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STATE-OF-THE-ART REVIEW

Cardiac Disease in Childhood Cancer Survivors

Risk Prediction, Prevention, and Surveillance: *JACC CardioOncology* State-of-the-Art Review

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ABSTRACT

Cardiac diseases in the growing population of childhood cancer survivors are of major concern. Cardiotoxicity as a consequence of anthracyclines and chest radiotherapy continues to be relevant in the modern treatment era. Mitoxantrone has emerged as an important treatment-related risk factor and evidence on traditional cardiovascular risk factors in childhood cancer survivors is accumulating. International surveillance guidelines have been developed with the aim to detect and manage cardiac diseases early and prevent symptomatic disease. There is growing interest in risk prediction models to individualize prevention and surveillance. This State-of-the-Art Review summarizes literature from a systematic PubMed search focused on cardiac diseases after treatment for childhood cancer. Here, we discuss the prevalence, risk factors, prevention, risk prediction, and surveillance of cardiac diseases in survivors of childhood cancer. (J Am Coll Cardiol CardioOnc 2020;2:363–78) © 2020 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/).

The survival of children with cancer has considerably increased over the last decades with 5-year survival rates currently exceeding 80% (1). However, the long-term health effects in the growing population of childhood cancer survivors (CCS) are of major concern (2). Cardiac disease, as a consequence of treatment with anthracyclines, mitoxantrone, and/or chest-directed radiotherapy (chest RT), can manifest as myocardial dysfunction and heart failure but also as valvular

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CCS = childhood cancer survivors

chest RT = chest-directed radiotherapy

ECG = electrocardiogram

FS = fractional shortening

GLS = global longitudinal strain

IGHG = International Late Effects of Childhood Cancer Guideline Harmonization Group

LV = left ventricle

LVEF = left ventricular ejection fraction

RCT = randomized controlled trial

disease, coronary artery disease, arrhythmias, and pericardial disease, depending on the exact cardiotoxic agent (3).

In this State-of-the-Art Review, we focus on long-term cardiac diseases after treatment for childhood cancer. We discuss the prevalence, risk factors, prevention, prediction, and surveillance of cardiac disease in this population (**Central Illustration**). We systematically searched PubMed for studies that described cardiac adverse events in children treated with cardiotoxic cancer treatments. We limited the search to full-text articles written in English and articles published within the last 10 years. We selected articles with a study cohort of which >50% were treated for childhood cancer before the age of 21 years. For studies describing the prevalence or cumulative incidence of heart failure, we reviewed articles with a minimum of 500 CCS; a minimum of 100 CCS was required for the other outcomes. Studies on primary prevention strategies were identified from previous Cochrane searches (4–6). Based on these criteria, 74 studies were considered to be described in this review (**Figure 1**). The full search strategy is provided in Supplemental Table 1.

HIGHLIGHTS

- The main risk factors for cardiac disease in childhood cancer survivors are anthracyclines, mitoxantrone, and chest-directed radiotherapy dose.
- Primary prevention strategies may reduce the risk of anthracycline-induced cardiomyopathy.
- There is an increased prevalence of traditional cardiovascular risk factors in childhood cancer survivors; screening and early management are important to modify risk.
- Multivariable risk prediction models may help to individualize prevention and surveillance strategies.

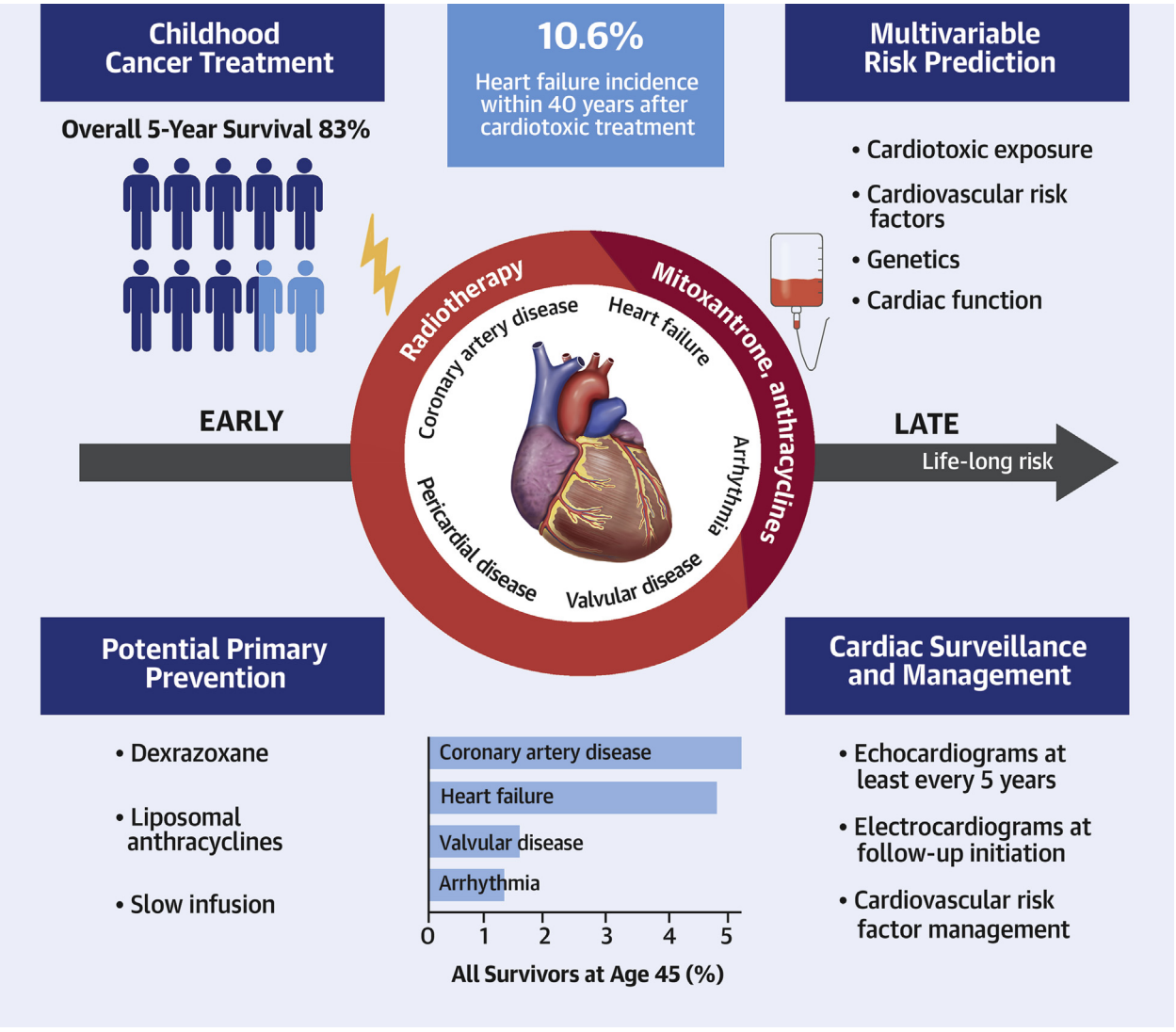
CARDIAC DISEASES AND TREATMENT-RELATED RISK FACTORS IN CHILDHOOD CANCER SURVIVORS

HEART FAILURE. Multiple studies have shown that left ventricular (LV) systolic function deteriorates as a result of cardiotoxic treatment (7–15). Anthracyclines are clearly associated with cardiomyocyte damage. Although the exact mechanism of anthracycline-induced cardiotoxicity has not been fully elucidated, early studies indicate that cardiotoxicity through reduction-oxidation reaction cycling and the generation of reactive oxygen species may be the cause. More recently, topoisomerase 2β has been proposed to be a mediator of doxorubicin-induced cardiac injury (16).

Systolic dysfunction can eventually progress to heart failure. Heart failure is one of the most frequent cardiac late effects in CCS (17,18), and contributes to significant morbidity and non-cancer-related mortality later in life (19,20). A large cohort from the Childhood Cancer Survivor Study investigated the occurrence of heart failure, defined by the Common Terminology for Criteria Adverse Events as grade 3 to 5. Based on questionnaires concerning long-term CCS, the reported cumulative incidence is 4.8% by 45 years of age (17). These results confirmed earlier reports that anthracyclines and chest RT are strongly associated with heart failure (21). Recently, it has been shown that even low-to-moderate chest RT doses increase the risk of heart failure substantially (22,23). In the Dutch LATER (Late Effects After Childhood Cancer) cohort, Feijen et al. (10) reported a cumulative heart failure incidence of 10.6% 40 years after childhood cancer diagnosis in CCS who received cardiotoxic cancer treatment. Higher exposure to mitoxantrone and cyclophosphamide were suggested as novel treatment-related risk factors (10). Although mitoxantrone has traditionally been classified as an anthracycline, it has been suggested that mitoxantrone results in cardiotoxicity through mechanisms different from anthracyclines (24,25). Mitoxantrone has a nonlinear dose-response relationship with heart failure risk (10,26–28), and compared to doxorubicin, mitoxantrone is 10 times more cardiotoxic. In addition, a younger age at diagnosis and presence of traditional cardiovascular risk factors may play a role in the development of heart failure (29). The influence of sex on the development of myocardial dysfunction is still incompletely conclusive (8,9,11,12,30).

CORONARY ARTERY DISEASE. The risk of coronary artery disease (CAD) is substantially increased in CCS. In the Childhood Cancer Survivor Study, the cumulative incidence of CAD by age 45 years was 5.3% in survivors with and without exposure to cardiotoxic cancer treatments (17). This risk is dependent on chest RT dose with no established safe dose; this risk is also higher in males. The cumulative incidence of symptomatic CAD at age 50 years

CENTRAL ILLUSTRATION **Overview of Clinical Practice in Childhood Cancer Survivors at Risk for Cardiotoxicity**



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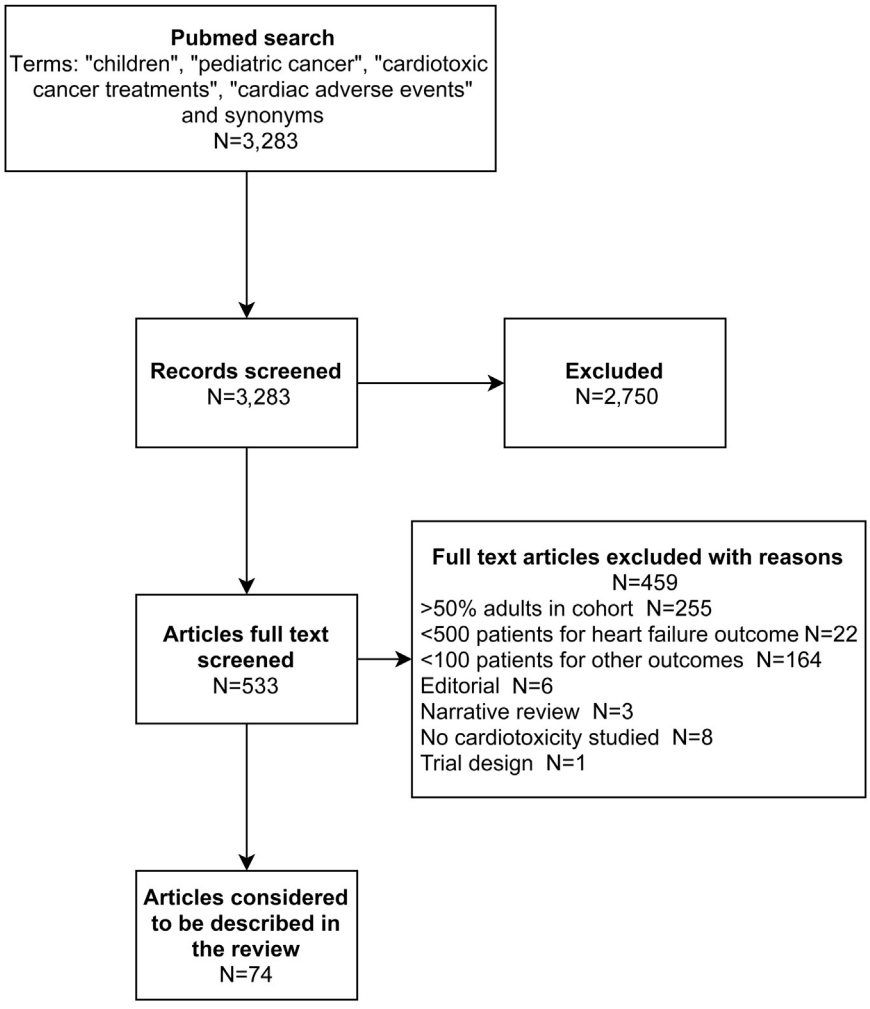
The prevalence of cardiac diseases, risk prediction models, preventive measures, and surveillance recommendations are illustrated based on available evidence and promising research topics of cardiotoxicity in childhood cancer survivors. Numbers derived from Siegel et al., 2019 (122); Feijen et al., 2019 (10); and Armstrong et al., 2013 (17).

increases to 20% in males exposed to >35 Gy of radiation (18,31). The St. Jude Lifetime cohort study detected CAD based on either history, electrocardiogram (ECG), or echocardiography in 3.8% of asymptomatic CCS 22.6 years after cardiotoxic therapy (30). However, evidence from (non)invasive coronary angiography is scarce. A study evaluating computed tomography in asymptomatic Hodgkin lymphoma CCS 55 years old or younger (n = 31) exposed to chest RT showed coronary artery lesions to be very proximal, placing large portions of the myocardium at risk (32).

VALVULAR HEART DISEASE. Several studies have investigated valvular abnormalities in CCS (11,17,30,33-35) with a reported prevalence of up to 31% (30,33,35). Chest RT has been identified as an

FIGURE 1 Flowchart of Study Inclusion



Flowchart describing the systematic literature search in PubMed and the inclusion of relevant studies.

important risk factor that increases at higher doses (35). Other risk factors are treatment with anthracyclines, hypertension, congenital heart disease, and younger age at diagnosis, although these have not been uniformly shown in all studies (11,30,33). Mild tricuspid regurgitation was most prevalent in 2 studies describing valvular disease, but this is also very common in the general population (30,33,36). In lymphoma CCS who were exposed to chest RT, valvular heart disease, defined as mild or higher for left sided valves and moderate or higher for right sided valves, was most frequently detected in the aortic and mitral valves (35). Valvular abnormalities after chest RT are most likely caused by direct irradiation injury to the valve cusps or leaflets, causing thickening, fibrosis, and calcification (30,37). These processes progress with age and increase in prevalence over time (30,35). Hence, CCS without echocardiographic abnormalities after a short follow-up period are still at risk of severe valvular heart disease.

PERICARDIAL DISEASE. Besides paraneoplastic and infectious causes, pericardial disease can arise from chest RT. Late constrictive pericarditis, in particular, can lead to disabling symptoms and a poor prognosis (38). However, data on pericardial disease in CCS are limited. The Childhood Cancer Survivor Study showed a 10-fold higher risk of pericardial disease in

all CCS versus siblings (30-year cumulative incidence, 3.0%) and a dose-response relation with chest RT (11). A single-center study in CCS older than 5 years after diagnosis (n = 1,362; 47% no cardiotoxic therapy), reported symptomatic pericarditis in only 2 CCS (18). Although the diagnosis of constrictive pericarditis is difficult by echocardiography, thickening of the pericardium as well as hemodynamic consequences (e.g., "septal bounce," abnormal respiratory variations in Doppler findings) can be suggestive. Upon high clinical suspicion, cardiac computed tomography, magnetic resonance imaging (MRI), and/or invasive hemodynamic evaluation may be needed to confirm the diagnosis (39).

ARRHYTHMIAS. The prevalence of symptomatic cardiac arrhythmias in long-term CCS is reportedly low (11,17,18,40). In 10,724 CCS, the cumulative incidence of grade 3 to 5 arrhythmia by 45 years of age was 1.3% (17). A subsequent study (n = 23,462) showed that chest RT >35 Gy, anthracycline dose ≥250 mg/m^2, dyslipidemia, and hypertension are risk factors for symptomatic arrhythmia (11). Myocardial fibrosis caused by chest RT may contribute to the occurrence of arrhythmias. Other frequently used cancer agents for pediatric cancers such as cisplatin, cyclophosphamide, and tyrosine kinase inhibitors may also be associated with supraventricular and ventricular arrhythmias (41,42). Prolonged QTc interval, which has arrhythmogenic potential, has been shown in CCS who received anthracyclines with and without chest RT (43,44). Also, rhythm disturbances such as premature ectopic beats and atrioventricular blocks have been reported in CCS (45–47). The literature on ECG abnormalities in large cohorts of long-term CCS is sparse (46,47), Data on the use of ambulatory ECG monitoring to define the prevalence of brady- and tachyarrhythmias induced by cardiotoxic cancer treatments are needed, but must be carefully weighed against the potential patient burden and clinical significance.

PREVENTION OF CARDIAC DISEASE IN CHILDHOOD CANCER SURVIVORS

PREVENTIVE MEASURES FOR CANCER TREATMENT-INDUCED CARDIOTOXICITY. As the risk of cardiac disease is high in chest RT and anthracycline-treated survivors, and as omitting or diminishing the use of cardiotoxic treatments is not always possible, prevention is critical (48). Advanced radiotherapy techniques to minimize exposure to the heart have been developed; the impact of those improvements is reflected by the decrease in CAD in more recent treatment eras (11).

Extensive research has been devoted to the identification of possible cardioprotective interventions during anthracycline treatment that do not have negative effects on antitumor efficacy or other noncardiac adverse effects. Below we discuss 3 preventive measures that have been studied during anthracycline treatment. We focus primarily on randomized controlled trials (RCTs) as they provide the highest level of evidence to answer this type of question. Because of developmental changes and the differences in the body composition of children, data from adults cannot be reliably extrapolated to children (49).

Dexrazoxane. Dexrazoxane is one of the most widely investigated cardioprotective pharmacologic interventions. It has been shown in adult cancer patients to prevent clinical and subclinical cardiac damage (4). The few published pediatric RCTs have included participants diagnosed with leukemia, lymphoma, and sarcoma (50–52). These studies suggest that there are no significant differences in clinical heart failure between dexrazoxane and control patients (4,53), although dexrazoxane might have a protective effect on asymptomatic cardiotoxicity (53,54). All studies included relatively short-term follow-up, and the impact on outcomes after longer follow-up is yet unknown.

Currently, dexrazoxane is not routinely used in clinical practice for all children treated with anthracyclines. This might be explained by a concern over interference with antitumor efficacy and the occurrence of secondary malignancies (55). However, high-quality evidence to support an increased risk of secondary malignancy is lacking. A Cochrane systematic review identified no significant differences between treatment groups (4), which is in line with more recently published randomized trials (50,53).

A recently published nonrandomized study in pediatric patients with acute myeloid leukemia (n = 1,014) added important knowledge about the efficacy and adverse effects of continuous use of dexrazoxane versus no dexrazoxane. Results showed that after a median follow-up period of 3.5 years, cardiac function was preserved with dexrazoxane without negative influence on antitumor efficacy or noncardiac toxicities. Importantly, the influence of possible differences in cumulative anthracycline dose per treatment group could not be evaluated in this study (56).

At the moment clear guidance on the use of dexrazoxane is missing. Since it will take many years to add relevant knowledge by new RCTs, additional observational studies are needed. The International Late Effects of Childhood Cancer Guideline

Harmonization Group (IGHG) is currently preparing recommendations based on the existing evidence.

Liposomal anthracyclines. Another option is to limit drug exposure in healthy tissues such as the heart and increase drug activity in malignant cells by altering the tissue distribution as with liposomal anthracyclines (57). Liposomal anthracyclines have shown promising results in adults with breast cancer (5). In a meta-analysis of 2 studies, liposomal-encapsulated doxorubicin significantly reduced both clinical and subclinical heart failure when compared to the same dose of conventional doxorubicin, without negative effects on antitumor efficacy and without cardiac adverse effects. In 1 of the studies, patients received a higher cumulative anthracycline dose in the liposomal group. However, again, follow-up was relatively short and we do not know how longer-term follow-up will influence these results (5). One study compared liposomal-encapsulated doxorubicin to the same dose of conventional epirubicin. No significant difference in cardiotoxicity was shown, but that might have been the result of inadequate power or a limited follow-up period (5). To our knowledge, no pediatric RCTs have been performed, so the benefits and harms of liposomal anthracyclines in children remain unclear. High-quality research in children is needed before definitive conclusions can be made.

Infusion duration. The use of longer anthracycline infusion durations may play a role in primary prevention of cardiotoxicity. A Cochrane systematic review compared different anthracycline infusion durations in children and adults with cancer (6). An anthracycline infusion duration of 6 h or longer seemed to reduce the risk of both clinical heart failure and subclinical cardiotoxicity. A clinical practice guideline for children treated with anthracyclines has suggested that although it was not possible to formulate a recommendation regarding a precise and optimal prolonged infusion duration, the use of an anthracycline infusion duration of at least 1 h was strongly recommended (58). Because data in children are limited, different anthracycline infusion durations should be evaluated further in children.

CARDIOVASCULAR RISK FACTORS AND HEALTHY LIFESTYLE.

For both primary and secondary prevention of cardiovascular disease in CCS, management of cardiovascular risk factors and counseling on healthy lifestyle are essential, although most evidence is still derived from the general population.

Metabolic syndrome. Hypertension, obesity, dyslipidemia, and diabetes, together clustered as metabolic syndrome, are well-known risk factors for cardiovascular disease (59). Some CCS are at increased risk of developing metabolic syndrome because of previous cancer treatment. Metabolic syndrome has been established in 9% of French childhood leukemia survivors and in 32% of the St. Jude Lifetime cohort at median attained ages of 21 to 32 years (60,61). Survivors treated with cranial radiotherapy are at risk of developing metabolic syndrome, especially obesity (62). Furthermore, abdominal radiation and nephrotoxic treatment may result in the development of cardiovascular risk factors (63,64). Hypertension is the most prevalent cardiovascular risk factor in CCS, approaching 40% in survivors aged 50 years or older, versus 26% in siblings (17). The Childhood Cancer Survivor Study ($n = 10,724$) investigated cardiovascular risk factors with longitudinal questionnaires and showed that hypertension had the strongest association with all cardiac events and mortality compared to diabetes, dyslipidemia and obesity (17). In the St. Jude Lifetime study, hypertension was also the only cardiovascular risk factor associated with an abnormal left ventricular ejection fraction (LVEF) (7).

Management of cardiovascular risk factors is essential in all CCS and particularly in those at risk for cardiac disease. No studies have assessed whether more aggressive approaches and treatment goals than in the general population are beneficial in CCS with a high lifetime risk of cardiovascular disease. Lifestyle interventions may prevent the occurrence of cardiovascular risk factors and cardiac disease and may complement pharmacologic risk factor modification.

Healthy lifestyle. A healthy lifestyle, including cessation and abstinence from smoking, a sufficient level of physical activity, a healthy diet, and less than moderate alcohol use may benefit cardiovascular health. It may prevent the onset and/or reduce the severity of cardiovascular disease directly or indirectly by lowering the risk of metabolic syndrome (59). Although the association between lifestyle factors and cardiovascular disease has been well established in youth and aging adults (59), there are few studies that have examined the association between lifestyle and either cardiovascular disease or cardiovascular risk factors in CCS. In the Childhood Cancer Survivor Study, smoking was not associated with cardiac events, most likely because of short exposure time and follow-up (17). In the St. Jude Lifetime cohort study, CCS who did not meet most of the lifestyle recommendations from the World Cancer Research Fund/American Institute for Cancer Research were more likely to have metabolic syndrome than CCS who did meet these recommendations (61). In recent studies in the St. Jude Lifetime

cohort, CCS were shown to have substantially less exercise capacity than community controls on maximal cardiopulmonary fitness testing in recent studies. Exercise capacity was associated with all-cause mortality, cardiac function (global longitudinal strain [GLS], but not LVEF), chronotropic incompetence, and worse pulmonary and muscle function (65). Furthermore, CCS with lower exercise capacity had more emotional distress and worse attainment of social roles and health-related quality of life (66). Although causal relations have not been established, based on the above results in the general population and CCS, it is widely assumed that healthy lifestyle interventions will contribute to less cardiac morbidity and mortality. However, the effectiveness of lifestyle interventions on cardiovascular risk factors or cardiovascular disease has not been established in CCS.

Several studies have been performed to support CCS to adapt to a healthy lifestyle, of which most have focused on increasing physical activity. In a meta-analysis of 9 studies, aerobic exercise was positively related to cardiopulmonary fitness in CCS (67). A systematic review by Raber et al. (68) identified 12 studies on physical activity interventions in CCS. Of these, 5 studies found that exercise training improved strength, functional mobility, and flexibility and/or anthropometric fitness (68). Another systematic review on lifestyle interventions in adolescent and young adult cancer survivors targeting 1 or more health behaviors identified 12 studies, of which 6 were successful in changing health behavior (69). Three of these were focused on influencing multiple behaviors, including an individually tailored counseling program on smoking and alcohol consumption. One-half of the reviewed studies delivered lifestyle interventions remotely, using phone calls or online contact. Personalized e-health interventions seem a relatively cost-effective and feasible way to improve lifestyle in CCS, but more studies are needed to examine its efficacy and effectiveness.

RISK PREDICTION MODELS

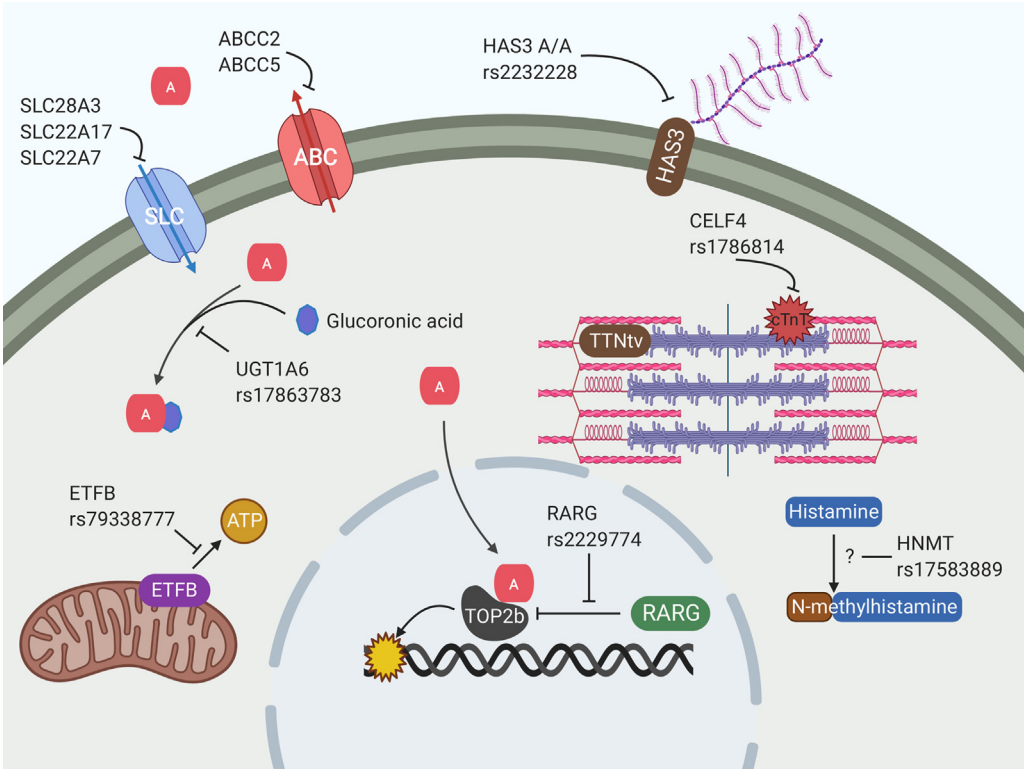
Knowledge of the risk of cardiac adverse events before or early after cardiotoxic cancer treatments can be very useful to guide the care for CCS. Multivariable risk prediction models have the potential to accurately estimate risk in individual survivors and should ideally be linked to a proven effective action to prevent or reduce the severity of cardiotoxicity (70,71).

Development of prediction models broadly includes a development and validation phase (70). In the development phase, relevant predictors are selected based on subject knowledge and/or stepwise regression (72). Subsequently, model discrimination and calibration are assessed. Discrimination is the ability of the model to discriminate between patients who develop the event and those who do not and is typically quantified by the C-statistic or area under the receiver operating characteristic curve (72,73). Calibration refers to how well the predicted risks match the actual risks and can be assessed with a calibration plot (71). In the validation phase, discrimination and calibration are assessed in a distinct cohort, a critical step before the prediction model can be applied to patients (70,71). In CCS, risk prediction models have been developed for heart failure, ischemic heart disease, and cardiovascular mortality. An overview of validated prediction models in CCS is provided in Supplemental Table 2.

HEART FAILURE PREDICTION MODELS. Practical models to predict heart failure onset before the age of 40 years in CCS at 5 years after cancer diagnosis have been developed by Chow et al. (29). Here, prediction models in 13,060 CCS (285 patients with heart failure) from the Childhood Cancer Survivor Study were derived and subsequently validated in 3,421 CCS (93 with heart failure) from the Dutch Emma Children's Hospital, the National Wilms Tumor Study, and the St. Jude Lifetime Cohort Study. Using a backward selection procedure, being female, younger age at cancer diagnosis, anthracycline dose, and chest RT dose were selected as predictors and assigned integer risk scores for clinical applicability. The final prediction model showed reasonable discrimination between CCS who developed heart failure and those who did not (C statistic: 0.76 and 0.68 to 0.82 in the development and validation cohorts, respectively). The discriminatory abilities of the model were further shown by a cumulative incidence of heart failure at age 40 years of 0.5% in the low-risk group, whereas this was 11.7% in the high-risk group. Importantly, 45.2% of the CCS were at low risk according to the model and thus unlikely to develop heart failure.

ISCHEMIC HEART DISEASE PREDICTION MODELS. A similar approach was used by the same investigators to develop and externally validate a prediction model for ischemic heart disease before the age of 50 years (31). Being male and having a higher chest RT dose were selected as predictors. The Cox regression model achieved modest discrimination between CCS who developed ischemic heart disease and those who did not (C statistic of 0.70 in the development cohort and 0.66 in the validation cohort). Cumulative incidences of ischemic heart disease at the age of 50 years ranged from 2.3%

FIGURE 2 Replicated Genetic Variants Associated With Anthracycline-Induced Cardiomyopathy in Childhood Cancer Survivors and Their Cellular Functions



Created with BioRender.com. A = anthracyclines; ABC = adenosine triphosphate binding cassette; ATP = adenosine triphosphate; CELF4 = CUGBP Elav-like family member 4; cTnT = cardiac troponin T; ETFB = electron transfer flavoprotein subunit beta; HAS3 = hyaluronan synthase 3; HNMT = histamine N-methyltransferase; RARG = retinoic acid receptor gamma; rs = reference single nucleotide polymorphism identification; SLC = solute carrier transporter; TOP2b = topoisomerase2b, TTNtv = titin truncating variant; UGT1A6 = UDP glucuronosyltransferase family 1 member A6.

(95% confidence interval [CI]: 1.5% to 3.1%) in the low-risk group to 19.9% (95% CI: 15.0% to 24.7%) in the high-risk group, whereas this was only 1.2% (95% CI: 0.4% to 2.0%) in siblings. Although a clear segregation was observed between the low- and high-risk groups, the C statistics were modest. For both the heart failure and ischemic heart disease prediction models, calibration was not assessed.

TRADITIONAL CARDIOVASCULAR RISK FACTORS IN THE PREDICTION FOR HEART FAILURE AND ISCHEMIC HEART DISEASE. Modifiable cardiovascular risk factors in CCS are known to increase the risk for cardiovascular events and their prevalence is strongly related to age (17). Thus, early, at 5 years after diagnosis, cardiovascular risk factors have been shown to provide little incremental information to prediction models for heart failure and ischemic heart disease (29,31).

In a more recent study, diabetes, hypertension, and dyslipidemia were used in the prediction of heart failure and ischemic heart disease in CCS who were 20, 25, 30, or 35 years of age at time of prediction, with relative risks comparable to moderate doses of anthracyclines (74). Cardiovascular risk factors were present in approximately 10% of the CCS at the age of 35 years and were strong predictors of heart failure and ischemic heart disease. Although the discrimination of the prediction models improved with the addition of cardiovascular risk factors, the C statistics were modest for both events ranging from 0.69 to 0.79 in the derivation cohort with successful replication in the other one-half of the cohort. Both the heart failure and the ischemic heart disease predictions models showed good calibration. A small, very-high-risk group was identified with cumulative incidences of heart failure or ischemic heart disease of

~10% at age 50 years; survivors in this very-high-risk group may benefit from more frequent surveillance and/or early interventions to modify their risk. However, low-risk survivors who may be excluded from further surveillance could not be identified with these models as cumulative incidences of heart failure (~1.5% to 2.5%) and ischemic heart disease (~1% to 1.5%) were still significantly higher compared to siblings at the age of 50 years.

CARDIOVASCULAR MORTALITY PREDICTION MODELS. A population-based study from the Surveillance, Epidemiology, and End Results Program in 28,811 CCS was used to develop and validate a clinical risk score for cardiovascular mortality ≥5 years after diagnosis (75). Being male, of non-white race, age at diagnosis, lymphoma history, and at any radiation dose were selected as predictors in the Cox regression model. This simple model showed modest discrimination (C statistic: 0.72 to 0.75) and good separation between low-risk and high-risk survivors (cumulative incidence at 30 years after cancer diagnosis of 0.7% and 6.0%, respectively).

GENETIC RISK PREDICTION MODELS. There is large interindividual variation in the susceptibility for cardiotoxicity after anthracycline treatment (76). Genetic predisposition may explain why some children will develop cardiotoxicity at lower anthracycline doses whereas others who are treated with high doses will not and thus enable risk stratification of children before anthracycline treatment. Several genetic variants implicated in DNA damage, oxidative stress, iron metabolism, sarcomere dysfunction, and anthracycline metabolism and transport have been described and replicated in anthracycline cardiomyopathy (**Figure 2**, Supplemental Table 3) (77,78). For a comprehensive overview of genetic variants implicated in anthracycline cardiomyopathy we refer the reader to an upcoming State-of-the-Art Review in *JACC: CardioOncology* and other systematic reviews (76,77).

In the absence of single genes explaining the susceptibility for anthracycline cardiomyopathy, combining genetic and clinical risk factors in a multivariable prediction model may increase the clinical usefulness of screening for genetic variants. Visscher et al. (79,80) developed several genetic risk prediction models. Validation of the first prediction model failed in an independent cohort (79,80). An updated prediction model based on 7 genetic variants and the clinical variables age at start of treatment, anthracycline dose, sex, chest RT, and ethnicity achieved an area under the curve of 0.79 (95% CI: 0.74 to 0.85) in the derivation cohort and 0.76 (95% CI: 0.68 to 0.83) in the validation cohort, compared to 0.68 (95% CI: 0.61 to 0.75) for the model with clinical variables only (81). Although these are promising results, this genetic risk prediction model is not ready to be applied to clinical practice due to several limitations. Calibration was not performed and coefficients of the final model were not provided. In addition, a logistic regression model was used that does not take into account the time-to-event, and also does not properly address survivors who dropped out before the study was performed. Therefore, the model estimates the probability of developing anthracycline cardiomyopathy at any time during follow-up, whereas it is likely more informative for a clinician to understand the probabilities within a certain timeframe. Studies that evaluate the predictive value of genetic variants in combination with clinical variables using time-to-event analyses are needed before genetics can be used in the risk stratification for anthracycline cardiomyopathy in CCS.

IMPROVING PREDICTION MODELS WITH ADDITIONAL PREDICTORS. Improvements in discrimination ability of the models may be achieved with the addition of echocardiographic parameters, ECG, blood biomarkers, and/or genetic variants (7,47). Updating risk estimates in a particular survivor with changes in echocardiographic, ECG, and/or blood biomarkers during follow-up may also improve predictions given the results in other areas of research (82). Moreover, acute or early-onset cardiotoxicity is suggested as a predictor for late-onset cardiotoxicity (83).

CLINICAL APPLICATIONS AND CLINICAL IMPACT ANALYSES OF PREDICTION MODELS. When a potentially high-risk patient is identified by a risk prediction model, preventive measures such as the use of dexrazoxane or liposomal anthracyclines may be considered. Prediction models using covariates that are known before cancer treatment, such as genetic variants or treatment protocols, may be useful for this purpose.

As a future application of prediction models, the predicted risk for cardiotoxicity can be weighed against the survival benefit associated with a particular treatment to guide therapy decisions. Risk estimates from a prediction model can also be used to individualize surveillance for asymptomatic cardiac dysfunction in CCS. Closer follow-up can be recommended in high-risk patients while at the same time the surveillance burden can be decreased in patients at low risk for cardiotoxicity.

Although the above-mentioned prediction models may be used to inform survivors and clinicians on individual risks for cardiotoxic events, there is a lack of evidence-based clinical actions that can be taken based on the risk estimates from current models. This emphasizes the need for clinical impact analyses to investigate changes in clinical management linked to the results from a prediction model. A trial with a cluster randomization design evaluating usual survivorship care compared to care based on results from a prediction model will provide the strongest evidence but may be impractical to perform in CCS because of the long follow-up needed (84).

Another approach to assess clinical impact is decision modeling (84,85). Decision curves can evaluate the net benefit of a prediction model across a range of disease probability thresholds for intervention (86). In the context of prediction model-guided surveillance, this can be seen as the benefit of early detection of asymptomatic cardiac dysfunction among those who will develop heart failure (true positives) weighted against the potential harm of an unnecessary diagnostic workup and/or treatment in those who will not develop heart failure (false positives).

Through decision modeling using simulations it has been shown that routine echocardiographic surveillance for asymptomatic cardiomyopathy every 10 years may be more cost-effective, especially in those treated with an anthracycline dose <250 mg/m^2 (85). Decision modeling provides weaker evidence on the clinical impact compared to an RCT, but it requires no follow-up and is less expensive to perform. Such analyses could be performed to assess clinical impact and cost-effectiveness before conducting an RCT.

DETECTION METHODS AND GUIDELINES

There are different methods and techniques available to detect anthracycline treatment induced cardiomyopathy. Much of the research in detection of cardiac diseases is focused on improving early detection of myocardial dysfunction. We will describe diagnostic methods that have been studied over the past decade in CCS.

CONVENTIONAL ECHOCARDIOGRAPHY. Echocardiographic measurement of the fractional shortening (FS) and biplane LVEF are widely used techniques to quantify cardiac dysfunction in survivors of childhood cancer. FS is discouraged in patients secondary to potential regional wall motion abnormalities (87). Moreover, LVEF and FS decreases may reflect later stages of cardiotoxicity. To overcome these limitations, developments in advanced imaging techniques are of great importance. Application of 3-dimensional echocardiography has improved inter-observer and intra-observer variability, which is desirable for longitudinal follow-up (88). Armstrong et al. (89) showed that the sensitivity and false-negative rate of 3-dimensional echocardiography for detection of LVEF <50% measured by cardiac MRI as the gold standard was improved compared to 2-dimensional echocardiography (89).

STRAIN IMAGING AND DIASTOLIC FUNCTION. One of the markers that may detect myocardial dysfunction at an early stage is GLS. In adult cancer patients, strain imaging has potential to predict subsequent LVEF deterioration (90,91). A relative GLS decrease of >15% from baseline is suggested as potentially abnormal, whereas a relative decrease of <8% seems not clinically relevant (92). Evidence on strain imaging in CCS is accumulating. Mavinkurve-Groothuis et al. (93) showed a significant difference in GLS between asymptomatic CCS (n = 111) approximately 15 years after anthracycline treatment and healthy controls. A large study of the St. Jude Lifetime cohort of 1,807 CCS with a median follow-up of 23 years determined an abnormal GLS in 28% of the cohort who were exposed to anthracyclines and/or chest RT and had normal LVEFs. Both cumulative anthracycline dose >300 mg/m^2 and any cardiac RT dose were associated with an increased risk for abnormal GLS (7). It is currently unknown whether an abnormal GLS is associated with development of an LVEF <50% or clinical heart failure in CCS.

Diastolic dysfunction after cardiotoxic cancer treatment has also been described in CCS (8,94). In the St. Jude Lifetime cohort, diastolic dysfunction grades 1 to 3 (based on peak mitral flow velocity, mitral septal and lateral early diastolic velocity, and left atrial volume) was detected in 11% of all CCS who were exposed to cardiotoxic treatment and in 8.7% with normal LVEF (7). One must be aware of the difficulties in the classification of diastolic dysfunction and there is a question of whether grading diastolic dysfunction according to the 2016 recommendations (95) has added value in CCS. Whether diastolic dysfunction is associated with asymptomatic systolic dysfunction and predictive of heart failure development warrants further investigation.

CARDIAC MRI. Cardiac MRI is a well-suited imaging technique because geometric assumptions are not needed and the high resolution images enables accurate function assessment with high reproducibility (96). A study in 114 adult survivors showed a significant difference in mean LVEF measured by MRI (55.9%) and 2-dimensional echocardiography (61.0%). Cardiomyopathy (LVEF <50% measured with MRI)

was identified in 12 CCS (11%) previously undiagnosed by 2-dimensional echocardiography (89). The added value of this modality could lie in the abilities of tissue characterization (i.e., edema and fibrosis), right ventricle systolic function assessment, precise volumetric and strain assessment of other cardiac chambers aside from the LV. Thus, cardiac MRI enables evaluation of structural and functional changes induced by cancer treatment. Yet, studies investigating the role of cardiac MRI in CCS are scarce (97–100).

BLOOD BIOMARKERS AND ELECTROCARDIOGRAPHY. The limited diagnostic value of the blood biomarkers N-terminal pro-B-type natriuretic peptide and (high-sensitive) cardiac troponins in the detection of myocardial dysfunction by echocardiography more than 1 year after cancer diagnosis was shown in a recent systematic review (101). Conflicting results on the predictive value of natriuretic peptides and troponins measured during cancer treatment for subsequent anthracycline cardiomyopathy exist in CCS (102,103). In adult cancer patients, the predictive value of elevated high-sensitive cardiac troponins during cancer treatment for early-onset cardiotoxicity may be more suggestive at specific timepoints (91,104).

ECG parameters may also aid in the prediction of myocardial dysfunction. A recent study in anthracycline-treated CCS showed that the QTc interval after chemotherapy was associated with subsequent LV dysfunction (105).

GUIDELINES FOR SURVEILLANCE AND TREATMENT OF CARDIAC DISEASE IN CHILDHOOD CANCER SURVIVORS. The IGHG aims to develop guidelines for surveillance of survivors of childhood cancer and young adult survivors by a global interdisciplinary collaboration (106). Within the guideline development process, recommendations are formulated based on existent national follow-up guidelines and evidence summaries (107–110). Recommendations cover the clinical questions: 1) Who needs surveillance?; 2) Which surveillance modality should be used?; 3) At what frequency and for how long should surveillance occur?; and 4) What should be done when abnormalities are found?

Cardiomyopathy surveillance guideline. The IGHG cardiomyopathy surveillance guideline was published in 2015 (111) and efforts are underway to update this guideline. It serves to define risk groups for the development of cardiomyopathy based on cardiotoxic exposure. CCS treated with anthracycline doses ≥250 mg/m^2, chest RT dose ≥35 Gy, or a combination of anthracyclines ≥100 mg/m^2 and chest RT dose ≥15 Gy are regarded as high risk. Anthracycline doses of 100 to 250 mg/m^2 or chest RT doses 15 to 35 Gy are regarded as moderate risk, and anthracycline doses <100 mg/m^2 as low risk. Echocardiographic surveillance is strongly recommended every 5 years or more frequently in high-risk CCS. It is reasonable to also surveil every 5 years in moderate- and low-risk CCS. Surveillance should start no later than 2 years after the completion of cardiotoxic therapy. The IGHG furthermore strongly recommends routine screening for and management of cardiovascular risk factors and counseling on smoking cessation and regular exercise.

Participation rates of high-risk CCS to guideline-based echocardiographic surveillance were shown to be less than one-third. In one RCT, telephone counselling more than doubled the participation rate in the subsequent year after correction for recommended surveillance frequency (112).

Until now, the IGHG did not formulate treatment recommendations for cardiomyopathy in CCS. When abnormalities are detected, this guideline recommends referral to a cardiologist. Clinical practice guidelines applied by (pediatric) cardiologists after referral are summarized in the section below on guidelines for management of cardiomyopathy in CCS.

Coronary artery disease surveillance guideline. The IGHG is currently finalizing a guideline for asymptomatic CAD surveillance in childhood, adolescent, and young adult cancer survivors (113). Preliminary studies suggest that there is insufficient evidence to recommend a particular surveillance modality in asymptomatic CCS treated with chest RT. Emphasis is placed on awareness of premature CAD risk in survivors treated with chest RT. Risk assessment and surveillance and management of modifiable cardiovascular risk factors is needed. Knowing that there is already a difference in the incidence of CAD between CCS and siblings in their late 20s, clinicians should be aware of the potential atypical presentation of CAD in younger patients (17,107).

Other cardiac disease surveillance guidelines. As the modality of choice for the evaluation of valvular disease is echocardiography, assessment of valve function and structure are usually incorporated in the surveillance of CCS who are at risk with chest RT doses >15 Gy (111). Furthermore, assessment of pericardial structural abnormalities is possible as well. When abnormalities are detected, a cardiologist should be consulted as specified in some national guidelines (107,109). To detect arrhythmia in an early phase, some national groups suggest performing an electrocardiogram at the initiation of long-term follow-up (107,109).

TABLE 1 Future Directions in Cardio-Oncology Research in Childhood Cancer Survivors

Future Research Directions	Study Design(s) to Answer Research Question
Cardiac diseases	
Detailed risk and risk factor analysis of cardiac diseases after childhood cancer	Cohort studies and case control studies
Prevention of anthracycline cardiotoxicity	
Safety and effectiveness of dexrazoxane	RCTs and observational studies in high-risk survivors and risk prediction model-guided studies
Effectiveness of liposomal anthracyclines	
Effectiveness of longer infusion duration	
Effectiveness of pharmacologic heart failure treatments	A RCT on low-dose carvedilol in high-risk CCS is ongoing (123)
Management of cardiovascular risk factors	
Effectiveness of risk factor modifications to prevent cardiovascular events in CCS	Prospective trials and RCTs in CCS with cardiovascular risk factors present
Effectiveness of lifestyle interventions in CCS	Prospective trials and RCTs in CCS
Risk prediction models	
Improvement with additional predictors (genetic, echocardiography, ECG, and blood biomarkers)	Cohort studies with validation in an independent cohort
Benefit of longitudinal measurements to update individual risk predictions	Landmark analysis or joint modeling within cohort studies with external validation
The incremental predictive value of machine learning algorithms compared to classical regression	Multicenter cohort studies with a large number of events.
Clinical impact of prediction models	Cluster RCTs, decision curve analysis
Early detection of cardiac disease	
Usefulness of (strain) imaging, ECG parameters, and blood biomarkers in early detection	Cohort studies, (cluster) RCTs of different surveillance strategies
Identification of novel blood biomarkers for cardiac disease	Proteomics/metabolomics in case-control studies with validation in cohort studies
Genetics	
Genetic susceptibility for other diseases than anthracycline cardiomyopathy	Cohort studies with uniform cardiotoxicity event definitions, replication in independent cohorts
Identification of novel genetic variants	GWAS or WGS in large (multicenter) cohort studies
Clinical usefulness of genetic risk stratification	Cohort studies with time to event analysis

CCS = childhood cancer survivors; ECG = electrocardiography; GWAS = genome-wide association studies; RCT = randomized controlled trial; WGS = whole-genome sequencing.

Guidelines for management of cardiomyopathy in CCS. The IGHG cardiomyopathy guidelines refers to (pediatric) cardiology guidelines for further investigation and management of cardiac abnormalities (114–116). However, an exact threshold for abnormal systolic function is not defined. In the general adult population, a LVEF <40% is a robust indicator that medical therapy reduces mortality, regardless of heart failure symptoms. Treatment decisions for patients with a LVEF 40% to 49% should be a "shared decision" balancing prognosis, heart failure symptoms, and the individual's treatment tolerance (115,116). In practice, these thresholds are often extrapolated to CCS in the absence of survivor-specific evidence.

There is a lack of evidence to support treatment recommendations in CCS. A Cochrane systematic review identified only 1 RCT that evaluated the initiation of angiotensin-converting enzyme-inhibitors for CCS with asymptomatic cardiac dysfunction (117). This study only showed improvement in LV wall stress by echocardiography. Possible reasons for failure to show an effect on clinical endpoints are the relatively short follow-up time (median, 2.8 years) and liberal inclusion criteria (118).

The European Society of Cardiology published a position paper for the diagnosis and management of cancer patients and survivors in adult cardiology (119). The paper recommends prompt initiation of an angiotensin-converting enzyme inhibitor and β-blocker in those with cardiac dysfunction during cancer therapy based on the high risk of developing heart failure. However, these recommendations were not based on RCT data. In long-term follow-up, general heart failure guidelines should be followed (115,116).

FUTURE PERSPECTIVES

Looking forward, there is a critical need for prospective and interventional studies to address most open research questions (Table 1). The current lack of

intervention studies in CCS may be due to the long follow-up required for clinical events. Therefore, initially, intermediate imaging or blood biomarker outcomes may be useful as a proof of concept before conducting larger trials.

The safety and effectiveness of primary prevention strategies, including dexrazoxane, and secondary prevention strategies, such as modification of cardiovascular risk factors and treatment of asymptomatic myocardial dysfunction, can ideally be studied in RCTs or large observational studies. Prevention and surveillance may be further individualized with prediction model-guided care after evaluation of their clinical impact.

Myocardial fibrosis and edema quantification with cardiac MRI are promising techniques to improve risk stratification and may facilitate earlier detection (39). The usefulness of echocardiographic strain imaging, ECG, and blood markers in the early detection of cardiotoxicity in long-term childhood cancer survivors is currently being investigated in the Dutch LATER cohort study (120). In addition, modeling complex interactions and nonlinear relationships between predictors and outcomes with machine learning algorithms may be a valuable addition to classic regression models in childhood cancer survivors when samples sizes are sufficient (121).

CONCLUSIONS

Cardiac disease after the treatment of childhood cancer is an important health problem for survivors of childhood cancer. Optimal survivorship care, including collaboration between pediatric oncologists and cardiologists, is needed to detect and treat cardiac abnormalities in an early phase. During the past decade, a large body of evidence on cardiac diseases in CCS has been collected through cohort studies that can improve current international surveillance guidelines. New insights into the impact of risk factors such as mitoxantrone should be incorporated in discussions on new treatment protocols for children with cancer and in guidelines for follow-up care. Apart from the treatment-related risk, lifestyle interventions may be important to modify cardiovascular risk factors and prevent cardiovascular events in aging survivors. Prediction models that have been developed for heart failure, ischemic heart disease, and cardiovascular mortality await clinical impact analysis to guide individualized preventive measures, surveillance, and treatment decisions. A better understanding of genetic susceptibility for anthracycline-induced cardiomyopathy and underlying pathophysiologic mechanisms have the potential to improve both risk stratification and the development of primary and secondary prevention strategies. Translating research into the care for survivors is complex and requires a multidisciplinary approach from researchers, epidemiologists, (pediatric) oncologists, and cardiologists.

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KEY WORDS cardiotoxicity, cardiovascular risk factors, childhood cancer survivors, prevention, risk prediction

APPENDIX For supplemental tables and references, please see the online version of this paper.

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