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EXPERT PANEL

Cardiovascular Considerations After Cancer Therapy

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

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ABSTRACT

Cancer survivors, particularly those treated with anthracyclines and chest radiation, face an elevated risk of cancer therapy–related cardiovascular toxicity. These complications affect not only physical health, but also life expectancy. Risk factors for cancer therapy–related cardiovascular toxicity include age at which cancer treatment was received, the use of (potentially) cardiotoxic cancer therapies, and the presence of concomitant cardiovascular risk factors. Current guidelines provide recommendations for cardiovascular surveillance after cancer therapy, including type and frequency. All cancer survivors are advised to undergo annual clinical screenings and optimization of cardiovascular risk factors. Those at higher risk should undergo additional cardiovascular testing. This document aims to summarize the available evidence, present practical recommendations, and outline existent gaps in the current literature regarding cardiovascular care after cancer therapies. (JACC CardioOncol. 2025;7:1–19) © 2025 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/).

Cancer survivors incur a 2- to 5-fold higher risk of mortality from cardiovascular disease compared with the general population.[1-3] The cardiovascular risk varies depending on underlying health conditions, age at treatment, cancer type, and the treatments received. Those who have completed cancer therapy require surveillance not only for cancer recurrences and secondary cancers but also for aggressive evaluation and treatment of long-term cardiovascular risks.[4-6] Some survivors present with cardiovascular risk factors (CVRFs) and cardiovascular disease before undergoing cancer

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ABBREVIATIONS AND ACRONYMS

ACEi = angiotensin-converting enzyme inhibitor(s)

ADT = androgen deprivation therapy

AF = atrial fibrillation

AI = aromatase inhibitor

ARB = angiotensin receptor blocker

BiTE = bispecific T cell engager

BTKi = Bruton's tyrosine kinase inhibitor

CAC = coronary artery calcification

CAD = coronary artery disease

CAR-T = chimeric antigen receptor T

CTR-CVT = cancer therapy–related cardiovascular toxicity

CVRF = cardiovascular risk factor

ESC = European Society of Cardiology

GDMT = guideline-directed medical therapy

GvHD = graft-versus-host disease

HCT = hematopoietic cell transplantation

HF = heart failure

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

LV = left ventricular

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular events

MCS = mechanical circulatory support

PI = proteasome inhibitor

RCT = randomized controlled trial

RT = radiation therapy

SGLT2 = sodium-glucose cotransporter 2

TKI = tyrosine kinase inhibitor

therapy, whereas others may develop these conditions during or after treatment, often after a long latency period (**Central Illustration**).

The age at which a cancer diagnosis is made is an important risk factor for the development of cardiovascular disease after cancer treatment. Three groups are distinguished: childhood, adolescent and young adult, and adult cancer survivors (**Table 1**). Attempting to stratify cancer survivors and associated cardiovascular risk, the 2022 European Society of Cardiology in collaboration with the International Cardio-Oncology Society created cardio-oncology guidelines. These guidelines emphasize that cardiovascular risk is dynamic across the cancer continuum and should be continually re-evaluated.[7] The risk is highest and most unique during cancer therapy but remains elevated compared with the general population even after cancer treatment.

The relative risks of cardiovascular disease and CVRFs are higher in younger patient populations, whereas the absolute risks tend to be higher in the older populations. Additionally, the type of cardiovascular disease and CVRFs that patients develop after cancer therapy varies by the treatments used across different age groups (**Table 1**).[8] Therefore, focusing on risk stratification, monitoring, and treatment remains imperative after cancer therapy. This review aims to evaluate the current evidence and highlight the gaps in both evidence and guideline recommendations for managing cardiovascular disease in cancer survivors who have completed their cancer therapy.

GENERAL POST-TREATMENT CONSIDERATIONS: CARDIOVASCULAR DISEASE RISK ASSESSMENT, SURVEILLANCE, AND PREVENTION

Recommendations:

- Educate all cancer survivors about the potential future risks of cardiovascular disease and the importance of identifying, preventing, and treating traditional CVRFs.
- Some cancer survivors, particularly those at higher risk due to treatment at a young age, high anthracycline dose, and/or chest radiation therapy (RT), may benefit from surveillance imaging.

HIGHLIGHTS

- Cancer survivors, depending on their age, risk factors, and types of cancer therapy received, are at an elevated risk of cancer therapy–related cardiovascular toxicity.
- All cancer survivors require annual screening and optimization of CVRFs, whereas those at higher risk should undergo further cardiovascular testing, such as cardiac imaging.
- Further research should focus on defining optimal long-term monitoring and surveillance strategies, and assessing the associated cost effectiveness of these strategies.

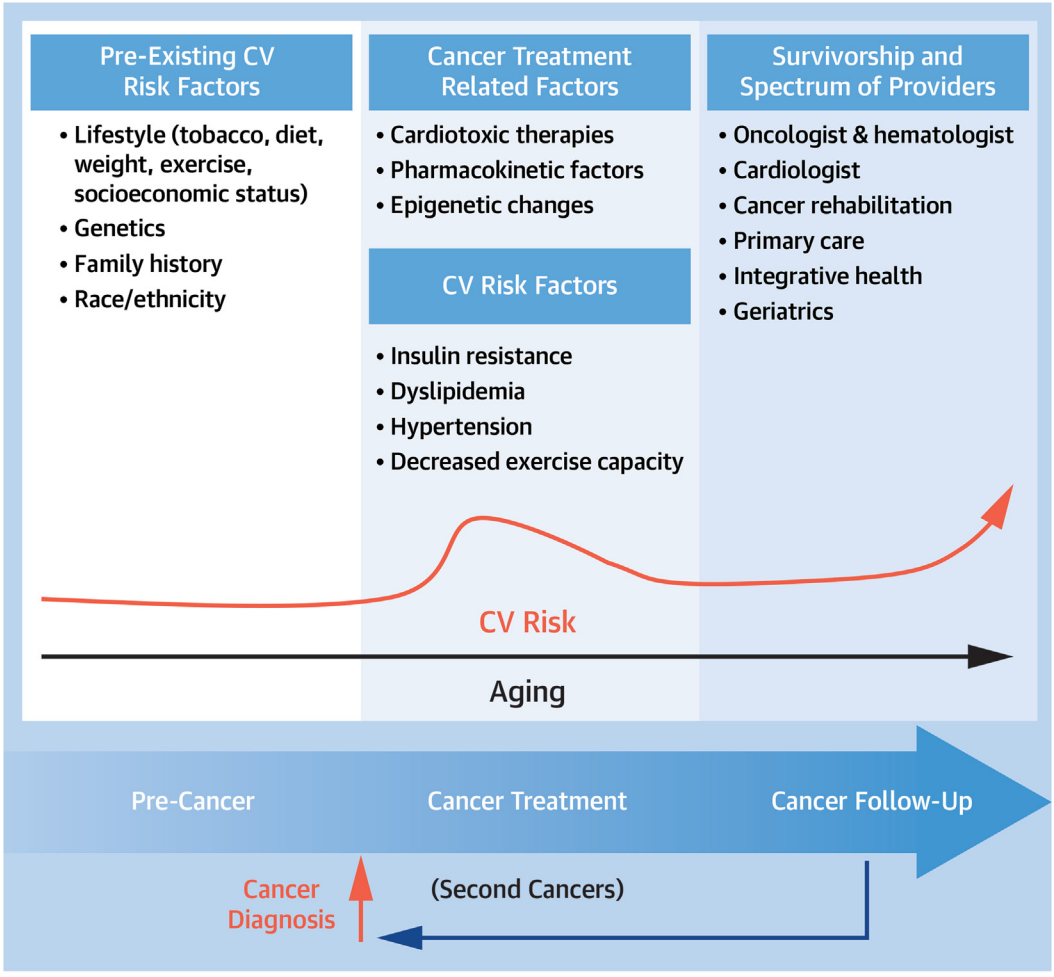
Gaps in knowledge:

- Understanding the risk of true de novo cardiovascular disease after cancer therapy completion by therapy type remains unknown.
- Developing risk prediction models to determine the risk of cardiovascular disease after cancer therapy, especially in certain populations with platinum agents or immunotherapy, is needed.
- Clarifying the timing, type, and frequency of screening cardiovascular tests to detect subclinical or asymptomatic cardiovascular diseases is needed.
- Determining the cost effectiveness of potential screening strategies, such as imaging, biomarkers, and the use of cardiac protective medications, particularly for low-risk populations (eg, those receiving trastuzumab without anthracyclines), remains unknown.

Cardiovascular disease in cancer survivors presents a significant risk of morbidity and mortality, and ideally should be prevented in the first place.[9-12] Although risk-based prevention strategies are appealing, their development is hindered by the lack of adequate data sets for derivation and external validation cohorts, incomplete capture of confounders, limited follow-up durations, and the broad spectrum of event types, with cancer-related mortality as a competing risk.

Assessment tools have been developed for pediatric cancer survivors to determine the risks of heart failure (HF), ischemic heart disease, and stroke risk by age 50 years; however, these tools do not assess risks over their entire lifetime.[13,14] Other simpler risk models for this group, based primarily on treatment

CENTRAL ILLUSTRATION Cancer Trajectory Across the Lifespan



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Prior to a cancer diagnosis, individuals have a variety of pre-existing cardiovascular risk factors. They experience diverse cancer treatment related effects through their cancer treatment; this requires an integrative and collaborative approach both during and after treatment. Within this trajectory, they are aging, and remain at risk for future cardiovascular and cancer events.

regimens, lack the desired rigor[15] (Table 2). In adult cancer patients, significant knowledge gaps still exist in approaches to cardiovascular disease risk stratification.

Traditional cardiovascular risk tools such as the ASCVD Risk Score and SCORE underperform because they fail to consider the impact of cancer therapies on cardiovascular risk and the competing risk of cancer-related mortality. Specific risk scores developed for breast cancer patients, such as BRisk (age and clinical risk factors) and CHEMO-RADIAT (HF, hypertension, elderly, myocardial infarction/peripheral artery occlusive disease, obesity, renal failure, abnormal lipid profile, diabetes mellitus, left breast radiation, anthracycline dose, and transient ischemic attack/stroke),[16] aim to predict long-term cardiovascular disease outcomes. However, these do not account for various cancer types and their distinct treatments.[16,17]

The 2022 European Society of Cardiology (ESC) cardio-oncology guidelines endorse the ESC/International Cardio-Oncology Society proformas for risk stratification of patients receiving 7 common classes of cancer therapy into categories ranging from low to very high risk for cancer therapy-related cardiovascular toxicity (CTR-CVT) (Table 2). These proformas,

TABLE 1 Cancer Survivor Groups Based on Age at Diagnosis

Cancer Group	Most Common Cancers	Related Cancer Therapies With Direct and Indirect Cardiovascular Risk	Related Types of Long-Term Cardiovascular Risk	Related Management Recommendations	Shortcomings, Challenges, Gaps
Childhood, <15 y	Leukemias, brain/CNS tumors, lymphomas, neuroblastoma, kidney tumors, malignant bone tumors	Anthracycline, chest radiation, brain radiation	Cardiomyopathy, radiation heart disease, growth hormone deficiency, obesity, metabolic syndrome	At least annual screen for CVRFs Optimal CVRF control Monitoring of growth and BMI charts Exercise recommendations Begin cardiomyopathy surveillance 2 y after treatment, continuing every 2-5 y for those at high and moderate risk, respectively[a] Cardiology consultation for those with asymptomatic LV systolic or diastolic dysfunction	Need for intensified surveillance and specific types needed for high-risk individuals Diversities and disparities Transition of follow-up care Lack of risk calculators for long-term adult survivors of childhood cancers Development of strategies to empower cancer survivors to advocate for their cardiovascular health
Adolescent and young adult, 15-39 y	Brain/CNS tumors, lymphomas, leukemias, malignant bone tumors, thyroid cancer, gonadal (testicular and ovarian) germ cell tumors, and breast cancer	Anthracycline, chest radiation, brain radiation, cisplatin, bleomycin	Cardiomyopathy, radiation heart disease, growth hormone deficiency, obesity, metabolic syndrome, vascular/coronary artery disease	At least annual screen for CVRFs Optimal CVRF control Exercise recommendations Counsel against drug, tobacco, and alcohol use Begin cardiomyopathy surveillance 2 y after treatment, continuing every 2-5 y for those at high and moderate risk, respectively Cardiology consultation for those with asymptomatic LV systolic or diastolic dysfunction	Identification of high-risk individuals Diversities and disparities Transition of follow-up care Development of strategies to empower cancer survivors to advocate for their cardiovascular health
Adult, >39 y	Breast and prostate cancer, lung and colorectal cancer, bladder and uterine cancer, and melanoma	Anthracyclines, chest radiation, antihormonal treatment, angiogenesis inhibitors, immunotherapies	Cardiomyopathy, radiation heart disease, hyperlipidemia, metabolic syndrome, hypertension, vascular/coronary artery disease	At least annual screen for CVRFs Optimal CVRF control Exercise recommendations Counsel against drug, tobacco, and alcohol use Conduct cardiomyopathy surveillance at years 1, 3, and 5 for asymptomatic individuals at high risk Conduct cardiomyopathy surveillance every 5 y for asymptomatic individuals at moderate risk Cardiology consultation for those with asymptomatic LV systolic or diastolic dysfunction	Identification of high-risk individuals Large spectrum of potential toxicities Low absolute incidence of some late toxicities Cost effectiveness of screening recommendations Diversities and disparities Integration of other providers into survivorship care Development of strategies to empower cancer survivors to advocate for their cardiovascular health

[a]Cardiomyopathy surveillance is not recommended for childhood, adolescent, and young adult cancer survivors at low risk.[11,18]

BMI = body mass index; CNS = central nervous system; CVRF = cardiovascular risk factor; LV = left ventricular.

developed predominantly based on expert consensus, serve as an important foundation and tool for clinicians. However, external validation is critical, especially to assess the proformas' ability to accurately identify lower risk patients.[18] For example, in the SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) study, risk stratification did not differentiate CTR-CVT incidence among lower-risk patients.[19]

Pediatric, adolescent, and adult cancer survivors who developed cardiovascular disease during cancer therapy will likely require long-term cardiovascular follow-up. Initially, this may be more frequent (annually) depending on recovery and the stability of outcome parameters (**Central Illustration**). For pediatric and adolescent cancer survivors without cardiovascular disease during therapy, cardiomyopathy surveillance should follow the International Late Effects of Childhood Cancer Guidelines Harmonization Group recommendations.[15] In adults without cardiovascular disease during cancer therapy, routine cardiovascular disease surveillance should be tailored based on the specific risks associated with cancer therapy, individual patient risk, and knowledge about the timing of onset for CTR-CVT. The ESC guidelines recommend that surveillance of adult cancer patients consider risks within the first year after cancer therapy and continue into the long-term follow-up.[7] Risk assessments within the first year after treatment are crucial for therapies such as anthracyclines, where effects can manifest shortly after therapy ends.[20,21] By contrast, therapies such as chest-directed radiation, which have delayed side effects, may allow for assessments to be conducted

TABLE 2 Risk Characteristics of Cancer and Cardiovascular Disease in Cancer Survivors per 2022 ESC Cardio-Oncology Guidelines

Risk Category	Risk Characteristics for Childhood, Adolescents, and Young	Risk Characteristics for Adults
Low risk	• RT <5 Gy MHD • Doxorubicin <100 mg/m^2	• Low baseline cardiovascular toxicity risk and normal end-of-therapy cardiac assessment • Mild CTR-CVT during therapy but recovered by the end of cancer therapy • RT <5 Gy MHD • Doxorubicin <100 mg/m^2
Moderate risk	• Doxorubicin 100-249 mg/m^2 • RT 5-15 Gy MHD • RT <5 Gy MHD + doxorubicin ≥100 mg/m^2	• Moderate baseline cardiovascular toxicity risk • Doxorubicin 100-249 mg/m^2 • RT 5-15 Gy MHD • RT <5Gy MHD + doxorubicin ≥100 mg/m^2
High risk	• Doxorubicin 250-399 mg/m^2 • RT >15-25 Gy MHD • RT > 5-15 Gy MHD + doxorubicin 100 mg/m^2	• High baseline cardiovascular toxicity risk pretreatment • Doxorubicin 250-399 mg/m^2 • RT >15 to 25 Gy MHD • RT >5-15 Gy MHD + doxorubicin 100 mg/m^2 • Poorly controlled CVRF
Very high risk	• Doxorubicin ≥400 mg/m^2 • RT >25 Gy MHD • RT >15 Gy MHD + doxorubicin ≥100 mg/m^2	• Very high baseline cardiovascular toxicity risk • Doxorubicin ≥400 mg/m^2 • RT >25 Gy MHD • RT >15 Gy MHD + doxorubicin ≥100 mg/m^2 • Symptomatic or asymptomatic moderate-to-severe CTR-CVT during treatment

CTR-CVT = cancer therapy-related cardiovascular toxicity; ESC = European Society of Cardiology; MHD = mean heart dose; RT = radiation therapy.

after the first year.[22] These recommendations are consistent with current oncology guidelines,[23] which advise cardiac function assessment in the first year after anthracycline treatment for patients at high cardiovascular risk.

Surveillance echocardiograms early during survivorship are recommended after treatment with trastuzumab and other human epidermal growth factor receptor 2 (HER2)-targeted monoclonal antibodies, though this practice has not been widely adopted in clinical practice, and its value has been questioned.[24] The risk is notably higher in patients who have received both anthracyclines and trastuzumab. However, it is less clear whether implementing these screening recommendations improves outcomes or is cost effective for those who received trastuzumab alone **Table 3**. Currently, there are no established recommendations for cardiovascular disease screening after treatment with other drugs like Bruton's tyrosine kinase inhibitors (BTKi), platinum-based agents, proteasome inhibitors (PIs), and immune checkpoint inhibitors (ICIs).

Clinicians should educate all cancer survivors about the potential future risk of cardiovascular disease and the importance of recognizing and managing CVRFs. It is crucial for survivors to understand how to identify typical cardiovascular symptoms, and the necessity of promptly reporting such symptoms to their primary practitioner.

Patients should also be informed about the benefits of annual physician visits for monitoring cardiovascular disease risk factors, such as blood pressure, cholesterol, blood sugar, and weight management. The value of lifestyle modifications, such as smoking cessation, healthy diet, and regular exercise cannot be overstressed. These changes not only support good long-term cardiovascular health but may also help reduce both primary and secondary cancer risks.

Clinicians should provide exercise guidelines, encourage compliance, and re-emphasize these concepts at every visit. Additionally, when available, cardio-oncology rehabilitation programs, supported by a corresponding American Heart Association scientific statement,[25] should be utilized. These programs are designed to improve cardiorespiratory fitness, enhance cardiovascular health, and reinforce these preventive efforts.

TREATMENT-SPECIFIC CONSIDERATIONS

ANTHRACYCLINES

Recommendations:

- Cancer survivors exposed to anthracyclines require long-term cardiovascular risk reduction, including optimal control of risk factors such as hypertension.

Gaps in knowledge:

- The incidence and natural course of cardiomyopathy with newer cancer protocols that implement lower doses of anthracyclines remain unknown.

TABLE 3 Future Needs in Cardiovascular Surveillance of Cancer Survivors

Recommended Pursuits to Address Current Gaps
• Develop optimal cardiovascular surveillance programs after cancer treatment, focusing on research into risk stratification, efficacy, and frequency of screening protocols.
• Identify optimal modalities and strategies for long-term surveillance, including the use of biomarkers, to screen survivor populations for complications of cancer therapies, especially those at long-term risk from treatments like anthracycline chemotherapy and mediastinal radiation.
• Advance research on primary preventive cardiovascular strategies for long-term cancer survivors, including the implementation of risk stratification calculators.
• Establish large cardio-oncology registries to collect data on diverse patient populations undergoing current era cancer treatments.
• Application of artificial intelligence and other new data analytics to identify cancer patients at risk of therapy-related cardiovascular toxicity, evaluate their responses to specific cardioprotective interventions, and assess long-term risk and safety of discontinuing cardiovascular therapies initiated during cancer treatment.

- The diagnostic yield of lifelong serial surveillance for populations exposed to anthracyclines on a large scale has yet to be determined.
- Cost-effective approaches are needed to identify individuals who will develop or have developed anthracycline-induced cardiomyopathy.
- Optimal treatment approaches for anthracycline cardiomyopathy, beyond the standard of care, need clear definition regarding necessity and, if needed, the types of treatments required.

Anthracyclines are used predominantly in individuals with leukemia, lymphoma, breast cancer, and sarcomas. These drugs lead to dose-dependent cardiomyopathy, with the highest risk among those who received more than 250 mg/m^2. Although less common, cardiomyopathy can occur at lower doses.[23] Although some risk occurs during treatment, anthracyclines may predispose individuals to a lifetime risk of CTR-CVT. Most CTR-CVT cases occur within 1 year of treatment completion, whereas late cardiotoxicity, emerging more than a year after treatment, occurs in 1.5% to 5% of patients, with rare reports surfacing decades later.

Risk factors for long-term anthracycline-related cardiotoxicity include advancing age, concomitant chest radiation, and prior CVRFs, such as hypertension, moderate-to-severe valvular heart disease, coronary artery disease (CAD), and abnormal or low-normal systolic function.[7] In a nested case (n = 91) control (n = 278) study of Hodgkin lymphoma survivors with moderate or severe HF, anthracycline exposure increased the risk of HF by a factor of 2.83 (95% CI: 1.43-5.59). The 25-year cumulative risks of HF following mean left ventricular (LF) radiation doses of 0-15 Gy, 16-20 Gy, and ≥21 Gy were 4.4%, 6.2%, and 13.3%, respectively, for patients treated without anthracycline-containing chemotherapy. By contrast, these risks were 11.2%, 15.9%, and 32.9%, respectively, for patients treated with anthracyclines,[26] suggesting an interaction between the receipt of anthracyclines and radiation.

In a Danish study of non-Hodgkin lymphoma survivors, the cumulative incidence of cardiovascular complications was 12% at 5 years and rose to 22% at 10 years.[27] The risk of chronic HF was more than 5-fold higher and the risk of stroke was 80% higher compared with the general population.[27] Non-ischemic cardiomyopathy occurred more frequently than CAD and ischemic cardiomyopathy.[27] More recent studies indicate a decline in cardiovascular complications in the modern treatment era, attributed to changes in protocols that involve less use of anthracyclines and radiation, alongside better management of CVRFs and survivorship care.[28] If anthracycline-induced systolic dysfunction is detected late and left untreated, it can progress to symptomatic HF.[29]

HER2-DIRECTED THERAPIES.

Recommendations:

- Cancer survivors treated with trastuzumab, particularly those who also received anthracyclines, should undergo long-term cardiovascular risk management.

Gaps in knowledge:

- The long-term cardiomyopathy risk associated with agents directed at HER2, particularly newer agents such as trastuzumab antibody-drug conjugates, has yet to be fully determined.
- The appropriate frequency of cardiac function surveillance during and after HER2-directed therapy needs to be clearly defined.

HER2 is overexpressed in approximately 25% of all breast cancers, where the use of trastuzumab-based therapies remains the standard of care. Although studies suggest that cardiotoxicity from trastuzumab is reversible, as it usually does not cause cardiac myocyte death, further data indicate an elevated risk for long-term cardiovascular disease in those who have received trastuzumab, especially in combination with anthracyclines. For example, in the HERA (Herceptin [Trastuzumab] in Treating Women With Human Epidermal Growth Factor Receptor [HER] 2-Positive Primary Breast Cancer) trial, CTR-CVT occurred in 7.2% in the 2-year trastuzumab arm and 4.1% in the 1-year arm, at a median follow-up of 8 years. Additionally, the NSABP B-31 (Doxorubicin and Cyclophosphamide Plus Paclitaxel With or Without Trastuzumab in Treating Women With Node-Positive Breast Cancer That Overexpresses HER2) trial observed a 4.1%

incidence of CTR-CVT at a median follow-up of 7 years.[30,31]

In population studies of older adults, this risk is even higher.[32] However, in trastuzumab-based regimens that do not incorporate anthracyclines, the risk of CTR-CVT appears very low. For example, in the APT (Adjuvant Paclitaxel and Trastuzumab for Node-Negative HER2-Positive Breast Cancer) trial, which used paclitaxel and trastuzumab, 0.5% of participants experienced CTR-CVT at a median follow-up of 4 years.[33] Given that the risk of long-term cardiotoxicity is primarily related to the use of anthracycline and radiation rather than trastuzumab itself, long-term surveillance for individuals receiving trastuzumab depends more on associated risk factors such as anthracyclines, radiation, and age, and less on the trastuzumab exposure alone.

Newer trastuzumab therapies, such as antibody-drug conjugates (trastuzumab emtansine and trastuzumab deruxtecan) and tyrosine kinase inhibitors (TKIs) (lapatinib, neratinib, tucatinib), demonstrate less cardiac toxicity, with rates of CTR-CVT between 1.2% and 1.5%.[34] These medications do not appear to carry long-term cardiac toxicities. However, antibody-drug conjugates used in the curative settings pose new challenges; for example, trastuzumab deruxtecan is known to cause pulmonary fibrosis, necessitating ongoing monitoring for long-term toxicity.[35]

ENDOCRINE AND ANDROGEN DEPRIVATION THERAPIES.

Recommendation:

- It is essential to develop patient education strategies that include risk reduction, cardiovascular disease management, and prevention of CVRFs for all survivors who have received antiestrogen therapies or androgen-deprivation therapies (ADTs).

Gaps in knowledge:

- Additional research is needed to understand the long-term impact of ovarian suppression combined with aromatase inhibitors (AIs) on cardiovascular health in premenopausal breast cancer survivors.
- The biological basis for short-term elevation of cardiovascular risk in patients receiving ADT has not been defined.

ENDOCRINE THERAPIES. Two-thirds of breast cancer survivors receive antiestrogen therapy with AIs or tamoxifen. Studies have noted higher rates of hypertension, hypercholesterolemia, and ischemic cardiovascular disease in postmenopausal breast cancer survivors receiving AIs, suggesting that these medications may induce endothelial dysfunction.[36] A study of 15,815 breast cancer patients diagnosed between 2006 and 2012 demonstrated an increase in HF rates when treated with AI compared with tamoxifen.[37] This increased cardiovascular risk might be more related to the protective effects of tamoxifen used as a comparator in some studies.[38] Conversely, other research suggests that endothelial dysfunction can occur within 6 months of starting AIs.

Further, there are scant data on the long-term impact of combining ovarian suppression with AI on cardiovascular health in premenopausal breast cancer survivors; ongoing investigations aim to understand this impact (Cardiovascular Impact of Near-complete Estrogen Deprivation for Breast Cancer; NIH 5R01HL159393).[39] Additionally, the use of CDK 4/6 inhibitors, known to cause QT prolongation, now used in the adjuvant setting raises concern about their long-term cardiovascular impact, which has yet to be fully understood.[40]

Optimizing CVRFs in breast cancer survivors continues to be essential in the survivorship period (**Central Illustration**).

ANDROGEN DEPRIVATION THERAPY. In the United States, it is estimated there are 3 million prostate cancer survivors, nearly 50% of whom will be exposed to ADT during their treatment.[41] Additionally, these patients often receive treatments that further reduce testosterone signaling, such as androgen receptor signaling inhibitors (ARSi), including androgen receptor antagonists (enzalutamide, apalutamide, and darolutamide) and steroid synthesis inhibitors (abiraterone acetate). The resulting hypogonadal state from these treatments can significantly alter metabolic factors, augmenting CVRFs by increasing cholesterol levels, reducing insulin sensitivity, and increasing abdominal adiposity.[42]

Studies indicate that exposure to ADT increases the risk of cardiovascular events, including inducing endothelial dysfunction, increasing arterial stiffness, and potentiating the formation of atherosclerotic lesions, effects linked to low levels of both testosterone and 17B-estradiol.[43] These cardiovascular risks may persist for months to years beyond treatment cessation, continuing until testosterone levels return to noncastrate levels. Recovery times vary, with median times to testosterone recovery being 1.5 years after 6 months, 3.1 years after 18 months, and 5.1 years after 36 months of ADT.[44]

Population-based observational studies offer robust evidence indicating cardiovascular risks during and after ADT exposure in prostate cancer survivors.[45] By contrast, meta-analyses of randomized

controlled trials (RCTs) focusing on prostate cancer survivors with nonmetastatic disease, and varying ADT durations generally do not show a significant difference in cardiovascular outcomes between those exposed to ADT and those with no or deferred ADT exposure.[46] Both cohort studies and RCT meta-analyses lack data on outcomes in the context of testosterone recovery, complicating assessments of the long-term effects of previous treatments among survivors.

A phase 3 RCT comparing testosterone recovery rates and major adverse cardiovascular events (MACE) during treatment among prostate cancer patients treated with the gonadotropin hormone-releasing hormone (GnRH) agonist leuprolide and the GnRH antagonist relugolix for 12 months sheds light on these dynamics.[47] In a subset of 184 patients who discontinued treatment at 48 weeks, testosterone recovery 90 days after treatment cessation was higher in patients treated with relugolix compared with those treated with leuprolide (54% vs 3%; $P = 0.002$), suggesting a potential for a more rapid return to baseline metabolic state. Additionally, the rate of MACE was lower in patients treated with relugolix (HR: 0.46; 95% CI: 0.24-0.88) during treatment. However, these events were not reported after the completion of the 48-week study follow-up.

Finally, treatment with ARSi has been associated with negative cardiovascular effects, including hypertension and arrhythmia during treatment. Whether these effects persist after treatment cessation remains to be determined.

Strategies that systematically address reversible CVRFs, such as hypertension, diabetes, and obesity, are recommended. The European Society for Medical Oncology guidelines advocate for annual cardiovascular risk assessments to manage these conditions.[48,49] Although there are no specific risk calculators for long-term cardiovascular risk in those on ADT, approximately 67% to 90% of prostate cancer survivors have cardiovascular comorbidities or risk factors. Addressing cardiovascular health through the effective management of these reversible CVRFs can potentially reduce cardiovascular risk, regardless of prior ADT exposure.[47,49]

PLATINUM-BASED CHEMOTHERAPIES.

Recommendations:

- For cancer survivors exposed to platinum-based chemotherapies, it is crucial to manage reversible CVRFs and promote healthy lifestyle choices, such as dietary changes and regular exercise, to optimize cardiovascular health.

Gaps in knowledge:

- The ideal type, frequency, and intensity of cardiovascular screening, as well as its cost effectiveness for cancer survivors treated with platinum chemotherapies, remain unknown.

Long-term cardiovascular health implications of platinum-based therapy are primarily documented in testicular cancer survivors.[50] Although testicular cancer is rare, with an expected 9,190 cases in the United States in 2023, it is the most common cancer among men aged 14 to 44 years.[51] In the year after the completion of cancer-directed therapy, these survivors face an increased risk of stroke, myocardial infarction, and cardiovascular mortality.[52] A study involving over 15,000 patients with nonseminoma assessed the absolute excess risk of cardiovascular complications between those receiving chemotherapy and those receiving surgery without radiation.[52] These results indicated an increased cardiovascular mortality in those treated with chemotherapy (standardized mortality ratio: 1.36; 95% CI: 1.03-1.78), but not in patients who only underwent surgery (standardized mortality ratio: 0.81; 95% CI: 0.60-1.07) in the year following diagnosis.[53]

Further research in this area includes an analysis from the Danish Testicular database, which showed an increased risk of hypertension, hypercholesterolemia, and metabolic syndrome in patients more than 10 years after treatment with cisplatin-based chemotherapy.[50] Additionally, a comparison of metabolic parameters between 225 testicular cancer survivors treated at an outpatient cancer center in the Netherlands and 360 healthy controls found that survivors had nearly twice the odds of developing metabolic syndrome (OR: 1.9; 95% CI: 1.1-3.2).[54]

Management of cardiovascular health in testicular cancer survivors centers on the screening, diagnosis, and treatment of hypertension, hyperlipidemia, and metabolic syndrome.[55] Testicular cancer survivors seen in cardiology or cardio-oncology clinics may benefit from a more intensive approach, which includes assessing cumulative cisplatin doses and managing CVRFs to predict and mitigate the risk of cardiovascular complications. Although currently evidence to support the use of cardiac biomarkers or screening echocardiography in these survivors is limited,[56] it remains essential to manage reversible

CVRFs and promote healthy lifestyle choices, such as dietary changes and regular exercise.[55]

RADIATION THERAPY.

Recommendations:

- Education on CVRFs, along with their reduction and prevention, is essential for all survivors who have received radiation to the chest.
- It is recommended to optimally manage all modifiable CVRFs, targeting high-risk thresholds for lipid and blood pressure levels, in patients exposed to chest radiation.

Gaps in knowledge:

- Assessing the incremental cardiovascular risk associated with chest radiation in the current era, especially considering advancements in RT, remains necessary.
- The development and identification of biomarkers, parameters, and prediction models to effectively stratify the risk of radiation-induced heart disease, both overall and for its various aspects, is needed.
- Defining the ideal RT-specific cardiovascular preventative measures, including the appropriate types and frequencies of surveillance protocols, as well as therapeutic interventions, is necessary.

Over one-half of all cancer patients receive RT. In thoracic cancers, such as lung cancers, left-sided breast cancers, mediastinal lymphomas, and esophageal cancers, RT often results in incidental radiation exposure of the heart. This exposure increases the risk of radiation-induced heart disease, which may manifest as CAD, valvular dysfunction, autonomic dysfunction, pericardial disease, arrhythmia, and/or cardiomyopathy.[7]

Advances in RT techniques aim to reduce cardiac risks. These include motion management strategies such as gating or deep inspiration breath hold, 3-dimensional radiation planning, intensity-modulated RT, and proton therapy, all of which help minimize cardiac exposure and the amount of heart tissue receiving higher doses of radiation. Despite recent improvements and a general decrease in cardiac radiation exposure, evidence still suggests that no level of radiation to the heart is completely without risk, with potential for future increases in cardiovascular events.[57,58]

Studies have demonstrated a linear relationship between radiation doses to the heart and both cardiovascular dysfunction and survival.[59] In cases of breast cancer and lymphomas, research has shown an approximately 4% to 17% relative risk increase in cardiac events for every Gray (Gy) increase in mean heart dose.[57,60] For radiation-induced CAD, increases may not appear until 5 or more years after treatment.[60] In a more recent breast cancer series, patients with higher mean heart doses were found to have an increased risk of HF with preserved ejection fraction.[61] In lung cancer patients, who often receive higher doses of radiation to the heart, studies found a >10% incidence of grade 3 or higher cardiac side effects within first few years of treatment.[60]

Since 2020, numerous guideline and consensus statements have been published, providing recommendations for the prevention, diagnosis, and surveillance of radiation-induced cardiac dysfunction.[7,22,62,63] Patients facing the highest risk of increased cardiovascular events include those who receive the highest doses of heart radiation, those who undergo other potentially cardiotoxic systemic therapies, those treated at a young age, and those with pre-existing CVRFs at baseline.[57,64,65] Unfortunately, no biomarkers currently exist that can further stratify risk among these patients. Additionally, there are no current RT-specific secondary preventative pharmacologic measures available to reduce the risk of cardiovascular events in cancer survivors after treatment.

Optimization of modifiable CVRFs is recommended for all survivors who have undergone chest radiation, regardless of the radiation dose received. Patients at higher risk, typically those exposed to >30 Gy or those receiving lower doses >15 Gy combined with anthracycline exposure or other risk factors (**Table 2**),[7,60] should undergo transthoracic echocardiograms approximately 1 to 5 years after treatment and periodically thereafter. However, follow-up schedules vary among the guidelines,[60] and there is a lack of definitive evidence on the ideal surveillance protocols for these patients. For asymptomatic patients, noninvasive screening for CAD is advised 5 years after treatment in higher risk radiation categories, with subsequent screenings every 5 years.[22,60] The approach to imaging for lower-risk patients lacks consensus across guidelines, highlighting an area in need of further research.[22,60,66]

Recent consensus statements recommend assessing both pretreatment and posttreatment coronary artery calcification (CAC) to better assess risk and manage cardiovascular disease.[22,63] Although studies have demonstrated that CAC may predict future cardiac risk,[67] its widespread adoption is limited by uncertainties about how to effectively assess CAC in CT planning scans,[68] and the fact that most radiation planning scans are not used for diagnostic purposes.

IMMUNE CHECKPOINT INHIBITORS.

Recommendations:

- Vigilance for a diverse spectrum of possible cardiovascular toxicities is recommended with the expanding use of immunotherapy (ICI therapy).
- As immunotherapy is increasingly utilized with curative intent, enhanced vigilance and proactive monitoring for immune-related adverse events (irAEs) in cancer survivors are recommended.

Gaps in knowledge:

- The long-term impact of ICIs, especially when used in conjunction with chemotherapy, on CTR-CVT needs to be clearly defined.
- Improving risk prediction for cardiovascular toxicities associated with ICIs is necessary.
- Establishing optimal surveillance strategies—covering the frequency, intensity, and duration—for monitoring cardiovascular toxicities in cancer survivors treated with ICIs is essential.
- Determining the long-term significance and management implications of isolated cardiac biomarker elevations in patients undergoing ICI therapy remains a critical gap.

In the last several years, immunotherapy has significantly changed the landscape of cancer care, achieving notable advancements in lung cancer, melanoma, triple-negative breast cancer, and gynecologic cancers. However, irAEs are a challenging consequence, affecting almost every organ system while on therapy. ICI myocarditis has prominently featured in discussions on cardiovascular toxicities due to early reports of fulminant myocarditis carrying a high mortality risk (up to 60%).[69] Although these irAEs typically occur during treatment, recent studies indicate they can also occur in survivors after treatment completion, termed delayed immune-related events.

Noninflammatory cardiomyopathies, including takotsubo's, have been described.[70] However, the long-term progression of these conditions, including both myocarditis and other non-inflammatory, non-takotsubo cardiomyopathies, remain poorly understood. A study from Leuven, Belgium, listed HF as the most common cardiovascular toxicity associated with ICI therapy in the current era, with nearly one-half of the cases diagnosed after completion of ICI therapy.[71]

Other side effects include endocrinopathies that may indirectly affect the cardiovascular system, occurring both acutely and over the long term, such as adrenal insufficiency, thyroid disorders, diabetes.[72] An increased risk of acute coronary events has been pointed out.[73] Drobni et al[74] showed a 3-fold increase in the risk for cardiovascular events after the initiation of ICI therapy and a 3-fold increase in the rate of total aortic plaque volume progression with ICIs (from 2.1%/y to 6.7%/y). Calabretta et al[75] further outlined heightened 2-18F fluorodeoxyglucose (FDG) activity in the aorta, presumed to be atherosclerotic plaques. However, not all studies corroborate these findings; some investigations report no changes in the FDG-positron emission tomography signals or atherosclerotic plaques volumes, though plaque composition may alter.

Despite the advancements in cancer therapy and the rapid implementation of immunotherapies, understanding their long-term impact on cardiovascular health, especially when combined with traditional cancer treatments, remains vital. Currently, there are no data on routine post-therapy screening for ICI-related cardiovascular disease, nor is it clear how other cardioprotective medications might affect cardiovascular outcomes in this setting.

THERAPIES IN HEMATOLOGIC MALIGNANCIES

Recommendations:

- Implementing validated risk models to stratify hematopoietic cell transplantation (HCT) patients and their cardiovascular risk is recommended.
- Regular assessments and optimal management of traditional CVRFs after HCT are recommended.

Gaps in knowledge:

- The acute and long-term cardiovascular risk dynamics associated with emerging therapies such as chimeric antigen receptor T (CAR-T) and bispecific T cell engager (BiTE) remain unclear for survivors.
- Defining the long-term clinical value of cardiac biomarker and imaging assessments in patients undergoing CAR-T and BiTE therapies to inform clinical management over time is needed.
- Determining the appropriate type, frequency, and duration of ongoing imaging surveillance for hematologic malignancy survivors treated with TKIs, BTKi, and PIs are not well-studied and needs further investigation.

Patients with hematologic malignancies commonly present with CVRFs such as diabetes and overt diseases including HF, myocardial infarction, and stroke at diagnosis—rates higher than those observed in noncancer patients.[76] Shared risk factors between cancer and cardiovascular disease include clonal hematopoiesis of indeterminate potential (CHIP),[77,78] which involves mutations such as ASXL1, DNMT3A, JAK2, and TET2. These mutations not only increase the risk of hematologic malignancies but also correlate with higher incidences of coronary heart disease

and ischemic stroke.[77,79] In patients with acute myeloid leukemia who have received cancer therapy and harbor CHIP mutations, there is a higher risk of subsequent cardiovascular events and poorer survival outcomes.[9] Additionally, myeloproliferative neoplasms are associated with an increased risk of thrombotic complications, HF, and pulmonary hypertension.[80]

TYROSINE KINASE INHIBITORS. As the number of hematologic malignancy survivors continues to grow, many live on treatment, changing the context of survivorship. For example, TKIs[81,82] such as dasatinib, imatinib, and nilotinib have revolutionized the treatment of chronic myeloid leukemia, but they are also associated with significant cardiopulmonary toxicities, including vascular events, HF, pleural effusion, QT prolongation, and pulmonary hypertension. Survivors on long-term TKIs for chronic myeloid leukemia face an ongoing risk of subclinical pulmonary hypertension. Routine echocardiography is suggested for surveillance, yet there is scant guidance on the optimal frequency and duration of ongoing imaging surveillance for this patient population.[83]

Similarly, BTKi have transformed the treatment of B cell malignancies, yet they come with increased risk of atrial fibrillation (AF), bleeding, hypertension, and HF.[84] Management of BTKi-related AF involves assessing and treating modifiable CVRFs, such as alcohol use, diabetes mellitus, hypertension, obesity, and obstructive sleep apnea. Whereas beta-blockers are preferred for rate control, non-dihydropyridine calcium channel blockers and digoxin can interact with BTKi. Catheter ablation offers an attractive definitive treatment option for patients with recurrent AF who require ongoing BTKi therapy for their malignancy. However, decisions about anticoagulation are complex due to increased bleeding risk associated with BTKi. Emerging evidence suggests that second- and third-generation BTKi may be associated with a lower likelihood of cardiovascular events, though longer-term studies are required to confirm these findings.[82,85]

PROTEASOME INHIBITORS. PIs, commonly used as frontline treatment for multiple myeloma, are linked to hypertension, pulmonary hypertension, HF, arrhythmias, and ischemic heart disease. Among PIs, carfilzomib has the highest potential for cardiovascular toxicity.[86] Aging, a major factor contributing to proteasome dysfunction, further increases cardiovascular risks associated with these drugs.

According to the ESC's cardio-oncology guidelines, patients on PIs, particularly those treated with carfilzomib, should undergo echocardiography monitoring at baseline and every 3 cycles. If echocardiographic images are suboptimal or tissue characterization is needed, cardiac magnetic resonance is recommended. During the first cycle of treatment, elevated cardiac markers, such as natriuretic peptides, indicate a significantly increased risk—up to 36-fold—of cardiovascular events.[87]

For patients at high risk of cardiotoxicity, the use of angiotensin-converting-enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and beta-blockers, such as carvedilol and nebivolol, is advised. Statins may also be considered for their cardioprotective effects. Further, fluid management during PI infusion should be conservative to mitigate risk, and drug dosage reduction or discontinuation of the drug may be required depending on the severity of HF symptoms.[88]

CAR-T AND BiTE THERAPY. CAR-T, ICIs, and BiTEs have been increasingly utilized in both relapsed/refractory and frontline settings for treating leukemias and lymphomas.[89-91] Although immune-mediated cardiovascular effects are infrequent, they are recognized as immediate toxicities associated with these treatments.[92,93] A recent prospective single-center study involving 44 patients undergoing CAR-T therapy reported a MACE rate of <5%. In this study, a case of HF with preserved ejection fraction occurred on day 6 and an instance of AF occurred on day 7 after cell infusion, with no further events noted throughout the year-long follow-up period.[94] The long-term impact of these treatments on cardiovascular complications in cancer survivors remains an important question that should be answered by future prospective studies.

HEMATOPOIETIC CELL TRANSPLANTATION. Advances in HCT have led to a 10% improvement in survival each decade since the 1980s for patients with hematologic malignancies.[95,96] Currently, there are an estimated 300,000 HCT survivors living in the United States, a number expected to exceed 500,000 by 2030.[97] Despite these advances, HCT survivors continue to experience markedly higher mortality rates compared with the general population, including more than double the cardiovascular-related mortality rates.[96-103]

HCT survivors face a 4-fold greater risk of developing serious cardiovascular disease compared with the general population.[104,105] This heightened risk is attributed to the combination of cardiotoxic exposures before HCT, the conditioning therapies used during HCT, and the development of new HCT complications, including de novo CVRFs that emerge after

HCT.[106] For those treated with anthracyclines before HCT, additional exposure to high-dose cyclophosphamide during conditioning can compound cardiac injury.[106] Studies in patients undergoing autologous HCT for lymphoma have shown that cumulative anthracycline dose ≥250 mg/m^2 is associated with a 10-fold risk of HF in HCT survivors.[107,108]

Among allogeneic HCT patients, graft-vs-host disease (GvHD) can lead to additional microvascular complications due to endothelial infiltration of alloreactive cytotoxic T lymphocytes, suggesting an immunological mechanism for accelerated arterial disease.[106,109] The treatments used for GvHD—systemic corticosteroids and calcineurin inhibitors—can increase the risk of de novo CVRFs such as hypertension, diabetes, or dyslipidemia.[106,110] Moreover, patients with GvHD are more likely to demonstrate physical inactivity due to the disproportionate muscle atrophy, particularly seen in the lower extremity and back extensor muscles.[106]

Traditional cardiovascular disease risk calculators designed for the general population do not account for HCT-specific exposures and risk factors, resulting in an underestimation of cardiovascular disease risk in HCT survivors.[111] There are now validated risk models tailored to HCT patients. These models categorize survivors into low, intermediate, and high cardiovascular risk groups, with corresponding 10-year cardiovascular disease incidences of 4%, 10%, and 26%, respectively.[112] These models account for both cancer treatments, such as anthracycline and radiation exposure, and cardiovascular disease risk factors such diabetes, hypertension, and smoking.[113]

As the population of long-term HCT survivors grows, developing personalized prevention strategies becomes imperative. For survivors at high risk of cardiovascular disease due to prior exposure to cardiotoxic treatments and conditions like diabetes, aggressive management of blood glucose has been shown to reduce the risk of future cardiovascular events, similar to other high-risk populations.[114]

UNIQUE PATIENT POPULATIONS: CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCER SURVIVORS

Recommendations:

- Lifelong surveillance is recommended for childhood, adolescent, and young adult survivors at high to moderate risk for cardiomyopathy. This group is defined as those with anthracycline exposure ≥250 mg/m^2, ≥30 Gy chest RT, or a combination of ≥100 mg/m^2 of anthracyclines and ≥15 Gy chest RT.
- For survivors treated with lower doses of anthracyclines (<100 mg/m^2) and/or chest RT (<5 Gy), routine screening is typically not necessary.
- All childhood, adolescent, and young adult survivors are recommended to engage in lifelong conventional CVRF reduction and prevention strategies.

Gaps in knowledge:

- The long-term natural history of CTR-CVT, including the incidence, spectrum of disease burden, risk factors, and trajectories, remains undefined.
- Including diverse populations, particularly adult survivors, to assess the natural history of CTR-CVT is needed.
- Identifying optimal surveillance strategies for various risk groups, along with evidence for their effectiveness and cost efficiency, is needed.
- Defining target goals for traditional risk factor reduction (eg, blood pressure and lipid goals) for cancer survivors without pre-existing cardiovascular disease is necessary.
- Establishing models of care for the long-term follow-up of cardiovascular disease in cancer survivors to define responsibilities for ongoing care is crucial.

In childhood cancer survivors, cardiovascular complications such as cardiomyopathy/HF, CAD, stroke, arrhythmias, and valvular disease are leading causes of late morbidity and mortality.[115] Compared with age- and sex-matched individuals from the general population, survivors face a >4-fold risk of cardiac-related death, with the rate of excess cardiac death increasing after their fourth decade of life.[116] This increased burden of cardiovascular disease is attributed to exposure to cancer treatments like anthracycline and chest-directed RT at a young age.[115] The period of greatest risk for developing cardiovascular disease coincides with a decline in engagement in survivorship-focused follow-up care,[117,118] emphasizing the urgency to implement accessible risk-stratification tools that can identify high-risk survivors in the community setting.

There are now validated HF[13] and arterial disease[14] (ischemic heart disease, stroke) risk-prediction models that take into account clinical factors, such as age at diagnosis and sex, and treatment-related risk factors like anthracycline or radiation dose. These models facilitate the implementation of early screening and intervention strategies to mitigate the risk of clinically significant cardiovascular disease. In certain diseases such as anthracycline-related

cardiomyopathy, routine screening for asymptomatic cardiac systolic dysfunction (abnormal left ventricular ejection fraction [LVEF]) using 2-dimensional echocardiography has proven to be cost effective,[119,120] allowing for pharmacological and lifestyle interventions to slow progression to symptomatic disease.

Guidelines recommend lifelong surveillance for survivors at high to moderate risk for cardiomyopathy,[15] defined as those with anthracycline exposure ≥250 mg/m^2, or ≥30 Gy chest RT, or a combination of ≥100 mg/m^2 of anthracyclines and ≥15 Gy chest RT. Screening is not recommended for survivors treated with lower doses of anthracyclines (<100 mg/m^2) and/or chest RT (<5 Gy), due to the low risk of cardiomyopathy and the high psychosocial and financial burden of lifelong screening.[15]

Studies in survivors of childhood cancer have shown that conventional CVRFs such as hypertension, diabetes, and dyslipidemia are more prevalent and occur at younger ages compared with the general population.[115,121] In a study of nearly 35,000 5-year survivors, the absence of hypertension or diabetes was associated with a 30% lower overall mortality rate, including a 30% to 50% decrease in cardiovascular mortality.[116] Survivors treated with anthracyclines who also have hypertension face an exceptionally high risk of developing HF.[121] Non-oncology population studies have shown a clear benefit for cardiovascular disease risk reduction with aggressive blood pressure control[122,123]—a strategy worth considering for survivors at the highest risk for anthracycline-related HF. Engaging in guideline-recommended vigorous exercise (ie, ≥9 MET hours/week) has been associated with a 50% reduction in the risk of any cardiovascular event[124] and a 20% reduction in all-cause mortality[125] compared with those not meeting those thresholds. Trials are underway to examine the efficacy of comprehensive cardiovascular disease risk reduction strategies in survivors,[126,127] paving the way for the implementation of evidence-based clinical care to improve long-term outcomes in this rapidly growing survivor population.

MANAGEMENT OF CARDIOVASCULAR DISEASE AFTER CANCER THERAPY

Recommendations:

- Individuals who have completed cancer therapy and exhibit posttreatment CTR-CVT should be managed according to current societal guidelines.

Gaps in knowledge:

- Significant knowledge gaps remain regarding the management of CTR-CVT after the completion of cancer therapy.
- Defining the optimal treatment approach for survivors with persistent CTR-CVT is necessary.
- The optimal duration of guideline-directed medical therapy (GDMT) in survivors with prior CTR-CVT needs to be clearly outlined.
- It is crucial to define the optimal long-term monitoring and surveillance strategies and assessing the cost effectiveness of these strategies for survivors with prior CTR-CVT.

The ESC cardio-oncology guidelines[7] recommend that individuals with post-treatment CTR-CVT be managed according to the current societal guidelines for HF.[128,129] It is important to acknowledge that clinical trials in HF have historically excluded patients with cancer, and the limited data available for the management of CTR-CVT is based on observational studies.

GDMT FOR CTR-CVT. Cardinale et al[20] found that ACEI with or without beta-blockers led to an improvement in LV systolic dysfunction in patients with anthracycline cardiomyopathy. However, recovery was often prolonged and typically only partial (71%), with complete recovery occurring in 11% of cases; 18% of patients experienced no recovery at all.[20] Another study on childhood cancer survivors with anthracycline-induced CTR-CVT found that starting ACEI treatment 7 years after cancer therapy and continuing it for 10 years only resulted in transient improvements in LV dimensions, mass, wall stress, and fractional shortening during the first 6 years, followed by a progressive deterioration.[130] Notably, all patients who had symptomatic CTR-CVT before initiating ACEI either died or underwent cardiac transplantation, whereas 8 of 12 patients with initially asymptomatic CTR-CVT developed symptomatic HF.

Novel HF therapies, including angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors, are under evaluation for their potential benefits in individuals with CTR-CVT . A retrospective analysis from a multicenter registry from Spain showed that transitioning patients with CTR-CVT from ACEI/ARB to sacubitril-valsartan led to improved LVEF, reduced levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and enhanced functional status.[131] A study involving breast cancer patients with CTR-CVT showed similar benefits after transitioning from ACEI/ARB to angiotensin receptor-neprilysin inhibitors.[132] Although

clinical studies evaluating the efficacy of SGLT2 inhibitors in treating CTR-CVT are currently not available, preclinical and early clinical data suggest their potential benefits, including reductions in apoptosis, fibrosis, and the expression of inflammatory cytokines in anthracycline-treated myocytes.[133-135]

DEVICES AND ADVANCED HF THERAPIES FOR CTR-CVT. Device therapies, including implantable cardioverter-defibrillators for both primary and secondary prevention of sudden cardiac death, and cardiac resynchronization therapy, have proven equally effective in cancer survivors with CTR-CVT as in noncancer patients with other types of cardiomyopathy.[136,137] Advanced HF therapies, such as mechanical circulatory support (MCS) and cardiac transplantation, may also be considered for cancer survivors, especially those in sustained complete remission. An analysis from INTERMACS (the Interagency Registry for Mechanically Assisted Circulatory Support) demonstrated that patients with chemotherapy-associated cardiomyopathy who underwent MCS have an increased likelihood of bleeding after MCS and right ventricular failure and are less likely to undergo transplantation; however, their survival rates are comparable to those who underwent MCS for other etiologies.[138-140] Outcomes following cardiac transplantation are similar between patients with chemotherapy-associated cardiomyopathy and those with other causes of HF, though patients with radiation-induced restrictive cardiomyopathy did not fare as well.[141,142]

OPTIMAL DURATION OF GDMT. The optimal duration of GDMT in survivors with CTR-CVT and improved LVEF remains unclear. Societal guidelines recommend continuing GDMT indefinitely in HF patients with improved LVEF,[128,129] based on the findings of the TRED-HF trial (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy).[143] In this trial, 44% of patients who underwent phased withdrawal of GDMT developed recurrent LV dysfunction over 6 months of follow-up.[143] However, the TRED-HF trial did not include patients with prior asymptomatic, mild-to-moderate LV dysfunction (LVEF >40%), indicating a need for further study in this population.

In the SAFE-HEaRt trial (Cardiac Safety Study in Patients With HER2 + Breast Cancer),[144] which included patients with pre-existing mild LV dysfunction (LVEF 40%-49%) and HER2$^+$ breast cancer, the concomitant use of beta-blockers and ACEI/ARBs allowed the completion of HER2-targeted therapy. These findings were also supported by the SCHOLAR (Safety of Continuing Chemotherapy in Overt Left Ventricular Dysfunction Using Antibodies to Human Epidermal Growth Factor Receptor-2) study.[145] During long-term follow-up, the use of beta-blockers and ACEI/ARB followed clinical practice and was continued in most patients.[145] The ESC cardio-oncology guidelines acknowledge the lack of studies in this population and suggest a personalized approach where withdrawal of GDMT can be considered in patients with history of mild CTR-CVT and normalized LVEF.[7] In support of this approach, a recent pilot matched-cohort study of 20 women with HER2$^+$ breast cancer treated with anthracyclines and trastuzumab, who had recovered asymptomatic CTR-CVT (nadir LVEF = 40%-50%), showed that withdrawal of neurohormonal blockade (n = 10) did not result in worsening of LV function or global longitudinal strain and was similar to a matched group (n = 10) that continued neurohormonal blockers.[146] This finding needs to be validated in RCTs.

PREGNANCY AND CANCER SURVIVORS. Cancer survivors contemplating pregnancy require comprehensive pre-pregnancy counseling and cardiovascular evaluation, including echocardiography, electrocardiogram, and natriuretic peptides measurements.[7] Pregnancy presents unique challenges in cancer survivors with a history of CTR-CVT. A recent meta-analysis revealed that childhood and young adult survivors with a history of pre-pregnancy CTR-CVT had 47.4-fold higher odds of developing LV systolic dysfunction or HF during or after pregnancy.[147] Therefore, close monitoring and multidisciplinary management involving maternal-fetal medicine and cardiology are crucial for the care of these patients.

OTHER CONSIDERATIONS

Cardiovascular risk in cancer survivors is influenced by pre-existing conditions, direct cancer treatments, and indirect effects of those treatments. Indirect effects include lifestyle changes where many cancer survivors, particularly those with breast cancer and lymphoma, may experience weight gain, develop sarcopenia, have a reduced Vo_2 max, and develop CVRFs such as hypertension and hyperlipidemia that can predispose them to cardiovascular disease. Collaborating with cardio-oncology rehabilitation programs and community-based exercise programs is essential for optimizing the cardiovascular health of these individuals.

Cancer survivors have ongoing needs such as surveillance for cancer recurrences and secondary cancers, evaluation and treatment of long-term and late effects from cancer and cancer treatments including both medical and psychosocial consequences, and

adherence to health promotion recommendations.[4-6] During active treatment, care for many chronic conditions is often managed by the cancer care team; however, after treatment, the majority of cancer survivors transition back to primary care for these needs.[3] This transition is crucial and requires successful integration of care.

Successfully supporting cancer survivors requires innovative models of cancer survivorship care delivery. These should include a team-based approach that engages members of the cancer team, primary care providers, the cancer survivor, and their family members (**Central Illustration**). Such models also necessitate significant education and stratification concerning CVRFs, risk modification, and potential interventions aimed at reducing the morbidity and mortality associated with cardiovascular disease in cancer survivors after therapy.

CONCLUSIONS

With advancements in cancer care, the number of both pediatric and adult cancer survivors continues to grow, and these individuals remain at an elevated risk for cardiovascular morbidity and mortality. Utilizing advancing technologies, such as genomic tools and artificial intelligence, to enhance our understanding of risk stratification using real-world data will be beneficial in the future. Finally, recognizing and addressing the gaps in current literature is imperative for providing cost-effective, evidence-based, and equitable care.

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