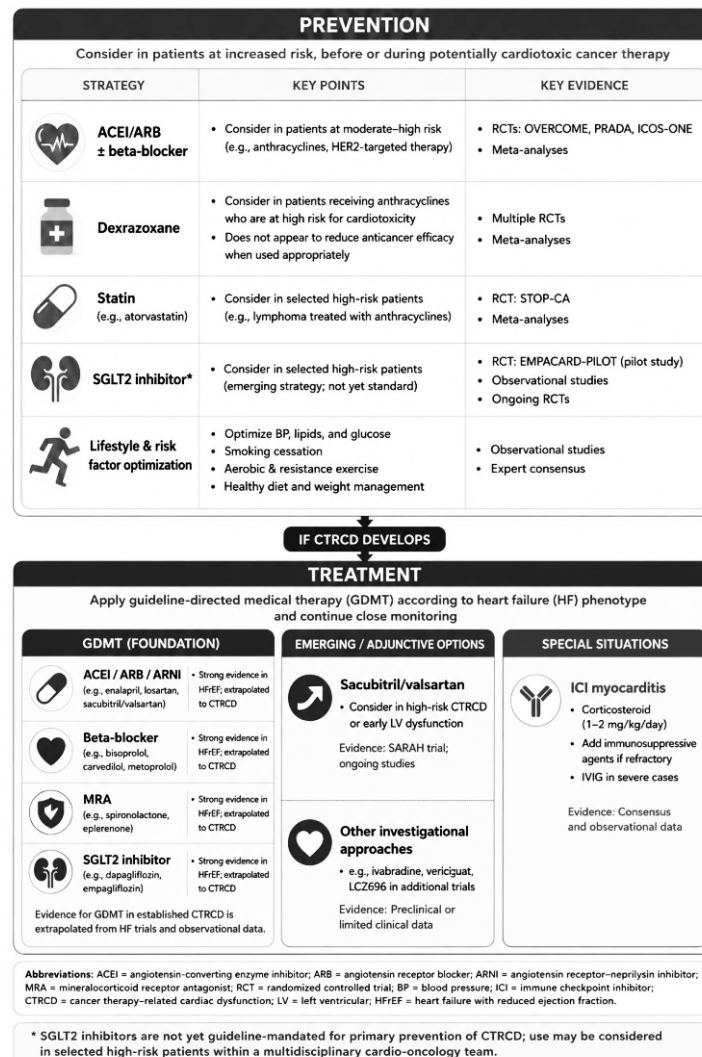


Figure 2. Pharmacological and non-pharmacological strategies for CTRCD prevention and treatment, grouped as guideline-recommended agents, emerging cardioprotective agents, and non-pharmacological intervention.

A Cardiologist's Perspective: Integrating Care in Practice

In day-to-day cardio-oncology practice, four principles guide the cardiologist's contribution. First, risk assessment must occur before the first dose of a cardiotoxic agent is given, not after a fall in LVEF is discovered; retrospective risk assessment forfeits the opportunity for primary prevention. Second, surveillance intensity should be tailored to baseline risk rather than applied uniformly-high-risk patients (cumulative anthracycline dose ≥ 250 mg/m², combination anthracycline-trastuzumab regimens, or pre-existing cardiovascular disease) warrant echocardiography with GLS approximately every three months during treatment, whereas long-term survivors at lower risk can be followed at intervals of two to five years (Lyon et al., 2022; Sánchez et al., 2025). Third, a GLS decline of more than 15% or an absolute LVEF fall of 10 percentage points to below 50% should trigger a defined pathway: repeat imaging, initiation of cardioprotective therapy, and a multidisciplinary discussion with the treating oncologist about whether to continue, modify, or interrupt cancer therapy-decisions that should never be made unilaterally by cardiology or oncology alone (Addison et al., 2023;

Lyon et al., 2022). Fourth, the cardiologist must remain alert to the reversibility profile of the specific agent involved: HER2-related dysfunction usually improves after treatment interruption and heart failure therapy, whereas anthracycline-related injury is more often only partially reversible, which should temper expectations and inform counselling of the patient and family (Contaldi et al., 2025; Wakasa et al., 2025).

Emerging Directions

Two developments are likely to reshape cardio-oncology practice over the coming decade. Pharmacogenomics is beginning to identify genetic variants-in genes such as RARG, SLC28A3, CBR3, and HAS3-that modulate individual susceptibility to anthracycline-induced cardiotoxicity, raising the prospect of genotype-guided selection of chemotherapy regimen or pre-emptive cardioprotection, although this remains at a preclinical and exploratory stage (Aminkeng et al., 2016). Artificial intelligence is already showing practical utility: AI-enhanced electrocardiography can predict the presence and future development of left ventricular systolic dysfunction, and AI-derived strain measurements demonstrate improved reproducibility compared with conventional GLS, potentially extending high-quality surveillance to centres with less specialized imaging expertise (Oikonomou et al., 2024; Zaha et al., 2021). Both approaches will require external validation before they can be incorporated into routine risk scores such as HFA-ICOS, but they represent a plausible path toward more individualized, rather than purely categorical, risk prediction.

Toward a Collaborative Cardiology-Oncology Framework for Cardiotoxicity Management in Indonesia

The arguments above are not merely of academic interest for Indonesia. GLOBOCAN estimates that Indonesia recorded approximately 408,661 new cancer cases in 2022, with breast cancer as the single most common malignancy and a case burden projected to rise substantially over the next two decades (Ferlay et al., 2024). Because anthracyclines and, increasingly, HER2-targeted and other targeted agents remain the backbone of treatment for many of the country's most common cancers, a correspondingly large number of Indonesian patients are already being exposed to agents with well-documented cardiotoxic potential. Despite this, it is the author's observation, from clinical practice in an Indonesian tertiary referral setting, that cardio-oncology services in the country remain unevenly distributed and largely informal: referral from oncology to cardiology appears to occur opportunistically-triggered by a clinician's individual judgement or by a patient becoming symptomatic-rather than through a standardized, pre-specified pathway applied consistently across centres. A dedicated, systematically collected account of cardio-oncology service provision across Indonesia is not yet available in the published literature, and the description that follows should therefore be read as the author's clinical impression rather than as an established epidemiological finding.

In the author's view, this fragmentation is likely to carry real clinical consequences. Without an agreed pathway, baseline cardiovascular assessment before cardiotoxic therapy may be inconsistently performed; the threshold for referral to cardiology probably varies widely between oncologists and between hospitals; echocardiographic surveillance, when it occurs, may not routinely include GLS reporting, since this requires both equipment capability and dedicated training; and decisions about interrupting or modifying chemotherapy in the face of falling LVEF may at times be made unilaterally, without the structured multidisciplinary

discussion that international guidelines recommend (Addison et al., 2023; Lyon et al., 2022). These are precisely the gaps that a locally developed, jointly authored standard operating procedure (SOP) is intended to close.

We therefore argue that the time has come for Indonesian professional societies in cardiology and in medical/haematology oncology to jointly develop and formally endorse a national SOP for the prevention, detection, and management of CTRCD. Such a document, ideally produced collaboratively by the relevant cardiology and oncology societies together with major cancer referral centres, should at minimum define: (i) which cancer regimens and which patient groups require mandatory baseline cardiology assessment before treatment begins; (ii) a single, nationally agreed risk-stratification instrument-the HFA-ICOS score is a reasonable starting point-to avoid the current variability in how risk is judged from one centre to another; (iii) a minimum, resource-appropriate surveillance schedule (biomarkers and echocardiography, with GLS where locally available) tied to each risk category, acknowledging that imaging capability and hs-troponin/NT-proBNP availability differ between tertiary cancer centres in Jakarta and regional hospitals elsewhere in the country; (iv) explicit criteria and a standardized referral form that trigger a joint cardiology-oncology case discussion whenever GLS, LVEF, or biomarker thresholds are crossed; and (v) a shared documentation template so that cardiac risk category, surveillance findings, and treatment decisions are recorded in a way that both specialties, and future audits, can readily interpret.

Embedding such a framework within existing multidisciplinary tumour boards, rather than creating a parallel structure, would likely be the most sustainable model, since it uses meeting infrastructure that already exists in most major Indonesian cancer centres. Training resident and consultant cardiologists in GLS acquisition and reporting, and training oncologists in the basic vocabulary of cardio-oncology risk categories, would further support consistent implementation. The benefits of this approach are threefold: it would reduce unwarranted variability in practice between hospitals; it would allow earlier detection of subclinical cardiotoxicity at a stage when cardioprotective therapy is most effective, rather than after symptomatic heart failure has developed; and it would provide a structured framework for national data collection on CTRCD incidence and outcomes in the Indonesian population, which at present is almost entirely absent from the published literature. Given the scale of the country's cancer burden and its continued reliance on anthracycline- and HER2-based regimens, a jointly developed cardiology-oncology SOP should be regarded not as an aspirational long-term goal but as an achievable and urgent near-term priority for Indonesian cancer care.

CONCLUSION

CTRCD is a heterogeneous but increasingly predictable consequence of modern cancer therapy, and its management has become a core competency for cardiologists working alongside oncology teams. A mechanistic understanding of the specific cardiotoxic agents involved; disciplined use of the HFA-ICOS risk assessment within a structured, reproducible algorithm such as the one proposed here; multimodal surveillance combining cardiac biomarkers with echocardiographic global longitudinal strain (GLS) and, when indicated, cardiac magnetic resonance (CMR); and judicious use of neurohormonal blockade and

emerging therapies, such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, collectively constitute key components of contemporary cardio-oncology care. As pharmacogenomic and artificial intelligence (AI)-based tools mature, the cardiologist’s role will likely shift further upstream—from managing established heart failure to preventing its development. In Indonesia, translating this evidence into consistent clinical practice will require more than individual clinician awareness. A jointly developed cardio-oncology framework embedded within existing multidisciplinary tumor boards represents a practical step toward standardizing CTRCD prevention and management nationally while continuing to safeguard the primary goal of cancer therapy: curing or controlling malignancy without compromising long-term cardiovascular health.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

Yogi Puji Rachmawan contributed to the conceptualization of the review, literature synthesis, clinical interpretation of CTRCD mechanisms and management, development of the practical cardio-oncology framework, and preparation of the original manuscript draft. Witri Pratiwi contributed to the literature synthesis, interpretation of the broader clinical and public health context, and critical review and revision of the manuscript. Both authors reviewed and approved the final version of the manuscript and accept responsibility for the integrity of the work.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

The authors state that generative artificial intelligence (AI) was used during the preparation of this manuscript solely to assist in improving language clarity and grammatical structure. Its use was undertaken in accordance with applicable ethical principles concerning the responsible use and disclosure of generative AI in scientific writing. Generative AI was not used to generate research data or replace the authors' scientific and clinical judgment. Both authors made substantial intellectual contributions to the work, carefully reviewed the entire manuscript for accuracy and consistency, and assume full responsibility for the integrity and final content of the manuscript.

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