Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy

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Summary:

Cardiotoxicity is now recognized as a leading cause of long-term morbidity and mortality among cancer survivors. This Guideline is intended to guide the care of cancer patients with established cardiovascular disease or those at risk of experiencing toxicities related to cancer treatment. It includes recommendations and important management considerations focusing on four main areas: identifying the high-risk population for cardiotoxicity; detection and prevention of cardiotoxicity; treatment of cardiotoxicity and a multidisciplinary approach to Cardio-oncology.

Abstract:

Modern treatment strategies have led to improvements in cancer survival, however these gains may be offset by the potential negative impact of cancer therapy on cardiovascular health. Cardiotoxicity is now recognized as a leading cause of long-term morbidity and mortality among cancer survivors. This Guideline, authored by a pan-Canadian expert group of healthcare providers and commissioned by the Canadian Cardiovascular Society (CCS), is intended to guide the care of cancer patients with established cardiovascular disease or those at risk of experiencing toxicities related to cancer treatment. It includes recommendations and important management considerations focusing on four main areas: identifying the high-risk population for cardiotoxicity; detection and prevention of cardiotoxicity; treatment of cardiotoxicity and a multidisciplinary approach to Cardio-oncology.

All recommendations align with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Key recommendations for which the panel provides a strong level of evidence include: (1) routine evaluation of traditional cardiovascular risk factors and optimal treatment of pre-existing cardiovascular disease be performed in all patients prior to, during and after receiving cancer therapy, (2) initiation, maintenance and/or augmentation of anti-hypertensive therapy be instituted per CHEP Guidelines for patients with pre-existing hypertension or for those experiencing hypertension related to cancer therapy and (3) investigation and management follow current CCS Heart Failure (HF) Guidelines for cancer patients who develop clinical HF or an asymptomatic decline in left ventricular ejection fraction during or after cancer treatment. This Guideline provides guidance to clinicians on contemporary best practices for the cardiovascular care of cancer patients.

Manuscript:

Approximately 40% of Canadians will be diagnosed with cancer in their lifetime. In the last 2 decades significant gains have been made in cancer detection and treatment. Between 2001 and 2010, age standardized mortality rates in women with cancer have declined by 1.2% per year and in men with cancer by 1.8% per year (www.cancer.ca). Improvement in survivorship, however, can come at a cost. While, the number of cancer survivors is increasing at twice the rate of new cancer diagnoses[1] extended follow-up from registry data, in selected populations, has shown that death from cardiovascular causes is more frequent than death from cancer[2,3]. Cardiotoxicity is now recognized as a leading cause of long-term morbidity and mortality among cancer survivors[4].

Cardio-oncology is a new discipline, which has developed in response to the need for optimal strategies to manage this at-risk population. This Position Statement, commissioned by the Canadian Cardiovascular Society (CCS), and endorsed by the Canadian Cardiac Oncology Network (CCON) is intended to optimize the care of cancer patients with established cardiovascular disease or those at risk of experiencing toxicities related to their cancer treatment.

The methodology and processes for development of this Position Statement are well described on the CCS website (www.ccs.ca). Recommendations are aligned with the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[5] system, which has been adopted by the CCS Guidelines Committee to promote quality and rigor in guideline development.

The objectives of this Position Statement are to provide recommendations on four key topics within cardio-oncology, specifically (1) the patient population at highest risk for cardiovascular toxicity related to cancer therapy, (2) strategies for detection and prevention of cardiotoxicity, (3) treatment of cardiotoxicity and (4) the need for a multidisciplinary approach in the management of those individuals who experience cardiotoxicity related to their cancer therapy.

1. Identifying the High Risk Population

Cancer & Cardiovascular Disease: The Multiple Hit Hypothesis

The multiple hit hypothesis is a framework for understanding cancer therapy-induced cardiac dysfunction. This framework suggests that traditional atherosclerotic risk factors and cardiac disease, in combination with cardiotoxic cancer therapy, can overwhelm cardiac reserve and lead to cardiac dysfunction (Figure 1)[6,7]. The childhood cancer survivorship study demonstrated that when hypertension and other cardiac risk factors operate on a cardiovascular system exposed to cancer therapy, survivors have a high risk of cardiac disease (Table 1)[8,9,10]. Such observations appear to validate this hypothesis as a suitable framework to understand, evaluate, prevent and treat cancer therapy induced cardiac dysfunction in adults.

Patient & Treatment Related Risk Factors For Cardiotoxicity from Cancer Therapy

Risk factors for cancer therapy induced cardiac dysfunction are well established for chemotherapy (e.g. anthracyclines), several targeted therapies (e.g. trastuzumab), and radiation therapy (Supplementary Tables S1-S6). Limited experience, variable definitions and inconsistent monitoring of cardiac function have hindered evaluation of risk factors for cardiotoxicity associated with newer cancer therapies. In general, patients with pre-existing cardiovascular disease, multiple or poorly-controlled cardiovascular risk factors, advanced age, and exposure to multiple cardiotoxic agents are at highest risk for cancer therapy induced cardiotoxicity. These toxicities, which may include left ventricular dysfunction, hypertension, myocardial ischemia, arterial thrombosis and arrhythmias are discussed in greater detail below.

A. Left Ventricular Dysfunction:

Risk factors for anthracycline induced heart failure (HF) and asymptomatic left ventricular (LV) dysfunction are well established (Supplementary Tables S1-S6). High-

risk patients include those at the extremes of age, non-Caucasians, women, and those with pre-existing cardiac disease and established cardiovascular risk factors. Anthracycline induced cardiotoxicity is largely irreversible, such that cumulative lifetime dose is one of the most important risk factors for LV dysfunction[11]; as such, contemporary chemotherapy regimens have evolved to minimize anthracycline exposure, particularly in the adjuvant setting. LV dysfunction associated with targeted therapies has been most extensively evaluated in the breast cancer population treated with trastuzumab; in the adjuvant setting, cardiotoxicity associated with these agents appears to be largely reversible[12,13]. At highest risk of LV dysfunction are those aged >50 years, with underlying heart disease or hypertension, baseline ejection fraction (EF) between 50-55%, and those who have received anthracycline therapy[14,15]. There is less information available on the short and long-term impact of novel targeted therapies (e.g. regorafenib) on cardiovascular health (Supplementary Tables S1-S6).

Baseline assessment of LV function, prior to treatment, with agents associated with the development of LV dysfunction, is a necessary component of established monitoring protocols for treatment related cardiotoxicity[16,17,18].

B. Hypertension:

A number of novel targeted cancer therapies are associated with hypertension (Supplementary Tables S1-S6). Therapy-associated hypertension was first described for the anti-angiogenic agent sunitinib and may relate to reduced function of nitric-oxide synthase, endothelial dysfunction and disruption of normal capillary function in non-tumor tissue[19,20] Other anti-angiogenic agents that may contribute to or worsen hypertension include: bevacizumab[21], regorafenib[22] in colorectal cancer, sorafenib[23] and axitinib[24] in renal cell carcinoma.

C. Myocardial Ischemia/Arterial Thrombosis:

Fluoropyrimidines, including 5-flurouracil and capecitabine, are the most well established cause of coronary arterial spasm leading to acute myocardial ischemia

during cancer therapy. Patients with pre-existing CAD and those receiving concomitant cisplatin therapy or prior mediastinal irradiation are at highest risk (Supplementary Tables S1-S6). Chest radiation is an important cause of accelerated CAD leading to increased long-term coronary events. However, with modern delivery techniques, the mean radiation cardiac volume exposure dose has decreased with a lifetime risk of major coronary events of 0.05%-3.5%. Risk factors for major coronary events among breast cancer survivors include exposure at a young age, combination with other cardiotoxic agents, and presence of traditional cardiovascular risk factors (Supplementary Tables S1-S6). There are early and late effects of chest radiation that lead to radiation induced heart disease (RIHD), including pericardial disease, myocardial fibrosis, cardiomyopathy, CAD, valvular disease and arrhythmias in the setting of myocardial fibrosis[25]. RIHD morbidity and mortality can be attenuated through careful control of cardiovascular risk factors, lifestyle modification, and avoiding cardiotoxic cancer treatment[26]. Anti-angiogenic agents (e.g. bevacizumab) have been associated with an increased incidence of arterial thromboembolism, especially in patients over age 65 with vascular disease[27]. As with LV dysfunction, the rate of arterial thrombotic events with this group of agents is less well established.

D. Arrhythmias:

Fluoropyrimidine therapy can cause ventricular arrhythmias as a consequence of myocardial ischemia. Novel cancer therapies, such as tyrosine kinase inhibitors, can prolong the QT interval leading to ventricular arrhythmias. High risk patients include those with congenital long QT syndrome, prior history of torsades de points, or baseline corrected QT (QTc) interval >450 ms. The use of supportive medications for cancer therapy (e.g. anti-emetics, anti-depressants) in combination with cancer treatments can lead to QT prolongation, and careful review of drug-interactions should be considered standard of care for all patients receiving cancer treatment.

Summary of Recommendations:

(1) We recommend evaluation of traditional cardiovascular risk factors and optimal treatment of cardiovascular disease, as per current CCS guidelines, be part of routine care for all patients prior to, during and after receiving cancer therapy. (Strong recommendation: moderate-quality evidence)

(2) We recommend that patients receiving potentially cardiotoxic cancer therapy undergo evaluation of left ventricular ejection fraction (LVEF) prior to initiation of cancer treatments known to cause impairment in LV function. (Weak recommendation: moderate-quality evidence)

2. Detection and Prevention of Cardiotoxicity

The most widely applied modality used to detect chemotherapy-induced cardiotoxicity is serial determination of LV function measured before and during cancer therapy[28]. The frequency of imaging varies according to the goals of cancer therapy (e.g. curative vs. palliative) and the type of therapeutic regimen used. The most commonly used marker of LV function is LV ejection fraction (LVEF), regardless of which imaging modality is used. Although the imaging modality chosen should adapt to local institutional expertise, transthoracic echocardiography (TTE) is the method of choice in view of its wide availability, reproducibility, and versatility. Moreover, TTE does not expose the patient to radiation and provides additional information on abnormalities of the right ventricle, pericardium, and heart valves[29].

There are currently no consistent recommendations on the frequency and modality with which cardiac imaging should be performed in patients at risk of LV dysfunction related to cancer therapy. Existing surveillance protocols are based on methodology from clinical trials and expert opinion[18]. In the case of trastuzumab however, there appears to be consensus in the adjuvant setting to assess LV function at baseline and every 3 months while on therapy[30].

Echocardiographic Evaluation

Although two-dimensional (2-D) measurement of LVEF has been widely used, its reproducibility is limited with the ability to reliably detect differences only greater than 10% in LVEF. Since this is the same magnitude of change that is used to adjudicate cardiotoxicity, the sensitivity of 2-D echocardiography for the diagnosis of chemotherapy-induced cardiotoxicity has been questioned [31,32,33].

Three-dimensional (3-D) echocardiography has emerged as the preferred technique for monitoring cardiac function and for the detection of cardiotoxicity[28]. Specifically in cancer patients, it has been shown to be more accurate for the detection of chemotherapy-induced cardiotoxicity[34] and has the best reproducibility[28].

For patients with sub-optimal image quality by 2-D echocardiography, the use of myocardial contrast agents may be useful[35]. Contrast agents should be used when two contiguous LV segments from any apical view are not visualized on non-contrast images[36].

Complementary Imaging Modalities for LVEF Assessment

There is extensive experience on the efficacy of radionuclide angiography scans (MUGA) for the identification of asymptomatic declines in LVEF among cancer patients. MUGA scans have consistently been shown to be more reproducible and accurate than standard 2-D echocardiography and have better correlations with 3-D imaging methods such as CMR and 3-D echocardiography [37,38,39]. This technique's inability to assess other cardiac structures, and the required radiation exposure, limit its widespread use.

In addition to echocardiography and MUGA scans, cardiac magnetic resonance imaging (CMR) may be useful for the non-invasive assessment of LV volumes and LVEF in the cancer setting[40,41,42]. CMR is considered the gold standard for the non-invasive assessment of LV systolic function[43]. In addition to accurate and highly reproducible determination of LV volumes and systolic function[44,45], CMR is also useful for the detection of myocardial edema, perfusion abnormalities, and cardiac fibrosis. The role

of these advanced CMR techniques in the assessment of cardiotoxicity is currently evolving.

As LV volumes and LVEF values differ significantly across techniques, the imaging modality and method used to determine LVEF should be maintained during treatment and for surveillance after treatment. Importantly, the digital images obtained to calculate LVEF regardless of imaging modality used should be compared with previous ones to minimize inter-observer variability.

Subclinical LV Dysfunction Using Novel Echocardiographic Techniques

Although LVEF remains the best surrogate for systolic function, it is a late marker of cardiotoxicity and one which is highly dependent on preload and afterload conditions. Detecting a decreased LVEF after cancer therapy may be a late finding; therefore, earlier markers of myocardial dysfunction are needed. Echocardiographic myocardial strain analysis, using 2-D speckle-tracking imaging, has shown promise in this regard. Global longitudinal strain (GLS) is a useful early marker predictive of a further decrease in LVEF[46,47,48]. For patients with available baseline strain measurements, a relative percentage reduction in GLS of <8% from baseline is not meaningful while those with >15% reduction from baseline are very likely to be abnormal[47].

Utility of Cardiac Biomarkers for the Early Detection of Chemotherapy-Mediated Cardiotoxicity

Although not routinely used in clinical practice, cardiac biomarkers are a reliable diagnostic tool for the early identification, and monitoring of cardiotoxicity. In the breast cancer setting, troponin (TnI) is a sensitive and specific marker for myocardial injury in chemotherapy-treated patients, and is an early predictor of LV systolic dysfunction[49,50]. Several studies have confirmed that the administration of anti-cancer drugs, specifically anthracyclines, induce subclinical myocardial injury, which can be associated with increasing levels of BNP[51]. Conversely, in a recent study evaluating HER-2 positive breast cancer patients treated with combined doxorubicin and

trastuzumab, TnT, C-reactive protien (CRP), and BNP were not able to predict early LV systolic dysfunction, which ultimately developed in 25% of the study population[47]. Further prospective studies are warranted to evaluate the potential use of cardiac biomarkers, including TnI and CRP, to identify a subset of patients at highest risk of developing cardiac dysfunction during and following chemotherapy[52,53].

Summary of Recommendations:

(1) We recommend the same imaging modality and method be used to determine LVEF prior to, during and after completion of cancer therapy. (Suggestion: low-quality evidence)

(2) We suggest that myocardial strain imaging be considered as a method for early detection of subclinical LV dysfunction in patients treated with potentially cardiotoxic cancer therapy. (Suggestion: low-quality evidence)

(3) We suggest that serial use of cardiac biomarkers (e.g. BNP, troponin) be considered for early detection of cardiotoxicity in cancer patients receiving cardiotoxic therapies implicated in the development of LV dysfunction (Weak recommendation: moderate-quality evidence)

Values and Preferences:

(1) We prefer the use of 3-dimensional echocardiography, whenever feasible and technically satisfactory, for LVEF determination due to enhanced reproducibility and accuracy.

Drug Therapy in Primary Prevention

Primary prevention strategies can be considered for HF, ischemia, arrhythmia, hypertension, or arterial thromboembolism. Primary prevention may include universal treatment of all patients receiving potentially cardiotoxic cancer therapy[54] or early detection of subclinical cardiac injury with targeted treatment[55]. The former is attractive because it has the potential to prevent any myocardial injury from occurring

and does not rely on repeated surveillance. The corollary however, is that primary prophylaxis may unnecessarily expose patients to treatment related side-effects in the absence of any clear benefit.

Much of the literature on prevention of HF has been generated in subsets of patients treated with anthracyclines[56]. This has included predominantly breast cancer, but also sarcoma, lymphoma, and leukemia patients. Drugs which have been tested for primary prevention include: beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and dexrazoxane. Overall, the evidence in support of primary prevention is quite limited due to small study size, variable follow-up and variable end-points; in some studies patients already had HF at the time of medication initiation. However, an important strength of the limited data is that it predominantly comes from randomized controlled trials[57]. Based on a recent meta-analysis, where trials with similar characteristics were combined, the relative risk reduction for LV dysfunction and/or HF with dexrazoxane ranged from 55-73% (n=1163), beta-blockers 37-84% (n=458), statins 23-87% (n=241) and angiotensin antagonists 71-96% (n=244) when compared to placebo[56]. Although this data is promising, it is unclear whether it is sufficient to support universal adoption of cardio-protection. Some studies have shown significant intolerance to cardiac medications necessitating discontinuation in ~1/3 of the patients[55]. This is a particular concern for patients who are at low risk for cardiotoxicity. Unfortunately, there are currently no robust methods for pre-treatment risk stratification which would allow for selective treatment of patients who are at high risk for cardiotoxicity. There are currently several ongoing studies such as MANTICORE-101[58], PRADA[59], SUCCOUR (www.anzctr.org.au) and ELEVATE (www.clinicaltrials.gov) that should provide further guidance on the optimal primary prevention approach.

Currently, there are no data on primary prevention strategies for myocardial ischemia, hypertension, arrhythmias, or arterial thromboembolism in patients receiving cancer therapies. The most significant challenge in articulating a primary prevention strategy is the relative paucity of tools to identify patients at high risk of adverse cardiovascular

outcomes. However, general principles should apply until more robust data becomes available. This includes guideline and evidence based treatment of underlying ischemia prior to initiation of cancer therapy, use of radiation treatment strategies to minimize cardiac injury, treatment of preexisting hypertension, and management of underlying cardiac arrhythmias and conduction system disease.

Summary of Recommendations:

(1) We suggest that in patients deemed to be at high risk for cancer treatment related LV dysfunction, an ACE inhibitor or angiotensin receptor blocker, and/or beta-blocker, and/or statin be considered to reduce the risk of cardiotoxicity. (Weak Recommendation: moderate-quality evidence)

Prevention Related to Radiation-Induced Heart Disease (RIHD)

The underlying mechanisms of RIHD are related to micro- and macro-vascular damage, which leads to clinical manifestations such as pericarditis, CAD, acute myocardial infarction, valvular heart disease, and cardiomyopathy[60]. Darby et al. demonstrated that the risk of major coronary events increased linearly with the mean radiation dose to the heart. This increased risk was observed as early as five years after radiotherapy and continued for three decades[61]. The most important factors influencing RIHD are dose to the heart and the target volume.

Several modern radiation techniques have been introduced with the aim of reducing the radiation dose to the heart. Modern 3-D conformal radiotherapy planning and intensity-modulated radiotherapy (IMRT) has been demonstrated to reduce radiation dose to the heart, especially in patients with unfavourable cardiac anatomy[62]. Active breathing control helps patients to reproducibly perform breath holding during radiotherapy with the aim of reducing the dose to the whole heart and the proximal portion of the left anterior descending coronary artery[62,63].

It is important to explore the risk: benefit ratio and individualize treatment decisions, taking into consideration other factors, such as smoking, diabetes, or history of ischemic heart disease[61,64].

Summary of Recommendations:

(1) We suggest that modern RT techniques (e.g. 3-D conformal RT, IMRT) be utilized when planning mediastinal and chest radiation in order to reduce the risk of short and long-term cardiotoxicity. (Weak recommendation: moderate-quality evidence)

3. Treatment of Cardiotoxicity

Despite the beneficial effects of many anti-cancer drugs, cardiotoxic complications of these treatments may require specific interventions. Here in, we broadly categorize the most common complications of anti-cancer treatment, including hypertension arrhythmias, ischemia and LV dysfunction, and describe an approach to management.

A. Hypertension:

The treatment of hypertension in the setting of malignancy will vary depending on the underlying cause and the overall goals of care.

Before considering treatment with an anti-cancer agent known to cause hypertension (e.g. anti-VEGF inhibitors or multi-targeted tyrosine kinase inhibitors), assessment and treatment of baseline cardiovascular risk factors, per established guidelines[65], is recommended. Baseline blood pressure (BP) measurements should be measured at two or more initial clinic visits to account for, and rule out, transient hypertension. Once diagnosed, treatment of hypertension should follow established CHEP Guidelines[65].

With respect to choice of anti-hypertensive agent, there are currently no studies suggesting the superiority of any given drug in the Cardio-Oncology setting. Cancer patients can be started on a diuretic, beta-blocker, ACE inhibitor, angiotensin receptor blocker, or calcium channel blocker accordingly[65]. The choice of agent should be tailored to the individual clinical situation including consideration for potential drug-

drug interactions. Careful attention to volume status and renal function, both at baseline and through the course of therapy are warranted, as this will affect the choice of an anti-hypertensive agent and the need for dose adjustments. After initiation of an anti-hypertensive agent, weekly monitoring of BP is recommended during the first cycle of therapy, and then every 2-3 weeks for the duration of cancer therapy.

B. Arrhythmia:

Arrhythmias represent a less common effect of cancer drugs. While there may be direct effects of chemotherapy and radiation therapy, there are also many other pre-existing patient factors that independently predispose to arrhythmia. Importantly, cancer itself creates an arrhythmogenic milieu. It can be difficult to determine whether one anti-cancer agent is responsible for an arrhythmia, when multi-drug regimens are used. In addition, arrhythmias may co-exist in the setting of other cardiotoxic effects (i.e. LV systolic dysfunction, ischemia, hypertension), rather than directly related to the administration of the chemotherapeutic agent itself.

Evaluation and management of new onset atrial fibrillation should follow CCS Guidelines[66]. If the atrial fibrillation is considered to be secondary to the chemotherapy agent, or it complicates the successful delivery of appropriate cancer therapy, it may be reasonable to consider restoration and maintenance of sinus rhythm with elective cardioversion and/or antiarrhythmic therapy, especially if the patient remains symptomatic despite adequate rate control. Decisions to continue with the presumed offending anti-cancer agent will depend on the clinical situation; however, the existence of atrial fibrillation alone does not warrant discontinuation of cancer therapy.

Use of warfarin and the novel oral anticoagulants (NOACs) in the setting of chemotherapy poses a unique challenge. It may be more appropriate to anticoagulate at-risk patients with alternative agents, such as low weight molecular heparin; particularly in those who may require multiple procedures or whose cancer treatments can affect the metabolic pathway of OACs, making anti-coagulant effects unpredictable.

Drugs associated with asymptomatic bradycardias require no specific monitoring, and no specific intervention is required if identified. The elective concomitant use of heart rate-controlling drugs (i.e. beta-blockers or non-dihydropyridine calcium channel blockers) should be avoided if bradycardia is detected.

Initial evaluation of patients receiving QT prolonging drugs should include a baseline ECG and periodic monitoring of the QTc interval should be performed during treatment with these agents. Treatment interruption and dose reduction is advised if no other reversible cause is identified. Permanent discontinuation is indicated if significant QTc prolongation recurs or is accompanied by an arrhythmia, HF, hypotension, shock, syncope, or torsade de pointes.[67,68,69]

C. Ischemia:

Proposed mechanisms for the spectrum of ischemic complications attributable to anti-cancer treatments have been inconsistent (coronary vasospasm, thrombosis, and vascular dysfunction), making management challenging. Importantly, these pathologies have not been reliably associated with underlying CAD risk.[70]

In the case of antimetabolites (5-FU and derivatives), it is important to establish the temporal relationship between drug administration and chest pain onset. If symptoms occur during 5-FU administration, it should be stopped, followed by an electrocardiogram, cardiac troponin, and cardiac monitoring until cardiac symptoms abate.

Acute symptoms should be treated with sublingual nitroglycerin and opioids[71]. If cardiac enzymes are found to be elevated, management as per ACC/AHA ACS guidelines should be initiated[72]. Treating physicians should be mindful of issues such as thrombocytopenia and need for future cancer surgery when choosing a revascularization strategy, if needed. In the non-ACS setting, elective assessment for the presence of underlying CAD may be warranted.

Once a diagnosis of myocardial ischemia due to cancer therapy is made (e.g. 5-FU), an

alternate anti-neoplastic treatment should be considered. Re-challenge of the offending agent may be considered if no alternate treatment is available. However, this is not routinely recommended, and must be approached with caution due to the frequent recurrence of symptoms[73,74] and should be performed in a controlled setting with close cardiac monitoring and with safer administration regimens (i.e. bolus 5-FU instead of infusion, dose reduction)[74]. Prophylactic therapy with nitrates and calcium channel blockers does not appear to be universally effective, but are the only available options[74].

For other classes of chemotherapy drugs associated with myocardial ischemia, there is insufficient data to propose management strategies. If ischemia is confirmed, the cancer therapy should be stopped and alternate options should be considered.

RIHD is an important cause of ischemia in patients treated with radiation to the chest[62]. It is important to manage cardiac risk factors prior to, during, and after radiation therapy. Coronary manifestations of RIHD are typically seen several years after completion of treatment and present similarly to other causes of ischemic heart disease[75]. Patients with stable angina should be assessed and managed in the same manner as patients with stable angina from atherosclerotic CAD[76], and those with unstable symptoms managed as per existing ACS guidelines[77,78]. Patients with RIHD may also have mediastinal fibrosis, aortic calcification, valvular heart disease, pericardial disease, and cardiomyopathy[79]. Careful review of cardiac imaging is necessary to assess these concomitant lesions, as they have an important impact on the choice of coronary intervention, if needed.

D. HF and LV Dysfunction:

We now recognize the dose dependency of LV systolic dysfunction with anthracyclines and the potential reversible decline in LVEF seen with trastuzumab, but evidence based guidelines for management of HF prior to, during, and after chemotherapy are still elusive in the literature. In cancer patients who develop clinical HF or an asymptomatic decline in LVEF during or after treatment, investigations and management should follow

current CCS Heart Failure Guidelines[80]. Other causes of LV dysfunction should be excluded.

Cardiac function should be optimized with standard guideline driven pharmacotherapy for HF. Treatment interruption and avoidance of agents known to cause LV dysfunction (particularly anthracyclines) is appropriate and alternative agents should be used where possible. Daily exercise should be encouraged among all patients prior to, during, and after chemotherapy as evidence mounts regarding the beneficial effects of exercise in attenuating the risk of cardiotoxicity[81,82].

Trastuzumab presents a unique challenge to the clinician in that LV dysfunction is generally assumed to be transient. Management of patients who experience a reduction in LVEF while on trastuzumab therapy have largely followed protocols from large clinical trials in the adjuvant breast cancer setting. It should be noted, however, that the schedule of cardiac assessment and criteria for withholding therapy vary across different trastuzumab studies. In general, patients in these trials with >10 % reduction in LVEF or to below institutional lower limit of normal using similar imaging modalities of LV function, had therapy held for one cycle, cardiac assessment repeated, and therapy restarted if cardiac function normalized. If not, further therapy was held. There is emerging evidence that early initiation of ACE-inhibitor therapy and/or beta-blockers can reverse the effects of trastuzumab on LV dysfunction[83,84].

Aside from trastuzumab adjuvant trials, there are very few studies evaluating the impact of holding or re-challenging patients with these agents. In general, if the risk of LV dysfunction or HF while on the agent exceeds the risk of cancer recurrence without the agent, the agent should be discontinued. This prioritization may shift in the metastatic setting or other scenarios where there may be significant benefit in continuing cancer treatment. Initiating evidence-based LV enhancement therapies, continuing cancer treatment and close clinical monitoring may be appropriate strategies in this setting.

Summary of Recommendations:

(1) We recommend that for patients with pre-existing hypertension or for those experiencing hypertension related to their cancer therapy, it is important to start, maintain or augment anti-hypertensive therapy as per CHEP Guidelines. A target BP of <140/90 mmHg should be established for all patients except those with diabetes where the goal should be adjusted to <130/80 mmHg. (Strong recommendation: high-quality evidence)

(2) We suggest in those patients receiving QTc prolonging agents, a baseline ECG prior to cancer treatment and periodic monitoring of the QTc during treatment. If the QTc interval exceeds 500 ms during treatment, metabolic and electrolyte disturbances should be identified and corrected, and the use of concomitant QT prolonging drugs be minimized where possible. (Weak recommendation: moderate-quality evidence)

(3) We recommend that in cancer patients who develop clinical HF or an asymptomatic decline in LVEF (e.g. >10% decrease in LVEF from baseline or LVEF <53%) during or after treatment, investigations and management follow current CCS Guidelines. Other causes of LV dysfunction should be excluded. (Strong recommendation: high-quality evidence)

(4) We suggest that alternate anti-neoplastic treatments be considered if patients experience myocardial ischemia due to their cancer therapy. (Suggestion: low-quality evidence)

Values and Preferences:

(1) Treatment targets (e.g. hypertension) should be tailored based on goals of care (e.g. curative vs. palliative) and by assessing the overall risks and benefits of cancer therapies within this context.

(2) We suggest cautious use of drugs metabolized by the cytochrome P450 system (e.g. diltiazem or verapamil) for hypertension management in patients receiving tyrosine kinase inhibitors due to potential drug-drug interactions.

(3) While CCS Guidelines recommend institution of ACE inhibitors/ARBs and beta-blockers in patients with an LVEF <40%, in clinical practice, the addition of LV

enhancement therapy may be considered in patients with an asymptomatic decline in LVEF (e.g. >10% decrease in LVEF from baseline or LVEF <53%) during cancer therapy.

(4) In the setting of trastuzumab related LV dysfunction, we recommend following the proposed algorithm by Jones *et al*.[30] recognizing there may be clinical scenarios where continuing trastuzumab alongside initiation of evidence based HF therapies may be considered.

4. Recommendations for a Multidisciplinary Approach to Cardio-oncology

Cardio-oncology is a collaborative medical discipline with focused expertise in the prevention, diagnosis and treatment of cardiovascular disease in cancer patients[85]. Historically, cancer patients at high risk of treatment-related cardiotoxicity were referred to cardiology services outside of a formalized program resulting in variability in cardiac assessment, delays in diagnosis and treatment of cardiac disease, as well as the risk of stopping a potential life-saving cancer treatment. Improved collaboration between oncology and cardiology is needed to address the clinical care gaps experienced by this at-risk patient population, thus leading to the evolution of Cardio-oncology as a distinct, inter and multidisciplinary patient-centered clinical specialty.

There are currently no established benchmarks to guide clinicians with regards to timely access and assessment of patients experiencing cancer related cardiotoxicity. For cancer patients, wait times to be assessed in a cardio-oncology clinic need to be balanced with the urgency of impending cancer treatments. The CCS HF Companion[86] provides wait time benchmarks for HF patients to be seen in a specialty clinic. The patient on active treatment will generally require more urgent access (1-2 weeks), while it may be appropriate for patients not on active therapy (e.g. surveillance) to be seen in a less timely fashion (weeks - months). We believe this framework may also be applicable in the cardio-oncology setting.

It is important to acknowledge the potential for late cardiac complications in long-term cancer survivors. Although beyond the scope of this document, healthcare providers caring for adult survivors of pediatric cancer should refer to the Children's Oncology Group (COG) Long-Term Follow-up Guidelines at: www.survivorshipguidelines.org

A Call to Action

In clinical practice, the cardiovascular surveillance of cancer patients is inconsistent and there is a lack of evidence to guide therapies. Recently published international guidelines for the cardiovascular surveillance of cancer patients receiving anthracyclines and/or trastuzumab recommend serial assessment with echocardiography and troponin[18]. However, the feasibility and cost effectiveness of this multimodality approach is not defined and has not yet been evaluated in the cancer community at large. Furthermore, it is unclear if early detection strategies decrease the burden of cardiovascular disease and ultimately improve the outcome of cancer survivors. Further complicating the clinical management of cardiotoxicity is the lack of high quality evidence for effective primary and secondary prevention strategies.

Thus we believe that there is an urgent need for collaborative studies to help guide patient management. Large prospective registries will enable the development of risk models for predicting cardiovascular events among cancer survivors as well as evaluate the downstream impact of surveillance strategies for cardiac toxicity prevention. Multi-centre randomized controlled trials are also needed to test traditional and novel pharmacotherapy as primary and secondary interventions. Effective knowledge translation strategies as well as education of trainees will be required to increase awareness and provide guidance on the management of these patients. Organizations such as the Canadian Cardiovascular Society (CCS), Canadian Cardiac Oncology Network (CCON)(www.cardiaconcology.ca) and the International Cardiooncology Society (ICOS) (www.icosna.org) will continue to play an important role in promoting the development of clinical care models, development of educational structures and promotion of evidence-based research.

Summary of Recommendations:

(1) We suggest that patients at high risk of cancer therapy related cardiovascular disease or patients who develop cardiovascular complications during cancer therapy (e.g. >10% decrease in LVEF from baseline or LVEF < 53%) be referred to a Cardio-oncology clinic or practitioner skilled in the management of this patient population, for optimization of cardiac function and consideration of primary or secondary prevention strategies. (Suggestion: low-quality evidence)

Figure 1 Legend:

Pre-existing cardiovascular disease and cardiac risk factors combine with chemotherapy and targeted therapy to produce subclinical and clinical cardiovascular disease, both during and long after cancer therapy. This model for cancer therapy induced cardiotoxicity emphasizes multiple risk factors, each of which is a potential target for intervention. Whether such intervention translates into clinical benefit requires further study.

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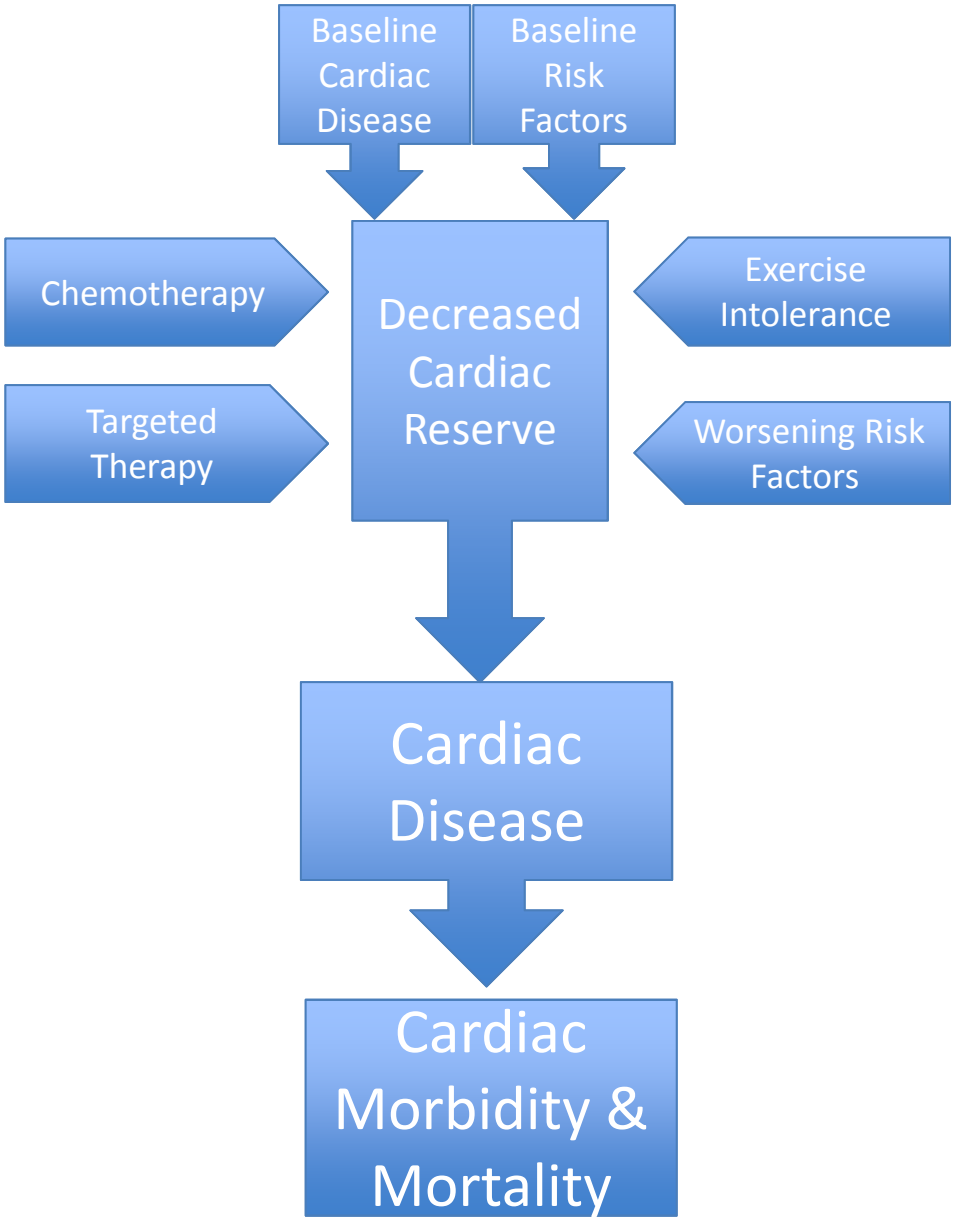
Table 1: Risk of Cardiac Disease and Cardiac Risk Factors in Long Term Survivors of Childhood Cancer vs Healthy Siblings

(Childhood Cancer Survivor Study)

	CAD[9]	Heart Failure[9]	Hypertension[10]	Diabetes[10]	Dyslipidemia[10]
R.R. (C.I.)	10.4 (4.1-25.9)	15.1 (4.8-47.9)	1.9 (1.6-2.2)	1.7 (1.2-2.3)	1.6 (1.3-2.0)
N	10,397	10,397	8,599	8,599	8,599

R.R. = relative risk; C.I. = confidence interval

Figure 1 – The Multiple Hit Hypothesis



adapted from Jones 2007, Cardinale 2013