Multidisciplinary Strategy for Managing Cardiovascular Risks When Treating Patients with Early Breast Cancer

DANIEL J. LENIHAN,a FRANCISCO J. ESTEVAb

aDepartment of Cardiology and bDepartment of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

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ABSTRACT
Adjuvant systemic therapies for the treatment of early-stage breast cancer (EBC) effectively treat the tumor and significantly decrease the risk for recurrence. However, some of these treatments are associated with an increased risk of cardiovascular adverse events. Cardiovascular complications related to cancer therapy may be a prominent concern in postmenopausal women with existing cardiovascular disease or in those who are at high risk for developing cardiovascular disease. The increased risk for cardiac toxicity in women receiving radiation, anthracyclines, and/or trastuzumab for the adjuvant treatment of EBC is well established. The risk of thromboembolic disease is higher in patients with estrogen receptor–positive EBC receiving tamoxifen in the adjuvant setting, whether it is given before or instead of an aromatase inhibitor. In addition, while available data suggest no substantial differences in the risk for ischemic cardiovascular events between aromatase inhibitors and tamoxifen, investigation is still ongoing. Based on this information, it is important for health care providers to understand the cardiovascular risks of treatment and how to monitor at-risk patients, particularly when multiple agents are used in combination or in succession. Improving cardiovascular outcomes in patients with EBC requires cardiovascular risk assessment, management, and long-term follow-up care. Because of the multimodal treatment of EBC patients, their care requires a multidisciplinary approach to reduce not only the risk for breast cancer recurrence but also the risk for treatment-related cardiac toxicities. The Oncologist 2008;13:1224–1234

INTRODUCTION
The treatment of early-stage breast cancer (EBC) includes local treatment with surgery and/or radiation therapy, and systemic treatment of potential residual breast cancer with cytotoxic chemotherapy, hormonal therapy, biologic therapy, or combinations of these therapies [1]. Selection of the exact treatment regimen varies between patients and is based on prognostic factors (e.g., lymph node status, tumor size) as well as predictive factors including estrogen receptor (ER) and human epidermal growth factor receptor (HER)-2 status [1]. In women with ER+ disease who receive hormonal therapy, the treatment of EBC lasts at least 5 years to mitigate the risk for...
recurrence [1]. Because a large percentage of these women become long-term breast cancer survivors, it is important to weigh the benefits of long-term therapy with the risks for serious adverse events. Although these EBC therapies have well-established clinical benefits, several are associated with an increased risk of cardiovascular adverse events. Therefore, the potential for cardiovascular risk should be considered when designing a treatment strategy for women with ER+ EBC, particularly for postmenopausal women with existing cardiovascular comorbidities.

Based on the known substantial incidence of existing cardiovascular disease in women, which is typically underrecognized, and the potential for cardiovascular-related adverse effects of breast cancer therapy, it is important to evaluate the cardiovascular status in women, especially those who are postmenopausal, who are receiving EBC treatment. In fact, recent data suggest that women with EBC are more likely to die of heart disease than recurrent cancer [2]. Thus, managing preexisting cardiovascular disease or related risk factors prior to receiving treatment is of paramount importance. A multidisciplinary team approach to coordinate the management of patients with breast cancer would likely optimize clinical outcomes and help minimize the impact and risk of adverse effects [3]. This review summarizes the latest data regarding treatment-related cardiovascular adverse events in women with EBC and includes highlights and considerations for assessing baseline cardiovascular risk, follow-up, and management, as well as multidisciplinary strategies to optimize patient outcomes.

TREATMENT OF ER+ EBC

After diagnosis by biopsy, patients with EBC (stage I, IIA, or IIB) may receive preoperative chemotherapy or undergo lumpectomy or total mastectomy with surgical staging of the sentinel and/or axillary lymph nodes [1]. All patients undergoing lumpectomy for locally invasive breast cancer undergo radiation therapy with treatment of the tumor bed, supraclavicular area, or internal mammary nodes, depending on the number of positive axillary lymph nodes. Radiation therapy may be omitted in patients undergoing a total mastectomy; however, this depends on the size of the tumor and number of positive lymph nodes. Tumors from patients with early invasive breast cancer are then tested for the presence of key predictive markers of response to therapy, including estrogen, progesterone, and HER-2 receptors.

Patients with ER+ tumors frequently receive a combination of adjuvant chemotherapy (depending on the tumor size and number of positive lymph nodes) and hormonal therapy. Patients with HER-2+ tumors > 1 cm or with node-positive disease may also be given trastuzumab.

Radiation therapy, some types of chemotherapy, and

TRUSTATZUMAB have all been associated with an increased risk for cardiovascular disease [4–6]. Many women with EBC require multimodal treatment and receive a combination of these therapies, which may cumulatively increase their risk for cardiovascular complications [7]. The potential cardiovascular risks of hormonal therapy are still under investigation.

Because treatments such as aromatase inhibitors (AIs) deprive the patient of circulating estrogen, there was initial concern that antagonism of estrogen synthesis would negatively impact the cardioprotective effects of estrogen [8]; however, large randomized trials such as the Heart and Estrogen/Progesterin Replacement Study, the Estrogen Replacement and Atherosclerosis trial, and the Women’s Health Initiative (WHI) observational study did not support the cardioprotective effects of estrogen replacement therapy [9–11]. Taken together, these reports suggest that AIs and other estrogen-reducing therapies may not pose as substantial a risk as originally theorized.

OVERVIEW OF THE CARDIOVASCULAR EFFECTS FROM BREAST CANCER TREATMENT

CLINICAL TRIALS

Radiation

Radiation therapy for breast cancer is associated with an increased risk for cardiovascular disease long after radiotherapy. Cardiovascular mortality is highest in patients receiving radiation of the left breast [12]. In a study of >20,000 women with breast cancer diagnosed between 1971 and 1988, those receiving radiation of the left breast had a 25% higher cardiovascular mortality rate at ≥15 years after diagnosis than women who received radiation of the right breast [12]. Similarly, an analysis of 961 medical records from patients with EBC was conducted to evaluate long-term (median, 12 years postradiation therapy) radiation-associated coronary damage. That study showed that, among the 46 patients with left-sided and 36 patients with right-sided disease who had undergone cardiac stress testing, significantly more patients treated with left-sided radiation had stress test abnormalities (59% versus 8%, respectively; p = .001) [13]. Furthermore, an initial review of medical records from 961 patients with breast cancer revealed no difference in overall cardiac mortality at 10 years after radiation therapy; however, at 20 years, a higher rate of cardiac mortality and morbidity was observed in patients receiving irradiation of the left breast [14]. In contrast, analysis of data from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database of >16,000 patients with breast cancer diagnosed between 1986 and 1993 revealed no difference in cardiac morbidity—including isch-
emic heart disease—between women with left- and right-sided breast cancer [15]. A later study of 4,414 breast cancer patients at a median follow-up of 17.7 years demonstrated that radiotherapy to either side of the mammary chain was correlated with a higher risk for cardiovascular disease, with an overall hazard ratio (HR) of 1.41 [16]. While the risk for myocardial infarction was lower in women treated after 1979 (due to the introduction of breast-conserving therapy), the risk of developing congestive heart failure (HF) persisted (HR, 2.66; 95% confidence interval [CI], 1.27–5.61). The risk for myocardial infarction was higher in women receiving irradiation of the left chest, regardless of treatment period or regimen (HR, 3.54; 95% CI, 1.13–11.1 versus no radiotherapy or negligible dose to the heart).

It is notable that the risk for death from ischemic heart disease associated with radiation for breast cancer has decreased substantially over time [17]. For example, Giordano et al. [4] divided the SEER 12 registry 1973–2000 dataset into three treatment eras and found that patients with left-side tumors treated with radiation between 1973 and 1979 had a higher cardiotoxicity rate than patients with right-side tumors. As a result, it appears that changes in techniques where radiation is administered tangentially, thereby minimizing cardiac exposure, ultimately reduce the potential cardiac toxicity [17]. However, during later eras, there was no difference between left- and right-sided radiation.

**Anthracycline-Based Chemotherapy**

Anthracycline-based regimens including epirubicin or doxorubicin are the standard of care for adjuvant chemotherapy. Anthracycline-based regimens can be used is limited by their associated risk of developing life-threatening HF, cardiomyopathy, and tumor resistance [20–22]. The risk of anthracycline-induced HF increases significantly with increasing cumulative dose [20, 21, 23]. In addition, ongoing studies (e.g., the National Surgical Adjuvant Breast and Bowel Project [NSABP] B-36 trial and the Cancer and Leukemia Group B 40101 trial [24, 25]) and existing data do not support an additional benefit of high cumulative doses of anthracyclines in the adjuvant setting [22]. As a result, all current adjuvant regimens using anthracyclines typically do not exceed 360 mg/m² [26].

Recent investigations indicate that previous methods for the detection of cardiac toxicity, primarily serial left ventricular ejection fraction (LVEF) measurements, may be substantially flawed and may not truly represent the incidence of cardiac toxicity. It is well established that a decrease in LVEF occurs when the tremendous compensatory ability of the myocardium has been impaired; therefore, a decline in LVEF is actually a marker of advanced damage [27]. Additionally, HF, a condition that can be challenging to diagnose during chemotherapy, frequently occurs even in a patient with a normal LVEF. As a result of these criticisms, there is interest in exploring the clinical utility of alternative measures of cardiac function. Several studies suggest that these potential biomarkers may give an early indication of cardiac toxicity and increased risk for a cardiac event. For example, elevations in the circulating levels of cardiac biomarkers such as troponin I, B-type natriuretic peptide (BNP), and N-terminal proBNP have shown promise as accurate predictors of cardiac toxicity [28–31]. Cardiac biomarkers may be best used as a mechanism to identify high-risk patients who are receiving chemotherapy or to more accurately predict cardiac toxicity [32]. Broad application of biomarkers as a less expensive, more accurate tool to monitor for cardiac toxicity is still under active investigation [33].

Certain cardioprotective medications have demonstrated benefit in ameliorating the cardiotoxic effects of anthracyclines and other high-dose chemotherapy [32, 34–37]. Reductions from baseline LVEF after chemotherapy indicative of cardiotoxicity were observed only in patients not receiving concomitant therapy with carvedilol [32], enalapril [34], and valsartan [35]. It is unclear whether prophylactic therapy with these or other cardioprotective agents will be helpful in preventing cardiac toxicity in certain high-risk patients receiving anthracyclines. There was significant interest in using dexrazoxane for cardioprotection during anthracycline chemotherapy. Dexrazoxane, an iron chelator initially believed to limit myocardial cell damage by scavenging reactive oxygen radicals produced during anthracycline therapy, has not been clearly established as beneficial. Although dexrazoxane is successful at reducing troponin release in children receiving anthracyclines, it has not substantially reduced clinical cardiac events [38]. Furthermore, this therapy is associated with myelosuppression and possibly secondary leukemia [36].

To mitigate the cardiotoxic risks associated with the anthracyclines, other studies are examining the efficacy of nonanthracycline-containing regimens in the adjuvant setting [39]. In one prospective, randomized clinical trial, four
cycles of docetaxel and cyclophosphamide produced both longer disease-free survival ($p = .018$) and longer overall survival ($p = .045$), compared with four cycles of doxorubicin and cyclophosphamide in patients with EBC [40]. There is still considerable debate as to whether anthracycline therapy is an essential part of EBC treatment, but regardless, anthracyclines are still commonly used.

**Trastuzumab**

Trastuzumab significantly improves the survival of HER-2$^+$, node-positive breast cancer patients and it is associated with an increased risk of cardiac dysfunction [6, 41]. An independent cardiac review and evaluation committee was established to assess the cardiovascular risk of trastuzumab in the clinical trials leading to U.S. Food and Drug Administration approval. This committee conducted a retrospective review of seven phase II and III clinical trials of trastuzumab in women with breast cancer. The analysis revealed a $3%–7%$ greater incidence of cardiac dysfunction associated with the use of trastuzumab monotherapy, but radiotherapy was not a significant risk factor [41]. When trastuzumab was given concomitantly with an anthracycline plus cyclophosphamide, the risk for cardiac dysfunction increased up to $27%$, versus $8%$ for an anthracycline alone. Similarly, when trastuzumab was given concomitantly with paclitaxel, $13%$ of patients developed cardiac dysfunction, versus $1%$ for patients receiving paclitaxel alone. The long-term use of trastuzumab has been associated with a higher risk for cardiac toxicity in patients with metastatic breast cancer, although this toxicity is manageable and an acceptable risk in this setting [6]. Furthermore, cardiac dysfunction detected during trastuzumab therapy is frequently reversible when managed carefully with typical HF medications such as angiotensin-converting enzyme inhibitors and beta-blockers [42].

Lower rates of cardiac toxicity have been reported in the adjuvant setting. The risk for HF was in the range of $0.5%–4%$ in the four largest clinical trials that evaluated the efficacy and safety of trastuzumab-based chemotherapy in the adjuvant setting. The NSABP B-31 trial was a randomized trial in which $>1,600$ patients with node-positive, HER-2$^+$ breast cancer received doxorubicin and cyclophosphamide followed by either paclitaxel alone or paclitaxel with trastuzumab. The study demonstrated a higher risk for HF following treatment with trastuzumab [43, 44]. Age, hypertension, and postdoxorubicin and cyclophosphamide LVEF values $<54%$ were identified as risk factors for the development of HF.

The North Central Cancer Treatment Group phase III trial N9831 evaluated doxorubicin plus cyclophosphamide followed by weekly paclitaxel with or without trastuzumab in women with HER-2$^+$ operable breast cancer [45]. That study showed that whereas postdoxorubicin and cyclophosphamide cardiac events were higher in treatment arms containing trastuzumab, the incidence was $<4%$ of that in the control arms [45]. In addition, whereas other chemotherapy agents are not given concurrently with radiotherapy, the coadministration of trastuzumab and radiotherapy in the metastatic setting does not further increase the cardiotoxicities associated with radiotherapy alone at 1.5 years of follow-up [46]; however, because the effects of radiotherapy on cardiac function persist for many years, longer follow-up is needed to confirm this finding.

The Herceptin Adjuvant trial evaluated the use of sequential trastuzumab after at least four cycles of an anthracycline-containing regimen in $1,693$ women with early-stage HER-2$^+$ breast cancer. In that study, the rate of HF was $0.6%$ for patients receiving trastuzumab for 1 year [47, 48]; however, a major consideration is that the time between starting trastuzumab and completing anthracyclines was longer in this study (mean, 89 days) than in previously reported studies. This may, in part, explain the low incidence of cardiac toxicity detected, because patients may have had a longer time to recover from an anthracycline-related cardiac insult [49]. Furthermore, the LVEF had to be at least $55%$ after completion of adjuvant chemotherapy and prior to initiation of trastuzumab, suggesting that the patients in this study may have had more cardiac reserve prior to trastuzumab therapy. Exploratory data indicate that the early detection of cardiotoxicity associated with trastuzumab may be predicted by a doubling of the BNP level [50]. Twenty-seven percent of patients with cardiotoxicity, defined as a $>15%$ decrease in LVEF or a $10%–15%$ decrease in LVEF to less than the institutional lower limit of normal, had a doubling of BNP, compared with $7%$ of controls. Because of the importance of prediction and early detection of treatment-related cardiotoxicities for the improvement of clinical outcomes, further study regarding the role of cardiac biomarkers is needed.

Both multigated acquisition (MUGA) scanning and echocardiography (echo) provide similar LVEF measurements [51] and are widely used in practice and in clinical trials for monitoring cardiac function in trastuzumab-treated patients. However, echo may be the preferred technique for cardiac monitoring because of additional structural hemodynamic information obtained by these studies as opposed to solely an LVEF measurement by MUGA. Moreover, because the cardiotoxicity of trastuzumab appears to be largely reversible [52], it is recommended that LVEF be re-evaluated every 12 weeks in patients receiving this therapy in the adjuvant setting.

In sum, anthracycline- and trastuzumab-based regimens
have been associated with clinical efficacy and both have been linked to cardiac dysfunction. It is apparent that the mechanism for cardiac toxicity is distinctly different between these two therapies [53]; however, the identification of toxicity and the optimal treatment of LV dysfunction is not [5]. It is also recognized that multiple factors may be responsible for cardiac dysfunction and all potential exacerbating factors should be identified and treated in these patients [7].

**Hormonal Therapy**

**Cardiovascular Effects**

It is thought that reduced estrogen levels during the hormonal treatment of women with EBC may increase the risk for cardiovascular disease. Initially, it was theorized that tamoxifen may be cardioprotective as a result of its estrogen agonist effects [54]; however, strong cardioprotective effects of tamoxifen have not been demonstrated. For example, a meta-analysis of data from the Early Breast Cancer Trialists’ Collaborative Group showed that tamoxifen tended ($p = .06$) to lead to fewer cardiac deaths than with control treatment [55]. Another meta-analysis showed that tamoxifen treatment resulted in significantly fewer fatal myocardial infarctions than control treatment (although the effect was lost when one trial that had markedly different results from the others was excluded) [56]. The AIs commonly used in treating EBC do not appear to be highly associated with a higher risk for thromboembolic events and are not contraindicated in patients who are obese or hypertensive. Limited data suggest that the AIs (anastrozole, letrozole, and exemestane) may differ from tamoxifen in their cardiovascular effects (Table 1); however, comparing published data from randomized clinical trials must be cautiously considered because cardiovascular events were defined and evaluated differently across studies [57–61].

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared 5 years of treatment with anastrozole, tamoxifen, or a combination of anastrozole plus tamoxifen in 9,366 women who had EBC [57]. The combination arm was discontinued after an initial analysis (median follow-up, 33 months) showed no additional benefit of the combination versus tamoxifen alone [57, 62]. At a median follow-up of 68 months ($n = 6,186$), there were no differences in the incidence of ischemic cardiovascular events, including angina, coronary artery disease, myocardial infarction, and myocardial ischemia, in patients treated with anastrozole (4%) or tamoxifen (3%; $p = .1$) [58]. Similarly, there were no significant differences in the incidence of cardiovascular-related deaths in patients receiving anastrozole (2%) or tamoxifen (1%). More patients receiving anastrozole developed hypertension (13%) than those receiving tamoxifen (11%; $p = .04$). Patients receiving anastrozole had fewer cerebrovascular (2% versus 3%, respectively; $p = .03$) and thromboembolic (3% versus 5%; $p = .0004$) events than patients receiving tamoxifen. The median follow-up of 100 months confirms these earlier findings and also shows no differences in the incidence of cardiovascular-related deaths in patients receiving anastrozole (2%) or tamoxifen (2%) [63].

Two large, randomized trials have compared the safety and efficacy of letrozole. The Breast International Group (BIG) 1–98 phase III study compared letrozole and tamoxifen in $>8,000$ women with EBC. Comparison of the mono-therapy treatment arms in the BIG 1–98 study at a median follow-up time of 51 months revealed no differences in the incidence of cardiac events in patients who received letrozole versus tamoxifen (5.5% versus 5.0%; $p = .48$); however, in that trial, patients receiving letrozole had a significantly higher incidence of grade 3–5 cardiac events (3.0%) than those receiving tamoxifen (1.4%; $p < .001$) [59, 64]. There were no differences between the rates of ischemic heart disease or cardiac failure between treatment groups; however, the incidence of other cardiovascular events was higher in patients receiving letrozole ($p = .014$) [59].

The National Cancer Institute of Canada Clinical Trials Group MA.17 trial compared a 5-year course of letrozole versus placebo in $>8,000$ women who completed 5 years of adjuvant tamoxifen treatment for breast cancer. In that study, the incidence of cardiovascular events was the same in patients receiving letrozole (5.8%) as in those receiving placebo (5.6%; $p = .76$) at a median follow-up of 30 months [60].

The Intergroup Exemestane Study evaluated the clinical benefit and long-term effects of switching to exemestane after 2–3 years of tamoxifen therapy in postmenopausal women with primary, ER$^+$ breast cancer [65]. After a median follow-up of 55.7 months, the incidence of cardiovascular events did not differ between treatment groups; however, patients receiving exemestane had fewer thromboembolic events than those receiving tamoxifen ($p = .004$) [61]. No differences were observed in the incidence of myocardial infarction between treatment groups, although 71% of exemestane patients who had a myocardial infarction had a history of hypertension, versus only 32% of the corresponding tamoxifen patients.

**Lipid Effects**

Because elevations in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, and low levels of high-density lipoprotein cholesterol (HDL-C) are
known risk factors for cardiovascular disease, it is important to evaluate the long-term effects of endocrine therapies on the lipid profiles of patients receiving these drugs [66]. The AIs and tamoxifen can significantly affect lipid levels. Tamoxifen significantly reduces serum cholesterol by 12% and LDL-C by 19%, with no change in HDL-C or triglyceride levels, perhaps via effects on lipoprotein lipase; however, studies in postmenopausal Japanese women with EBC have shown that tamoxifen raises triglyceride levels [54, 67, 68]. Like the cardiovascular effects of these drugs, the effects of AIs on lipids differ among agents, and vary among the individual studies. In the ATAC trial, anastrozole was associated with a greater incidence of hypercho-

<table>
<thead>
<tr>
<th>Study/event</th>
<th>AI</th>
<th>Comparator</th>
<th>p-value</th>
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<tr>
<td>Anastrozole</td>
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<tr>
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<td>Tamoxifen (n = 3,116)</td>
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<td>Cerebrovascular deaths</td>
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<td>29 (0.9)</td>
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<tr>
<td>Exemestane</td>
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<tr>
<td>Intergroup Exemestane Study [61]</td>
<td>Exemestane (n = 2,320)</td>
<td>Tamoxifen (n = 2,338)</td>
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<tr>
<td>Cardiovascular events (excluding VTE)</td>
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<td>350 (15)</td>
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<tr>
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<td>VTE</td>
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<tr>
<td>Other cardiovascular event</td>
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Abbreviations: AI, aromatase inhibitor; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG, Breast International Group; CABG, coronary artery bypass graft; DVT, deep vein thrombosis; NR, not reported; PTCA, percutaneous transluminal coronary angioplasty; VTE, venous thromboembolic event.

Data from the BIG 1–98 phase III study indicate that letrozole was associated with a higher incidence of hypercho-

1229Lenihan, Esteva

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Studies of exemestane, on the other hand, revealed no significant differences in the incidence of hypercholesterolemia among women receiving exemestane (7.2%) versus tamoxifen (6.0%; \( p = 0.12 \)), and a modest reduction in HDL-C and increase in LDL-C when compared with placebo [61, 70].

The Letrozole, Exemestane, and Anastrozole Pharmacodynamics trial compared the effects of all three of these AIs on lipid profiles in 90 healthy postmenopausal women [71]. Initial results showed that these three drugs have different effects on total cholesterol, triglycerides, the LDL-C: HDL-C ratio, HDL-C, and the apolipoprotein (Apo)B: ApoA1 ratio. Overall, anastrozole had a neutral effect on lipid values in this study; however, when compared with anastrozole, letrozole significantly increased triglyceride levels at week 12 (\( p = 0.037 \)) and exemestane significantly increased the LDL-C:HDL-C ratio at week 12 (\( p = 0.048 \)) and week 24 (\( p = 0.047 \)) [71]. While these studies suggest that tamoxifen and the AIs may be involved in lipid metabolism, limitations of these studies include a lack of appropriate comparators (e.g., placebo), carryover effects of prior therapies, small sample sizes, and differences in trial designs that make meaningful interpretation of the data difficult (see summary in Table 2). Based on the available data, however, the demonstrable effects of lipid alterations do not appear to have a significant impact on clinical outcomes, especially because no notable cardiac events occurred. It is significant that the WHI trials, which evaluated the effects of hormone replacement therapy, concluded that changes in lipid profiles resulting from hormones are not a reliable predictor of cardiovascular events [72, 73].

**Recommendations and Suggested Interventions for Assessing and Managing High-Risk Patients**

Oncologists and cardiologists should remain vigilant regarding the risks for cardiovascular disease in patients receiving long-term adjuvant therapy for EBC. Although inconsistent and limited data may impede treatment decisions, a concerted effort must be made to educate the health care community involved in caring for breast cancer patients. It is important that oncologists understand the need to adequately assess cardiac function and vascular risk because many patients with EBC are more likely to die of heart disease than cancer [2, 74]. Similarly, education of cardiologists about the increased risk for cardiovascular events in the breast cancer patient population is also necessary. Oncologists and cardiologists should work together when possible [75] to ensure that women with breast cancer receive the necessary information to prevent cardiac events, as well as the appropriate treatment and rehabilitation if they develop cardiovascular disease or experience a cardiac event.

Based on our experience at the M. D. Anderson Cancer Center and our review of the literature, we suggest several recommendations for assessing and managing patients with EBC who are at high risk for a cardiovascular event (Table 3). Patients should be encouraged to follow standard guidelines for reducing cardiovascular risk [74]. Blood pressure control, lipid level reduction, and lifestyle modifications to include exercise and smoking cessation are suggested for the prevention and early identification of cardiovascular disease.

A clinical endpoint for patients with breast cancer, particularly those at high risk for a cardiovascular event, should be the prevention and optimal management of cardiovascular risk factors (Table 3). A thorough history and baseline assessments should be conducted to determine the overall risk level. Because exposure to radiation, anthracycline-based therapies, and trastuzumab are all associated with adverse cardiac outcomes, including HF, physicians should remain cognizant of the potential for cardiovascular events during long-term follow-up. Based on an emerging body of literature and the fact that cardiac disease can be
clinically silent, it is recommended that LVEF be assessed in any patient who is about to receive anthracyclines or has previously. Additionally, periodic (every 12 weeks) monitoring of cardiac function is suggested for those patients receiving trastuzumab in the adjuvant setting. Although there are no guidelines for biomarker monitoring of cardiac-related toxicity in breast cancer patients, both the literature and our experience suggest that there may be a prognostic value of biomarkers in identifying the high-risk patient and predicting the degree of LVEF reduction, especially in those patients receiving anthracyclines and perhaps trastuzumab [37].

It is important to critically evaluate all available and forthcoming data from clinical trials on the effects of AIs. To date, key trial data suggest some subtle differences among the AIs regarding cardiac and lipid abnormalities; however, there is neither sufficient nor available data from ongoing head-to-head studies to determine whether there are clear differences among these agents and if these results translate to clinical practice.

A multidisciplinary approach should be used to manage ER+ EBC patients with high cardiovascular risk. This approach involves the patient’s primary care physician, oncologist, and cardiologist. The goals of the multidisciplinary management of the EBC patient are to improve clinical outcomes; maximize consistency, continuity, coordination, and cost-effectiveness of treatment; and foster better communication among clinicians [3]. Several studies evaluating the effectiveness of a multidisciplinary team approach for the management of patients with cancer reported increased survival following the introduction of the multidisciplinary management of patients [76–78]. Furthermore, increased communication among a patient’s oncologist, primary care physician, and cardiologist will help ensure proper management of cardiovascular risk factors, appropriate follow-up care, and risk-reduction interventions for the prevention of cardiovascular events associated with the use of chemotherapeutic regimens commonly used for the treatment of EBC.

**CONCLUSIONS**

Cardiovascular disease is the leading cause of death in women worldwide, with more than two million deaths annually [79]. Many adjuvant therapies for treating EBC are associated with an increased risk for cardiovascular events, particularly with long-term therapy. It is important for clinicians involved in the care of EBC patients to assess and manage the risk factors for cardiovascular disease. Overall, no significant differences in the risk for ischemic cardiovascular events have been reported between AIs and tamoxifen to date. Although variable effects on lipid levels have been observed with AIs, there has been no evidence to link these changes with clinical outcome. Furthermore, AIs may reduce the risk for venous thromboembolism and perhaps have a clinically beneficial effect on triglycerides. Greater awareness among primary care physicians, oncologists, and cardiologists of the cardiovascular risks associated with treating the EBC patient is needed. Improving cardiovascu-

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<th>Table 3. Recommendations and suggested interventions for the multidisciplinary management of cardiovascular risk in patients with EBC at high risk for cardiovascular events</th>
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<tr>
<td><strong>Recommendations</strong></td>
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<tr>
<td>Obtain baseline assessments of cardiovascular health before initiating therapy</td>
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<td>Assess cumulative cardiovascular risk</td>
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<td>Begin cardiovascular risk-reduction strategies/interventions</td>
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<td>Monitor cardiovascular health of patients with cardiotoxic therapy</td>
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<td>Continue long-term cardiovascular follow-up</td>
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Abbreviations: BNP, B-type natriuretic peptide; EBC, early breast cancer; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition; NCEP, National Cholesterol Education Program.
lar outcomes in patients with EBC requires appropriate risk assessment, monitoring, and long-term follow-up care.

**AUTHOR CONTRIBUTIONS**

Conception/design: Francisco J. Esteva, Daniel Lenihan

Data analysis: Francisco J. Esteva, Daniel Lenihan

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