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Cardio-Oncology in 2025: From Molecular Mechanisms to Clinical Practice

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The year 2025 marked an important step forward for cardio-oncology, with advances spanning mechanistic discovery, prevention-oriented trials, risk stratification, and expert consensus statements that collectively signal a transition toward precision cardiovascular (CV) care. This editorial presents a focused narrative selection of high-impact 2025 contributions—covering anthracycline (AC)/human epidermal growth factor receptor 2 (HER2) therapies related cardiotoxicity, immune checkpoint inhibitors (ICIs), prevention strategies, survivorship, and key statements—rather than a systematic review (Figure 1); several practice-relevant areas (e.g., radiation-associated CV disease, thrombosis, and arrhythmias) remain outside the scope of the present discussion.

At the preclinical level, one of the most informative advances was the reframing of AC cardiotoxicity as a ferroptosis-driven process. Gao et al.[1] employed complementary *in vivo* and *in vitro* models of doxorubicin-induced cardiotoxicity, including a chronic murine model and cultured cardiomyocytes, to investigate both functional and molecular endpoints. The investigators identified STAT3 as a central regulator of ferroptotic susceptibility. Importantly, pharmacological intervention with liraglutide consistently attenuated doxorubicin-induced myocardial dysfunction and ferroptotic signaling, thereby repurposing GLP-1 receptor agonists—already widely used in cardiometabolic disease—as potential cardioprotective agents in oncology.

Targeting ferroptosis through alternative platforms further supported this concept. Wang et al.[2] developed a biomimetic Cu–Zn metal–organic framework nanoparticle with antioxidant and anti-ferroptotic properties. In murine models of doxorubicin exposure, the nanoparticle preserved systolic function and reduced iron accumulation and myocardial injury without compromising antitumor efficacy. Although still early in its translational trajectory, this work reinforces ferroptosis as a convergent and therapeutically targetable mechanism in AC cardiotoxicity and illustrates how mechanistically informed platforms may complement more conventional pharmacological strategies.

Extending this cardioprotective paradigm beyond direct modulation of cell death pathways, complementary experimental evidence highlighted metabolic preservation as an additional and mechanistically distinct avenue for myocardial protection. In a porcine model of AC cardiotoxicity, Medina-Hernández et al.[3] showed that empagliflozin preserved systolic function in a dose-dependent manner, fully preventing left ventricular (LV) dysfunction at higher doses. These functional benefits were accompanied by preservation of myocardial energetics and mitochondrial structure and function, providing robust translational evidence that targeting metabolic derangements can effectively interrupt the pathophysiological cascade of AC cardiotoxicity.

Cardiotoxicity is not determined solely by drug exposure or molecular pathways; rather, susceptibility is strongly influenced by baseline CV reserve. L'Abbate et al.,[4] using stratified murine phenotypes ranging from healthy myocardium to overt systolic dysfunction, demonstrated that trastuzumab induced myocardial injury even in the absence of prior AC exposure. Prophylactic angiotensin-converting enzyme inhibitor and beta-blocker therapy effectively preserved systolic function, normalized electrical abnormalities, mitigated myocardial inflammation and fibrosis, and restored mitochondrial structure as well as gene expression profiles across both healthy and vulnerable phenotypes. Collectively, these findings position baseline CV reserve as a key determinant of trastuzumab cardiotoxicity and provide strong mechanistic support for tailored, risk-adapted prophylactic cardioprotection in HER2-targeted therapy. Together, these experimental studies advance the mechanistic understanding of cardiotoxicity; however, their clinical integration will require early-phase and prospective validation in oncology-specific populations, with careful evaluation of safety and potential interactions with anticancer efficacy.

Importantly, prevention of cardiotoxicity, rather than treatment of established myocardial dysfunction, emerged as the central objective of several of the most influential clinical trials published in 2025. Xia et al.[5] conducted a prospective, multicenter, randomized clinical

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trial specifically designed to evaluate the feasibility, safety, and preliminary efficacy of a biomarker-guided cardioprotection strategy in patients with breast cancer or lymphoma initiating AC therapy. Exploratory efficacy analyses indicated that N-terminal pro-B-type natriuretic peptide-guided care was associated with attenuation of early biomarker elevation and a modest but statistically significant preservation of LV ejection fraction (LVEF) at three months compared with usual care. By shifting the trigger for cardioprotective therapy from overt functional decline to early myocardial stress signaling, this trial challenged the traditional reliance on LVEF-based surveillance and provided the first randomized proof-of-concept that biomarker-guided cardioprotection during active AC therapy is both clinically actionable and safe.

Complementary evidence emerged from PRADA II, in which prophylactic sacubitril/valsartan did not significantly reduce LVEF decline as measured by cardiac magnetic resonance imaging but consistently preserved global longitudinal strain and attenuated biomarker release, indicating mitigation of subclinical myocardial injury.[6] In parallel, a prespecified STOP-CA substudy demonstrated that atorvastatin reduced AC-associated myocardial extracellular volume expansion, a surrogate marker of diffuse myocardial fibrosis that was strongly associated with subsequent LV dysfunction.[7]

A further landmark clinical contribution in 2025 addressed the critical challenge of risk stratification in ICI-associated myocarditis. Using the largest international myocarditis registry to date, Power et al.[8] derived and externally validated a pragmatic risk score predicting severe cardiomyotoxic events within 30 days. Multivariable modeling identified a small set of readily available clinical variables—including the magnitude of troponin elevation, active thymoma, cardiomuscular symptoms, low QRS voltage, and LVEF < 50%—as independent predictors of major adverse events. The resulting point-based risk score demonstrated strong discrimination, with event rates ranging from < 5% in low-risk patients to > 80% in those at highest risk, and was externally validated in two independent cohorts. Importantly, low-risk patients were safely managed with immunotherapy withdrawal alone, demonstrating immediate clinical utility. The marked gradient in 30-day event rates across risk strata enables alignment of monitoring intensity with short-term risk. In practical terms, higher risk categories may support decisions toward monitored in-hospital care (telemetry), lower thresholds for pacing readiness in the presence of conduction disease, and earlier multidisciplinary escalation of immunosuppression when clinical deterioration or biomarker trajectories warrant. Conversely, "low-risk" reflects relative registry risk and should not be equated with routine outpatient management.

Contemporary cardio-oncology practice extends beyond myocardial dysfunction. Radiation-associated CV disease, thrombotic and bleeding complications, therapy-related arrhythmias and conduction disturbances, and selected pulmonary vascular complications (including pulmonary hypertension in specific therapeutic contexts) represent important components of cardio-oncology care. In addition, sex-based differences in cardiotoxic susceptibility further underscore the need for individualized CV risk assessment. These domains, while central to clinical practice, are not examined in this focused editorial.

As the evidence base expands, expert consensus documents published in 2025 moved to codify practical approaches to risk assessment, monitoring, and management across contemporary cancer therapies. In a scientific statement, the Heart Failure Association

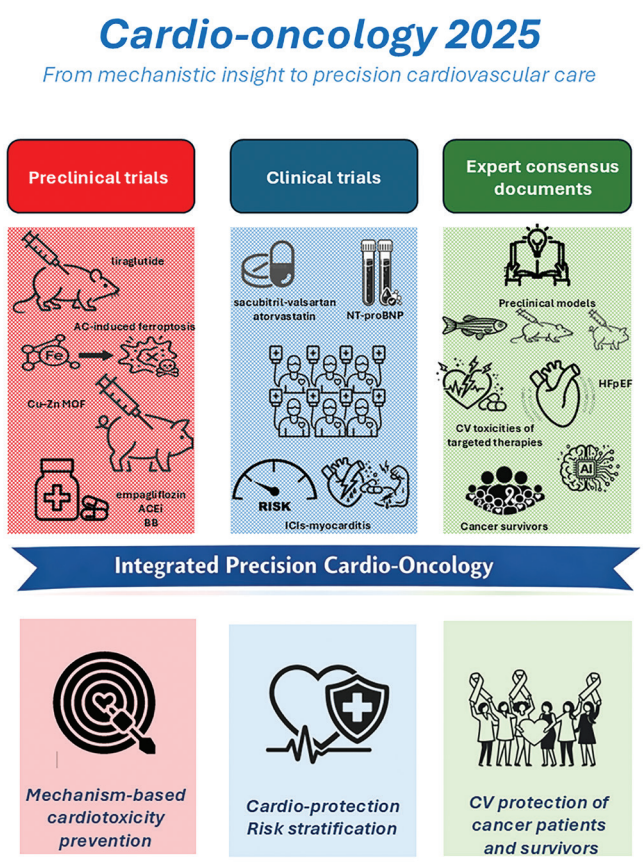

FIG. 1. Conceptual framework synthesizing evidence from the most influential preclinical studies, clinical trials, and expert consensus publications of 2025. The upper panels summarize key evidence domains: mechanistic insights from preclinical models, prevention-focused clinical trials emphasizing early cardioprotection and cardiovascular risk stratification, and expert consensus documents addressing preclinical models of cardiotoxicity, targeted therapy–related toxicity, heart failure with preserved ejection fraction, the role of artificial intelligence (AI) in cardio-oncology, and long-term survivorship surveillance. These complementary data streams converge into an integrated precision cardio-oncology approach (central ribbon). The lower panels depict the core pillars of this paradigm: mechanism-based cardiotoxicity prevention, effective cardioprotection, and sustained cardiovascular protection of cancer patients and survivors across the cancer continuum. AI (ChatGPT, OpenAI) was used as an assistive tool in the conceptual design and graphical refinement of the figure. AC, anthracyclines; Cu-Zn MOF, Cu–Zn metal–organic framework; ICIs, immune checkpoint inhibitors; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; ACEi, angiotensin converting enzyme inhibitors; BB, beta blockers; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(HFA) emphasized the need for translationally relevant preclinical models reflecting real-world phenotypes, including late-onset toxicity, immune-mediated injury, and tumor–heart interactions.[9] By advocating multimodal and human-relevant experimental platforms, the statement addressed persistent translational gaps between experimental findings and clinical reality. In parallel, the 2025 American College of Cardiology Concise Clinical Guidance translated emerging evidence into pragmatic care pathways for targeted therapy-related CV toxicities.[10] By emphasizing therapy-specific surveillance, baseline risk assessment, and the concept of permissive CV toxicity, it reframed clinical decision-making toward balancing oncologic efficacy with CV safety through active management rather than premature treatment discontinuation.

The HFA–European Society of Cardiology scientific statement on heart failure with preserved ejection fraction (HFpEF) in cancer patients further broadened the field's perspective.[11] HFpEF was repositioned not only as a risk factor for cardiotoxicity but also as a common and underrecognized manifestation of cancer therapy-related CV toxicity driven by systemic inflammation, endothelial dysfunction, and cumulative therapy exposure. Reliance on LVEF alone was highlighted as a major barrier to timely diagnosis and effective risk stratification.

This expanded recognition of chronic and progressive CV phenotypes naturally extended the focus of cardio-oncology beyond active treatment and into survivorship. The *JACC: CardioOncology* Expert Panel emphasized that CV risk in cancer survivors is cumulative, lifelong, and extends far beyond cardiomyopathy.[12] Traditional short-term surveillance was shown to underestimate late coronary disease, arrhythmias, valvular disease, and HFpEF. Accordingly, a shift toward structured long-term risk assessment and the integration of preventive cardiology principles was strongly advocated.

Finally, the American Heart Association scientific statement positioned artificial intelligence (AI) as an enabling—rather than substitutive—tool for precision cardio-oncology.[13] Multimodal AI integrating imaging, electrocardiography, biomarkers, genomics, and electronic health records offers opportunities for earlier detection of subclinical CV injury and refined risk prediction, provided that rigorous validation, transparency, and bias mitigation are ensured.

Collectively, the 2025 evidence base outlines a clear trajectory toward precision cardio-oncology. The field is shifting from reactive treatment of established ventricular dysfunction toward mechanism-based prevention, biomarker- and strain-guided surveillance, and risk-adapted management. Validated tools such as biomarker-guided cardioprotection and ICI-myocarditis risk stratification now allow alignment of monitoring intensity with short-term risk. For clinicians, early identification of vulnerability, structured longitudinal surveillance, and multidisciplinary coordination are central to protecting CV health across the cancer continuum. The remaining challenge is implementation—integrating these advances into routine care pathways so that gains in cancer survival are not offset by preventable CV disease.

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