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Cardioprotection in Patients at High Risk of Anthracycline-Induced Cardiotoxicity

JACC: CardioOncology Primer

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Anthracyclines form the backbone of many chemotherapy protocols and are frequently used with curative intent in lymphoma, childhood leukemia, breast cancer, and other solid tumors. The potential for anthracycline-related myocardial injury and development of left ventricular (LV) dysfunction and heart failure (HF) remains a concern. This short-form primer will focus on the evidence for cardioprotection strategies to mitigate anthracycline cardiotoxicity in high-risk patients.

NEW PERSPECTIVES ON THE INCIDENCE AND PREDICTION OF ANTHRACYCLINE CARDIOTOXICITY

Two recently published cardioprotection trials have provided details on the natural history of anthracycline cardiotoxicity using precise magnetic resonance imaging quantification of cardiac function up to 2 years following chemotherapy completion.[1,2] These trials altogether randomized 399 anthracycline-treated patients. Only 1 patient (0.2%) developed clinical HF, and the mean decline in LV ejection fraction (LVEF) was <3.5 percentage points in placebo-treated patients. The longer term clinical consequences of this LVEF decline are uncertain. The majority of patients in these studies would be categorized at low risk for anthracycline cancer therapy-related cardiac dysfunction (CTRCD) using the European Society of Cardiology (ESC) Heart Failure Association-International Cardio-Oncology Society risk assessment tool[3] recommended in the 2022 ESC cardio-oncology guidelines.[4] This tool incorporates age; baseline cardiac function; the presence of established coronary, hypertensive, or valvular heart disease; cardiovascular risk markers; and previous cardiotoxic treatment to provide a risk grading of low, medium, high, or very high for anthracycline CTRCD.[3] The strength of this recommendation (Class 2a, Level of Evidence [LOE]: C) reflects the need for validation of this tool and research on how risk assessment should inform management.

Low-risk patients may benefit from ongoing healthy lifestyle advice, as well as aggressive management of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and obesity. There is insufficient evidence to suggest that low-risk patients benefit from targeted cardioprotective pharmacotherapy before or during exposure to anthracycline-based chemotherapy. High-risk patients are underrepresented in trials and may benefit from cardioprotection strategies, including: 1) the use of medications with established roles in the treatment and prevention of HF and cardiovascular disease (CVD); and 2) the application of strategies to directly reduce anthracycline-induced cardiomyocyte injury, including the use of dexrazoxane and pegylated or liposomal anthracyclines.

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CONVENTIONAL CARDIOVASCULAR THERAPIES AND CARDIOPROTECTION

There is overwhelming evidence demonstrating the benefits of neurohormonal antagonists, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers, in the treatment of patients with HF with reduced ejection fraction. In this context, their benefits are derived primarily from effects upon neurohormonal activation, which arises as a secondary consequence of cardiac dysfunction. These agents have modest direct effects on cardiomyocytes and cause LV afterload reduction. They may not be the optimal agents for prevention of the direct cardiotoxic effects of anthracyclines, given that there may not be significant neurohormonal activation. A 2019 meta-analysis of 17 randomized trials including patients receiving anthracycline-based chemotherapy showed that patients receiving neurohormonal blockade had a 4% higher LVEF.[5] However, recent studies randomizing anthracycline-treated patients produced no strong evidence for cardioprotective effects of carvedilol (CECCY [Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity]),[6] candesartan (PRADA [Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy]),[1] or the combination of candesartan and carvedilol (Cardiac CARE).[7] Although the majority of patients enrolled in CECCY and PRADA would not be considered to be at high risk for CTCRD, Cardiac CARE excluded patients treated with low-dose anthracycline regimens and randomized only patients at higher risk, on the basis of troponin elevations during chemotherapy.[7] The 2022 ESC cardio-oncology guidelines give a Class 2a ("should be considered") (LOE: C) recommendation for preventive neurohormonal blockade in patients at high and very high risk for anthracycline CTRCD, recognizing the lack of randomized trial evidence for this strategy.[4] Many patients at high or very high risk for CTRCD will have established indications for treatment with neurohormonal antagonists, such as prior myocardial infarction, hypertension, and LV dysfunction. In these patients, treatment with neurohormonal antagonists should be optimized before anthracycline-based chemotherapy.

A propensity score-matched cohort study demonstrated that women prescribed statins had a lower risk for HF presentation after anthracycline chemotherapy for breast cancer.[8] Two recent moderately sized randomized placebo-controlled trials examining the cardioprotective effects of statins produced conflicting results.[2,9] Hundley et al[2] compared atorvastatin 40 mg with placebo and found no difference in mean LVEF decline 2 years after anthracycline-based chemotherapy for breast cancer or lymphoma in the PREVENT (Preventing Anthracycline Cardiovascular Toxicity With Statins) study. In contrast, the STOP-CA (Statins to Prevent the Cardiotoxicity From Anthracyclines) trial demonstrated a significant reduction in the primary endpoint of a 10 percentage point decrease to an LVEF <55% at 1 year in patients randomized to atorvastatin 40 mg compared with placebo (9% vs 22%; $P = 0.002$).[9] By selecting a categorical primary outcome, the STOP-CA investigators focused on the group of patients who potentially had the most to gain from cardioprotection with atorvastatin. In comparison with PREVENT, STOP-CA enrolled only patients with lymphoma receiving high-dose (>300 mg/m^2) doxorubicin. The difference in outcomes between the trials may at least partly reflect enrichment for a higher risk group in STOP-CA. The recently published SPARE-HF (Statins for the Primary Prevention of Heart Failure in Patients With Cancer Receiving Anthracycline Based Chemotherapy) trial also examined the effect of atorvastatin 40 mg vs placebo in 112 patients.[10] Inclusion criteria enriched for higher risk status and incorporated age, higher planned doses of anthracycline, prior LV dysfunction or borderline LVEF at enrollment, and other factors, including, diabetes, hypertension, obesity, smoking, and prior chest and mediastinal radiotherapy. The primary endpoint was LVEF (a continuous measure) by cardiac magnetic resonance imaging within 4 weeks of anthracycline completion. There was no difference in the primary outcome between groups. Direct comparison between SPARE-HF and STOP-CA is limited because of the short follow-up after anthracycline completion[10] in SPARE-HF.

ABBREVIATIONS AND ACRONYMS

CTRCD = cancer therapy-related cardiac dysfunction

CVD = cardiovascular disease

ESC = European Society of Cardiology

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LOE = Level of Evidence

LV = left ventricular

LVEF = left ventricular ejection fraction

PEG = polyethylene glycol

SGLT2 = sodium-glucose cotransporter 2

DIRECT CARDIOPROTECTION STRATEGIES

DEXRAZOXANE. Dexrazoxane is an iron-chelating agent that may reduce cardiotoxic reactive oxygen species generation following the interaction between iron and anthracycline. However, given that other iron-chelating agents do not appear to offer the same protection from anthracycline-associated cardiotoxicity, its cardioprotective activity may also come via competition with Adenosine triphosphate for binding sites on myocardial topoisomerase 2 beta. This prevents the formation of cardiotoxic anthracycline-myocardial topoisomerase 2 beta complexes.[11]

Data to support its use in adults come from small- to medium-sized trials conducted mainly in women with breast cancer and in patients with soft tissue sarcoma. Compared with placebo, dexrazoxane has been associated with fewer anthracycline-related HF events and preservation of LV function. In a combined report of 2 similar placebo-controlled trials of dexrazoxane in 534 women with advanced breast cancer, the incidence of HF or LVEF decline was 2.0 to 2.6 times higher with placebo.[12] Dexrazoxane is usually given as a 15-minute infusions administered 30 minutes prior to each anthracycline dose and usually 10 times the doxorubicin- or epirubicin-equivalent dose. It has been associated with myelosuppressive effects and injection site pain. The approved indication for dexrazoxane is in the treatment of patients with advanced breast cancer who have already received a cumulative dose of 300 mg/m^2 of doxorubicin (or 540 mg/m^2 of epirubicin) when further anthracycline treatment is required. Notably, however, most trials examining the use of dexrazoxane enrolled patients who had not previously received treatment with an anthracycline. The ESC cardio-oncology guidelines suggest that dexrazoxane should be considered (Class 2a, LOE: B) in adult patients with cancer who are considered to be at "high" or "very high" cardiovascular risk when anthracyclines are indicated.[4]

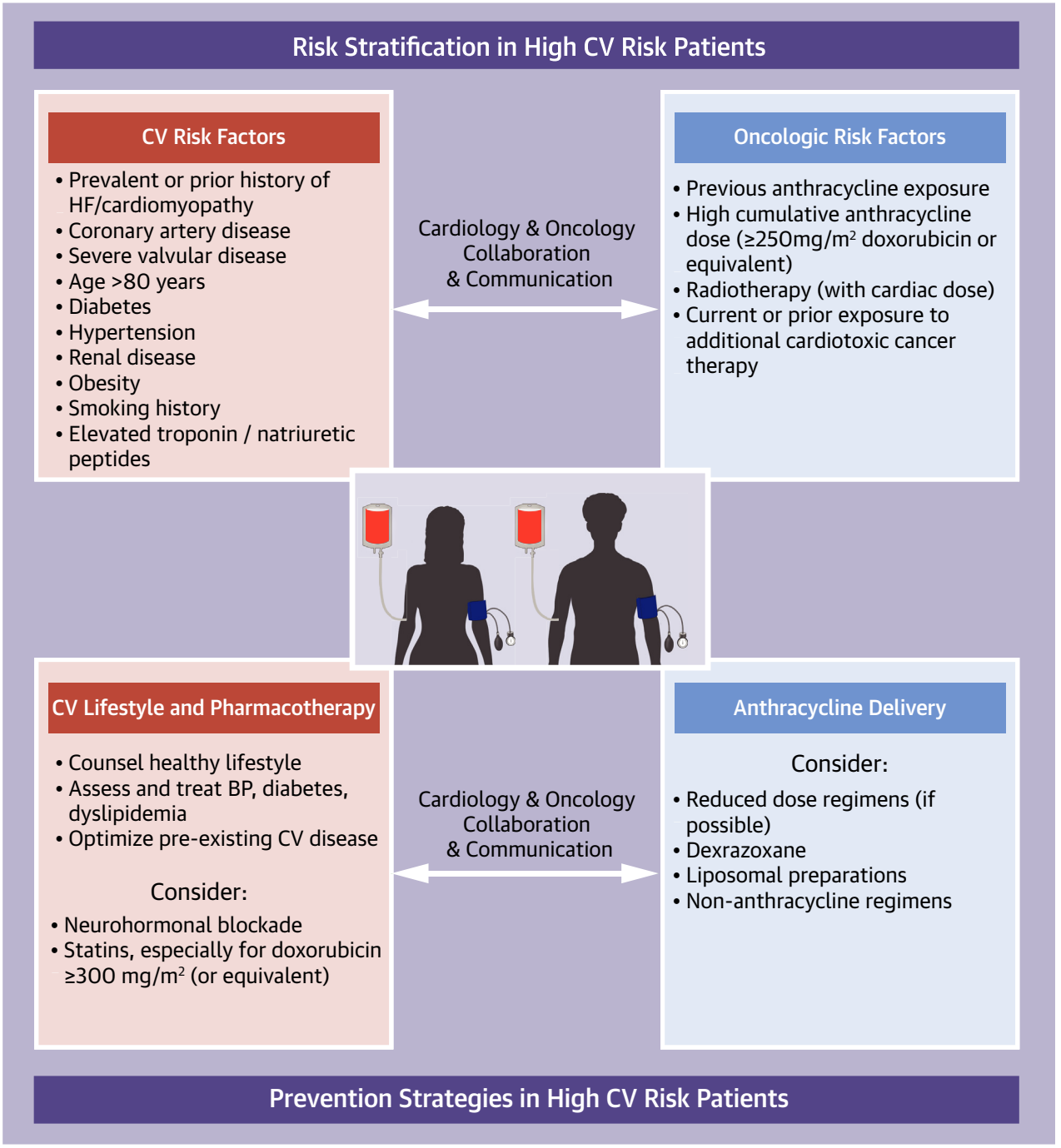
LIPOSOMAL PREPARATIONS. Liposomes are phospholipid vesicles and are established as a vehicle for drug delivery through encapsulation and stabilization of therapeutic compounds. The liposomal carrier particle can be further stabilized by adding polyethylene glycol (PEG). Liposomal and PEGylated liposomal doxorubicin do not escape the vascular space in tissues with intact tight junctions as found in the healthy myocardium. They preferentially exit in cancer tissue where capillary integrity is compromised. This reduces the volume of distribution of the anthracycline and prolongs its half-life. Studies of liposomal doxorubicin have demonstrated favorable toxicity profiles with less cardiotoxicity, nausea, vomiting, and myelosuppression compared with conventional doxorubicin. A 2015 network meta-analysis compared cardiotoxicity in patients with breast cancer treated with liposomal doxorubicin and conventional formulations of epirubicin.[13] Of 19 studies in the meta-analysis, 6 included patients treated with liposomal doxorubicin (n = 881). Compared with conventional doxorubicin, there was a statistically nonsignificant tendency toward lower odds of severe cardiotoxicity (symptomatic HF, cardiac death, myocardial infarction, and arrhythmia) in patients treated with liposomal doxorubicin (OR: 0.6; 95% CI: 0.34-1.07). The OR was also nonsignificant when epirubicin was compared with liposomal doxorubicin (OR: 0.95; 95% CI: 0.39-2.33). There was considerable heterogeneity of anthracycline dose in this meta-analysis, and the number of severe cardiotoxicity events was low. PEGylated and non-PEGylated liposomal doxorubicin are approved for patients with metastatic breast cancer. PEGylated doxorubicin is also approved for advanced ovarian cancer, multiple myeloma, and acquired immune deficiency syndrome-related Kaposi sarcoma. The 2022 ESC cardio-oncology guidelines give a Class 2a (LOE: B) recommendation for consideration of the use of liposomal doxorubicin preparations as a primary preventive cardioprotection strategy in patients at high and very high risk for CTRCD treated for the aforementioned cancers.[4] The guidelines also suggest using liposomal doxorubicin (Class 2b, LOE: C) in patients who have developed cardiac dysfunction with anthracyclines and when resuming anthracyclines represents the best option for achieving cure.

There has been at least theoretical concern that the tumoricidal effect of anthracyclines could be affected by the aforementioned strategies. Cancer outcomes have been scrutinized closely in dexrazoxane and liposomal anthracycline studies. For dexrazoxane, a recent Cochrane analysis found no evidence for a negative effect on cancer response, recurrence, and overall survival. In the context of poor-quality data, this review cautioned that there may be a signal for excess secondary malignancies associated with the use of dexrazoxane in pediatrics.[14] Importantly, however, no signal to suggest this adverse effect was seen in a subsequent analysis of long-term outcomes for >1,000 children included in dexrazoxane trials.[15] Irrespective, long-term follow-up and reporting of all-cause mortality with all cancer-related outcomes remains important in cardioprotection studies.

CURRENT PRACTICE AND FUTURE PERSPECTIVES

The optimal management of patients at high risk for anthracycline-induced CTRCD (**Figure 1**) relies on close collaboration between cardiology and oncology. After exploring options to minimize cardiotoxic drug use, treatment of existing cardiovascular conditions should be optimized before initiating anthracycline treatment. For patients with pre-existing CVD, this is likely to include neurohormonal blockade, statins, and proactive treatment of conventional cardiovascular risk factors, including hypertension and diabetes. However, in the absence of pre-existing CVD, evidence for the wider use of neurohormonal antagonists for primary prevention of CTRCD remains

FIGURE 1 Risk Stratification and Prevention for High-Risk Anthracycline CTCRD



BP = blood pressure; CV = cardiovascular; HF = heart failure.

weak. Dexrazoxane appears to reduce the development of cardiac injury and dysfunction, while liposomal doxorubicin should also be considered to reduce anthracycline-related myocardial injury.

The ideal cardioprotective strategy remains to be defined, but those that have direct effects upon the cardiomyocyte seem most attractive for further investigation. Ongoing studies, including with angiotensin-neprilysin

inhibitors as well as intriguing early data relating to potential cardioprotective effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors may be important. A retrospective study of patients with diabetes treated with anthracyclines noted a lower incidence of CTRCD and HF events in those treated with SGLT2 inhibitors compared with other diabetes drugs.[16] Preclinical models demonstrate potentially cardioprotective effects mediated via SGLT2 inhibitor-associated reductions in cardiac fibrosis, apoptosis, and inflammation in the context of doxorubicin exposure.[17] Trials of other pharmacologic cardioprotective strategies include assessments of ivabradine (NCT04030546), trimetazidine (EudraCT 2016-002270-12) and sulforaphane (NCT03934905).

Future development and trials of strategies to prevent anthracycline-induced CTRCD should focus on high-risk patients who have the most to gain and in whom treatment effects should be most discernible. However, accurate prediction of clinically meaningful CTRCD, at an individual patient level, remains challenging for the majority of high-risk patients who have normal baseline cardiac function. Biomarker and cardiac imaging monitoring provides prognostic information and is recommended in guidelines, but factors determining the transition between early asymptomatic and subclinical changes in these measures and subsequent development of clinical HF remain unclear.

For these reasons, future trials should seek to understand long-term clinical benefits of preventive cardioprotective interventions and the long-term impact upon incident HF and cardiovascular mortality. Given the advances in cancer-specific survival, and the continued importance of anthracycline-based chemotherapy, mitigating cardiotoxicity has never been more important.

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