ARTICLE TITLE: Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection, and Management

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After reading the article “Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection and Management,” the learner should be able to:
1. Review the most common and most serious types of cardiotoxicity associated with treatment of cancer.
2. Describe options for prevention, diagnosis, and treatment of cardiovascular disease associated with anticancer systemic therapies and radiotherapy.

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Cancer and heart disease are the leading causes of morbidity and mortality in the industrialized world. Modern treatment strategies have led to an improvement in the chances of surviving a diagnosis of cancer; however, these gains can come at a cost. Patients may experience adverse cardiovascular events related to their cancer treatment or as a result of an exacerbation of underlying cardiovascular disease. With longer periods of survival, late effects of cancer treatment may become clinically evident years or decades after completion of therapy. Current cancer therapy incorporates multiple agents whose deleterious cardiac effects may be additive or synergistic. Cardiac dysfunction may result from agents that can result in myocyte destruction, such as with anthracycline use, or from agents that appear to transiently affect left ventricular contractility. In addition, cancer treatment may be associated with other cardiac events, such as severe treatment-induced hypertension and vasospastic and thromboembolic ischemia, as well as rhythm disturbances, including QTc prolongation, that may be rarely life-threatening. Early and late effects of chest radiation can lead to radiation-induced heart disease, including pericardial disease, myocardial fibrosis, cardiomyopathy, coronary artery disease, valvular disease, and arrhythmias, in the setting of myocardial fibrosis. The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of cancer patients, whether they are receiving active treatment or are long-term survivors. Strategies to prevent or mitigate cardiovascular damage from cancer treatment are needed to provide the best cancer care. This review will focus on the common cardiovascular issues that may arise during or after cancer therapy, the detection and monitoring of cardiovascular injury, and the best management principles to protect against or minimize cardiotoxicity during the spectrum of cancer treatment strategies.
cardiomyopathy, coronary artery disease (CAD), valvular disease, and arrhythmias in the setting of myocardial fibrosis. Oncologists face the challenge of treating patients with the best cancer therapies available without adversely impacting CV health. The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of patients with cancer, whether they are receiving active treatment or are long-term survivors after successful treatment. This review will focus on the common CV issues that may arise during or after cancer therapy, the detection and monitoring of CV injury, and the best management principles to protect or minimize the impact of CV issues during the spectrum of cancer therapies.

**Epidemiology of Cancer Therapy-Induced Cardiotoxicity**

Cancer and heart disease are the leading causes of morbidity and mortality in the industrialized world. However, there is cause for optimism. Modern treatment strategies have led to an improvement in the chances of surviving a diagnosis of cancer; the 5-year survival for early stage breast cancer increased from 79% in 1990 to 88% in 2012 and similar improvements have been seen with some other solid and hematological cancers, including non-Hodgkin lymphoma and testicular cancer. Long-term cancer survivors are expected to increase by approximately 30% in the next decade to an estimated 18 million by 2022 in the United States alone. These improvements in survival come at a cost. Current anticancer therapies are associated with unique and various degrees of direct (eg, myocardial toxicity, ischemia, hypertension, arrhythmias) as well as indirect CV insults (eg, unfavorable lifestyle changes). The incidence of cancer treatment-induced CV injury varies widely, depending on the specific cancer therapy used, duration of therapy, and underlying patient comorbidities. In a recent comprehensive review of breast cancer survivors in the United States, women were noted to be at significantly increased risk of death caused by CVD, exceeding their risk of death from the initial cancer itself or from recurrent disease. CVD is the predominant cause of mortality in breast cancer patients over 50 years of age and is a more common contributor than cancer to mortality among older cancer survivors. CVD is not always caused by toxicity from cancer therapy exposures, and it can be a normal disease process in older adults. However, the impact of cancer therapies on CVD in the general adult cancer survivor population is largely unknown. We can gain some insight from longitudinal studies in the pediatric population. The Childhood Cancer Survivor Study showed that, 15 to 25 years after diagnosis, survivors of childhood cancer have an 8.2-fold higher rate of cardiac death compared with the age-matched and sex-matched national average. Compared with controls, long-term childhood cancer survivors had 15-fold increased rates of congestive HF, 10-fold higher rates of CVD, and 9-fold higher rates of stroke. These results have significant implications for adult cancer survivors who face the CV effects of aging compounded by the potential detrimental impact of cancer therapy. Recognition of the importance of CV health in adult cancer patients is paramount if we are to sustain the survival gains achieved with modern cancer therapies.

**Common CV Adverse Events**

**LVD and HF**

Cardiac dysfunction and HF are among the most serious CV consequences of systemic cancer treatment. Conventional chemotherapeutics, such as anthracyclines, antimetabolites, and cyclophosphamide, can induce permanent myocardial cell injury, leading to acute or chronic LVD. Anthracyclines, commonly used in the treatment of solid tumors (ie, breast cancer, osteosarcoma, etc) and hematologic malignancies (Hodgkin/non-Hodgkin lymphoma, acute lymphoblastic leukemia, etc), can trigger significant LVD. Anthracycline-related LVD has historically been considered to be dose-dependent, cumulative, and progressive, which manifest as decreased LV ejection fraction (LVEF) and, ultimately, symptomatic HF in up to 5% of patients. The mechanism of anthracycline-induced cardiac injury has been studied extensively and is still not clearly understood. Structural cardiomyocyte alterations and cell death induced by anthracyclines are mediated in part by reactive oxygen species (ROS) generated in iron-dependent chemical reactions. ROS lead to the peroxidation of myocyte membranes and, after calcium influx, into the intracellular space, which can ultimately lead to permanent myocyte damage. In addition, mechanisms have been identified, including disturbances in DNA topoisomerase 2-β (Top2b) metabolism. The risk of doxorubicin-induced HF (which can occur within hours, weeks, or years after exposure) increases with cumulative dose of anthracycline: 3% to 5% with 400 mg/m², 7% to 26% at 550 mg/m², and 18% to 48% at 700 mg/m². High-risk patients include those at the extremes of age (<5 or >65 years), those who received prior or concurrent chest radiation, and those with preexisting cardiac disease or established CV risk factors.

In a Surveillance, Epidemiology, and End Results (SEER) database review of elderly breast cancer patients, the adjusted hazard ratio (HR) for HF was 1.26 (95% confidence interval [CI], 1.12–1.42) for those who received adjuvant anthracyclines compared with those who received nonanthracycline adjuvant regimens. The cumulative incidence of HF at 10 years was 38% after anthracyclines, 32.5% with nonanthracycline chemotherapy regimens, and 29% with no chemotherapy. The likelihood of anthracycline-induced HF almost doubles with each 10-year increase in age.
Peripheral and coronary artery disease (CAD) (HR, 1.31 and 1.58, respectively), diabetes (HR, 1.74), hypertension (HR, 1.45), as well as emphysema and chronic bronchitis (HR, 1.68), represent additional predictors of increased risk for cardiac dysfunction. The risk of HF remains higher for patients who receive anthracyclines compared with those who receive other agents, even after excluding elderly patients and those with relevant comorbidities. Cancer treatment-induced HF occurs with several other traditional chemotherapeutic agents, including cyclophosphamide (7%-28%) and docetaxel (2.3%-8%) (Table 1). The potential for permanent cardiac damage with exposure to anthracyclines has led to the adoption, in some clinical settings (ie, early stage breast cancer), of chemotherapy regimens with lower cumulative anthracycline exposure.

Many targeted therapies, particularly monoclonal antibodies and tyrosine kinase inhibitors (TKIs), targeting human epidermal growth factor receptor 2 (HER-2) (ie, trastuzumab, pertuzumab, etc), vascular endothelial growth factor (VEGF), and VEGF receptors (ie, bevacizumab, sunitinib, sorafenib, etc), and Abl kinase activity (ie, imatinib, nilotinib, dasatinib, etc), have been demonstrated to interfere with molecular pathways crucial to CV health. LVD associated with targeted therapies has been most extensively evaluated in the breast cancer population treated with trastuzumab. Trastuzumab binds to the extracellular domain of the erb-b2 receptor tyrosine kinase 2 (ErbB2)/HER2 and leads to reduced ErbB2 signaling via several mechanisms. It has been speculated that the cardiac dysfunction associated with trastuzumab is a direct consequence of ErbB2 inhibition in cardiomyocytes. Mice with cardiac-specific deletion of ErbB2 develop dilated cardiomyopathy and demonstrate exaggerated systolic dysfunction in response to pressure overload compared with normal mice. Therefore, it would appear that ErbB2 receptor signaling is important in the maintenance of myocardial function. In contrast to anthracycline–induced cardiotoxicity, trastuzumab exposure can result in LVD and HF that appears mostly reversible. At highest risk for cardiotoxicity from trastuzumab exposure are those aged >50 years, patients with underlying heart disease or hypertension, those with baseline LVEF between 50% and 55% or lower, and those who have also received anthracycline therapy. The introduction of adjuvant trastuzumab for patients with HER2-positive, early stage breast cancer has reduced the risk of breast cancer recurrence by 50% and mortality by 33%. However, in the 5 major adjuvant trastuzumab trials (summarized in Table 2), symptomatic, severe HF/cardiac events, ranging from 0% to 3.9%, were observed with the addition of trastuzumab to traditional chemotherapy. Long-term follow-up of the pivotal adjuvant trials have demonstrated the cardiac safety of trastuzumab with no substantial increase in CV events over 8 to 10 years, even with longer term trastuzumab therapy. However, it is difficult to generally define cardiac toxicity across studies, as criteria vary by trial. Current clinical trials in early breast cancer are taking advantage of the role of dual HER2 blockade, including the synergistic activity of pertuzumab and trastuzumab. To date, there has not been any additional cardiac safety concern when those agents were combined; however, we await the results of a large, prospective, randomized trial (Aphinity trial) exploring this combination in the adjuvant setting. Two neoadjuvant studies (Neosphere, Tryphaena) demonstrated higher pathological complete response rates in women with breast cancer treated with chemotherapy and dual HER2 blockade (pertuzumab, trastuzumab) compared with chemotherapy.

**TABLE 1. Potential Cardiac Toxicity Induced by Anticancer Chemotherapeutic Agents**

| DRUG          | STUDY                      | TOXIC DOSE RANGE | CARDIAC TOXICITY                  | FREQUENCY OF OCCURRENCE |
|---------------|----------------------------|------------------|-----------------------------------|-------------------------|
| Doxorubicin   | Chlebowski 1979           | > 450 mg/m²²     | Left ventricular dysfunction       | Common                  |
| Epirubicin    | Tjuljandin 1990           | > 900 mg/m²²     | Left ventricular dysfunction       | Common                  |
| Idarubicin    | Anderini 1995             | 150-290 mg/m²²   | Left ventricular dysfunction       | Intermediate            |
| Paclitaxel    | Perez 1998                | Conventional dose| Left ventricular dysfunction       | Intermediate            |
| Docetaxel     | Kenmotsu & Tanigawara 2015| >100-120 mg/kg   | Left ventricular dysfunction       | Intermediate            |
| Cyclophosphamide | Gottdiener 1981, Goldman 1986 | >10 mg/m²²   | Cardiac ischemia                   | Uncommon                |
| Ifosfamide    | Khandilis 1989, Tasclari 2007, Cancer Care Ontario 2004 | | Cardiac ischemia                   | Common                  |
| Capetitabine  | Sentürk 2009              | Conventional dose| Cardiac ischemia                   | Intermediate            |
| Fluorouracil  | Sentürk 2009, Schimmel 2004, Chanan-Khan 2004 | | Cardiac ischemia                   | Intermediate            |
| Paclitaxel    | Perez 1998                | Conventional dose| Cardiac ischemia                   | Uncommon                |
| Docetaxel     | Kenmotsu & Tanigawara 2015| Conventional dose| QTC prolongation                   | Common                  |
| Trabectedin   | Lebedinsky 2011           | Conventional dose| QTC prolongation                   | Uncommon                |
| Arsenic Tioxide | Brana & Taberno 2010 | Conventional dose| QTC prolongation                   | Uncommon                |
| Paclitaxel    | Perez 1998                | Conventional dose| QTC prolongation                   | Common                  |

*Common indicates that more than 5% reported incidence; intermediate, between 1% and 5% reported incidence; uncommon, less than 1% reported incidence.
and trastuzumab therapy alone. In the Tryphanea study, the primary endpoint of cardiac safety was met, with a low incidence of symptomatic and asymptomatic LV systolic dysfunction across all arms.58

Cardiac dysfunction has also been reported with angiogenesis inhibitors, including bevacizumab (1.7%–3%) and sunitinib (4%–11%).59 Inhibitors of VEGF receptors, such as sunitinib and sorafenib, block several tyrosine kinase receptors,52 thus making it difficult to identify which targets mediate cardiotoxicity.59 Preclinical studies have associated sunitinib therapy with LV systolic dysfunction related to the inhibition of 5’ adenosine monophosphate-activated protein kinase (AMPK), a regulator of cardiomyocyte response to stress.60 This inhibition leads to a condition of energy depletion and consequent cardiomyocyte dysfunction. Mitochondrial dysfunction may explain the transient episodes of LV systolic dysfunction observed in clinical practice. A marked increase in systemic vasoconstriction, increasing the afterload on a susceptible LV, provides another plausible explanation for LV systolic dysfunction.61

The hypothesis of reversibility for cardiac damage is not unique to toxicity exposure from chemotherapy or targeted agents, because the features of stunning or hibernation of the myocardium are well established in cardiac physiology.62 Myocyte injury may also be reversible if the extent of damage has not met a threshold of irreversibility; if cell death exceeds this threshold, then it will result in potential permanent LV contractile dysfunction. The distinction between reversible and irreversible cardiac dysfunction, however, is somewhat arbitrary. In fact, if LVD is detected early and appropriate HF-based treatment is instituted, even anthracycline cardiac damage may be reversible.63

### Hypertension

The TKIs, which include certain VEGF signaling pathway (VSP) inhibitors, such as sorafenib and sunitinib, commonly cause hypertension.64 Although these are effective anticancer agents, their clinical use may be limited by their potential negative impact on CV health. Hypertension is the most frequent cardiotoxicity observed with VSP inhibitors, with a reported incidence of 19% to 47% (see Table 3).60,65–76 The mechanisms of hypertension induced by VSP inhibitors have recently been reviewed15 and include: reduced nitric oxide production in the wall of arterioles, increased endothelin-1 production, and capillary rarefaction that results in the reduction of effective capillary beds.12,77 In addition, VSP inhibitor-induced hypertension is perhaps related to VEGF-mediated suppression of nephrin, a transmembrane protein that is important for the maintenance of the glomerular slit diaphragm, which may contribute to proteinuria seen with this class of drugs. Strategies to attenuate or prevent VSP inhibitor-induced hypertension are necessary to prevent cardiac dysfunction and early termination of effective anticancer therapy.

### Vascular Thrombosis and Ischemia

Several of the newer TKIs (dasatinib, nilotinib, and ponatinib) that have revolutionized the treatment of some hematologic cancers appear to be associated with important vascular events.78,79 There is also an increased rate of thrombotic adverse events in patients treated with combination therapy for multiple myeloma that includes dexamethasone, revlimid, and proteasome inhibitors like carfilzomib.80,81

### Table 2. Cardiotoxicity in the Major Adjuvant Trastuzumab Trials for HER2-Positive Patients

| TRIAL           | DESIGN                        | ASYMPTOMATIC DROP IN LVEF, % | SYMPTOMATIC DROP IN LVEF, % | SEVERE CHF/CARDIAC EVENTS (CHF OR DEATH), % | DISCONTINUED H FOR CARDIAC REASONS, % |
|-----------------|-------------------------------|------------------------------|------------------------------|---------------------------------------------|--------------------------------------|
| NSABP B31 (Perez 201147), n = 2043 | AC × 4 + T vs AC × 4 + TH + H | 34 vs 17                     | 3.9 vs 1.3                     | 18a                                         |                                      |
| NCCTG N9831 (Perez 201147), n = 2766 | AC × 4 + T vs AC + T + H vs AC × 4 + TH + H | 3.3 vs 2.8 vs 0.3             |                              |                                              |                                      |
| BCIRG 006 (Samon 201148), n = 322; update with SABCS 2009 | AC × 4 + T vs AC × 4 + TH + H vs TCAH | 18 vs 10 vs 8.6               | 1.87 vs 0.38 vs 0.38           |                                              |                                      |
| HERA (Goldhirsch 201349, Baselga 200650), n = 5102 | Adj CT → H vs Adj chemo alone2 | 3.04 vs 0.53 OR              | 1.7 vs 0.06                    | 0.6 vs 0                                     | 4.3                                  |
| FinHer (Baselga 200650), n = 232 | V or T ± H → FEC × 38        | 7.03 vs 2.05                 | 3.5 vs 6.0                     |                                              |                                      |

| ±, with or without; A, anthracycline; AC, anthracycline plus cyclophosphamide; Adj, adjuvant; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; Ca, carboplatin; chemo, chemotherapy; CHF, cardiac heart failure; E, epirubicin; F, 5-flouroracil; FEC, 5-fluorouracil, epirubicin, plus cyclophosphamide; FinHer, Finland Herceptin trial; H, trastuzumab; HERA, Herceptin Adjuvant trial; LVEF, left ventricular ejection fraction; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; SABCS, San Antonio Breast Cancer Symposium; T, taxane; TCAH, taxane, carboplatin, plus trastuzumab; V, vinorelbine. aBecause of unacceptable drops in LVEF, 3.23% did not receive H after A. bBecause of unacceptable drops in LVEF, 5.0% did not receive H after A. The study included an A-free arm. cNinety-six percent of chemotherapy was A-containing. dThere were no patients who had prior A exposure before H exposure; H exposure was limited to 9 weeks. eThe study included an A-free arm. fThere were no patients who had prior A exposure before H exposure; H exposure was limited to 9 weeks.
of these events varies, depending on the exact agent used and the severity of the hematologic malignancy being treated. The range of vascular problems is related to the vascular beds affected. For instance, dasatinib rarely induces pleural effusions or pulmonary hypertension, although the vascular issues noted with nilotinib are completely different and likely represent progressive atherosclerosis. In addition, combination therapies used in myeloma may increase the risk of venous and arterial thrombotic events. Overall, it is fair to say that these myriad vascular complications are important and ultimately require specific strategies to manage them effectively.

### Rhythm Disturbances and QTc Prolongation

Cancer therapies may be associated with a variety of rhythm disturbances but most notably can prolong the QT interval, potentially leading to ventricular arrhythmias. The use of some medications used in supportive care during cancer therapy (eg, antiemetics, antidepressants) in combination with cancer treatments can lead to QT prolongation. A careful review of drug interactions should be considered the standard of care for all patients receiving cancer treatment. There are specific therapies that have been associated with certain rhythm disturbances, but the mechanism for this association is frequently related to electrolyte abnormalities or concomitant medications that occur in a particular population. Potential QT interval changes may be related to the pharmacologic targets, but this association is difficult to prove. In general, electrolyte abnormalities should be carefully managed, and concomitant medications should be chosen that have minimal impact on rhythm disturbances.

### Radiotherapy-Induced CV Damage

The association of radiotherapy (RT) and cardiac dysfunction is well recognized. Radiation-associated cardiac injuries are especially important in young patients with curable malignancies, in whom the risk of developing clinically significant late cardiotoxicity is high. The development of CV damage after RT may be progressive and can include coronary artery disease, valvular disease, myocardium damage, defects in the conduction system, and diastolic dysfunction. The relative risk of fatal CV events after mediastinal irradiation for Hodgkin disease and for left-sided breast cancer, which are the two most common reasons for RT in young patients, is between 2.0 and 7.0 and between 1.0 and 2.2, respectively. In addition, it is worth highlighting that these data may not reflect contemporary radiation treatment protocols, because RT methods have significantly changed over time. Damage to the arterial endothelium can induce premature atherosclerosis in the coronary circulation, particularly in the left anterior descending and right coronary arteries. This usually occurs 10 to 15 years after RT. Acute pericarditis and either symptomatic or asymptomatic chronic pericardial effusion may appear 6 to 12 months after RT. Stenosis and regurgitation of mitral and aortic valves have been reported. Fibrosis of the conduction system with disturbed heart rate and heart block (either complete or incomplete) may also occur. These late radiation-induced cardiac effects have been seen with doses from 30 to 40 grays. Newer RT techniques, including 3-dimensional (3D) treatment planning with dose-volume histograms to precisely calculate both heart volume and dose, should decrease the risk of direct cardiac damage.

### Table 3. Rates of Hypertension With Selected Angiogenesis Inhibitors

| Disease          | Drug         | Study                                      | Antiangiogenic, % | Control, % |
|------------------|--------------|--------------------------------------------|-------------------|------------|
| Colon cancer     | Bevacizumab  | Dewdney 2012, Mir 2011, Chen 2015          | 11                | 2.3        |
| Renal cell cancer| Bevacizumab  | Fraeman 2013, Chen 2015                    | 36                | NA         |
| Lung cancer      | Bevacizumab  | Fraeman 2013, Gampernieder 2014            | 14.8              | 14.6       |
| Breast cancer    | Bevacizumab  | Fraeman 2013                               | 26.4              | 16.7       |
| Ovarian cancer   | Bevacizumab  | Larchelle 2012                             | 8                 | 1          |
| Renal cell cancer| Sunitinib    | George 2012, Sunyub & Chamberlain 2015     | 3                 | 0          |
| GIST             | Sunitinib    | Funakoshi 2013                             | 6                 | NA         |
| Breast cancer    | Sorafenib    | Langenberg 2009                            | 17                | 12         |
| Lung cancer      | Cediranib    | Langenberg 2009                            | 35                | NA         |
| Breast cancer    | Cediranib    | Castellano 2013, Azad 2008                 | 42                | NA         |

GIST, gastrointestinal stromal tumor; NA, not available.
complication probability (NTCP) method, which takes into account the dose and the volume of normal tissues that are subject to radiation exposure.\textsuperscript{92} The NTCP model predicts the correlation between the given dose and the risk of cardiac mortality within 15 years after RT.\textsuperscript{93}

**Detection of Cardiac Dysfunction and Evidence for Cardiotoxicity**

**Echocardiographic Imaging**

Echocardiography, particularly 2-dimensional imaging (2D-Echo), is the most commonly used imaging technique to monitor cardiac function during and after chemotherapy. It is a widely available, reproducible, noninvasive modality that permits safe, serial assessment of cardiac function. There are many technical limitations to any technique, and 2D-Echo is no exception. Recent reviews have detailed these considerations.\textsuperscript{94} Common parameters that are followed include LVEF and myocardial strain.

**LVEF**

LVEF is the most commonly accepted parameter of cardiac function that independently predicts short-term and long-term mortality from CV events, including myocardial infarction, ischemic and idiopathic cardiomyopathy, as well as anthracycline-induced cardiomyopathy.\textsuperscript{95-99} However, the measurement of LVEF presents several challenges related to image quality, assumption of LV geometry, load dependency, and expertise. Moreover, LVEF measurement remains a relatively insensitive tool for detecting cardiotoxicity at an early stage.\textsuperscript{100} This is largely because a decrease in LVEF does not occur until a critical amount of myocardial damage has taken place and cardiac compensatory mechanisms are exhausted. Interestingly, in a recent study involving a large, predominantly breast cancer population treated with anthracyclines, prospective and close monitoring of LVEF with standard 2D-Echo during the first 12 months after the completion of chemotherapy allowed early detection of almost all cases of cardiotoxicity (98%), and prompt treatment led to normalization of cardiac function in most cases (82%). In this study, candidate variables were age, sex, CV risk factors, cumulative anthracycline dose, mediastinal RT, left chest RT, body mass index, and year of recruitment; and baseline and final (at the end of chemotherapy) LVEF measurements were collected. LVEF at the end of chemotherapy was an independent predictor of further development of cardiotoxicity.\textsuperscript{101}

However, only 11% of patients had a full recovery—ie, showed an LVEF value equal to or better than the baseline value (before chemotherapy initiation); in the remaining 89% of patients, cardiac function was below the baseline value. This evidence suggests that strategies aimed at preventing the development of LVD appear strategically more effective than therapy interventions aimed at counteracting existing damage, which can be progressive and irreversible in many cases.

Diastolic dysfunction may precede LVEF reduction in patients with chemotherapy-induced cardiotoxicity.\textsuperscript{101} Accordingly, abnormal diastolic filling without evidence of LVEF decrease has been demonstrated in chemotherapy-treated patients.\textsuperscript{102} However, no diastolic parameters have been proven to definitively predict cardiotoxicity, and the role of diastolic dysfunction in screening for the detection of early subclinical cardiotoxicity currently remains controversial.

**Myocardial strain**

Newer technology has emerged that allows for an improvement in the accuracy of calculating LVEF. One of the most promising is strain-echocardiography. Strain is a measurement of myocardial deformation. As the ventricle contracts, muscle shortens in the longitudinal and circumferential dimensions and thickens and lengthens in the radial direction. Strain imaging can provide an assessment of global and regional cardiac function and can be measured using either tissue Doppler or 2D-based methods.\textsuperscript{103} Several small studies evaluating tissue Doppler and LV strain rate imaging have detected early subclinical changes in cardiac function that preceded a decrease in LVEF.\textsuperscript{104-106} By using tissue Doppler-based strain imaging, a common measurement known as the peak systolic longitudinal strain rate can be used to reliably recognize most early myocardial deformation variations during anticancer therapy; whereas, with speckle tracking echocardiography, an advancement of strain imaging, peak systolic global longitudinal strain (GLS) would appear to be the most accurate measure. A 10% to 15% early decrease in GLS by speckle tracking echocardiography during therapy seems to be the most useful parameter for the early detection of cardiotoxicity, defined as a drop in LVEF or HF.\textsuperscript{103} However, currently, long-term data on large populations confirming the clinical significance of such changes are not available. Moreover, there are currently important limitations of these techniques: data analysis is currently offline, time-consuming, and still depends on the quality of the acoustic windows. In addition, different echo machines and software packages may yield different strain results, making them difficult to compare. Consequently, these new echo imaging techniques are not typically included in a routine assessment of cardiac function during chemotherapy.\textsuperscript{94}

**The role of other imaging techniques**

Multiple-gated acquisition (MUGA) scans can limit interobserver variability in assessing LVEF, but it has the disadvantages of exposing the patient to radiation and provides limited information on cardiac structure and diastolic function. Magnetic resonance imaging is considered to be the
gold standard for the evaluation of cardiac volumes, mass, and both systolic and diastolic function. However, because of high cost and lack of availability, this imaging modality is not routinely used.103,105

Cardiac Biomarkers

A strategy based on the use of biochemical markers, in particular cardiac troponins, has developed in the last 15 years for early real-time identification, assessment, and monitoring of antitumor drug-induced cardiotoxicity. This approach negates the interobserver variability reported with strategies using imaging; but, unfortunately, the exact timing of biomarker measurement and the variability in techniques have not been adequately determined.103,107,108

Troponins

Cardiac troponins are regulatory proteins within the myocardium that are released into the circulation when damage to the myocyte has occurred.109 Troponins are the first blood biomarkers identified to detect cardiac damage. They are medium-sized proteins regulating the contractile elements actin and myosin. Although they are normally undetectable, troponins may increase within 2 or 3 hours after cardiac damage occurs.110-112 Studies have shown that troponins may detect cardiotoxicity at a preclinical phase, long before any reduction in LVEF has occurred, in patients treated with antitumor drugs (Table 4).104,108,110,113-130

Measurement of troponins may provide additional information, including:

1. Prediction of the severity of future LVD, because the peak value of troponin after chemotherapy is closely correlated to the extent of LVEF reduction;
2. Stratification of cardiac risk after chemotherapy, which allows for the personalization of the intensity of post-chemotherapy monitoring of cardiac function;
3. Selection of patients more prone to develop cardiotoxicity, in whom a cardioprotective therapy can be considered; and
4. Exclusion of most patients from prolonged cardiologic monitoring.

In a study of 703 predominantly breast cancer patients, troponin I (TnI) was assessed before chemotherapy, during the 3 days after the end of chemotherapy (early evaluation), and after 1 month (late evaluation).110 Three different troponin release patterns were identified. TnI was regularly within the normal range in 70% of patients, increased only at early evaluation in 21%, and increased at both early and late evaluations in 9%. Patients without a TnI increase after chemotherapy showed no significant reduction in LVEF and had a low incidence of cardiac events (1%) during the

| STUDY             | NO. OF PATIENTS | CANCER TYPE | DRUGS | TROPONIN TYPE | CUTOFF, ng/mL | TIMING OF ASSESSMENT |
|-------------------|----------------|-------------|-------|---------------|---------------|----------------------|
| Lipshultz 1999    | 15a            | ALL         | AC    | T             | 0.03          | Before CT; 1–3 d after each dose |
| Cardinale 2000    | 201            | Various     | HD CT | I             | 0.04          | Before CT; 0, 12, 24, 36, and 72 h after CT |
| Cardinale 2002    | 232            | Breast cancer| HD CT | I             | 0.04          | Before CT; 0, 12, 24, 36, and 72 h after CT |
| Auner 2002        | 30             | Hematological | HD CTX | T             | 0.03          | Before CT; 1-14 d after CT |
| Sandri 2003       | 179            | Various     | HD CT | I             | 0.04          | Before CT; 0, 12, 24, 36, and 72 h after CT |
| Cardinale 2004    | 703            | Various     | HD CT | I             | 0.04          | Before CT; weekly × 4 |
| Specchia 2005     | 79             | Hematological | AC    | I             | 0.15          | Before CT; 3-5 d after first and last dose |
| Kilickap 2005     | 41             | Various     | AC    | T             | 0.10          | Before each dose |
| Lee 2008          | 86             | Hematological | AC    | I             | 0.20          | Before CT; bimonthly during CT |
| Schmidinger 2008  | 74             | Renal carcinoma | Sunitinib/sorafenib | I             | 0.03          | Before CT; before and after each cycle |
| Cardinale 2010    | 251            | Breast cancer | TRZ   | I             | 0.04          | Every 2 wk during CT |
| Morris 2011       | 95             | Breast cancer | AC + taxanes + TRZ/LAP | I             | 0.30          | Before CT; after 3 and 6 mo during CT |
| Sawaya 2011       | 43             | Breast cancer | AC + taxanes + TRZ | HS-I          | 0.015         | Before CT; after 6 mo during CT |
| Lipshultz 2012    | 205a           | ALL         | AC/AC + dexrazoxane | I/T          | Any detectable amount 30 pg/mL | Before CT; 1-7 d after each dose; end CT |
| Sawaya 2012       | 81             | Breast cancer | AC + taxane + TRZ | HS-I          | 0.03          | Before CT; after 3 and 6 mo during CT |
| Geiger 2012       | 50             | Various     | AC    | T             | NA           | Before CT; after 6 h, 7 d, 3 mo |
| Drafts 2013       | 53             | Various     | AC    | I             | 0.06          | Before CT; after 6 h, 7 d, 3 mo |
| Morros & Petrescu 2013 | 74  | Various     | AC    | HS-T         | NA           | Before CT; after 6, 12, 24, and 52 wk |
| Mavinikurve-Groothuis 2013 | 60a | ALL         | AC    | HS-T          | 0.01         | Before CT; after 3 and 12 mo |
| Ky 2014           | 78             | Breast cancer | AC + taxanes + TRZ | HS-I          | NA           | Before CT; after 3 and 12 mo |
| Mornos 2014       | 92             | Various     | AC    | HS-T         | NA           | Before CT; after 12 and 36 wk |

Abbreviations: AC indicates anthracycline-containing chemotherapy; ALL, acute lymphoblastic leukemia; CT, chemotherapy; CTX, cyclophosphamide; HD, high-dose; HS-I, high-sensitivity troponin I; HS-T, high-sensitivity troponin; I, troponin I; LAP, lapatinib; NA, not available; T, troponin T; TRZ, trastuzumab. aThis was a pediatric population.
>3-year follow-up. In contrast, TnI-positive patients had a greater incidence of major adverse cardiac events. In particular, among TnI-positive patients, the persistence of the TnI rise 1 month after chemotherapy was associated with a greater LVEF reduction and a higher incidence of cardiac events compared with patients who had only a transient increase in the marker (84% vs 37%; P < .001). An additional study in leukemia patients suggested that a troponin elevation may identify those at risk for LVD.131

**High-sensitivity troponins**

Recent improvements in assay technology have led to more sensitive and precise troponin assays. These new high-sensitivity (HS) assays can now reliably measure small increases that are undetectable by using other troponin assays.132 The most recent study in which HS troponin was assessed was that by Ky et al,108 who investigated the association between multiple biomarker increases and successive development of cardiotoxicity in breast cancer patients being treated with anthracyclines, taxanes, and trastuzumab.108 In that study, however, the most important risk of cardiotoxicity was associated with HS TnI change in absolute values at the end of anthracyline treatments as well an increase in myeloperoxidase, a marker of oxidative stress.

**Natriuretic peptides**

Increased natriuretic peptide (NP) levels can detect chemotherapy-induced LVD in both adult and pediatric populations.133,134 Unfortunately, many studies failed to find a correlation between the increase in NP and the development of cardiac dysfunction, probably because significant volume changes can occur in patients who are receiving chemotherapy without any significant change in LVEF. It is noteworthy that, when considering only the two most used NPs—B-type NP (BNP) and N-terminal pro-BNP (NT-proBNP)—the significant differences in analytical characteristics and measured values among the most widely used commercial methods underline that clinicians must be careful and cautious when comparing results obtained by laboratories that use different methods. Understanding the utility of NP as an adjunct to clinical care in patients being treated with potential cardiotoxic therapy is necessary.135 New prospective and multicenter studies that include large populations, using well standardized methods for dosage, and with well defined timing of sampling and cardiac endpoints are paramount to clarify the appropriate use of NP and to interpret the results in the clinical context.

**An Integrated Approach of Markers and Cardiac Imaging**

An integrated approach combining biomarkers as well as imaging data may yield progressive utility in predicting subsequent cardiotoxicity. In a recent multicenter study, HS tropoins, NT-pro-BNP, ST2 (interleukin 1 receptor–like 1), LVEF, and echocardiographic parameters of myocardial deformation were used to detect LVD in patients receiving anthracyclines, taxanes, and trastuzumab. Decreases in peak longitudinal strain and increases in HS TnI concentrations at the completion of the anthracyline treatment were predictive of subsequent LVD. The combined assessment of the two endpoints showed an improved specificity (93%) compared with either parameter alone (both 73%).124 However, this result was associated with a reduction in sensitivity to 35%.126

**Other Proposed Biomarkers**

Other potential markers of cardiotoxicity have been investigated in small studies. These include markers of endothelial dysfunction (tissue-type plasminogen activator, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule–1, and circulating endothelial cells), markers of myocardial ischemia (fatty acid binding protein), as well as markers of oxidative stress and inflammation (glutathione peroxidase, high-sensitivity C-reactive protein, interleukins).132,133 Although many of these proposed biomarkers have shown significant changes during chemotherapy, the impact of these changes on cardiac function are unknown; thus, further research is needed.136

In summary, a novel approach based on the use of cardiac biomarkers has emerged in the last decade, resulting in a promising, cost-effective diagnostic tool for early, real-time identification, assessment, and monitoring of cardiotoxicity. Further trials are necessary to confirm their use in clinical practice. Standardization of the use of routine biomarkers in this clinical setting is a current unmet need, and future larger, prospective, multicenter studies should provide clear indications of the appropriate use of these biomarkers in clinical practice.

**Management of Anticancer Drug-Related Cardiotoxicity**

**The Role of Cardioprotective Therapy for Prevention**

The cardioprotective effects of many pharmacologic agents have been demonstrated during cancer therapy in a laboratory setting; however, most of these agents have not been proven to be cardioprotective for cancer treatment-related cardiotoxicity. Several agents—dextrazoxane, beta-blockers, angiotensin antagonists, statins, and aldosterone antagonists—have been shown to be potentially cardioprotective in patients exposed to anthracyclines or trastuzumab (Table 5).137-146

**Dextrazoxane**

Dextrazoxane significantly reduces anthracycline-related cardiotoxicity in adults with different solid tumors and in children with acute lymphoblastic leukemia and Ewing sarcoma.147-149 There is a large amount of evidence that
patients who received dexrazoxane had a decreased incidence of HF compared with those who did not receive the drug. Despite these consistent positive findings, the use of dexrazoxane has not been widely adopted, and it is recommended as a cardioprotectant by the American Society of Clinical Oncology (ASCO) only in patients with metastatic breast cancer who have already received more than 300 mg/m² of doxorubicin. This might be explained by the suspicion—never confirmed—of interference with the efficacy of anthracyclines, by the occurrence of secondary malignancies, or by its possible additive effects of myelosuppression.

**Beta-blockers**

Carvedilol, a nonselective beta-blocker with antioxidant activity that is considered crucial in the treatment of patients with HF and LVD, is an effective cardioprotective agent during doxorubicin treatment. This effect was confirmed in a randomized study in which prophylactic use of the drug protected both systolic and diastolic LV function in a small population of anthracycline-treated patients. The protective effect of nebivolol, a beta-selective beta-blocker with a nitric oxide donor capacity, has also been demonstrated to be beneficial in a recent randomized study of 47 breast cancer patients receiving anthracycline-therapy; notably, LVEF and NT-proBNP remained unchanged after 6 months in patients who received nebivolol. Conversely, in the placebo group, a significant decrease in LVEF and an increase in NT-proBNP were observed.

**Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers**

The possible role of telmisartan, an angiotensin receptor blocker, in preventing myocardial injury induced by epirubicin was evaluated by Cadeddu et al in a randomized trial that included 49 patients with a variety of solid cancers. Twenty-five patients who started telmisartan 1 week before chemotherapy showed no significant reductions in myocardial deformation parameters (peak strain rate), as evaluated using a tissue Doppler echo technique, and no significant rise in ROS or interleukin-6, as found in 24 control patients. These results suggest that telmisartan might protect against epirubicin-induced ROS production and inhibit the generation of inflammation, thus preventing the development of early myocardial impairment. The cardioprotective effects of enalapril, an angiotensin-converting enzyme inhibitor (ACE-I), were studied in a randomized, controlled trial that included 473 patients (53% had breast cancer) treated with high-dose anthracyclines. One-hundred fourteen patients (24%) showed an early troponin increase and were randomized to receive enalapril or no treatment. Enalapril was started 1 month after the end of chemotherapy and continued for 1 year. In the enalapril-treated group, LVEF did not change during the follow-up period. Conversely, in patients who did not receive enalapril, a progressive decrease in LVEF and an increase in end-diastolic and end-systolic volumes were observed. Moreover, enalapril-treated patients had a significantly lower incidence of adverse cardiac events compared with controls at 1-year follow-up (2% vs 52%; P < .001).

The preventive effects of combined enalapril and carvedilol recently were tested in a randomized trial of 90 patients with hematologic malignancies who were treated with anthracyclines. After 6 months, LVEF did not change in the intervention group; conversely, LVEF significantly decreased in controls (P = .035). Importantly, compared with controls,
patients in the intervention group had a lower incidence of the combined event of death or HF (6.7% vs 22%; \( P = .036 \)) or of death, HF, and a final LVEF below 45% (7% vs 24%; \( P = .02 \)).144

Statins
Statins exert antioxidative, anti-inflammatory, and other pleiotropic effects in addition to reducing low-density lipoprotein (LDL) cholesterol. In an animal model, it was demonstrated that pretreatment with fluvastatin blunted anthracycline-induced toxicity, reducing oxidative stress, enhancing the expression of antioxidative enzyme mitochondrial superoxide-dismutase-2, and limiting cardiac inflammation.153 In a retrospective case-control study, 67 women with breast cancer treated with anthracyclines who also were receiving a statin drug were compared with 134 matched controls.146 Women treated with statins showed a lower incidence of HF at a mean of 2.5 years of follow-up.146 Finally, in a small clinical trial of 40 patients who had normal LVEF before undergoing chemotherapy (which included anthracyclines), the 6-month LVEF value was unchanged among patients treated with atorvastatin compared with an 8% absolute decrease in controls.145

Aldosterone antagonists
Aldosterone antagonism has been evaluated in a very recent trial that included 83 patients with breast cancer who were randomized to spironolactone or placebo and a concomitant anthracycline-containing chemotherapy control groups.140 During at least 24 weeks of treatment, including 3 weeks after completing anthracycline-containing chemotherapy, spironolactone prevented a decrease in LVEF, blunted the increase in TnI and NT-proBNP, and preserved diastolic function.140

Ongoing Studies
Currently, several studies are ongoing to evaluate CV drugs as cardioprotectant agents. The MANTICORE-101 (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial is evaluating the use of perindopril versus bisoprolol in patients with HER2-positive breast cancer who are undergoing treatment with trastuzumab in the prevention of LVD as assessed by cardiac magnetic resonance imaging.154 At the end of trastuzumab therapy, neither drug had an impact on LV end-diastolic volume (the primary outcome of change from baseline in the study). In univariate analysis, only bisoprolol was associated with preservation of baseline function (from 62% to 61%; secondary outcome). However, in multivariate analysis, the use of both cardiac drugs significantly predicted preserved LV function (for perindopril, \( P = .013 \); for bisoprolol, \( P < .001 \)). These data were presented during the 2015 San Antonio Breast Cancer Symposium.

The PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial is assessing whether the use of candesartan, metoprolol, or their combination can prevent the development of LVD in patients on adjuvant epirubicin-containing chemotherapy with or without trastuzumab.155 The results demonstrated that candesartan—but not metoprolol—concomitantly administrated with adjuvant chemotherapy, including epirubicin with or without trastuzumab, can protect against early decline in LVEF, assessed with cardiac magnetic resonance.

The International Cardi Oncology Society (ICOS)-ONE trial is the only randomized study that is designed to compare the use of enalapril administration concomitantly with anthracycline-containing chemotherapy (primary prevention) versus enalapril administration after preclinical cardiotoxicity detection, as revealed by the increase in troponins (secondary prevention; national clinical trial NCT01968200; clinicaltrials.gov).

In the NCT01708798 study (clinicaltrials.gov), the potential ability of the aldosterone antagonist eplerenone to prevent doxorubicin-induced cardiotoxicity will be explored in a randomized controlled trial of breast cancer patients.

Finally, at Memorial Sloan Kettering Cancer Center, an ongoing randomized trial (NCT02177175; clinicaltrials.gov) is assessing the use of carvedilol for the prevention of anthracycline/trastuzumab therapy-associated cardiotoxicity among women with HER2-positive breast cancer using myocardial strain for early risk stratification. In this trial, carvedilol is started in women who show an absolute decrease in GLS below 19% or in those who have a decrease ≥11% from baseline. It is hoped that the findings from these trials will provide important insights into the best strategy for managing cardiotoxicity induced by anticancer drugs.

Treatment
The Role of ACE-I and Beta-Blockers
Limited data exist regarding the treatment of patients with antitumor drug-associated cardiomyopathy. Typically, these patients have been excluded from large randomized trials evaluating the effectiveness of HF therapies. The use of ACE-I and beta-blocking agents in this particular clinical setting were first evaluated in a very few retrospective studies, which involved small populations (Table 6).155,63,99,101,156-163 More recently, the effectiveness of ACE-I and beta-blockers were prospectively assessed in this setting. In 201 consecutive patients with anthracycline-induced LVD, enalapril (combined with carvedilol when possible) was initiated at the time of LVEF impairment detection and was up-titrated to the maximal tolerated dose.63 The investigators found that the time elapsed from the end of chemotherapy to the start of HF therapy was a crucial variable for the recovery of cardiac function. Indeed, among patients who were treated within
months after the end of chemotherapy, 64% had a complete recovery of LVEF. Conversely, after 2 months, the percentage of patients who recovered progressively decreased, with no complete recovery seen after 6 months. Consistent with these findings, a greater improvement in cardiac function was observed in a large population of patients with anthracycline-induced LVD who were receiving a combination of enalapril and carvedilol or bisoprolol. Initiation of HF medications promptly after the detection of symptomatic and asymptomatic anthracycline-induced cardiomyopathy was associated with recovery in 82% of patients over a mean period of 8 ± 5 months. Long-term studies are needed to determine if therapy with ACE-I and beta-blockers should be prolonged lifelong, or discontinued after achievement of complete recovery of LVEF.

**QTC Prolongation Management**

Prolongation of the QT interval can lead to life-threatening cardiac arrhythmias, including “torsade de pointes.” Although prolongation of the QT interval is not the best predictor of proarrhythmic risk, it represents the principal clinical surrogate marker by which to evaluate the arrhythmic risk of a drug and has led to withdrawal of several anticancer drugs from the market. Although drugs leading to prolonged QT may possess significant risks of serious adverse events, the clinical benefit of therapy in the oncologic setting, including the possibility of cure for a cancer patient, may outweigh the potential risks of QTc prolongation, even when the prolongation is significant. Patients with a history of QT interval prolongation; patients who are taking antiarrhythmics; or patients with relevant CVD, bradycardia, thyroid dysfunction, or electrolyte disturbances should be screened and monitored. Periodic monitoring with on-treatment electrocardiograms and electrolytes should be considered.

**Hypertension Treatment and Management**

A collaboration between oncologists, a primary care health care provider, and cardiologists is essential to properly monitor and manage hypertension, which is an unwanted adverse effect of many antiangiogenic agents associated with VSP inhibition. Aggressive management of hypertension beginning from the initiation of therapy is important to avoid cardiac dysfunction; and, again, an understanding of the potential cardiac toxicities of the chemotherapeutic regimen used is essential, giving further support to the concept of a multidisciplinary strategy for management. Patients who are candidates for treatment with VEGF/TKI inhibitors should be considered at higher risk for CV complications if they have systolic blood pressure (BP) ≥160 mm Hg or diastolic BP ≥100 mm Hg; diabetes mellitus; established CV disease, including any history of ischemic stroke, cerebral hemorrhage, or transient ischemic attack; myocardial infarction, angina, coronary revascularization, or HF; peripheral artery disease; subclinical organ damage previously documented by electrocardiogram or 2D-Echo revealing LV hypertrophy; cigarette smoking; and dyslipidemia. Repeated BP measurements and aggressive management of BP elevations are recommended to prevent clinically limiting complications.

**Anticoagulation in Cancer Patients**

Venous thromboembolism (VTE) is an important cause of morbidity and mortality in cancer patients. Patients receiving chemotherapy or antiangiogenic agents have a 7-fold higher risk of developing VTE compared with patients

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**TABLE 6. Clinical Studies Evaluating Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in Anticancer Drug-Induced Cardiomyopathy**

| TREATMENT | AUTHOR (YEAR) | NO. OF PATIENTS | MEAN AGE, Y | STUDY | DRUGS | FOLLOW-UP, MO | B-LVEF, % | F-LVEF, % | REPORTED EVENT |
|-----------|---------------|----------------|-------------|-------|-------|--------------|-----------|-----------|----------------|
| Dig + Diur + ACEI | Saini 1987 | 3 | 49 | CR | AC | 12-16 | 20 | 48 | Relief of symptoms, LVEF↑ |
| Dig + Diur; Dig + | Jensen 1990 | 9 | 58 | P | AC | 26 | 27 | 47 | CD, HF |
| Diur + ACEI | | | | | | | | | |
| Dig + Diur + ACEI; BB | Fazio 1998 | 1 | 35 | CR | AC | 12 | 14 | 45 | Relief of symptoms |
| BB; BB + ACEI | Noori 2000 | 2; 6 | 51 | R | AC | 32 | 28 | 41 | LVEF↑ |
| Dig + Diur; Diur + | Jensen 2002 | 10 | 54 | P | AC | 30 | 27 | 41 | HF |
| Diur + ACEI | | | | | | | | | |
| BB; BB + ACEI | Mukai 2004 | 3; 2 | 53 | CR | AC | 27 | 37 | 53 | LVEF↑, NYHA1 |
| ACEI; ACEI + BB | Tallaj 2005 | 10; 15 | 47 | R | AC | 70 | 25 | 34 | CD, TXS |
| ACEI; ACEI + BB | Ewer 2005 | 38 | 52 | R | AC, TRZ | 10 | 43 | 56 | LVEF↑ |
| ACEI + BB | Tabet 2006 | 1 | 52 | CR | AC | 8 | NA | 30 | HF |
| ACEI + BB | Cardinale 2010 | 201 | 53 | P | AC | 12-96 | 38 | 46 | LVEF↑ up to ≥50% |
| ACEI; ACEI + BB | Thakur & Witteles 2014 | 79 | 52 | R | AC, TRZ, TKI | NA | 41 | 53 | LVEF↑ |
| ACEI + BB | Cardinale 2015 | 226 | 50 | P | AC | 4-228 | 40 | 52 | LVEF↑ of 5 points + ≥50% |

Note: ACE-I, angiotensin-converting enzyme inhibitor; BB, beta-blockers; B-LVEF, baseline left ventricular ejection fraction; CD, cardiac death; CS, case report; Dig, digoxin; Diur, diuretics; F-LVEF, final left ventricular ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; P, prospective; R, retrospective; TKI, tyrosine kinase inhibitor; TRZ, trastuzumab; TXS, cardiac transplantation.
Several randomized trials have demonstrated a significant thromboprophylactic effect of low-molecular-weight heparins (LMWH) in ambulatory cancer patients who are receiving chemotherapy. However, routine thromboprophylaxis is currently not recommended for ambulatory cancer patients by ASCO because of the limited absolute risk reduction demonstrated with LMWH and the concern with bleeding complications.

The prophylactic use of LMWH may be considered for highly selected, high-risk patients only, according to the risk-assessment model validated by Khorana et al (Table 7), ie, in patients with scores ≥3 and a low bleeding risk. Data about the new oral anticoagulants (dabigatran, apixaban, rivaroxaban) for either prophylaxis or treatment of VTE in patients with cancer are still limited, and their use is currently not recommended (ASCO).

**Conclusions**

Modern cancer treatment strategies have led to a significant improvement in the chances of surviving a diagnosis of cancer for many years. These gains in overall outcome may be offset by the potential negative impact of cancer therapy on CV health. Cancer therapies may have short-term and long-term side effects involving the heart and circulation, as well as exacerbating and/or unmasking existing heart disease. The development of CV disease during the course of cancer treatment can adversely impact the management of the underlying malignancy by interfering with the optimal doses and timing of lifesaving cancer therapy. In addition, the development of a potentially important cancer therapy...
may be halted or abandoned because of a perceived increased CV risk. The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of patients with cancer, whether they are receiving active treatment or are long-term survivors after successful treatment (Fig. 1). Cardiology and oncology organizations around the world (ie, European Society for Medical Oncology, American College of Cardiology, ASCO, European Society of Cardiology, Canadian Cardiovascular Society) are now recognizing the importance of this collaboration, resulting in the ongoing development of several clinical practice guidelines and position statements. Although these initiatives will provide important guidance for clinicians on best practices for patients today, many questions remain unanswered: How can we predict who will develop cardiotoxicity, what is the best prevention strategy, how should we monitor those at risk of cardiotoxicity, and what are the best management strategies? There is an urgent need for collaborative research to address these questions. Vibrant collaborative partnerships between oncologists, cardiologists, and other allied health care professionals will play an important role in the development and promotion of clinical care models, educational programs (for patients and health care providers), and evidence-based research to improve the care of patients being treated for cancer.

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