Curr Treat Options Cardio Med (2019) 21: 79
DOI 10.1007/s11936-019-0788-2

Women's Health (M Wood, Section Editor)

Cardiovascular Disease Risk in Survivors of Breast Cancer

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Published online: 9 December 2019

This article is part of the Topical Collection on *Women's Health*

Keywords Breast cancer survivors · Cardio-oncology · Chemotherapy cardiotoxicity

Abstract

Purpose of review Early detection and improved treatment in breast cancer have resulted in an increased number of survivors. Cardiovascular disease now remains an important cause for morbidity and mortality in this population. There is a growing gap in the knowledge about the optimal long-term cardiovascular management of this population.
Findings Breast cancer and cardiovascular disease share a number of common risk factors. Different breast cancer treatment modalities, including anthracyclines, radiation, and hormonal therapy, can act in synergy with preexisting and/or new cardiovascular risk factors to result in significant cardiovascular disease.
Summary We summarize the recent evidence about cardiovascular effects of breast cancer therapy and recommendations for their diagnosis and management during the cancer treatment continuum into survivorship. We also present current research initiatives and how they inform clinical care.

Introduction: The current landscape of survivorship in breast cancer

There were more than 3.5 million breast cancer (BC) survivors in the USA in 2016, with an increase of approximately one million survivors compared to the 2006 report [1]. This unprecedented, rapid growth in survivorship can be largely attributed to the improved screening and treatment [2] with overall 5-, 10-, and 15-year early stage BC survival rates of 91%, 86%, and 80%, respectively [3].

Table 1. Shared risk factors between breast cancer and cardiovascular disease

Shared risk factor	Interventions	Facts/outcomes
Age	**	• Increasing age is risk for BC, higher with CVD after menopause [24] • < 40 and > 80 years at BC diagnosis had poorer prognosis [25]
Alcohol intake	*Abstinence or moderate intake*	• Any alcohol intake increases risk of BC [9••, 26, 27] • Higher risk of hormone receptor^{+} BC with alcohol consumption [28] • Modest intake reduces risk of CVD [29]
Western diet	* *Prudent diet [higher take of fruits, vegetables, fruits, fish, poultry, and whole grains]* † *Adherence to the 2020 AHA 7 health metrics* ‡ *Reduced fat intake; increased fruits, vegetables and grains* *Anti-inflammatory diet*	• Less consistent data for relationship between BC and Western Diet [9••] • * Prudent diet reduces risk of CVD [11] • Healthy diet reduces risk estrogen receptor negative BC [12] • † Inverse incidence of BC [10] • ‡ Reduced risk of death from BC in postmenopausal women [15•] • ¶ May decrease risk of cancer recurrence and overall mortality in BC patients [30]
Familial history	**	**
Hormone replacement therapy	*Avoid long-term hormone replacement therapy when feasible*	• HRT significantly increases risk for BC and coronary heart disease [31] • Continued, prolonged use of HRT increases risks for BC and death [32]
Overweight/obese	*Lifestyle modifications (e.g., dietary)*	• Postmenopausal women: increasing BMI increased risks of BC [17] • Premenopausal women: increased BMI decreases risk of BC [18] • Premenopausal women: short term weight gain increased risk of BC [19] • Early, continued weight gain after definitive therapy in triple negative BC [20]
Physical inactivity	*Physical activity, structured programs promoting lifestyle modifications (e.g., dietary and exercise based interventions)*	• 12-month commercial lifestyle modification program, decreased total adipose tissue and TNFα in BRCA1/2^{+} BC survivors [33] • 12-week diet/exercise program improved metabolic risk biomarkers and insulin resistance indicators in overweight/obese BC survivors [34] • 3x/week (for 16 weeks) resistance and aerobic exercise program reduced metabolic syndrome, sarcopenic obesity, and corresponding markers (insulin, IGF-1, leptin, adiponectin) in sedentary, overweight, or obese BC survivors [35]

Table 1. (Continued)

Shared risk factor	Interventions	Facts/outcomes
		• Cardiac rehabilitation model (personalized aerobic and resistance exercise sessions plus educational sessions to promote behavioral adoption to healthy lifestyle) significant improvements in cardiorespiratory fitness, QoL and mental health among BC survivors [36]
Tobacco usage	*Avoid active and passive smoking*	• Link between smoking and BC is less certain [37, 38] • Smoking is a known risk factor for CVD [38]

BC = breast cancer, CVD = cardiovascular disease, AHA = American Heart Association, HRT = hormone replacement therapy, BMI = body mass index, TNF = tumor necrosis factor, IGF = insulin like growth factor, QoL = quality of life

BC is a heterogenous group of diseases that can be classified according to the spread of disease, tumor grade, hormonal molecular expression of estrogen and progesterone receptors (ER and PR), expression of human epidermal growth factor receptor 2 (HER2), and genomic testing. The American Joint Committee on Cancer has developed prognostic stages (0–IV) of BC that go beyond the traditional TNM classification and incorporate the tumor grade and molecular characteristics, anatomic extent of the tumor, as well as genetic testing when available [4]. This staging directs treatment options and prognosis: 5-year disease-specific survival rates are 96.6% for stage I, ~ 91% for stage II, and 33.3% for stage IIIC disease [4]. Survivorship in cancer, including BC, is defined "from the time of diagnosis, through the balance of his or her life" as stated by the National Cancer Institute and endorsed by the National Comprehensive Cancer Network Survivorship Panel and American Society of Clinical Oncology [5]. This definition encompasses patients during treatment with curative intent or chronic management of disease; however in clinical practice survivorship, more refer to the period after completion of definitive therapy. With increasing number and age of BC survivors, non-cancer morbidity and mortality have become an important focus for clinicians [6•]. Among older women diagnosed with BC, for example, cardiovascular disease (CVD) represents the leading cause of death [6•, 7]. In this review we summarize current knowledge of the shared risk factors for CVD and BC, CVD effects from BC treatments, and management approaches to CVD in BC survivorship.

Shared cardiovascular disease and breast cancer risk: Can it be modified?

There is significant overlap between risk factors for BC and CVD including western diet, physical inactivity, sedentary lifestyle, smoking, age, family history, and hormone replacement therapy [8, 9••]. Prospective data from the Atherosclerosis Risk in Communities (ARIC) study has shown that control of CVD risk factors, as identified by seven health metrics (e.g., dietary intake, smoking, obesity, etc.), has shown an inverse incidence of cancer occurrence with increasing control of these health behaviors [10]. Furthermore, a prospective cohort study in women demonstrated that a diet high in vegetables, fruits, legumes, fish, poultry, and whole grains decreased mortality from CVD [11]. The relationship between diet and BC is less well understood. A number of observational and epidemiologic studies showed mixed results [9••]. There is evidence that consumption of a healthy diet lowers the risk of developing estrogen negative breast cancer [12]. A review of epidemiologic evidence and laboratory investigations suggests hyperlipidemia as an increased risk of BC, specifically ER^+ BC [13]. Cancer registry data from Canada showed that women with high dietary cholesterol intake were at increased risk (relative risk 1.48) for postmenopausal BC [14]. Recent post hoc analysis of a large randomized trial of 48,835 women in the Women's Health Initiative reported significantly reduced risk of death in postmenopausal women who developed BC and were randomized to a diet consisting of reduced fat intake and increased fruit, vegetable, and grains [15•].

Table 2. Examples of systemic therapy options (chemotherapeutics, biologics, and endocrine therapy) and radiation in breast cancer with associated cardiovascular side effects

Cancer treatment type	Typical regimens	Cardiovascular effects
Alkylating agents (e.g., cyclophosphamide)	ACTH, ACTHP, dd AC-T, FEC, FEC-DH, TC, TAC	Cerebrovascular events [44•] Hypertension [44•] Left ventricular systolic dysfunction [9••, 44•, 45••] Myocardial ischemia [44•] Pericardial disease [9••, 45••] QTc prolongation [46] Troponin elevation [46]
Anthracycline (e.g., doxorubicin and epirubicin)	ACTH, ACTHP, dd AC-T, FEC, FEC-DH, TAC	Atrial fibrillation [47] Endothelial dysfunction [44•] Increased total left ventricular extra-cellular volume [48] Left ventricular systolic dysfunction and HF [9••, 44•, 49, 50••, 51–53] Valvular heart disease [51]
Antimetabolites (e.g., 5-fluoururacil and capecitabine)	FEC, FEC-DH	Atrial fibrillation, ventricular arrythmias [9••] Chest pain, palpitations, MI, cardiogenic shock, cardiac arrest [54] Coronary artery spasm, myocardial ischemia [44•] HF [55]
Endocrine therapy – tamoxifen	Used in prevention, early stage, or advanced metastatic HR^+ BC	Decrease total serum cholesterol and LDL-C [56, 57] VTE [58•, 59•]
Endocrine therapy – aromatase inhibitors (anastrozole, letrozole, exemestane)	Used in prevention, early stage, or advanced metastatic HR^+ BC	Angina and MI [58•] Hyperlipidemia [9••, 60]
HER-2-targeted therapy (e.g., trastuzumab, pertuzumab, lapatinib)	ACTH, ACTHP, FEC-DH, T-DM1, TCH, TCHP, TH, THP	Left ventricular systolic dysfunction and HF [9••, 44•, 45•, 61] Right ventricular dysfunction [62]
Taxanes (e.g., paclitaxel and docetaxel)	ACTH, ACTHP, dd AC-T, FEC-DH, TC, TAC, TCH, TCHP, TH, THP	Asymptomatic bradycardia [63] AV block, LBBB and ventricular arrhythmias [63] HF (docetaxel) [52] QTc prolongation [46] Troponin elevation [46]
CDK 4/6 inhibitors (e.g., ribociclib)	Administered with AI or fulvestrant	QTc prolongation (ribociclib) [9•, 64] VTE (palbociclib and ribociclib) [65]

Increased body mass index (BMI) has established risk for CVD [16] and BC, although the latter is confounded by menopausal status and less well understood. A review of 50 epidemiological studies concluded that in postmenopausal, nonhormonal therapy using women, each 5 kg weight gain was associated with an increased relative risk of BC by 1.11 [17]. Meta-analysis data in premenopausal women showed that BMI and risk of BC may be inversely related, while in a population-based study, short-term weight gain significantly

Table 2. (Continued)

Cancer treatment type	Typical regimens	Cardiovascular effects
Radiation therapy	*	Cardiomyopathy and HF [9••, 45••, 51, 66•] CAD [9••, 44, 51, 66•] HFpEF [67] Pericardial disease [9••, 66•] Vascular/endothelial dysfunction [44•] Valvular heart disease [9••, 45••, 51, 66•]

ACTH (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab), ACTHP (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab), dd AC-T (doxorubicin/cyclophosphamide-paclitaxel), FEC (5-fluorouracil, epirubicin, cyclophosphamide), FEC-DH (5-fluorouracil, epirubicin, cyclophosphamide-docetaxel/trastuzumab), TAC (docetaxel, doxorubicin, cyclophosphamide), TC (docetaxel, cyclophosphamide), TCH (docetaxel, cyclophosphamide, trastuzumab), TCHP (docetaxel, cyclophosphamide, trastuzumab, pertuzumab), TH (docetaxel, trastuzumab); THP (docetaxel, trastuzumab, pertuzumab), T-DM1, ado-trastuzumab emtansine. HF = heart failure, MI = myocardial infarction, LDL-C = low density lipoprotein-cholesterol, VTE = venous thromboembolism, AV = atrioventricular, LBBB = left bundle branch block, CAD = coronary artery disease, HFpEF = heart failure with preserved ejection fraction

increased BC risk [18, 19]. In a retrospective analysis of triple negative BC survivors, there was observed weight gain in survivors soon after definitive therapy [20]. This continued for 1 year into their survivorship.

Reduced physical activity (PA) can increase risk of BC and CVD [9••]. Regular PA has shown to attribute to a 12.2% decrease of myocardial infarction (MI) in the population-based INTERHEART case control study across 52 countries [21]. Systematic review of current epidemiological data reported a 25% average risk reduction of BC among physically active women, compared to the least active [22]. While BC survivors may be meeting general PA recommendations, they may have increased risks for obesity and subclinical risk factors for CVD, such as lower peak oxygen consumption [23]. A variety of structured programs aimed at physical inactivity have been demonstrated an improved cardiometabolic profile in BC survivors (Table 1) [33–35, 39]. Cardiac rehabilitation (CR) has proven beneficial in BC survivors, showing improved cardiorespiratory fitness, quality of life, and decreased incidence of depression in a tailored CR model among 247 BC survivors [36]. A statement on CR focused on cancer patients and survivors [40••] has introduced a new vision for a comprehensive approach. The model outlined here has potential for the translation of CR tools and resources to improve outcomes in cancer survivors. In this statement the authors outline opportunities for delivery of exercise, measurement, and tracking of cardiorespiratory fitness in cancer survivors, and an opportunity to promote several services (e.g., nutrition, weight management, etc.).

Alcohol intake is a known risk factor for BC [26, 27] with consumption linked to specific tumor types (e.g., hormone receptor positive) in a meta-analysis of several epidemiologic studies [28]. The relationship between alcohol and CVD is more complex with dose-dependent relationship where modest intake of alcohol is beneficial and heavy intake is harmful [29]. In contrast, smoking is a known risk factor for CVD, while the relationship between BC and smoking has been suggested but is less understood and confounded by menopausal status and genetics [9••, 37, 38].

Postmenopausal hormone replacement therapy (HRT) is a shared risk factor for both BC and CVD. The National Institutes of Health launched the Women's Health Initiative to identify risks and beneficial strategies on the incidence of CVD, cancer, osteoporosis, and fracture among postmenopausal women. A number of clinical trials and observational studies were performed to accomplish this. One large randomized trial from this program on HRT was stopped earlier than anticipated due to significantly exceeding risks of BC and coronary heart disease associated with hormone replacement therapy [31]. In the Nurses' Health Study, biannual questionnaires with 725,550 person-years of follow-up data showed that continued HRT increased risks for BC and death from BC especially if prolonged at 5 or more than 10 years [32].

Non-modifiable risk factors include age and genetics. Increasing age corresponds with higher risks; however menopause marks a divergence where the rate of BC risk

slows but CVD risk increases [24]. The mutations in BRCA1 and two genes are well-known BC risk factors and considered causative in 5–10% of cases [41]. In a prospective study comparing *BRCA 1/2* gene mutation carriers to sporadic BC patients who underwent anthracycline therapy there was no significant difference in cardiac function parameters including left ventricular ejection fraction and global longitudinal strain measured by echocardiography [42]. However, the current recommendations of prophylactic bilateral salpingo-oophorectomy in *BRCA* gene mutation carriers and resultant decreased endogenous estrogen may increase the risk of CVD and coronary artery disease (CAD) [43].

Cardiovascular adverse effects and multimodality breast cancer treatment

Contemporary treatment options for BC include a multimodal approach with surgery (breast conserving or mastectomy), radiation therapy (external beam, or internal methods like brachytherapy, or intraoperative radiation), systemic chemotherapy (anthracyclines, alkylating agents, taxanes, and antimetabolites), endocrine therapy (tamoxifen, aromatase inhibitors, and ovarian suppression therapy), HER2-targeted therapies (monoclonal antibodies and small-molecule tyrosine kinase inhibitors), and new therapies (cyclin-dependent kinase inhibitors) [3, 9••]. The CV effects of commonly used BC treatment modalities are summarized in Table 2. Below we review current CV diagnostic and management strategies for BC patients into their survivorship.

Anthracyclines

Doxorubicin and epirubicin are the most commonly used anthracyclines in BC. The exact molecular mechanism underlying doxorubicin-related cardiotoxicity has not been completely elucidated; however, production of reactive oxygen species, mitochondrial dysfunction, and inhibition of topoisomerase 2ß have all been proposed as important mediators in cardiac injury [68]. The common BC chemotherapy regimens (Table 2) in the USA include coadministration of doxorubicin with taxanes and cyclophosphamide, with addition of targeted HER2 therapy to patients with HER2-positive breast cancer. In clinical practice, the most important cardiac side effects of anthracyclines are cardiomyopathy (also referred as left ventricular systolic dysfunction, LVSD) and heart failure (HF) [9••, 44•, 49]. These effects are directly related to the cumulative lifetime dose of anthracyclines received. This is an important consideration in patients who had a previous cancer diagnosis and had received prior treatment. Unfortunately, BC itself is a recognized late complication among survivors of childhood cancers and is one of the most common secondary malignancies among women treated for a childhood cancer [69••, 70], thus putting this population at a high-long-term risk for cardiotoxicity as well. The American Society of Clinical Oncology (ASCO) clinical practice guideline on cardiac dysfunction in adult cancer survivors provides a helpful framework for identifying patients at risk for cardiac dysfunction [50••]. Criteria for patients at high risk for cardiac dysfunction from anthracycline therapy include:

- Receipt of high dose anthracyclines (defined as equivalent of doxorubicin ≥ 250 mg/m^2 or epirubicin > 600 mg/m^2)
- Receipt of lower dose of anthracyclines (doxorubicin < 250 mg/m^2 or epirubicin < 600 mg/m^2) in combination with lower dose radiation therapy (< 30 Gray) where the heart is present in the treatment field
- Receipt of lower dose of anthracyclines (doxorubicin < 250 mg/m^2 or epirubicin < 600 mg/m^2) in addition to at least one of the following:
  - > Two CVD risk factors (smoking, hypertension [HTN], diabetes, dyslipidemia, obesity)
  - > 60 years old at time of treatment
  - Compromised cardiac function (e.g., left ventricular ejection fraction [LVEF] of 50–55%, previous MI, or at least moderate valvular heart disease)
- Receipt of lower dose of anthracyclines (doxorubicin < 250 mg/m^2 or epirubicin < 600 mg/m^2) followed by sequential trastuzumab therapy

Contemporary treatment regimens for BC now mostly include lower dose anthracycline therapy (equivalent to 240 mg/m^2), and the ASCO guidelines emphasize the importance of CV risk factor identification as part of routine evaluation and risk stratification [69••].

During survivorship, routine LVEF assessment among asymptomatic patients at high risk of cardiac dysfunction (as defined above) is recommended to be considered once, between 6 and 12 months after completion of therapy. In contrary, for patients with clinical signs or symptoms of HF, prompt cardiac evaluation is recommended, including LVEF assessment, cardiac biomarkers, and early referral to a cardiologist to identify

potential cardiac dysfunction [50••]. For asymptomatic patients at increased risk as defined above, cardiac imaging should be performed. Currently, repeated cardiac imaging past the first year of survivorship is not recommended in asymptomatic patients. This is due to lack of evidence that surveillance imaging improves outcomes. A recent large, retrospective cohort study reported a fourfold increase risk of HF in BC patients that received anthracycline therapy, which persisted 10–15 years after treatment [51]. The long-term HF risk in this study population was compounded to an overall ninefold risk when anthracycline therapy was combined with radiation therapy (RT).

There has been increasing interest in primary prevention of anthracycline-induced cardiomyopathy. Several recent randomized control trials (RCTs) have tested the hypothesis that treatment with neurohormonal agents in patients with early stage BC undergoing anthracycline chemotherapy may prevent cardiac dysfunction [71•, 72•]. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA) [71•] was a RCT in 130 BC patients that underwent adjuvant epirubicin-based chemotherapy and were randomized in 2 × 2 factorial design to receive metoprolol succinate, candesartan cilexetil, or placebo. In this study the candesartan group achieved the primary outcome with less overall decline in LVEF as measured by cardiac magnetic resonance (CMR), compared to the metoprolol and placebo groups. Patients who received candesartan also showed significant reduction in total left ventricular cellular volume on CMR suggesting its effects on remodeling [48]. Another RCT, Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity (the CECCY trial) [72•], studied the effects of carvedilol used as primary prevention for LVSD in 200 BC patients receiving doxorubicin. Here carvedilol failed to demonstrate a significant impact on doxorubicin-related LVEF decline, measured at 6 months after treatment. However, this study did show carvedilol led to significantly lower levels of troponin I and diastolic dysfunction by echocardiogram. This evidence may suggest that beta-blockers may attenuate early myocardial injury [72•].

Dexrazoxane is an iron chelator that has been shown to be cardioprotective in BC patients undergoing high dose anthracycline therapy. This has been shown in meta-analysis of several RCTs [73]. It is rarely used with contemporary breast cancer regimens which most often include lower doses of anthracyclines. FDA-recommended usage mirrors this by stating its use in "women with metastatic breast cancer who have received a cumulative doxorubicin dose > 300 mg/m^2 and who will continue to receive doxorubicin therapy to maintain tumor control" [74]. Clinical practice guidelines from ASCO mention similar recommendations, noting intermediate evidence quality and moderate strength of this recommendation [50••].

Anthracycline therapy plays a large role in BC treatment and is incorporated into many chemotherapy regimens (Table 2). Several risk prediction models to determine long-term CVD and cardiac dysfunction have been performed. Recent retrospective analysis of an epirubicin-based regimen showed diabetes, HTN, CAD, and stroke history were independent risk factors for long-term HF incidence [52]. Concurrent therapy with capecitabine, gemcitabine, and bevacizumab in this study was associated with increased odds of long-term HF. These risk factors were incorporated into a score-based model to identify patients at risk for HF and did so with moderate sensitivity (0.79) and specificity (0.65). Another risk prediction model used multi-variate analysis to assess the risks versus benefits of doxorubicin in BC patients [53]. They identified increasing age, higher BMI, and lower baseline LVEF associated with increased cardiotoxicity at 1 year. This study's model stratified these patients receiving doxorubicin into low to high predicted risk of cardiotoxicity at 1 year versus their predicted BC mortality absolute risk reduction, using the PREDICT model [53]. This model has future potential of giving providers an estimated benefit/harm ratio of doxorubicin therapy, thus guiding shared decision-making.

HER2-targeted therapy

Targeted monoclonal antibodies for BC patients with HER2 receptor expression include trastuzumab, pertuzumab, and novel antibody conjugate trastuzumab-emtansine or T-DM1. Trastuzumab and pertuzumab act at the extracellular domain of the HER2 receptor [75]. T-DM1 uses trastuzumab as a vehicle for the delivery of a cytotoxic anti-microtubule drug to cancer cells with HER2 overexpression [76]. Other agents include oral small-molecule kinase inhibitors that target HER2 such as lapatinib [77]. These agents are sometimes given in conjunction with other chemotherapeutic agents, of note anthracyclines (Table 2). This class of medications has well-

Table 3. Examples of professional societies and regulatory recommendations for cardiac imaging in patients at risk

Recommendations by	Patients at risk	Time and frequency of cardiac imaging	Imaging modality
American Society of Oncology Clinical Practice (ASCO) Guideline on Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers [50••]	• High dose anthracyclines* • Lower dose anthracyclines with lower dose RT (< 30 Gy), heart in treatment field • Lower dose anthracyclines with at least two CV risk factors¶, > 60 years old, or baseline compromised cardiac function¥ • Lower dose anthracyclines followed by trastuzumab therapy • Trastuzumab with presence of at least two CV risk factors¶, > 60 years old, or baseline compromised cardiac function¥	• Prior to cancer treatment initiation • After completion of therapy for patients at high risk consider one LVEF assessment between 6-12 months	• Echocardiogram[1] • CMR • MUGA
Food and Drug Administration (FDA) trastuzumab US package insert [78]	• Patients planned to receive trastuzumab therapy	• Baseline LVEF • Every 3 months until completion • Every 6 months for 2 years, following completion as adjuvant chemotherapy.	• Echocardiography • MUGA
American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy [79•]	• Patients planned to receive trastuzumab therapy	• Baseline LVEF evaluation • Every 3 months until completion • Once 6 months after completion, if received cardiotoxic agents prior (e.g., anthracyclines)	• Echocardiography (including 3D and/or GLS)[1] • CMR or MUGA acceptable alternatives
	• Patients planned to receive anthracycline therapy with baseline LVEF > 53%, normal GLS, and negative troponin	• Baseline LVEF evaluation • Follow-up at completion of therapy • 6 months after completion • With every 50 mg/m^2 above total dose of 240 mg/m^2	• Echocardiography (including 3D and GLS)[1] • CMR or MUGA acceptable alternatives

*High dose anthracycline therapy = equivalent of doxorubicin ≥250 mg/m^2 or epirubicin > 600 mg/m^2 and lower dose anthracycline therapy = doxorubicin < 250 mg/m^2 or epirubicin < 600 mg/m^2

¶ Cardiovascular (CV) risk factors = smoking, hypertension, diabetes, dyslipidemia, obesity; ¥ Compromised cardiac function = LVEF 50–55%, previous myocardial infarction, or at least moderate valvular heart disease. 1: indicates preferred imaging method.

CMR = cardiac MRI, Gy = Gray, GLS = global longitudinal strain, LVEF = left ventricular ejection fraction, MUGA = multigated acquisition scan, RT = radiation therapy

Table 4. Recent primary and secondary cardioprevention trials in patients with breast cancer

	Population studied	Intervention	Findings/endpoints
PRADA [71•]	130 patients with early BC receiving a epirubicin-based chemotherapy; 22% of patients also received trastuzumab	Randomized to metoprolol succinate, candesartan, and placebo (2 × 2 factorial design)	Candesartan attenuated LVEF decline (2–3%) compared to metoprolol or placebo, measured by CMR at end of therapy (10-64 weeks)
CECCY [72•]	200 patients with early BC receiving doxorubicin based chemotherapy, no trastuzumab	Randomized to carvedilol or placebo (1:1)	No significant difference in number of women with decline in LVEF of > 10% measured by echocardiography at 6 months (Carvedilol 14.5%, placebo 13.5%). Secondary endpoint: significantly lower troponin I with carvedilol
MANTICORE [83•]	94 patients with HER2 positive BC patients receiving trastuzumab. 23% of patients also received anthracyclines	Randomized to bisoprolol, perindopril or placebo (1:1:1)	No significant difference in change in LVEDVi measured by CMR at the end of treatment. Secondary endpoint: significant attenuation of LVEF decline with both
Lisinopril or Carvedilol in Reducing Cardiotoxicity [84•]	468 patients with HER2 positive BC, stratified based on the receipt of anthracyclines	Randomized lisinopril, carvedilol or placebo	No significant difference in number of women who declined measured by echocardiography and/or MUGA except subgroup who received con-current anthracycline therapy with both interventions compared to placebo,
SAFE-HEaRT [85•]*	31 patients with preexisting or during treatment LVSD (LVEF 40–49%) and need to receive HER2-targeted chemotherapy.	All treated with carvedilol and ACEi/ARB as tolerated, concomitantly with HER2 therapy. Routine echocardiograms and cardiology assessment.	Met primary outcome of completion of planned oncology therapy without cardiac events (N = 27 or 90% of patients). 2 heart failure events, 1 persistent asymptomatic LV dysfunction despite holding therapy.

PRADA, Prevention of cardiac dysfunction during adjuvant breast cancer therapy; CECCY, Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity; MANTICORE, Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research; SAFE-HEaRT, Safety of HER2-taRgeted Therapies in patients with HER2-positive breast cancer and compromised heart function. *Secondary prevention

documented cardiotoxicity, primarily in the form of LVSD and/or HF [9••, 44•]. This is evident among retrospective review of several clinical trials [61] ultimately giving way to a change in administration methods and routinely recommended cardiac monitoring. The FDA package insert of trastuzumab reflects such recommendations [78]. This includes baseline LVEF via echocardiogram or multigated acquisition scan (MUGA) prior to therapy initiation, followed by LVEF assessment every 3 months until completion. Monitoring is recommended to continue at 6-month intervals for at least 2 years following the completion as adjuvant

therapy (Table 3). Cardiac monitoring recommendations from the American Society of Echocardiography and European Association of Cardiovascular Imaging [79•] reflect the FDA package insert and endorse the same interval (every 3 months), pending LVEF > 53%, normal global longitudinal strain (GLS) values, and negative troponin at baseline. If any of these are abnormal prior to initiation of therapy, prompt cardiology referral is recommended. If HER2 therapy is used sequentially after other potential cardiotoxic agents (e.g., anthracyclines), then an additional onetime assessment at 6 months is recommended after therapy is completed [79•]. A more recent consensus statement from the European Society of Cardiology is in line with this strategy of 3-month intervals, followed by once at completion [45••]. Current recommendations endorse first-choice imaging modality as echocardiography with GLS but state CMR or MUGA as acceptable alternatives [50••, 79•]. Switching between imaging methods is discouraged [45••].

Long-term data on CVD from HER2 therapy show relatively low incidence of occurrence, with most events typically occurring near/around treatment and are reversible [9••, 45••]. Recent long-term follow-up data from the TRYPHAENA clinical trial, where trastuzumab and pertuzumab were used as sequential blockade of HER2 for improved pathologic complete response, showed overall low rates of LVSD (0–2.7%) [80]. While LVSD is well documented, prospective observational imaging data show concomitant right ventricular (RV) dysfunction, measured by RV free wall longitudinal strain on CMR [62], which recovered 18 months after completion of trastuzumab.

Monitoring during therapy plays a significant role for capturing acute cardiotoxicities, but long-term strategies are less defined due to lower incidence. A recent Danish nationwide cohort study showed low overall risks of long-term HF as compared to early HF (hazard ratio of 1.93 vs. 8.69, respectively) [81]. Risk factors in this cohort for long-term HF included age, ischemic heart disease, and diabetes. Data from the Surveillance, Epidemiology, and End Results database used in the development of a risk prediction model for patients undergoing adjuvant trastuzumab therapy demonstrated increased risks in patients over 80, CAD, diabetes, or receiving concomitant anthracycline therapy [82]. Recent ASCO clinical practice guidelines give some guidance on long-term strategies, specifically among increased risk patients who received trastuzumab [50••]. Criteria of these patients at increased risk include:

- Receipt of trastuzumab with at least one of the following:
  - > Two CVD risk factors (smoking, hypertension [HTN], DM, dyslipidemia, obesity)
  - > 60 years old at time of treatment
  - Compromised cardiac function (e.g., LVEF 50–55%, previous MI, or at least moderate valvular heart disease)
- Patients treated with trastuzumab sequentially after lower dose anthracycline therapy (doxorubicin < 250 mg/m2 or epirubicin < 600 mg/m2)

ASCO guidelines on long-term monitoring are similar to previous consensus recommendations [45••, 79•]. This panel recommends cardiac assessment should be performed in increased risk patients (noted above) between 6 and 12 months after completion of HER2 therapy [50••] (Table 3).

Several primary prevention RCTs have attempted to reduce these cardiotoxicities (Table 4). Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE) randomized patients on trastuzumab therapy to perindopril (angiotensin-converting enzyme inhibitor, ACEi), bisoprolol (beta-blocker, BB), or placebo [83•]. The majority of patients studied underwent trastuzumab therapy without anthracyclines (77%). The primary outcome of cardiac remodeling, as measured by indexed left ventricular end-diastolic volume by CMR, was not significantly affected by these interventions. However, they did find significant attenuation of LVEF decline and less interruptions in therapy administration with both ACEi and BB [83•]. A recent RCT, with the largest study population of 468 BC patients treated with trastuzumab, were randomized to lisinopril (ACEi), carvedilol-extended release (BB), or placebo [84•]. Patients were stratified based off receiving anthracycline therapy. A significant decrease in the incidence of cardiac dysfunction was found among both interventions in the anthracycline subgroup. This was not found in the non-anthracycline group, trastuzumab group, nor was the overall study primary outcome of interest (change in LVEF) found to be significant with these interventions. Several aspects of these two studies differ. This includes the different imaging modality used (echocardiography and MUGA) as compared to CMR in MANTICORE and overall higher rates of cardiotoxicity (38% vs. 25%, with and without

anthracyclines) in the latter RCT [84•]. In both studies, patients had overall fewer interruptions in therapy with ACEi and BB. This may prove useful in its own right to allow for continued chemotherapy administration and greater achievement toward oncologic goal of improved BC outcomes. The recently completed prospective SAFE-HEaRt study demonstrated this concept [85•]. Among 30 asymptomatic women with diagnosis of HER2-positive BC (any stage) and reduced LVEF (40–49%), 27 women (90%) were able to succesfuly complete one year of planned oncology therapy in the setting of concomitant administration of beta-blockers and renin-angiotensin inhibitors as well as cardiac follow-up and imaging.

Hormonal therapy

BC patients with hormone receptor expression of ER and/or PR are managed with medications such as tamoxifen and aromatase inhibitors (AIs) (e.g., anastrozole, letrozole, or exemestane). Tamoxifen is the choice in premenopausal women [9••, 69••]. Both result in decreased estrogen production. Tamoxifen via competitive binding at the estrogen receptor and decreased production [86]. AIs inhibit endogenous production via enzymatic inhibition [87]. The use of these medications as adjuvant therapy, usually for years in BC survivors, stresses the importance for attention to adverse long-term CVD.

A recent large meta-analysis data examined several CVD outcomes in patients on long-term hormonal therapy [58•]. For example, AIs when compared to tamoxifen, were shown to have increased relative risk for angina and MI. Furthermore, tamoxifen over placebo decreased the risk of anginal symptoms. The protective effects of tamoxifen are believed to be from its estrogen agonist like actions [9••, 56]. This has also been observed in regard to tamoxifen's favorable effect on lipids, with decreased serum total cholesterol and low-density lipoprotein (LDL) [56, 57]. On the other hand, AIs reduce overall production of estrogen and possibly increasing risk for CVD, including CAD and MI. While adjuvant hormonal therapy may favor employment of tamoxifen over AIs, in regard to MI and CAD, the effects on CVA appear to be mixed in this meta-analysis [58•].

Tamoxifen's estrogen like agonism puts BC survivors at increased risks of venous thromboembolic events (VTE) [9••, 88]. Significant reduced long-term risk of VTE exists with AIs over tamoxifen [58•]. These meta-analysis findings are consistent with recently published prospective data on median follow-up of 5.4 years examining the incidence of VTE in patients on adjuvant hormonal therapy [59•]. AIs were associated with at least 41% lower VTE risk when compared with tamoxifen. Clinicians will need to take into account each of these risks, when managing BC survivors on long-term adjuvant hormonal therapy.

Alkylating agents

Cyclophosphamide is the main agent of this class used in BC treatment. It is often administered with taxanes, antimetabolites, and notably anthracyclines (Table 2). Cerebrovascular events, HTN, myocardial ischemia, VTE, and LVSD are some of the reported CV events [44•, 45••] but are rare. Recent prospective data found significant QTc prolongation and troponin elevation after coadministration with anthracyclines [46]. Overall events are uncommon and limited to days around administration [9••, 45••]. It is important to note in BC that because cyclophosphamide is given in combination with other agents (Table 2), cardiotoxicity may be a result of their coadministration or primarily these other agents.

Taxanes

Paclitaxel and docetaxel are given as part of systemic therapy (Table 2). Their tumor effects include cellular death and apoptosis by stabilizing microtubule polymerization and halting progression in the cell cycle [89]. Previously reported CV effects include arrhythmic events, however without significant morbidity and mortality [63]. Taxanes when administered with epirubicin (anthracycline class) may increase risk for long-term HF in recent long-term retrospective study data [52]. This was specifically seen with docetaxel but not paclitaxel. Taxanes seem to show limited overall cardiotoxic events (Table 2). Arrhythmias, in particular bradycardia, have been reported during administration, however without long-term serious sequelae.

Antimetabolites

Antimetabolites used in BC include 5-fluorouracil (5FU) and its prodrug capecitabine (Table 2). CV effects are mostly related to coronary artery spasm which ranges from limited symptoms to life-threatening ones, occurring infrequently in < 2% of patients (Table 2) [54]. Existing CAD and infusion method have been described

as risk factors for events [9••, 44•]. In a retrospective review, bolus method administration of 5FU resulted in fewer coronary vasospastic events and may be safer over traditional infusion methods in patients who have had adverse events prior [90]. HF has been reported albeit at very low incidence (0–0.7%) during active treatment duration [55]. As most adverse events occur around or during treatment, there is little long-term information on CVD. Further follow-up information on BC survivors exposed to these agents is needed.

Emerging treatment options

Newer medications used in BC include cyclin-dependent kinase (CDK) inhibitors, specifically CDK 4/6 inhibitors, and include palbociclib, ribociclib, and abemaciclib. These are administered in hormone receptor-positive BC with an AI or fulvestrant, an intramuscular selective estrogen receptor degradation agent [91]. Review data suggest adverse effects are primarily noncardiac such as leukopenia, anemia, thrombocytopenia, fatigue, vomiting, and diarrhea [9••, 92]. However, QTc prolongation and thromboembolic events have been observed.

QTc prolongation was observed primarily with ribociclib. As a result, current recommendations include starting this agent with a baseline QTc of < 450 msec and routine ECGs during treatment [9••, 64, 69••]. Recent results from MONALEESA-7, an international RCT, indicated significant improvement in survival from 46% to 70% at 42 months when ribociclib was added to standard endocrine therapy as compared to endocrine therapy alone [93]. These results suggest that ribociclib is likely to become integrated into routine care for hormone receptor BC. Therefore, the need to establish monitoring and treatment practices for QTc prolongation is warranted. Thromboembolic events, including pulmonary emboli, have been reported with use of palbociclib and ribociclib, in 1.8% and 5.0% of patients, respectively [65]. While no long-term arrhythmias or other embolic events have been observed from current evidence, long-term CV sequelae need to be further researched.

Radiation therapy

The rate of CVD significantly increases in a dose-response relationship of 7.4% increased risk for CVD with every Gray (Gy) mean heart dose (MHD) of radiation [94]. RT results in cardiotoxicity via a number of proposed mechanisms including general inflammation, microvascular/macrovascular injury, atherosclerotic changes, endothelial damage, and myocardial ischemia/injury that can result in CAD, HF, valvular heart disease, large and medium vessel vasculopathy, and pericardial disease [9••, 44•, 66•, 94].

Recent retrospective data from a long-term follow-up study examined CVD in patients exposed to an older form of RT known as internal mammary chain (IMC) radiation [51]. IMC was associated with significant risks of ischemic heart disease, valvular heart disease, and HF. The cumulative risk for these events was higher with time, persisting up to 20 years after treatment. Importantly, ischemic heart disease (defined here as MI or angina) was significantly higher in patients with an existing CV risk factor. Cumulative incidence of ischemic heart disease was 11.3% versus 6.4% in BC patients who underwent IMC with and without CV risk factors, respectively [51]. With significant overlap in shared risk factors for BC and CVD, this should be noted.

Contemporary RT techniques have included a number of approaches to reduce detrimental CVD effects. These include tailored fields to exclude the heart from the treatment field, cardiac shielding, intracavitary brachytherapy, intensity-modulated RT and proton therapy, intraoperative single-dose radiation, and breath-holding techniques [9••, 44•, 50••, 66•]. With these advances, the effects on the heart and vasculature are likely to be significantly less, however, probably not completely eliminated. Recent studies indicate that even relatively low MHD (2.5 Gy) given as part of contemporary RT may result in previously unrecognized forms of RT toxicity such as HF with preserved EF (HFpEF) [67•].

Patients who received high dose RT of more 30 Gy are at risk for valvular dysfunction, coronary and cerebrovascular events, cardiac dysfunction, as well as pericardial disease [50••, 66•]. Multimodality imaging has been recommended in these patients even if asymptomatic to identify specific pathology and rate of progression [66•]. There is a lack of data to inform screening imaging frequency; however, most documents extrapolate from general valvular and ischemic disease recommendations. It is important to note that patients with history of high doses of therapeutic radiation are at high risk of operative and postoperative complications, in particular. They are best served in specialized centers with expertise on radiation-induced CV disease where novel approaches such as percutaneous options for valvular disease can be considered.

Cardiovascular risk factors and cardiovascular disease within survivorship care

CVD in BC needs to be considered in the context of overall survivorship care. Survivorship guidelines from the National Comprehensive Cancer Network and American Cancer Society/American Society of Clinical Oncology [95, 96] outline the importance of patient education on health lifestyle modifications (e.g., PA, weight loss, smoking cessation) and patient reporting of symptoms concerning for CVD. They also provide information for providers who follow these patients years after definitive therapy on topics such as monitoring for and managing CVD such as HTN, obesity, diabetes, and dyslipidemia. Indeed, management of BC survivors needs to include a number of specialists and providers who work collaboratively and share decision-making with the patient. These include and are not limited to the primary care provider, oncology team (medical oncologist, surgeons, radiation oncologists), cardiology team (advanced practitioners, cardiologist), and ancillary services (dietician, physical medicine, and rehabilitation) [69••]. Future research in this area needs to address effectiveness of lifestyle modifications and CV risk factor control in improving outcomes. We also need models that will allow implementation of CV risk assessment and real-time management of BC survivors at increased risk for cardiac disease.

Compliance with Ethical Standards

Conflict of Interest

Ana Barac has no conflict of interest related to this article. She has received honoraria from Bristol Myers Squibb and serves on the DSMB of CTI Biopharma.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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