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EXPERT PANEL

Cardiovascular Considerations Before Cancer Therapy

Gaps in Evidence and *JACC: CardioOncology* Expert Panel Recommendations

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ABSTRACT

Baseline cardiovascular assessment before the initiation of potentially cardiotoxic cancer therapies is a key component of cardio-oncology, aiming to reduce cardiovascular complications and morbidity in patients and survivors. Recent clinical practice guidelines provide both general and cancer therapy–specific recommendations for baseline cardiovascular toxicity risk assessment and management, including the use of dedicated risk scores, cardiovascular imaging, and biomarker testing. However, the value of such interventions in altering disease trajectories has not been established, with many recommendations based on expert opinion or Level of Evidence: C, studies with a potential for high risk of bias. Advances in understanding underlying mechanisms of cardiotoxicity and the increased availability of genetic and immunologic profiling present new opportunities for personalized risk assessment. This paper evaluates the existing evidence on cardiovascular care of cancer patients before cardiotoxic cancer therapy and highlights gaps in evidence and priorities for future research. (JACC CardioOncol. 2024;6:631-654) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACHD = adult congenital heart disease

ADT = androgen deprivation therapy

AF = atrial fibrillation

AIC = anthracycline-induced cardiotoxicity

BP = blood pressure

BRAF = rapidly accelerated fibrosarcoma B type

BTKi = Bruton tyrosine kinase inhibitor

CAC = coronary artery calcium

CAD = coronary artery disease

CAR-T = chimeric antigen receptor T cell

CIED = cardiac implantable electronic device

CLL = chronic lymphocytic leukemia

CMR = cardiac magnetic resonance

CRS = cytokine release syndrome

CT = computed tomography

cTn = cardiac troponin

cTnI = cardiac troponin I

CTRCD = cancer therapy-related cardiovascular dysfunction

ECG = electrocardiogram

ESC = European Society of Cardiology

GLS = global longitudinal strain

GnRH = gonadotrophin-releasing hormone

HbA1c = glycated hemoglobin

HSCT = hematopoietic stem cell transplantation

HER2 = human epidermal growth factor receptor 2

HFA-ICOS = Heart Failure Association–International Cardio-Oncology Society

ICI = immune checkpoint inhibitor

IHD = ischemic heart disease

IMID = immunomodulatory agent

LV = left ventricular

LVEF = left ventricular ejection fraction

Cancer and cardiovascular disease are the leading noncommunicable causes of ill health and premature death worldwide.[1] Patients with cancer face an increased risk of cardiovascular disease because of shared risk factors, cancer-related biologic processes, and the cardiotoxic effects of cancer treatments.[2,3] Improving the cardiovascular care of cancer patients is essential to enable optimal cancer treatment and to reduce long-term morbidity and mortality.[2]

Cardiovascular assessment is recommended for all patients before starting cancer treatment to assess cardiotoxicity risk; address modifiable cardiovascular risk factors; and, in certain scenarios, obtain baseline cardiac biomarker data to quantify interval changes during treatment.[2]

International societies have produced expert consensus documents and guidelines in cardio-oncology.[4-6] Notably, in 2022, the European Society of Cardiology (ESC) published its first cardio-oncology guidelines.[2] Although these guidelines mark a significant advance in standardizing clinical pathways, most recommendations are based on Level of Evidence: C, derived from consensus opinion or small studies, retrospective studies, or registries. Fully implementing guideline recommendations in clinical practice also requires a thorough evaluation of the feasibility and available resources and needs across the entire multidisciplinary team and the patient.

Providing blanket recommendations for risk stratification in cancer care is challenging because of the variability in patient-specific factors such as treatment intent, line of therapy, tumor burden, life expectancy, and patient preferences. Often, cancer patients undergo combination treatments, and those with more advanced cancers may have received multiple previous treatments, each with its own discrete cardiotoxicity profiles. Furthermore, oncologic drug development progresses rapidly, and for many newer therapies, knowledge of cardiovascular safety is incomplete, meaning that risk estimates are largely extrapolated from data relating to older agents.

This expert panel review initiates a 3-part series aimed at evaluating the evidence base for cardiovascular care of cancer patients: 1) before; 2) during; and 3) after cardiotoxic cancer therapies. There is a particular focus on emerging areas and critical appraisal of the existing evidence. Recommendations are provided where there is consensus evidence available, and gaps in evidence are highlighted to direct future research.

HIGHLIGHTS

- Risk stratification and cardiovascular optimization are recommended for all patients before undergoing cardiotoxic cancer therapies.
- Current guidelines are supported by Level of Evidence: C across many clinical scenarios, and greater evidence is needed to inform future cardio-oncology guidelines.
- Although cardiovascular imaging and biomarkers may facilitate risk stratification, their prognostic value is unclear.
- Developing validated risk scores and novel biomarkers is a critical research priority aimed at achieving personalized assessments of cardiotoxicity.

GENERAL PRETREATMENT CONSIDERATIONS

RECOMMENDATIONS.

- It is recommended that all patients undergo cardiovascular risk assessment and optimization before starting cardiotoxic cancer therapy.
- Baseline cardiovascular investigations are recommended to be tailored based on individual risk, including the proposed cancer therapies and cardiovascular status.
- It is recommended that all patients undergo a clinical history and examination; have blood pressure (BP), lipids, and glycated hemoglobin (HbA1c) measured; and receive advice on a healthy lifestyle and exercise.
- The use of the Fridericia technique for QTc measurement for electrocardiograms is recommended.
- Following existing clinical practice guidelines is recommended when feasible for patients with known or suspected cardiovascular disease.

GAPS IN KNOWLEDGE.

- The understanding of how baseline cardiovascular risk influences cardiotoxicity with many newer therapies remains incomplete.

- The risk of cardiotoxicity in special populations, such as pediatric and adult congenital heart disease (ACHD) patients, has not been fully evaluated.
- A significant gap exists in the availability of large-scale studies on exercise prehabilitation for cardioprotection.

Current clinical guidelines advocate for cardiotoxicity risk assessment for all patients before cancer treatment.[2] This risk stratification helps guide both cancer therapy choices and the frequency and type of surveillance required during treatment. A "baseline" evaluation should be repeated whenever a change in cancer treatment is considered.

The level of assessment required varies based on patient demographics, cardiovascular risk, and the planned cancer treatments. Patients with known cardiovascular disease or risk factors face a higher risk of new cardiovascular events and worsening of pre-existing conditions during cancer treatment. Common cancer treatment complications, such as sepsis, and hemodynamic and metabolic disturbances may exacerbate pre-existing cardiovascular diseases alongside direct treatment-related toxicities. Therefore, these high-risk patients should undergo specialist cardiology assessment before starting cancer treatment. Conversely, individuals at lower risk should proceed to treatment without delay.

The increased risk of cardiotoxicity in patients with high cardiometabolic burden and pre-existing cardiovascular disease has been demonstrated in large retrospective cohorts, primarily involving breast and hematologic cancer patients, often in the context of anthracycline therapy.[7] Hypertension, diabetes, and pre-existing coronary artery disease (CAD) are consistent predictors of cardiotoxicity, whereas the role of obesity is less certain.[8] Evidence with other cancer drugs is limited and relies heavily on extrapolations from anthracycline studies. This approach may be unreliable because it overlooks drug-specific mechanisms of cardiotoxicity. Indeed, select studies involving other systemic cancer therapies, such as fluoropyrimidines, have reported a higher cardiotoxicity risk in younger patients with lower baseline morbidity.[9] Disentangling the cardiovascular risks associated with specific cancer treatments is complicated by overlapping shared risk factors and the coadministration of agents with adverse metabolic effects, such as corticosteroids. The age at which cardiotoxic treatment is administered also modifies risk, with an increased risk of cardiovascular sequelae observed at extremes of age. Childhood cancer survivors face a greater risk of cardiovascular morbidity and mortality compared with their age-matched peers.[10] Additionally, patients with cancer and ACHD represent a specific high-risk population. Attempts to better understand best practices for this cohort require international collaboration to compile data from multicenter registries supported by standardized protocols and cardiotoxicity adjudication to facilitate data collation.

For baseline cardiotoxicity risk stratification, all patients should undergo a clinical history and examination, including measurements of BP, serum lipids, and HbA1c. A 12-lead electrocardiogram (ECG) is crucial for detecting pre-existing abnormalities and establishing a baseline for future comparisons. This is particularly relevant for therapies associated with QT prolongation in which the Fridericia technique is recommended for monitoring the heart rate-QTc interval.[11] Blood biomarker and cardiovascular imaging are obtained for some patients based on risk stratification, with additional targeted investigations for those with pre-existing cardiovascular disease.

Considering an individual's genetic, immune, and molecular profile is likely informative for defining personalized cardiotoxicity risk. However, the predictive value of such biomarkers is incompletely understood, and they are not currently included in established cardiotoxicity risk scores.[12] Developing tailored risk assessments that account for treatment-specific cardiotoxicity mechanisms could significantly improve both cancer and cardiovascular prognosis. This would require a deeper understanding of biologic pathways that lead to cardiotoxicity and the validation of identified biomarkers in generalizable clinical cohorts.

Another key pretreatment consideration is primary prevention of cardiotoxicity. Dose reduction remains the most reliable method to reduce cardiotoxicity risk, particularly in treatments with a clear dose-response relationship, such as radiation therapy and anthracyclines. The role of pre-emptive cardioprotective medications to prevent cardiotoxicity is uncertain. Clinical trials involving most cardiac drugs have failed to reach consensus, and none have demonstrated a clinically relevant benefit from such interventions. Exercise has been proposed as a non-pharmacologic intervention to offset the risk of anthracycline-induced cardiotoxicity (AIC). Although animal studies indicate a potential role for forced exercise in reducing AIC in vivo and ex vivo,[13] human

MEK = mitogen-activated extracellular signal-regulated kinase

MM = multiple myeloma

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PI = proteasome inhibitor

RCT = randomized controlled trial

TKI = tyrosine kinase inhibitor

TTE = transthoracic echocardiography

VEGFi = vascular endothelial growth factor inhibitor

TABLE 1 Imaging Modalities and Derived Phenotypes for Baseline Risk Assessment of Patients With Cancer

	TTE	CMR	Cardiac CT
Recommended parameters	• LVEDV and LVEF (ideally 3D TTE) • LAV, E/A measurement • RV diameter • GLS • RV FWLS and LA strain if available • S′ for mitral and tricuspid • TAPSE • Peak TRV • E/E′ • IVC diameter • Valvular and pericardial diseases	• LVEDV and RVEDV • LV mass • LVEF and RVEF • Longitudinal and circumferential strain if available • Myocardial characterization • T2w (STIR), T1, T2 maps, LGE	• Agatston score for cardiac CT and CAC-DRS for all noncontrast CT scans • LVEDV and LVEF • Coronary anatomy description
Clinical scenarios in which these imaging tests are recommended at baseline[a]	• All patients with pre-existing cardiovascular diseases • All patients receiving anthracyclines, HER2 therapies, proteasome inhibitors, CAR-T therapy, and HSCT • Patients at high cardiovascular toxicity risk receiving immunotherapy-targeted therapies (VEGF, bcr-abl TKIs, BRAF-MEKi, BTKi)	• Poor-quality TTE imaging or borderline results • Patients with pre-existing cardiovascular disease • New left ventricular impairment or cardiac symptoms on baseline TTE • Multiple myeloma where cardiac amyloidosis is suspected	• Symptomatic patients before any potentially cardiotoxic therapy • High-risk patients or those with known CAD before fluoropyrimidines, targeted therapies (VEGFi, second- and third-generation bcr-abl TKIs), IMIDs

[a]European Society of Cardiology guidelines included only class 1 indications for TTE.

3D = 3-dimensional; BRAF = rapidly accelerated fibrosarcoma B type; BTKi = Bruton tyrosine kinase inhibitor; CAC-DRS = coronary artery calcium data and reporting system; CAR-T = chimeric antigen receptor T cell; CMR = cardiac magnetic resonance; CT = computed tomography; E = mitral inflow early diastolic velocity obtained by pulsed wave; E′ = early diastolic velocity of the mitral annulus obtained by tissue Doppler imaging; FWLS = free wall longitudinal strain; GLS = global longitudinal strain; HER2 = human epidermal growth factor receptor 2; HSCT = hematopoietic stem cell transplantation; IMID = immunomodulatory agent; IVC = inferior vena cava; LA = left atrial; LAV = left atrial volume; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MEKi = mitogen-activated protein/extracellular signal-regulated/kinase inhibitor; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; S′ = systolic velocity of tricuspid annulus obtained by Doppler tissue imaging; STIR = short tau inversion recovery; TAPSE = tricuspid annular plane systolic excursion; TKI = tyrosine kinase inhibitors; TTE = transthoracic echocardiography; TRV = tricuspid regurgitation velocity; VEGF = vascular endothelial growth factor; VEGFi = vascular endothelial growth factor inhibitor.

studies show that although training improves exercise capacity, there is scant evidence of its cardioprotective effects during cancer therapy.[13-16]

TOOLS FOR RISK STRATIFICATION PRECANCER TREATMENT

RECOMMENDATIONS.

- Echocardiography is recommended as the first-line modality for assessing baseline cardiac function, measuring 3-dimensional left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) when available.
- Cardiac magnetic resonance (CMR) is recommended for its incremental imaging precision in high-risk patients or when echocardiography results are suboptimal.
- It is recommended that coronary artery calcium (CAC) be reported on nongated computed tomography (CT) scans to guide the administration of preventative medications.

GAPS IN KNOWLEDGE.

- A cost-effectiveness analysis of universal baseline screening for all patients receiving anthracyclines and anti-human epidermal growth factor receptor 2 (HER2) therapies has yet to be performed.
- There is need for the development and evaluation of precision biomarkers that target underlying pathophysiological mechanisms of cardiotoxicity.
- External validation of cancer-specific risk scores, including the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk assessment tool, is essential for their widespread implementation.
- The validity of conventional cardiovascular risk scores in cancer patients remains incompletely defined.

IMAGING TOOLS FOR BASELINE ASSESSMENT AND RISK STRATIFICATION. Cardiovascular imaging plays an important role in baseline assessment, particularly for higher-risk patients and for therapies associated with cancer therapy-related cardiovascular dysfunction (CTRCD) (Table 1). The rates of previously unknown asymptomatic left ventricular (LV) dysfunction range from 3% to 6% in the general population, making detection before cardiotoxic chemotherapy crucial.[17] Documenting pretreatment cardiac function is also essential for not only detecting changes during cancer therapy but also evaluating disease severity and determining fitness for proposed cancer treatments in patients with pre-existing cardiovascular disease.

Cardiac function. Routine monitoring of cardiac function is recommended both before and during treatment for patients receiving therapies with a high risk of LV dysfunction, including anthracyclines, targeted therapies, and anti-HER2. CTRCD is defined as symptomatic heart failure or an asymptomatic decline in LVEF, with severity grading based on symptoms, the degree of change in LVEF, and the absolute LVEF value.[2] Additionally, a decrease ≥15% in GLS relative to baseline is also considered indicative of confirmed or likely mild CTRCD.[2,18,19]

Accurate detection of CTRCD from serial monitoring during treatment necessitates reproducible measurements of LVEF and GLS. LVEF estimates obtained using different modalities are calculated using various methods and are not interchangeable.[20] Therefore, the imaging modality selected for baseline assessments should consistently be used for serial tracking of interval changes during treatment, although the choice of modality will ultimately depend on local resources and available expertise.

Transthoracic echocardiography (TTE) is the recommended first-line modality for assessing cardiac function, ideally incorporating 3-dimensional LVEF and GLS.[2,6] It is widely accessible, inexpensive, and radiation free. However, the image quality depends on acoustic windows, which can be obscured in patients with a large body habitus or after breast surgery. If the endocardium of ≥2 contiguous LV segments is not clearly defined, contrast-enhanced TTE or CMR should be used. Although CMR is the reference modality for LVEF calculation,[21] its widespread use is limited by factors such as cost, availability, and the need for specialized expertise. Newer protocols and automated analysis tools may alleviate some of these limitations,[22] and CMR should be considered when decision making is complex.[23] Multigated acquisition nuclear imaging scanning, although providing limited anatomical or functional imaging beyond chamber quantification, involves ionizing radiation and is thus recommended only when alternative methods are unavailable.[2]

GLS, a marker of myocardial deformation, is generally measured using speckle tracking echocardiography or feature tracking on CMR. Research has highlighted the prognostic value of baseline GLS, demonstrating enhanced incremental performance when combined with LVEF and biomarkers compared with LVEF and biomarkers alone.[24-26]

Additionally, several studies have examined the prognostic utility of CMR measures of myocardial tissue characterization. Myocardial T1 values are commonly elevated in cancer patients even before treatment[27]; however, there is no proven association between baseline values and subsequent CTRCD or long-term clinical outcomes.[28] Consequently, myocardial mapping techniques are not currently recommended for routine baseline imaging in asymptomatic patients.

The prognostic value of baseline cardiac function assessment for all patients receiving therapies associated with CTRCD regardless of risk remains controversial.[29] Similarly, its cost-effectiveness has yet to be proven. However, 1 simulation study[30] showed that despite a low incidence of heart failure (2%), measuring LVEF in all breast cancer patients receiving anthracyclines was cost-effective because of the low cost of TTE and the high cost of managing chronic heart failure. There is need for more thorough scrutiny of the health economics of surveillance recommendations, taking into account various scenarios and patient populations.

Coronary artery disease. Vascular toxicities, such as accelerated atherosclerosis, arterial thrombotic events, and coronary spasm, are associated with both established treatments like chest radiation therapy and fluoropyrimidine chemotherapy as well as contemporary therapies such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs).[18] In patients presenting with symptoms suggestive of angina who are scheduled to receive therapies associated with coronary events, the existing guidelines for noninvasive assessment should be followed. This includes coronary computed tomography angiography for those with low pretest probability and functional tests for others. However, there is minimal evidence supporting baseline imaging in asymptomatic patients.

CAC scoring is crucial for stratifying atherosclerotic risk in the general population. Many cancer patients undergo chest CT imaging for cancer diagnosis or staging. Although these scans are non-ECG gated, assessing coronary calcium from them is feasible and recommended by radiology guidelines,[31] thus aiding in risk stratification and modification before treatment with anticancer agents associated with coronary events. For patients at intermediate risk, a CAC score of 0 may allow for monitoring only, whereas any higher scores should prompt the initiation of statin therapy, with or without aspirin.[32]

BASELINE BLOOD BIOMARKERS. Traditional cardiovascular blood biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin (cTn), are crucial for assessing myocardial function and myocyte damage. These biomarkers have been incorporated into clinical practice guidelines for risk stratification, monitoring,

and diagnosing patients receiving cardiotoxic cancer therapies. Routine baseline measurement of these biomarkers is recommended in certain populations[2] despite conflicting evidence regarding their effectiveness beyond detecting pre-existing occult cardiovascular disease and tracking interval changes during treatment.[33-39]

Newer biomarkers provide additional insights into myocardial stress and injury and, similar to traditional biomarkers, serve as early indicators of pathology. Soluble ST2, a member of the interleukin-1 receptor family, acts as a biomarker of inflammation and stress, possessing prognostic value in heart failure and coronary disease. However, although it has been suggested as a potential early biomarker for cardiotoxicity,[40] studies have not demonstrated that baseline ST2 levels can predict cardiotoxicity events.[41]

Other novel genetic, proteomic, and immunologic biomarkers based on biological mechanisms have been proposed to predict cardiotoxicity. Extensive research has been conducted on identifying genetic variants that indicate individual susceptibility to cardiotoxicity, encompassing both known gene variants associated with dilated cardiomyopathy and polymorphisms linked to cardiotoxicity risk from other cancer therapies, such as HER2 polymorphisms.[42-44] Armenian et al[45] reported that a combined clinical and genetic risk prediction model for heart failure with anthracyclines outperformed models that relied solely on clinical or genetic factors. However, despite their theoretical promise, the existing research is based on cohorts with very small event numbers, which are underpowered to detect all single-nucleotide polymorphisms (SNPs), and most studies have not been validated.

Immunosenescence, the age-related decline of immune system efficacy, may contribute to the development of somatic preleukemic mutations in the hemopoietic bone marrow. These mutations, known as clonal hematopoiesis of indeterminate potential, are associated with an increased risk of leukemia and an increase in cardiovascular risk independent of traditional risk factors. It has been proposed that individuals carrying clonal hematopoiesis of indeterminate potential mutations face an increased risk of cardiotoxicity and could benefit from enhanced surveillance.[46] Further research is needed to better understand this association and to inform management recommendations.

RISK SCORES FOR CARDIOVASCULAR DISEASE PREDICTION IN CANCER PATIENTS. A key goal of cardio-oncology is the estimation of personalized cardiotoxicity risk before treatment begins. The HFA-ICOS cardiotoxicity risk assessment tool[12] received a Class 2a recommendation in the ESC 2022 cardio-oncology guidelines[2] despite being supported only by Class C level evidence. Validation studies for these risk scores are emerging,[47-50] but further research is needed.

A systematic review of additional novel risk prediction tools for cardiotoxicity in breast cancer included 7 models. Most of these models lacked external validation. The discrimination of these models, as measured by the C-statistic, ranged from 0.70 to 0.87. However, most of the derivation studies exhibited high heterogeneity and were at high risk of bias, raising concerns about model overfitting.[51]

Many gaps in knowledge remain in our understanding of the validity of risk scores for cardiotoxicity prediction. Further validation, standardization of endpoints, and model refinements are essential for wider clinical implementation. Current risk scores primarily extrapolate from anthracycline studies because of limited evidence for individual drugs. The complexity of the cardio-oncology field presents challenges for traditional research methods, and machine learning approaches may provide useful solutions. Additionally, the practicalities of incorporating cardiotoxicity risk prediction into clinical pathways, including determining the thresholds for referral, additional investigations, initiation of cardioprotection, or cancer treatment change, still need to be determined.

OPTIMIZATION OF PRE-EXISTING CARDIOVASCULAR CONDITIONS INCLUDING ANTICOAGULATION. Current guidelines advocate for the identification and treatment of cardiovascular risk factors alongside optimizing the management of pre-existing cardiovascular diseases.[2] Although such interventions are anticipated to prevent adverse cardiovascular events in the general population, their effectiveness in reducing cardiotoxic events remains uncertain. Managing pre-existing cardiovascular conditions can also be more complex in the context of active cancer and its treatments. Pretreatment consideration of drug interactions is crucial to avoid preventable complications. The administration of heart failure therapies, such as angiotensin-converting enzyme inhibitors and beta-blockers, is

often interrupted because of sepsis, renal impairment, adverse effects, and potential drug interactions,[52] necessitating clear baseline guidance. Additionally, controlling pre-existing hypertension and metabolic disorders may need to be intensified because of the effects of cancer therapies and adjuncts, including steroids.[53]

Patients with active cancer have an increased risk of venous (5-fold)[54] and arterial (2-fold) thromboembolism,[55] but they also face elevated bleeding risks, particularly if they have intracranial or gastrointestinal malignancies, thrombocytopenia, or severe renal impairment. This presents unique challenges for anticoagulation management for cardiovascular conditions such as atrial fibrillation (AF). Conventional risk scores, including the CHA_2DS_2-VASc score, tend to underestimate the risk of thromboembolic events in cancer patients.[56] Nonetheless, these scores can be useful in identifying patients who may safely avoid anticoagulation.

Many cancer treatments interact with oral anticoagulants or affect platelet numbers and function, such as ibrutinib, making the historical preference for low molecular weight heparin for thromboprophylaxis in cancer patients understandable. More recently, subgroup analyses from large, randomized trials have shown that non-vitamin K antagonist oral anticoagulants are noninferior to vitamin K antagonists for thromboprophylaxis in AF among cancer patients,[57-60] with superior safety data.

The interruption of antiplatelet therapy in patients who have recently undergone percutaneous coronary intervention is considered high risk. Contemporary drug-eluting stents and coronary interventional devices have allowed for shorter durations of dual antiplatelet therapy with increased safety. Therefore, the duration of antiplatelet therapy in cardio-oncology patients could be attenuated to allow earlier surgical treatments or to decrease bleeding risks in those anticipated to experience declines in platelet count.

For patients with cardiac implantable electronic devices (CIEDs), both cancer diagnostic and treatment pathways can be affected. Although most patients with CIEDs can safely undergo cardiac magnetic resonance,[61] the absence of local expertise and dedicated pathways often limits access to this diagnostic modality. For patients requiring radiation therapy, it is crucial to provide guidance on safety protocols and on monitoring and programming the CIED before treatment begins.[62] Radiation therapy planning might need to be adapted to prevent chest tumor shielding by the CIED generator, and, occasionally, repositioning of the CIED may be necessary to enable radiation therapy.

Patients with pre-existing cardiovascular disease who require procedural interventions before cancer treatment should have their prognosis and quality of life carefully considered in planning management. The outcomes for such interventions in patients with active cancer are gradually emerging.[63]

TREATMENT-SPECIFIC CONSIDERATIONS

ANTHRACYCLINES.

Recommendations.

- It is recommended to minimize the dose of anthracycline when feasible.
- A baseline cardiac function assessment should be performed, and management of pre-existing cardiovascular diseases and risk factors should be optimized.
- Measuring NT-proBNP in high-risk patients may be considered to identify/diagnose subclinical cardiovascular disease because this is part of the diagnostic work-up for heart failure.
- In high-risk patients receiving high-dose anthracyclines, consider the use of conventional cardiovascular medications for cardioprotection.

Gaps in knowledge.

- The cost-effectiveness of baseline imaging and biomarker measurement in low-risk patients exposed to low-dose anthracycline regimens remains unknown.
- The role of genetic testing in predicting cardiotoxicity requires further research.
- Investigation into specific cardioprotective agents that target underlying pathophysiological mechanisms is needed.
- The efficacy and effectiveness of assessing baseline cardiovascular biomarkers have not been established.
- Further evaluation is required to understand differences in cTn subtype and sex-specific thresholds.

Anthracyclines are widely used anticancer drugs (**Table 2**) included in treatment regimens for breast and other solid tumors as well as hematologic malignancies in both adults and children. However, their use is limited by cumulative dose-dependent cardiotoxicity, which can vary in onset and may present with either symptomatic or asymptomatic CTRCD.

Cardiovascular imaging is recommended for all patients before initiating anthracycline treatment.[2] In a study of 2,234 patients with LVEF between 50% and

TABLE 2 Baseline Cardiovascular Assessment of Patients Before Anthracycline-Based Chemotherapy

	Summary of Evidence	Clinical Practice Recommendations	Research Recommendations
Blood biomarkers			
NT-proBNP[35,64,66]	• Few studies have examined the prognostic value of baseline NT-proBNP, and evidence supporting this metric as a stand-alone predictor is weak.	• Baseline NT-proBNP is recommended to detect interval change during treatment, which may indicate preclinical cardiotoxicity.	• Elevated baseline troponin is linked to higher levels during treatments but not directly to cardiotoxicity outcomes in the same studies. • Existing studies exclude high-risk individuals who might benefit most from baseline assessment. Further research into the predictive value of troponin and NT-proBNP in unselected patient cohorts is needed.
Cardiac troponin[65,173]	• There is conflicting evidence for the utility of routine cardiac troponin measurement for risk stratification or early detection of clinical cardiotoxicity.	• Baseline cardiac troponin may have some role in determining cardiotoxicity risk during treatment.	
Genetic testing[45,69-71]	• More than 40 genetic polymorphisms are linked to increased susceptibility to anthracycline-related cardiotoxicity, with studies varying from focusing on pharmacogenetics and mechanisms to those examining cardiomyopathy-related variants and conducting GWASs targeting cardiotoxicity as the phenotype.	• Routine genetic testing is not currently recommended.	• Although a growing number of studies link biologically plausible genetic variants to anthracycline-induced cardiotoxicity, almost all lack appropriate validation data. • The incremental utility of genetic testing over standard clinical assessments remains to be conclusively demonstrated. • Identifying patient groups most likely to benefit from genetic testing is important and would allow for more effective resource allocation.
Cardiovascular imaging			
LVEF[25,64,65,173]	• Good evidence to support the use of baseline LVEF as an indicator of cardiotoxicity.	• Measure baseline LVEF using 3D TTE or CMR as the initial choice for all patients before anthracycline treatment.	• Head-to-head comparisons of baseline LVEF using different modalities and measurement methods to establish reproducibility, performance, and the prospective association with cardiotoxicity events.
GLS [25,64,65,173]	• Good evidence to support GLS as an indicator of cardiotoxicity, with some evidence suggesting that GLS may detect cardiotoxicity onset before a decline.	• For all patients, measure baseline LVEF using 2D echocardiogram with 3 long-axis views before anthracycline treatment.	• In addition to the previous recommendation, assess the impact of variations in GLS by modality and vendor and the incremental value of this metric over LVEF in terms of translating to improved clinical outcomes.
Primary prevention			
Reduce exposure[164]	• Reducing or omitting doses of anthracyclines is the most effective way to prevent related cardiotoxicity.	• Consider alternatives to anthracyclines when equally effective anticancer agents are available.	• The cumulative risk from anthracycline exposure is well-documented.
Cardioprotection (RAAS blockers, beta-blockers)[80,81]	• Existing evidence from multiple randomized trials does not support routine use of cardioprotection with RAAS blockers or beta-blockers.	• There is no evidence to support the routine use of pre-emptive cardioprotection with RAAS blockers or beta-blockers before anthracycline treatment.	• Most existing studies focus on low-risk cohorts; further research is needed to identify higher-risk patient subsets who may benefit from pre-emptive cardioprotection.
Liposomal doxorubicin[73]	• Multiple randomized trials support the protective role of liposomal doxorubicin in preventing incident cardiotoxicity compared with standard doxorubicin.	• Liposomal anthracyclines should be considered for patients at high and very high toxicity risk.	• Current research is limited to very select patient cohorts (considering malignancy type, status, and cardiotoxicity risk). The potential broader role of this drug in reducing risk beyond these contexts needs further exploration.
Dexrazoxane[74,75,77]	• Dexrazoxane has proven effective in reducing the risk of clinical heart failure in breast cancer patients receiving anthracycline chemotherapy.	• Dexrazoxane may be considered for high- or very high-risk patients for whom anthracyclines are essential.	• The use and role of dexrazoxane across different patient cohorts should be explored.
Exercise[13-16]	• Animal models show a reduced risk of cardiotoxicity with exercise. In humans, exercise is linked to improved cardiorespiratory fitness metrics but has not been shown to reduce cardiotoxicity risk.	• There is inadequate evidence to recommend prescribed exercise specifically for reducing cardiotoxicity risk.	• Research should explore various exercise regimens in different cohorts, with better assessment of compliance (eg, using smart watch monitoring), and consider longer term outcomes.
Hypertension control[174,175]	• Observational studies in breast and hematologic cancer patients indicate a correlation between hypertension and an increased risk of AIC. Hypertension susceptibility loci are linked to AIC in childhood cancer survivors.	• Early control of blood pressure is recommended.	• Additional studies are necessary to further elucidate the mechanisms of hypertension and AIC comorbidity.

2D = 2-dimensional; AIC = anthracycline-induced cardiotoxicity; GWAS = genome-wide association study; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Table 1.

TABLE 3 Overview of Evidence for Treatment-Specific Baseline Investigations and Primary Prevention of Cardiotoxicity Events

Cancer Therapy Class	Conventional Cardiovascular Risk Factors	Imaging	NT-proBNP	cTn	HFA-ICOS	Primary Prevention
Anthracyclines	++	High/ medium risk: LVEF ++ Low risk: O GLS ++	+/-	+/-	O	Dose reduction: ++ Liposomal doxorubicin: ++ Dexrazoxane: + Beta-blockers: +/- ACEI/A2RB: +/- Statins: +/-
HER2-targeted therapies	++	++	+/-	+/-	+	Beta-blockers: +/- ACEI/A2RB: +/-
Fluoropyrimidines	+/-	O	O	O	Not applicable	Nitrates/CCB: +
BRAF/MEK inhibitors	++	O	O	O	X	O
Androgen-deprivation therapy	++	O	O	O	Not applicable	Statins: +
Immune checkpoint inhibitors	Myocarditis: +/- Coronary events: ++	O O	O O	+ O	Not applicable Not applicable	O Statins: +
BCR:ABL tyrosine kinase inhibitors	++	O	O	O	O	O
Multiple myeloma therapies	++	O	PI: +	O	O	PI—high risk: DOAC PI—low risk: aspirin, LMWH
VEGFi	++	O	O	O	O	O
CAR-T cell therapies	++	++	+	O	Not applicable	O
Radiation therapy	++	O	O	O	Not applicable	Dose reduction: ++
Hematopoietic stem cell transplantation	++	O	O	O	Not applicable	O

Multiple studies with consensus results supporting effect (++), single study with evidence of effect (+), evidence differs between studies (+/-), evidence shows no effect (X), no evidence available (O), and not applicable (no risk calculator).

A2RB = angiotensin 2 receptor blocker; ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium-channel blocker; cTn = cardiac troponin; DOAC = direct oral anticoagulant; HFA-ICOS = Heart Failure Association-International Cardio-Oncology Society; LMWH = low molecular weight heparin; MEK = mitogen-activated protein/extracellular signal-regulated/kinase; PI = proteosome inhibitor; other abbreviations as in Tables 1 and 2.

59%, baseline LVEF and GLS were linked to incident cardiovascular events independent of age over a median of 659 days after anthracycline treatment.[25] Similar findings have been reported in other smaller studies of breast cancer patients[64] in whom even a baseline ejection fraction ≤5 points above the lower limit of normal has been prognostic for subsequent symptomatic heart failure and cardiovascular death during anthracycline chemotherapy.[64,65] These findings underscore the overall value of baseline LVEF and GLS as predictors of AIC. However, the incremental value of these measures in low-risk populations receiving low-dose anthracycline regimens is still unclear and important to determine, particularly in resource-limited health care settings.

Current guidelines recommend measuring baseline NT-proBNP and cTn concentrations if these biomarkers are to be monitored during treatment.[2] The evidence base for routine blood biomarker monitoring is mixed, with emerging evidence increasingly questioning the role of cTn concentration monitoring. Data on the prognostic value of baseline NT-proBNP and cTn measurements are mostly limited to small studies in low-risk patient groups. These studies generally focus on biomarker or imaging endpoints, without demonstrating a link to clinically relevant CTRCD. For instance, 1 study found that only 2% (8/348) of lymphoma patients had elevated baseline high-sensitivity cardiac troponin T concentrations, which rose to 28% (100/348) by the end of treatment, with a clear association between levels at these 2 time points.[66] Conversely, a study of 52 patients treated with anthracyclines for early breast cancer found a significant association between baseline NT-proBNP and LVEF at 2 years but not with cTn.[38] Other studies involving breast cancer patients found no correlation between baseline NT-proBNP or cTn concentrations and cardiotoxicity.[35,64,67] These findings are corroborated by recent prospective clinical trials, which question the utility of routine cTn monitoring for assessing cardiotoxicity. We highlight these studies because they have implications for baseline monitoring as well.

In the Cardiac Care Trial,[68] patients receiving anthracyclines for breast cancer or non-Hodgkin lymphoma with cardiac troponin I (cTnI) concentrations in the upper tertile during chemotherapy were randomized to receive cardioprotection or standard therapy. The study found no differences in the degree of LVEF decline in those deemed high risk (upper

tertile) or low risk (lower 2 tertiles) based on cTn concentrations during anthracycline therapy. This indicates that cTn concentrations may be a poor marker of CTRCD risk. However, it is important to highlight that the cTnI thresholds used to categorize high risk were conservative (≥5 ng/L for cycle 2 and ≥23 ng/L for cycles 3 to 6) and fell well within the normal reference range. Further research is needed to explore the prognostic role of baseline cTn levels outside of the normal range and to investigate the differences between troponin I and T.

In a recent analysis of the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial, Mecinaj et al[69] evaluated the impact of implementing the ESC-International Cardio-Oncology Society guideline criteria for defining CTRCD, which includes troponin measurement. They found that mild asymptomatic CTRCD during cancer therapy, primarily driven by cTn elevation rather than LV dysfunction, was common and did not predict subsequent CTRCD. These results fail to show a clear relationship between changes in baseline troponin levels, changes in LV function, and clinical outcomes, calling into question the current guideline recommendations for troponin assessment with cancer therapy.

Genetic testing is not currently recommended as a routine procedure before anthracyclines. However, emerging data suggest a promising future role for it in personalized risk stratification, informed by pharmacogenomic and cardiovascular biology. Garcia-Pavia et al[70] identified variants linked to cardiomyopathy, particularly titin truncations, associated with cardiotoxicity in a heterogeneous cohort of patients, 90% of whom had received anthracyclines. Additionally, a study of 1,697 patients with non-Hodgkin lymphoma revealed 5 SNPs in the NAD(P)H oxidase and doxorubicin efflux transporters that increase susceptibility to AIC.[71] Further research with 170 anthracycline-exposed childhood cancer survivors identified polymorphisms in the genes encoding carbonyl reductase—enzymes that catalyze the reduction of anthracyclines to cardiotoxic alcohol metabolites—as contributing to increased AIC risk, particularly in those with low- to moderate-dose anthracyclines.[72] However, current studies are based on small cohorts and lack adequate validation data, necessitating much more research before genetic testing can be recommended for pretreatment risk stratification.

To mitigate the risk of cardiotoxicity in high-risk patients, primary prevention strategies should be considered (**Table 3**).[73] The most effective approach includes reducing the dose of anthracyclines or opting for alternative agents; however, these options might compromise cancer outcomes. The use of liposomal doxorubicin is recommended for patients at high risk of cardiotoxicity or those who have previously received high cumulative doses of anthracyclines.[2] This recommendation is supported by meta-analysis data from 19 randomized controlled trials (RCTs), which demonstrate a 40% reduction in cardiotoxicity risk compared with doxorubicin.[74] Dexrazoxane, a free radical scavenger, has also been shown to reduce the risk of cardiac events in breast cancer patients receiving anthracyclines,[75,76] without affecting cancer outcomes or increasing other adverse events.[77] Its use is currently recommended for adults at high risk of CTRCD for whom anthracycline chemotherapy is essential.[78,79] There are currently no trials with head-to-head comparison of dexrazoxane and liposomal doxorubicin in adults; however, 1 such trial is underway involving a pediatric population with acute myeloid leukemia.[80]

There is a lack of consistent evidence supporting the use of standard heart failure medications for primary prevention across several prospective studies. In a meta-analysis of 12 RCTs involving 1,035 cancer patients treated with anthracyclines, cardioprotection was associated with a smaller decline in LVEF but not with a reduced risk of heart failure.[81] Another meta-analysis of 17 RCTs involving a heterogenous cohort of cancer patients receiving chemotherapy found that cardioprotection was linked to a smaller LVEF decline, although the absolute difference was clinically nonsignificant.[82] Additionally, a small retrospective case-control study involving patients with diabetes receiving anthracyclines found lower rates of cardiotoxicity in those treated with sodium glucose co-transporter 2 inhibitors compared with those who were not.[83] However, ongoing clinical trials are expected to provide more definitive evidence. The potential benefits of cardioprotection may be underestimated in existing studies because of the under-representation of patients at high cardiovascular risk who may benefit most from such interventions.

More recently, several trials have studied the use of statins for cardioprotection in patients treated with anthracyclines who do not have conventional indications for statin therapy.[84-87] A meta-analysis of 3 observational studies and 4 RCTs found a lower incidence of cardiotoxicity in patients treated with statins for primary prevention. However, there was no significant change in LVEF between the intervention and control groups. Given the differences in patient populations, statin regimens, small sizes of the studies, and the lack of hard clinical endpoints or

medium-term effects, further research is needed before statin administration can be confidently recommended for this purpose.

HER2-TARGETED THERAPIES.

Recommendations.

- Measuring baseline cardiac function in all patients before starting HER2-targeted therapies is recommended.

Gaps in knowledge.

- More evidence is needed to assess the utility of blood biomarker measurement in low-risk populations, especially with newer HER2-targeted agents or antibody-drug conjugates.
- The efficacy of cardioprotective agents when used in conjunction with HER2-targeted therapies has not yet been established.

Approximately 15% to 20% of breast tumors overexpress HER2 receptors, responding effectively to HER2-targeted therapies.[88] These therapies have shown clinical efficacy across early, locally advanced, and metastatic breast cancers as well as other HER2-positive solid tumors.[89-91] Initial trial data revealed that patients treated with trastuzumab in combination with anthracyclines experienced a 27% incidence of cardiac dysfunction.[89] To address this, subsequent trials introduced stringent exclusion criteria for cardiovascular disease and mandated that HER2 therapies only be administered sequentially after anthracyclines, which significantly reduced the rates of LV dysfunction to 8% to 13%.[92] The Food and Drug Administration now recommends baseline and 3 monthly LVEF surveillance throughout treatment for all patients regardless of baseline risk to facilitate early detection of cardiotoxicity.[2,93-95] Similarly, the ESC guidelines recommend baseline risk stratification using the specific HFA-ICOS proforma for anti-HER2 therapies,[2] suggesting that the patients at highest risk are those with pre-existing cardiovascular conditions; older age (particularly >80 years); and those with a history of smoking, hypertension, diabetes, or chronic renal disease.[96,97]

Baseline measurement of LVEF and GLS before initiating HER2 therapy provides benchmark values for comparison during surveillance and may identify patients with pre-existing or anthracycline-induced LV dysfunction. Borderline baseline values of LVEF (50%-54%) are associated with higher rates of subsequent LV dysfunction,[92,98] although no evidence suggests these are associated with worse long-term outcomes.

Unlike with anthracyclines,[99] HER2 therapy-related LV dysfunction does not involve myocardial ultrastructural changes and is reversible in up to 80% of patients.[100] Hence, in patients receiving HER2-targeted agents with mild to moderately decreased LVEF at baseline (40%-50%), a degree of "permissive cardiotoxicity" may be accepted, allowing cancer treatments to commence under close clinical and imaging supervision.[98,101] Nevertheless, alternative anticancer therapies should be considered.

For symptomatic patients or those with LVEF <30%, the risk of cardiotoxicity with HER2-targeted therapies is considered prohibitively high,[100] although this threshold lacks evidence in asymptomatic patients and cannot be directly compared with data from anthracycline treatments in which cardiotoxicity is less reversible. Similarly, imaging studies suggest HER2-targeted therapies might cause right ventricular dysfunction,[102] necessitating a comprehensive baseline assessment in patients with ACHD or pulmonary hypertension. Further research into their long-term outcomes is also warranted.

There are significant evidence gaps concerning the role of cardiac biomarkers for risk stratification before anti-HER2 therapies,[103] with existing guidelines showing discrepancies.[2,93] Overall, widespread biomarker screening remains controversial.[104,105] Many patients exhibit elevated troponin levels before treatment,[35,106] and in the HERA (Herceptin Adjuvant) study, abnormal baseline cTnI and cTnT measurements were found in 13.6% and 24.8%, respectively. These abnormalities associated with a 2.5-fold to 4.5-fold increased risk of significant LVEF decline during therapy.[39] Thus, normal baseline biomarkers might help identify patients at lower risk of cardiotoxicity who could benefit from less intensive monitoring during treatment.

However, a study of 251 trastuzumab-treated patients found that although 17% developed CTRCD, 38% of those who developed cardiac dysfunction did not show a rise in cTn concentrations during trastuzumab therapy, even though patients with elevated baseline levels were at increased risk.[107] In a trial of neoadjuvant lapatinib with or without trastuzumab for breast cancer, cardiac biomarkers did not predict subsequent cardiotoxicity in patients without prevalent CVD.[37] A combined imaging and biomarker approach, incorporating both high-sensitivity troponin I and GLS measurements, predicted HER2-related cardiotoxicity more effectively than either a single measure dose alone,[106] although further evidence is needed to support this strategy.

Additionally, baseline genetic testing might have value. Polymorphisms in the *ERbB2* gene, which alters the sequence of the HER2-neu protein, have been linked to an increased risk of trastuzumab

cardiotoxicity.[108] Further unique SNPs, identified through genome-wide association studies in different populations, have also been linked to HER2 cardiotoxicity.[109,110]

Evidence supporting the empirical use of cardioprotection for primary prevention of anti-HER2-related CTRCD remains weak. Several studies involving angiotensin 2 receptor blockers,[111] angiotensin-converting enzyme inhibitors,[112,113] and beta-blockers[112,113] in patients receiving trastuzumab have shown small benefits in reducing rates of asymptomatic, but not symptomatic, CTRCD. However, these trials have been limited by their size (<1,000 patients in total), short follow-up periods, and the use of significantly lower drug doses than those recommended for heart failure treatment.

Most of the existing evidence comes from patients who have received HER2-targeted therapies concurrently with or immediately after anthracyclines. Therefore, it is difficult to separate the direct and/or synergistic effects of the individual agents. Treatment approaches have also progressed, with current evidence supporting HER2 combination regimens (trastuzumab with pertuzumab) and the development of novel HER2-targeted agents, including anti-HER2 TKIs and antibody-drug conjugates. Emerging evidence from clinical trials and U.S. pharmacovigilance data indicate that these newer therapies are associated with lower rates of cardiotoxicity[114] and heart failure.[115]

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS.

Recommendations.

- Performing baseline BP and ECG assessments in all patients receiving vascular endothelial growth factor inhibitors (VEGFis) is recommended.
- Optimizing modifiable risk factors, particularly hypertension, before initiating treatment is recommended.

Gaps in knowledge.

- The role of baseline imaging before the administration of VEGFi-targeted therapies is not established.

The VEGF pathway plays a crucial role in angiogenesis, which is essential for tumor growth and metastasis, making it an attractive target for anticancer therapies across various malignancies. Inhibition of this pathway can lead to hypertension, venous and arterial thromboembolism, QT prolongation, and heart failure.[2,116] Hypertension, a reversible class effect, generally occurs early during treatment because of vasoconstriction from reduced nitric oxide production.[2] There are within-class differences in the incidence of other cardiovascular complications.

All patients due to receive VEGFis should undergo a baseline risk assessment for cardiotoxicity, including BP and QTc measurement. For patients with known hypertension, strict control is necessary to avoid VEGFi treatment interruptions or complications caused by VEGFis. Although baseline echocardiography is recommended in high-risk patients and may be considered for all patients, the measurement of NT-proBNP is advised only for those at high risk.[2] However, there is no specific evidence supporting this strategy, and it is primarily extrapolated from general cardiology principles.

FLUOROPYRIMIDINE CHEMOTHERAPY.

Recommendations.

- Cardiology assessment in patients with cardiac symptoms, including anginal-type chest pain, is recommended before initiating treatment.

Gaps in knowledge.

- The relationship between pre-existing cardiovascular disease and fluoropyrimidine cardiotoxicity is not well understood.
- There are currently no specific tools for risk stratification of fluoropyrimidine-related cardiotoxicity.
- The role of prophylactic administration of vasodilator agents during treatment in high-risk patients is not established.

Fluoropyrimidines, including 5-fluorouracil and capecitabine, are commonly used for gastrointestinal malignancies. Cardiotoxicity usually manifests early in the treatment as angina pectoris or myocardial infarction, thought to be caused by vasospasm even in the absence of significant atherosclerotic disease.[2] The reported incidence of cardiotoxicity is highly variable, ranging from 1% to 19%, and the relationship between conventional cardiovascular risk factors and events remains unclear.[9,117,118] Existing studies report conflicting results, likely because of variations in study design, patient cohorts, outcome definitions, and follow-up duration.

Vasodilator agents (nitrates and calcium-channel blockers) have been used clinically for primary prevention of coronary vasospasm before the administration of fluoropyrimidine chemotherapy but without supportive evidence. Oncologists commonly administer nonfluoropyrimidine second-line chemotherapy to patients with known CAD or multiple cardiovascular risk factors because of concerns about

cardiotoxicity. It is now recognized that genetic polymorphisms in the *DPYD* gene (encoding the DPD enzyme responsible for >85% of 5-fluorouracil elimination) contribute to systemic fluoropyrimidine toxicities. Consequently, patients are now gene tested before treatment, with dose reductions recommended for heterozygous gene carriers. However, the value of *DPYD* testing for specifically reducing the risk of cardiotoxicity remains unknown.

There is no specific HFA-ICOS risk proforma for patients receiving fluoropyrimidines, and recent ESC guidelines recommend only general cardiovascular risk assessment for asymptomatic patients, reserving investigations for symptomatic patients or those with known CAD.[2] Further evidence is required to better understand the disease mechanisms, risk factors, and cardioprotective agents for fluoropyrimidine cardiotoxicity.

RAPIDLY ACCELERATED FIBROSARCOMA B TYPE AND MITOGEN-ACTIVATED PROTEIN/EXTRACELLULAR SIGNAL REGULATED/KINASE INHIBITORS.

Recommendations.

- Achieving BP control, ideally to a target of below 130/80 mm Hg, before initiating therapy with rapidly accelerated fibrosarcoma B type (BRAF) and mitogen-activated protein/extracellular signal-regulated/kinase (MEK) inhibitors is recommended.

Gaps in knowledge.

- The utility of baseline cardiac function and blood biomarker measurements outside of high-risk patients requires further research.

BRAF and MEK inhibitor therapies have significantly transformed the treatment of melanoma and non-small-cell lung cancer, with recent Food and Drug Administration approvals expanding their use to other solid tumors with BRAF mutations.[119] However, cardiotoxicity, including hypertension, heart failure, arrhythmia, QTc prolongation, bleeding, and thromboembolic disease, remains a significant concern that may limit their therapeutic potential.[120] The true incidence of cardiotoxicity is difficult to determine from clinical trials because these often exclude patients with pre-existing cardiovascular disease and do not routinely perform echocardiography.[121] Nevertheless, a recent small retrospective study found CTRCD in 27% of patients.[50] Furthermore, a recent systematic review and meta-analysis comparing cardiovascular complications of BRAF-MEK inhibitor combination therapy with BRAF monotherapy[120] found an increased risk of pulmonary embolism and hypertension. For patients with pre-existing cardiovascular disease, monotherapy may be considered a lower-risk treatment option.

A baseline risk assessment tool for BRAF-MEK inhibitors has been proposed by HFA-ICOS,[12] yet this is primarily based on patient factors associated with a generalized risk of cardiotoxicity. However, recent data indicate that the majority of cardiotoxicity occurs in patients categorized as low or medium risk.[50] It is recommended that all patients have their BP aggressively managed before treatment with BRAF-MEK inhibitors, targeting a BP of <130/80 mm Hg.[121] Although the ESC guidelines recommend echocardiography for high-risk patients,[2] the individual drug's summary of product characteristics suggest serial monitoring of LV function for all patients. A recently published pathway for BRAF-MEK inhibitor cardiotoxicity recommends comprehensive baseline assessment incorporating BP, ECG, echocardiography, and biomarkers (NT-proBNP and cTn) for all patients[121]; however, direct evidence to support this approach is currently lacking.

ANDROGEN DEPRIVATION THERAPY.

Recommendations.

- BP, lipid, and HbA1c should be measured and optimized before initiating androgen-deprivation therapy (ADT) therapy.

Gaps in knowledge.

- Further research is needed to establish the cardioprotective roles of exercise, diet, and statin administration.
- The relative benefit of gonadotrophin-releasing hormone (GnRH) antagonists over GnRH agonists in reducing cardiotoxicity remains unclear.

ADT is an effective treatment for advanced prostate cancer, working by reducing circulating testosterone levels. GnRH agonists are most commonly used; however, they are associated with an increased risk of CAD, largely driven by indirect modifications of cardiovascular risk factors through metabolic effects.[2,122] Therefore, baseline assessments should include measurements of BP and metabolic markers, with treatment of any abnormalities detected. Emerging data from cohort studies and prospective clinical trials support the administration of statin to reduce both cardiovascular events and cancer progression.[123-125] Lifestyle interventions, including dietary measures and exercise, are recommended via survivorship guidelines,[126] although no outcome data are currently available. No dedicated cardiovascular risk calculators have been developed for patients receiving ADT,[2] with recommendations to use

existing tools like SCORE2 (Systematic Coronary Risk Evaluation 2). However, GnRH antagonists are associated with lower rates of cardiovascular events[127] and may be safer for high-risk patients, especially those with known coronary disease.

DRUGS USED FOR CHRONIC HEMATOLOGIC MALIGNANCIES.

Recommendations.

- ECG and baseline BP should be measured in all patients, with cardiovascular risk factors optimized.
- Echocardiography is recommended for patients receiving proteasome inhibitors, with NT-proBNP measurement in high-risk patients.
- Risk-assessed administration of thromboprophylaxis should be considered with immunomodulatory drugs.
- Baseline echocardiography is recommended for patients receiving dasatinib.
- Careful consideration of drug selection is recommended for patients at high cardiovascular risk when using BCR-ABL inhibitors.

Gaps in knowledge.

- The value of baseline echocardiography across all patients receiving proteasome inhibitors (PIs) and BCR-ABL TKIs remains undefined.

The treatment of chronic hematologic malignancies such as multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia has been transformed by the introduction of new and effective drugs. Patients with these conditions often receive long-term treatments. The various drugs available, even within the same class, exhibit varying cardiotoxicity profiles.

Older age at diagnosis increases cardiovascular risk, primarily because of the rise in comorbidity. In patients with MM, the prevalence of cardiovascular risk factors includes hypertension in 38%, arrhythmias and/or ischemic heart disease (IHD) in 14%, and diabetes in 16%, rising to 30% after corticosteroid treatment.[128] Additional MM-specific risk factors include hyperviscosity, anemia, and renal failure.

Current treatment regimens for MM incorporate combinations of immunomodulatory agents (IMIDs), PIs, anti-CD38 monoclonal antibodies, and steroids. The IMIDs, including thalidomide, lenalidomide, and pomalidomide, are closely associated with arterial and venous thrombosis because of their procoagulant effects on endothelial surfaces, a risk that is enhanced by the concomitant corticosteroid use.[128] As a result, risk-assessed thromboprophylaxis with IMIDs is mandatory but may increase mortality from bleeding.[129]

PIs are linked to adverse events such as heart failure, AF, hypertension, IHD, and thrombosis, with these effects being dose related.[130] Meta-analysis data[131] have shown a higher incidence of cardiotoxicity with carfilzomib (overall 18.1%, heart failure 4.1%) compared with bortezomib or ixazomib, attributed to the irreversibility of carfilzomib's proteasome inhibition and the higher doses used. Daratumumab, an anti-CD38 monoclonal antibody, is associated with new onset hypertension, although no cardiovascular signals have been reported for the alternative anti-CD38 molecule, isatuximab. Venous thrombosis, HF, and AF have been linked to elotuzumab, which targets SLAMF7. The histone deacetylase inhibitor, panabinostat, increases the QT interval, necessitating caution regarding potential drug interactions.[128]

For MM patients, baseline assessments should include optimization of cardiovascular risk factors and pre-existing cardiovascular diseases alongside BP and ECG acquisition for all patients. Echocardiography is recommended for all patients receiving PIs and NT-proBNP measurement for those at high risk.[2,132] A recent prospective study of patients receiving PIs showed that elevated baseline NT-proBNP levels predicted subsequent cardiotoxicity.

Bruton tyrosine kinase inhibitors (BTKis) offer effective and relatively safe therapy in CLL. BTKis are administered orally on a daily basis until progression or discontinuation because of intolerance. Ibrutinib, the first BTKi introduced, is associated with a high incidence of AF (up to 16%), hypertension (28%), and an increased risk of ventricular arrhythmias and sudden death.[133] Acalabrutinib, a second-generation BTKi, shows a 2-fold lower incidence of AF and a 5-fold lower risk of treatment discontinuation compared with ibrutinib.[134] The latest BTKis, zanubrutinib and pirtobrutinib, exhibit better safety profiles than ibrutinib, although clinical experience with them is still limited. Venetoclax, a BCL-2 antagonist, appears to be relatively free of cardiovascular toxicity in CLL to date. Current evidence for investigations beyond general pretreatment assessment with BTKi is limited, although the ESC guidelines recommend echocardiography for high-risk patients.

The treatment of chronic myeloid leukemia has been transformed by BCR-ABL multitargeted kinase inhibitors, with patient prognosis now largely

determined by comorbidities, including cardiovascular toxicities. Imatinib, the first-generation drug, is noted for its good cardiac safety profile[135] and may be cardioprotective. However, second- or third-generation agents such as bosutinib, dasatinib, nilotinib, and ponatinib (in this order) show rising incidences of cardiovascular complications because of off-target kinase inhibition.[136]

Ponatinib, also a VEGFi, is strongly associated with cardiotoxicity, showing exposure-adjusted incidences of 15.8 per 100 patient-years at 12 months,[137] with high rates of heart failure (9%-12%) and arrhythmia (7%-15%). Nilotinib is known for its potential to exacerbate or initiate hypertension and diabetes. At the 10-year follow-up, IHD, stroke, and peripheral vascular disease were up to 5 times more common with nilotinib compared with imatinib.[138] Dasatinib, which is strongly associated with pleural effusions, also presents a low (0.5%) but significant incidence of pulmonary arterial hypertension, which is usually but not always reversible on discontinuation.[139] Prescribing information for the myristoyl-binding inhibitor asciminib indicates increased incidences of arterial occlusive events, heart failure, hypertension, and QTc prolongation,[140] although long-term data are still pending.

For all second- and third-generation drugs, baseline assessment should include a thorough history and examination and measurements of BP, ECG, lipid profile, and HbA1c, with consideration of echocardiography for high-risk patients and mandatory for all patients receiving dasatinib. Performance of the HFA-ICOS risk assessment tool has demonstrated superiority to SCORE risk charts in this context[47] and should be used to inform drug choice prior to the administration of second- and third-generation drugs.

IMMUNOTHERAPY. Immunotherapies, such as ICIs and chimeric antigen receptor T-cell (CAR-T) therapy, leverage inherent immune system "cancer immunosurveillance" mechanisms to target cancer cells. The dramatic success of these therapies has expanded clinical use, thereby increasing the number of patients experiencing immunotherapy-related adverse events. Identifying high-risk patients and gaining a better understanding of common and serious cardiotoxicities are crucial steps in improving patient outcomes.

IMMUNE CHECKPOINT INHIBITORS.

Recommendations.

- It is recommended that ECG and cardiovascular risk optimization be performed in all patients before therapy.
- For high-risk patients, baseline echocardiography and cTn measurements are recommended to provide useful comparison data for outcome adjudication.

Gaps in knowledge.

- The relationship between conventional cardiovascular risk factors and ICI-related myocarditis remains incompletely understood.
- Further evidence is needed to assess the role of troponin measurement in predicting cardiotoxicity for all patients.
- Specific tools for risk stratification of cardiotoxicity related to immunotherapy are lacking.
- The role of cardioprotective strategies in this setting is not yet known.

Blockade of immune checkpoints enables the "reactivation" of antitumor T-cell immune responses. Current approved ICIs include inhibitors such as cytotoxic T lymphocyte antigen 4 (ipilimumab), programmed death 1 (nivolumab, pembrolizumab, and cemiplimab), and programmed death ligand 1 (atezolizumab, avelumab, and durvalumab). ICIs, both as single agents and in combination therapies, are effective against an expanding array of solid tumors, including melanoma, non-small-cell lung cancer, renal cell cancer, triple-negative breast cancer, and selected hematologic malignancies such as Hodgkin lymphoma.[141]

Systemic amplification of T-cell immune responses underlies toxicities and cardiotoxicities associated with ICIs, including myocarditis, pericarditis, arrhythmias such as heart block, and certain vasculitis.[142] These complications are more common in patients who also experience other toxicities like thyroiditis or myositis.[143] More recently, ICIs have been linked to atherosclerotic cardiovascular events,[144] possibly because of increased vascular inflammation and accelerated plaque progression.

Myocarditis occurs in 0.27% to 1.14%[145] of patients receiving ICIs, with a mortality risk of at least 50% in those receiving combination immunotherapy.[146] Diagnosis is often complicated by atypical clinical and imaging manifestations.[145,147] Blood biomarkers play an important role, especially baseline cTn concentrations,[147,148] which serve as pretreatment comparators. Elevated high-sensitivity cTnI levels are predictive of subsequent cardiovascular events.[149] The specific risk factors and the relationship between ICI-induced myocarditis and conventional baseline cardiovascular risks remain poorly understood.[145,146]

Currently, the most significant risk factors for ICI-mediated myocarditis include pre-existing

autoimmune diseases[150] and combination therapy with cytotoxic T lymphocyte antigen 4 inhibitors, which present more than a 4-fold increased risk compared with single-agent programmed death 1/programmed death ligand inhibition.[151] This highlights the need for specific risk calculators tailored for immunotherapy. Although current guidelines suggest a baseline ECG and reserve biomarkers and echocardiography for high-risk patients, the supporting data are limited. Available evidence suggests that reduced baseline LVEF and GLS are predictive of both ICI-induced myocarditis and major adverse cardiovascular events.[152]

Recent evidence indicates an increase in coronary events associated with ICIs, warranting comprehensive assessments for atherosclerotic risk factors. CAC assessment from ungated CT scans may provide prognostic value in patients receiving immunotherapy.[153] Additionally, the use of statins, colchicine, or other anti-inflammatory medications for primary prevention in this context has been proposed.[154]

CAR-T THERAPY.

Recommendations.

- A comprehensive baseline cardiovascular assessment, including ECG, echocardiography, and cardiac biomarkers, is recommended to assess cardiovascular reserve.

Gaps in knowledge.

- The data guiding risk stratification for cardiotoxicity during CAR-T therapy are limited.
- The long-term cardiovascular sequalae of CAR-T therapy remain unknown.

Adoptive cell transfer leverages a patient's own immune cells to target cancer. Among the adoptive cell transfer strategies, CAR-T immunotherapies are predominant, currently used for refractory and relapsed hematologic malignancies such as ALL, CLL, and non-Hodgkin lymphoma across pediatric and adult populations.[155] The chimeric antigen receptor recombinant fusion protein, genetically engineered to recognize a tumor-specific antigen, is expressed on the patient's autologous T cells, enabling them to specifically identify, target, and eliminate tumor cells.

CAR-T-associated toxicities include tissue damage from chimeric antigen receptor target cross-reactivity, acute anaphylaxis, and tumor lysis syndrome after infusion, neurotoxicity, and, most commonly, the systemic inflammatory response of cytokine release syndrome (CRS). Clinical trials have documented CRS occurrence in at least 50% of patients, with 20% experiencing both CRS and cardiopulmonary adverse events,[156-159] leading to fatality rates as high as 80% when cardiogenic shock is present.[158] The presence of pre-existing cardiovascular disease increases the risk of cardiomyopathy and heart failure with CAR-T therapy; however, the impact of previous treatment with cardiotoxic agents such as anthracyclines remains unclear.[159] Higher disease burden and increased CAR-T doses correlate with more severe CRS and cardiotoxicity, often preceded by new troponin elevations and reduced LVEF.[160,161]

Other markers linked with an increased risk of CRS and cardiotoxicities include lower baseline GLS and elevated natriuretic peptides.[160] A comprehensive baseline cardiovascular risk assessment is recommended, especially for patients with multiple prior treatment lines or other risk factors. This assessment should include ECG, echocardiography, and cardiac biomarkers, not only to assess the cardiovascular reserve necessary to withstand CRS but also to provide a baseline reference for subsequent comparisons during treatment.

RADIATION THERAPY.

Recommendations.

- It is recommended to minimize the mean heart dose to reduce the risk of long-term complications from radiation therapy.

Gaps in knowledge.

- Established cardiovascular risk scores and preventive strategies do not currently reflect the augmented cardiovascular risk from chest radiation therapy.
- Although improvements in radiation therapy techniques are anticipated to reduce cardiac complication rates, these reductions have not yet been documented in large population cohorts.

The association between radiation exposure and cardiovascular complications has long been established, with complications occurring acutely during treatment and, more commonly, decades later. Radiation-induced injury triggers inflammatory pathways and oxidative stress, potentially damaging both microvasculature and macrovasculature and leading to fibrosis that can affect all cardiac substructures.[162] Current evidence suggests a dose-response relationship in the risk of chronic radiation-induced heart disease, such as coronary events, valvular heart disease, and heart failure,[163,164] which persists for several decades[163] and is magnified

by pre-existing cardiovascular disease or risk factors.[163,164]

The primary cardiovascular consideration before treatment is minimizing cardiac exposure, specifically the "mean heart dose." Radiation therapy delivery techniques have evolved, leading to considerable reduction in overall cardiac dose in modern treatments. For example, although earlier studies indicated an increased risk of major coronary events for patients treated in the left breast compared with the right breast,[164] recent findings from the Danish Breast Cancer group suggest that laterality no longer poses a risk because of the widespread adoption of heart-sparing radiation delivery techniques.[165] In response, the recent ESC cardio-oncology guidelines recommend risk stratification based on mean heart dose, which provides a more individualized measure of cardiac exposure compared with the radiation dose prescribed to the tumor.[2] Additionally, it is recommended that general cardiovascular risk stratification using validated measures such as SCORE2 be used and that the treatment of pre-existing risk factors and conditions be optimized before radiation therapy.

HEMATOPOIETIC STEM CELL TRANSPLANTATION.

Recommendations.

- Comprehensive baseline cardiovascular assessments, including ECG, echocardiography, and cardiac biomarkers, are recommended to assess cardiovascular reserve.

Gaps in knowledge.

- The evidence supporting prehabilitation for patients with cardiovascular disease before undergoing hematopoietic stem cell transplantation (HCT) is not conclusive.

Studies across multiple settings have highlighted the heightened risk of cardiovascular events, both in the acute phase after HCT and among long-term survivors. These individuals experience early onset of hypertension, diabetes, dyslipidemia, and metabolic syndrome and face a 4-fold increased risk of developing cardiovascular disease and a 2-fold increased risk of cardiovascular disease mortality compared with the general population. However, the transplant marks a moment within a long disease course, and its effects are difficult to distinguish from the effects of the underlying disease, pretransplant treatments, conditioning regimen involving drugs and radiation therapies, and post-transplant complications, particularly chronic graft-versus-host disease in allograft recipients.

A comprehensive pretransplant cardiovascular assessment should be performed[166] including cardiovascular history and examination; BP, ECG, NT-proBNP, and troponin levels; and echocardiography. Although lifestyle interventions and prehabilitation exercise regimens have been tested in patients undergoing HCT—showing increases in strength and endurance—no demonstrable impact on cardiovascular outcomes has been demonstrated.[167]

PATHWAYS, DELIVERY, AND EQUITY

Recommendations.

- A multidisciplinary partnership is essential for optimizing cardiovascular health before cancer treatment, including specialized cardio-oncology care for high-risk patients.
- Empowering patients with pretreatment education regarding lifestyle interventions to prevent cardiovascular events is important.
- Consideration of demographic, social, and health inequalities is vital when planning cardio-oncology services.

Gaps in knowledge.

- There is a need for strategies to educate the broad range of stakeholders involved in implementing cardio-oncology clinical guidelines, including oncology and hematology physicians and nurses, general cardiologists, primary care physicians, and pharmacists.
- The feasibility and utility of dedicated cardio-oncology services in low-resource settings remain unclear.

The effective implementation of the ESC cardio-oncology guidelines in routine clinical practice requires strategies for streamlined risk assessment across the continuum of cancer treatment into survivorship. However, the substantial resources required for the successful implementation of such strategies can limit their reach and sustainability. Although most patients will not require specialist cardiology input and can undergo basic risk stratification by the treating oncologist or hematologist-oncologist within standard pathways, specialized services are needed for higher-risk patients. There is a call to action from international societies to expand

the development of cardio-oncology programs. Developing partnerships and education to develop simple, evidence-based tools that can be implemented at scale is essential. These efforts must be complemented by ensuring appropriate access and signposting to specialist services.

Recent reports have highlighted the influence of social determinants on cardio-oncology outcomes.[168-170] Patients with cancer from disadvantaged backgrounds face a higher burden of baseline cardiovascular risk factors, which significantly contributes to disparities in the occurrence of cardiotoxicity.[171] Inequities in access to preventive therapies, cardiovascular screening, and cardio-oncology services further exacerbate these health disparities, particularly in geographically remote settings and socioeconomically disadvantaged communities.[172] To promotion the equitable access to cardio-oncology care, it is essential to develop practical and cost-effective models that can establish and maintain high-quality cardio-oncology programs across different settings and resource levels.

RECOMMENDATIONS FOR FUTURE RESEARCH

The ESC 2022 cardio-oncology guidelines offer a highly comprehensive framework for the cardiovascular care of cancer patients, aligning with and expanding on previous guideline considerations.[4-6] Although these guidelines consolidate the existing evidence and reflect consensus opinions from global field leaders, they have also revealed the significant gaps in evidence that underpin many of the recommendations, resulting in uncertainty on the impact on clinical outcomes (**Central Illustration**). Given the many factors that influence cardio-oncology decisions and the limitations of the existing evidence, incorporating individual patient factors in a multidisciplinary approach with reliance on clinical judgment remains the best strategy for managing many cases until such evidence is available.

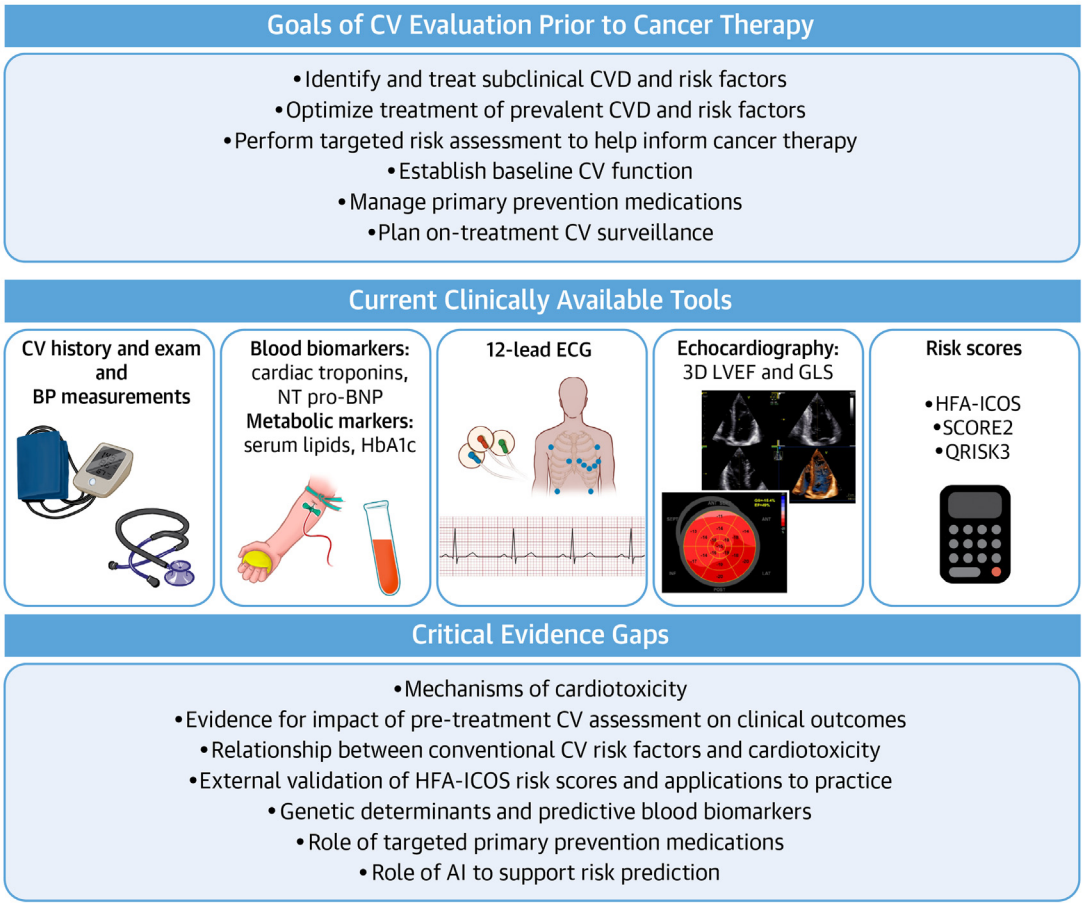
A major research priority in cardio-oncology is the refinement and validation of cardiotoxicity risk stratification based on the understanding of treatment-specific disease mechanisms to produce optimal personalized risk estimates. Initial results from novel biomarkers are promising; however, demonstration of their incremental value above and beyond existing inexpensive and easily collected metrics is essential before their incorporation into routine practice. Biomarkers offering higher predictive accuracy may enable more targeted, less frequent cardiac monitoring during treatment.

Existing evidence supports the value of monitoring interval changes in blood and imaging cardiovascular biomarkers for the early detection of cardiotoxicity. However, the stand-alone predictive value of these metrics pretreatment is uncertain. Implementing routine cardiac imaging and blood biomarker measurements for large cohorts of cancer patients, especially those at low risk, would mark a major departure from current practice, has the potential to delay cancer treatment, and would require significant health care investment. It is unclear whether a more pragmatic approach such as focusing resource-intensive assessments on higher-risk groups may be more acceptable in clinical practice. Developing evidence in this area should be coupled with health economic analysis to ensure recommendations are both feasible and judicious in using health care resources.

Research in cardio-oncology requires special considerations. Patient groups, treatment exposures, and individual circumstances are highly variable and dynamic, making it impossible to control all potential variables in research designs. Additionally, lengthy follow-ups are expensive and particularly challenging in cancer patients, which means that very “clean” observational studies are not possible, and most studies will inherently possess biases. Appreciating the limitations and strengths of these study designs is crucial for accurate interpretation of the results. Similarly, clinical trials face additional difficulties, including competing for recruitment with cancer clinical trials, limited sample sizes, and brief follow-up durations. Given the diverse nature of the patient population and the complexities of research questions, a concerted international, cross-disciplinary effort is needed to bring together data sets for high-quality observational, registry, and clinical trial research. Collaborative efforts to standardize outcome definitions and treatment classifications are critical steps toward achieving this.

Clinicians and researchers must remain vigilant and insist on proper scientific scrutiny of all presented research and recommendations. The upcoming decade offers a significant opportunity for

CENTRAL ILLUSTRATION **Overview of Pretreatment Evaluation Recommendations, Assessment Tools, and Evidence Gaps**



Raisi-Estabragh Z, et al. JACC CardioOncol. 2024;6(5):631-654.

Cardiovascular input is essential before cancer treatment for several purposes, including risk stratification for cardiotoxicity, optimizing the management of pre-existing cardiovascular conditions, and administering cardioprotective medications before potentially cardiotoxic cancer therapies. Although several international guidelines offer recommendations for baseline cardiovascular assessments and management of cancer patients, significant evidence gaps remain. These gaps include the need for developing and validating targeted genetic and blood biomarkers alongside specific risk stratification tools to support a personalized approach aimed at minimizing cardiotoxicity and improving long-term cardiovascular outcomes. 3D = 3-dimensional; AI = artificial intelligence; BP = blood pressure; CV = cardiovascular disease; CVD = cardiovascular disease; ECG = electrocardiogram; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

researchers to usher in a new evidence-based era that will shape the future of cardio-oncology care.

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