Review article

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Women survive breast cancer but fall victim to heart failure: the shadows and lights of targeted therapy

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In many cases, early-stage breast cancer is now curable, and metastatic disease can be chronic consequent to the advent of new therapeutic tools. Unfortunately, some treatments have been associated with adverse cardiovascular effects. Indeed, in many breast cancer survivors, the risk of cardiovascular disease is higher than the risk of cancer recurrence. The clinical challenge of preventing cardiovascular complications in patients undergoing antineoplastic treatment has two aims, more effective life-saving treatment of patients, and prevention of morbidity and cardiovascular mortality in the short term and long term. The aim of the present study is to review the rapidly evolving therapeutic strategies designed to treat early-stage breast cancer. The review highlights the need for more data on the impact of new biological drugs (targeted therapy) on the cardiovascular apparatus. Finally, given the complexity of targeted and other novel treatments, cancer patients are best managed through a multidisciplinary approach. *J Cardiovasc Med* 11:861–868

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Introduction

The ongoing discussion about the cardiologic treatment of patients affected by cancer focuses on two issues, the side-effects, in particular left ventricular dysfunction, of drugs, and the long-term survival of patients with cardiac disease induced by oncologic medication. Consequently, cardiologists and oncologists must address the problem, also from a medicolegal perspective, of treating cancer without damaging the heart. This issue applies particularly to early breast cancer that, in some centers such as ours, has reached a 5-year survival rate of 93%.

Unfortunately, the survival rate decreases dramatically in case of cardiac insufficiency [1,2]. It is noteworthy that in the USA, 2.3 million women have a history of breast cancer and a life expectancy long enough to develop cardiovascular complications [3]. The incidence of breast cancer is increasing; every year, about 210 000 women in the USA and about 40 000 in Italy become affected [4]. Therefore, this neoplasia has a tremendous socio-economic impact.

The association between traditional risk factors and cardiovascular disease has been extensively investigated in women [5]. Risk factors are diabetes, dyslipidemia, cigarette smoking, hypertension and a family history of coronary artery disease. It is well known that by the age of 50 years, 40% of women have at least one cardiovascular risk factor and 17% have two or more risk factors [3]. Therefore, at the time of diagnosis, a remarkable percentage of women with breast cancer will be at a significant risk of cardiovascular disease and the risk will increase due to the direct and indirect effects of breast cancer treatment [3]. Moreover, cardiovascular risk factors are a strong predictive factor for the development of cardiovascular damage induced by cancer therapies.

It is noteworthy that, in addition to the well-recognized risk factors associated with breast cancer, there are less well-known risks such as physical inactivity and obesity [6]. Physical inactivity and obesity can be more frequent in women affected by early breast cancer and this implies an increased risk in cardiovascular events not related to cancer therapy toxicities [6].

The purpose of the present review is to examine the data about the cardiovascular effects of early breast cancer therapy so that clinical cardiologists can improve their preventive, diagnostic and therapeutic approach toward this emerging population of new patients that is at high cardiovascular risk.

In recent years, drugs that target a specific pathway in the growth and development of a tumor (e.g. trastuzumab, bevacizumab and sunitinib) have been added to the so-called 'traditional' drugs, that is, anthracyclines, cyclophosphamide, taxanes, 5-fluorouracil and capecitabine. Targeted therapy has reduced mortality and increased

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Table 1 Differences between type I and II cardiotoxicity

	Type I Doxorubicin	Type II Trastuzumab
Clinical course, response to CRCD therapy	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months (reversible)
Dose effects	Cumulative, dose related	Not dose related
Mechanism	Free radical formation, oxidative stress/damage	Blocked ErbB2 signal
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve overtime)	No apparent structural abnormalities
Noninvasive cardiac testing	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion
Effect of rechallenge	High probability of recurrent dysfunction that is progressive may result in intractable heart failure and death	Increasing evidence for relative safety of rechallenge
Effect of late sequential stress	High likelihood of sequential stress related cardiac dysfunction	Low likelihood of sequential stress-related cardiac dysfunction

CRCD, chemotherapy-related cardiac dysfunction. Adapted from [27].

the disease-free survival of cancer patients [7–10], and its use is destined to increase. The cardiotoxic effects of traditional drugs are well documented [11], whereas targeted therapy's off-target effects, particularly those concerning the cardiovascular apparatus, have only recently started to emerge [12–18].

Trastuzumab

The most relevant cardiotoxic effect of trastuzumab is systolic dysfunction of the left ventricle that, in some cases, can cause severe cardiac insufficiency and even death [19–22]. The term 'II-type cardiomyopathy' has been coined for this condition to distinguish it from 'I-type cardiomyopathy' caused by the anthracycline agent doxorubicin (Table 1). The incidence of trastuzumab cardiotoxicity was first evaluated in a metastatic setting (pivotal trial) [23,24]. Seidman *et al.* [24] reviewed the data from six phase II trials and one phase III trial for a total of 1219 women with metastatic breast cancer receiving trastuzumab alone or in combination with cytotoxic chemotherapy. They found that the incidence of any cardiac dysfunction during therapy was between 3 and 7% with trastuzumab alone, and significantly higher in patients receiving trastuzumab concurrently with doxorubicin and cyclophosphamide or paclitaxel (Table 2). In a seminal phase III trial assessing the benefit of adding trastuzumab to cytotoxic therapy [23], the incidence of any cardiac dysfunction with trastuzumab and anthracycline versus anthracycline alone was 27 versus 8%, and it was also higher with trastuzumab and paclitaxel versus paclitaxel alone (13 versus 1%; Table 2). Moreover, the incidence of New York Heart Association (NYHA) class III/IV heart failure was higher with trastuzumab and anthracycline (16%) and markedly lower with trastuzumab alone (2–4%) and paclitaxel and trastuzumab (compared with 4% for anthracycline alone).

These data led to the general recommendation that concurrent doxorubicin and trastuzumab be avoided because of the increased risk of cardiotoxicity, although newer data are challenging this view. However, there is evidence that concurrent administration of trastuzumab and doxorubicin is well tolerated when the cumulative doxorubicin dose is limited to 180 mg/m^2 [25,26].

Table 2 Incidence of cardiac failure (New York Heart Association class III/IV) in the pivotal trials

				With CREC-diagnosed cardiac dysfunction		With NYHA functional class III/IV	
Treatment	Prior anthracycline exposure (% of patients)	Treated (no. of patients)	Reviewed by CREC (no. of patients)	No. of patients	%	No. of patients	%
Trastuzumab alone	Unknown	46	8	3	7	2	4
Trastuzumab + cisplatin	Unknown	39	4	1	3	1	3
Trastuzumab + AC	1%	143	47	39	27	23	16
AC alone	1%	135	22	11	8	5	4
Trastuzumab + paclitaxel	91%	91	18	12	13	2	2
Paclitaxel alone	97%	95	9	1	1	1	1
Trastuzumab alone	Unknown	213	24	11	5	8	4
Trastuzumab alone	Unknown	114	6	3	3	2	2
Trastuzumab ± other chemotherapy	Unknown	246	35	16	6	8	3
Trastuzumab ± other chemotherapy	Unknown	343	29	15	4	10	3
	Not applicable	1219	202	112		62	

AC, anthracycline + cyclophosphamide; CREC, Cardiac Review and Evaluation Committee; NYHA, New York Heart Association. Adapted from [23,24].

Table 3 Cardiotoxic effects in adjuvant trials

	Arm	*N*	Severe CHF, %
HERA [9]	H 1 Year	1678	0.6
NSABP B-31 [8]	AC > PH	947	3.8
NCCTG N9831 [7]	AC > PH	570	3.3
BCIRG 006 [10]	AC > DH	1068	1.9
	DcarboH	1056	0.4

A, anthracycline; C, cyclophosphamide; carbo, carboplatin; CHF, congestive heart failure; D, docetaxel; H, trastuzumab (herceptin); P, paclitaxel. Adapted from [7–10].

In the adjuvant setting, the effects of trastuzumab, which is administered to 25% women affected by breast cancer, have been analyzed in several trials, Herceptin Adjuvant (HERA) trial, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831 and Breast Cancer International Research Group (BCIRG) 006 [7–10] (Table 3). Based on data obtained in patients affected by metastatic breast cancer and given concerns about enhanced cardiotoxicity with concurrent anthracyclines, anthracyclines and trastuzumab were sequentially administered in all adjuvant trials.

NSABP B-31 is an American, phase III, randomized, multicenter, open-label trial in the adjuvant setting that compared the outcomes of anthracycline–cyclophosphamide with or without trastuzumab. Patients were randomized to one of the two arms. Arm one received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) for four 3-week cycles, followed by paclitaxel (175 mg/m^2) for four 3-week cycles. Arm two received the same chemotherapy regimen and concomitant trastuzumab, administered as a loading dose (4 mg/kg) with the first dose of paclitaxel, then as weekly doses of 2 mg/kg for 51 weeks.

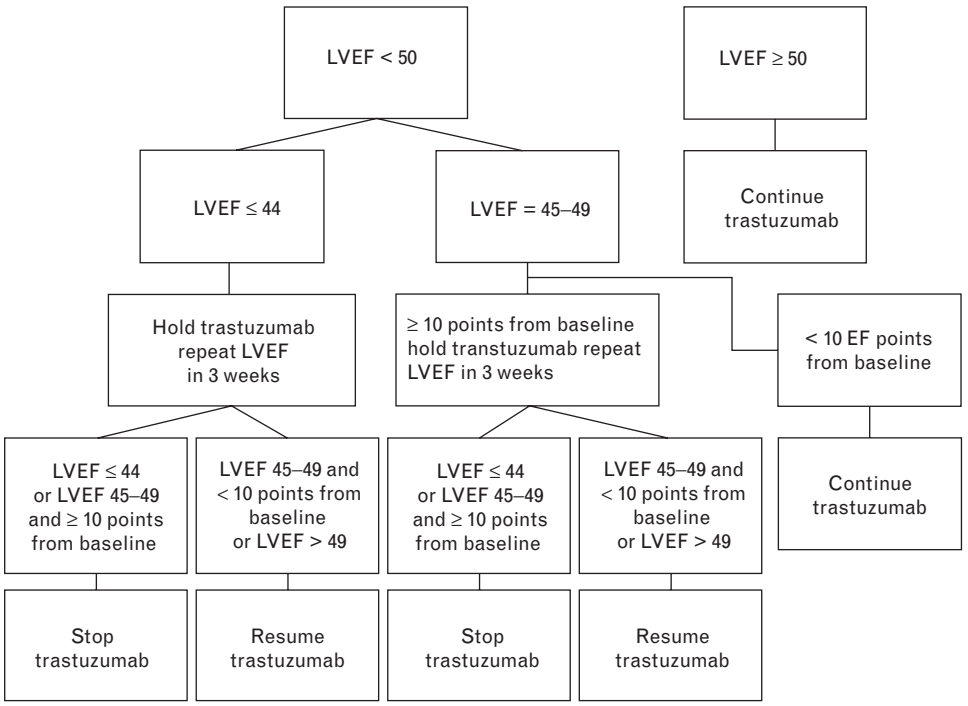
NCCTG N9831 is an American, phase III, randomized, multicenter, open-label trial of 1 year of adjuvant Herceptin (Roche, Basel, Switzerland) given either concurrently with or after paclitaxel therapy compared with chemotherapy alone in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. Patients were randomized to one of the three arms. Arm A received anthracycline–cyclophosphamide (as in NSABP B-31 arm one) followed by 12 weekly doses of paclitaxel (80 mg/m^2). Arm B received the same chemotherapy regimen as arm A, followed by a course of postpaclitaxel trastuzumab therapy. Trastuzumab was given as a loading dose (4 mg/kg) followed by weekly doses of 2 mg/kg for 51 weeks. Arm C received the same chemotherapy regimen as arm A with the addition of concomitant trastuzumab (dosed as described for arm A).

In the NSABP B-31 and NCCTG N9831 trials, the control arms (arms one and A, respectively) and treatment arms two and C, respectively, are similar. The 3-year cumulative incidence of NYHA class III/IV heart failure in B-31 was significantly higher in the trastuzumab arm (3.8 versus 0.8% with chemotherapy alone). In the N9831 study, the incidence of class III or IV heart failure was significantly higher with trastuzumab (3.3 versus 0% with chemotherapy alone). Overall, 19% patients discontinued trastuzumab for a cardiac reason, 14.2% because of an asymptomatic decline in left ventricle ejection fraction (LVEF) and 4.7% because of cardiac symptoms.

The HERA trial is an international, phase III, randomized, multicenter, open-label trial comparing adjuvant Herceptin for 1 or 2 years versus observation only in HER2-positive early breast cancer. Patients who had previously received a predefined neoadjuvant or adjuvant chemotherapy regimen (for a minimum of four cycles or 4 months) with or without radiation therapy were randomized to one of the three arms. Arm A received no trastuzumab (observation only control arm). Treatment arms B and C received a loading dose of trastuzumab (8 mg/kg) followed by 6 mg/kg in 3-week cycles for 1 year (arm B) or 2 years (arm C). As in the North American trials, the incidence of both symptomatic and asymptomatic cardiotoxicity was significantly higher in patients receiving trastuzumab in conjunction with chemotherapy compared with chemotherapy alone. The incidence of cardiac failure NYHA class III/IV was 0.6%.

The BCIRG 006 trial is an international, phase III, randomized, multicenter, open-label trial of 1 year of adjuvant Herceptin given with chemotherapy compared with chemotherapy alone in HER2-positive early breast cancer. Patients were randomized to one of the three treatment arms. Like the NSABP B-31 and NCCTG N9831 trials, the BCIRG 006 study design was based on four 3-week cycles of anthracycline therapy followed by four 3-week cycles of taxane therapy. Doxorubicin (60 mg/m^2) was used in combination with cyclophosphamide (600 mg/m^2), and docetaxel (100 mg/m^2) replaced paclitaxel in the taxane phase of chemotherapy for arm A and arm B. After completion of docetaxel therapy, arm B patients received weekly trastuzumab for up to 1 year (2 mg/kg). Arm C assessed a nonanthracycline chemotherapy combination because anthracyclines have been associated with an increased risk of cardiac dysfunction in patients receiving concurrent trastuzumab. Arm C was based on the synergy among the three agents and efficacy in treating metastatic disease, and patients received six 3-week cycles of docetaxel (75 mg/m^2) and carboplatin [calculated at a dose of area under curve (AUC6)] with a weekly standard dose of trastuzumab during chemotherapy (2 mg/kg), switching to 3-week cycles for 1 year of follow-up. The maximum incidence of severe cardiac failure was 1.9% reached in the arm with anthracycline and cyclophosphamide followed by docetaxel with trastuzumab (Table 3).

Fig. 1



Current recommendations for cardiac monitoring in trastuzumab-treated patients. EF, ejection fraction; LVEF, left ventricle ejection fraction. Adapted from [30].

In conclusion, in the groups treated with trastuzumab there was a significant increase in clinically evident cardiac insufficiency, and a higher percentage of asymptomatic reduction in ejection fraction versus chemotherapy alone. However, the incidence of NYHA III/IV cardiac failure was less than 4% of the treated patients in all the trials [7–10] (Table 3). The dysfunction caused by trastuzumab is completely different from the dysfunction caused by anthracyclines. The dysfunction caused by trastuzumab is reversible and does not seem to cause ultrastructural damage to cardiomyocytes [27,28]. In this context, the term 'II-type cardiomyopathy' was coined to distinguish trastuzumab-induced effects from the effects of anthracyclines ('I-type cardiomyopathy'). Chien [29] noted that trastuzumab and the heart can constitute a modified model of cardiac insufficiency.

In the attempt to facilitate decision-making for cardiologists and oncologists in daily practice when confronted with cases of collateral cardiovascular complications of trastuzumab, Suter *et al.* [30] devised an algorithm for the monitoring of asymptomatic reduction of ejection fraction (Fig. 1). In addition, Mackey *et al.* [31] reported the medication [angiotensin-converting enzyme (ACE) inhibitors and β-blockers], the starting dose, target dose and suggested titration plan in order to try to reach the target dose in 4 weeks (Table 4).

However, in these adjuvant trials [7–10] in a remarkable percentage of women there was an asymptomatic reduction in ejection fraction that persisted at 3-year follow-up (17.3% in one arm of BCIRG 006, 14% in NSABP B-31 and less in the others) [32]. This finding casts doubt on the concept of reversibility. Moreover, because remodeling in cardiac insufficiency is a progressive phenomenon and the follow-up of adjuvant studies is relatively short, it is difficult to envisage the long-term evolution of the trastuzumab-induced cardiomyopathy [32,33].

Angiogenesis inhibitors

Vascular endothelial growth factor (VEGF) and other proteins involved in tumor angiogenesis play a crucial role in tumor growth and development of metastases and have thus become an important therapeutic target in cancer. Consequent to the efficacy of angiogenesis inhibitors such as bevacizumab and sunitinib in other tumors, these agents have been tested in early breast cancer trials. As shown in Table 5, cardiovascular complications have already been associated with angiogenesis inhibitors, namely, arterial hypertension, reduction of left ventricular ejection fraction and increased incidence of thromboembolic events [34,35].

Bevacizumab is a monoclonal antibody against circulating VEGF and is now used to treat breast cancer. Miller *et al.*

Table 4 Treatment of trastuzumab-related cardiotoxicity

Medication	Starting dose (mg)	Target dose (mg)	Suggested titration plan
ACE inhibitors			Increase the dose at 1–2-week intervals
Captopril	6.25–12.5 × 3/day	25–50 × 3/day	Monitor renal function and electrolytes weekly or every 2 weeks
Enalapril	1.25–2.5 × 2/day	10 × 2/day	Maintain blood pressure normal
Ramipril	1.25–2.5 × 2/day	5 × 2/day	Try to reach target dose in 4 weeks
Lisinopril	2.5–5 × 1/day	20–35 × 1/day	
β-blockers			
Carvedilol	3.125 × 2/day	25 × 2/day	
Bisoprolol	1.25 × 1/day	1.25 × 1/day	

ACE, angiotensin-converting enzyme. Adapted from [31].

[36] conducted a randomized phase III trial to compare the efficacy and safety of capecitabine with or without bevacizumab in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. In this study, bevacizumab caused grade three hypertension in 17.9% patients. In six other series of patients bevacizumab caused hypertension of all grades in percentages of patients that ranged from 4 to 35% [37–42]. The incidence of thrombotic events was 4% [36].

Sunitinib is a tyrosine kinase inhibitor against VEGF receptors 1–3. In clinical trials, it was associated with hypertension with an incidence between 5 and 47% [43–47]. In a retrospective review, sunitinib was found to increase blood pressure (>150/100 mmHg) in 47% patients, with grade three hypertension seen in 17% patients [48] (Fig. 2). Hypertension occurred within the first 4 weeks of therapy. In the same study there was an ejection fraction asymptomatic reduction of at least 10% in 28% of patients, and of at least 15% in 19% of patients. In another series of 48 patients treated with sunitinib, seven (15%) experienced symptomatic grade 3–4 ventricular dysfunction 22–435 days after initiation of sunitinib [49].

The mechanism of antiangiogenic therapy-related hypertension is not fully understood. However, it is thought to be related to VEGF inhibition, which decreases nitric oxide production in the wall of the arterioles and other resistance vessels [50]. Nitric oxide is a natural vasodilator; therefore, blockage of its production promotes vasoconstriction, increased peripheral vascular resistance and blood pressure [50]. Animal studies have shown that sunitinib induces mitochondrial damage in cardiomyocytes, but not apoptosis [48]. Khakoo *et al.* [15] suggest that hypertension may also play an important causative role in left ventricular dysfunction because sunitinib inhibits a receptor kinase that helps to regulate the response of cardiomyocytes in the setting of hypertensive stress. In this case, the systolic dysfunction might be partly due to a direct effect of sunitinib on cardiomyocytes exacerbated by arterial hypertension. Therefore, patients treated with sunitinib should be monitored for cardiac dysfunction and should undergo aggressive treatment for arterial hypertension. Finally, studies are urgently required to evaluate the toxicity of sunitinib in order to develop strategies for preventing and handling these complications, particularly because the oncologic indications for this drug continue to expand.

Endocrine therapy

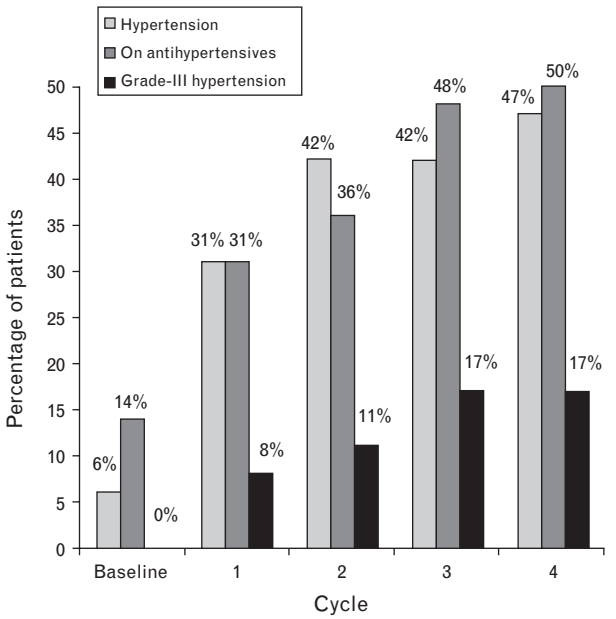
The traditional endocrine therapy (tamoxifen) has not been associated with cardiovascular damage, whereas it exerts a promoting effect on deep-vein thrombosis [51]. Several studies have shown the superiority of third-generation aromatase inhibitors used after, or as alternatives to tamoxifen in early breast cancer. The Breast International Group (BIG) 1–98 study is a phase III clinical trial designed to compare letrozole, a third-generation aromatase inhibitor, and tamoxifen, given alone or sequentially for 5 years [52]. Between 1998 and 2003, researchers at 27 institutions worldwide enrolled 8010 postmenopausal women who had undergone surgery for early estrogen receptor-positive invasive breast cancer and who had no evidence of metastases. The women were randomly assigned to one of the four treatment groups, as follows, letrozole for 5 years (letrozole monotherapy), tamoxifen for 5 years (tamoxifen monotherapy), letrozole for 2 years, followed by tamoxifen for the remaining 3 years or tamoxifen for 2 years, followed by letrozole for the remaining 3 years. Letrozol monotherapy was found to cause a significant increase in grade 3–5 cardiac events (cardiac failure and cardiac death) and hypercholesterolemia compared with tamoxifen alone (Table 6). Further randomized trials are required to evaluate whether this effect is related only to this drug

Table 5 Incidence of cardiovascular complications with angiogenesis inhibitors

		Arterial hypertension grade 3	Cardiomyopathy	Thromboembolism
Single target VEGF-specific Ab	Bevacizumab	17.9%	3%	4%
Multitarget tyrosine kinase inhibitor	Sunitinib	17%	15%	2%

Ab, antibody; VEGF, vascular endothelial growth factor. Adapted from [36,48].

Fig. 2



Cumulative percentage of patients diagnosed with hypertension and on antihypertensive medication during the first four cycles of sunitinib ($n = 36$). Adapted from [48].

or whether it is a drug class effect. As shown in Table 7, in four other studies, letrozol, besides increasing total cholesterol, decreased high-density lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein cholesterol (LDL-C) [53–56].

Conclusion

Many women at the time they are diagnosed with breast cancer are at risk of cardiovascular disease because of preexisting risk factors. Some of the drugs that will be used to treat these patients are associated with cardiotoxicity of various degrees. Therefore, patients will undergo a number of sequential or concomitant cardiovascular stresses caused by oncologic drugs that, in association with the basic risk factors and a detrimental lifestyle, produces overt or subclinical cardiovascular disease; this concept is known as the 'multiple hit' hypothesis [6] (Fig. 3). This clinical problem, which can have devastating immediate or delayed cardiac effects, is exacerbated by many of the most recent biological drugs used in targeted therapy, which, as mentioned above, have several off-target effects, cardiovascular effects being the most dangerous for patients. Therefore, it is necessary to identify preventive and treatment strategies that will reduce the clinical consequences of multiple cardiac and oncological hits [57–61].

Table 6 Breast International Group 1–98: cardiac events and hypercholesterolemia

	Letrozol ($n = 3975$)	Tamoxifen ($n = 3988$)	P
Cardiac events, total	134	122	0.48
Cardiac event grade 3–5	74	35	<0.001
Cardiac deaths	11	5	<0.001
Hypercholesterolemia	1238	601	<0.0001

n, number of patients. Adapted from [52].

Table 7 Changes in lipid parameters from baseline after treatment with anastrazole (130 weeks), letrozole (16 weeks) and examestane (24 weeks)

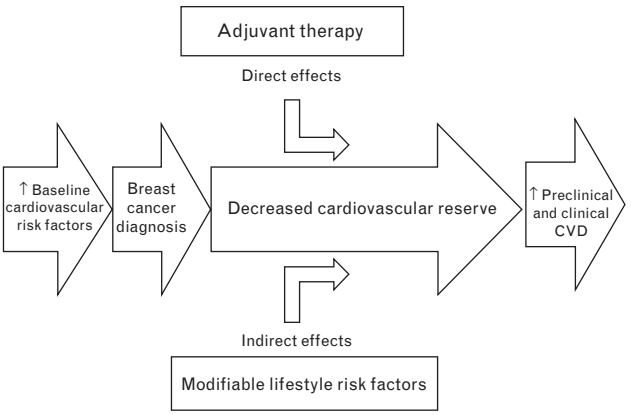
Lipid parameter	Anastrazole	Letrozole	Exemestane
Total cholesterol (mg/dl)	–	↑[a]	–
HDL-C (mg/dl)	–	↓	–
LDL-C (mg/dl)	–	↑[b]	NA
Triglyceride (mg/dl)	–	–	↓[c]
Apolipoprotein A1 (mg/dl)	NA	↓	–
Apolipoprotein B (mg/dl)	NA	↑[a]	–
Apolipoprotein E (mg/dl)	NA	–	NA
Lipoprotein (a) (mg/dl)	NA	–	–
Total cholesterol/HDL-C	–	↑[d]	–
LDL-C/HDL-C	–	↑[c]	NA
Apolipoprotein A1/B	NA	↑[d]	–

↑, increase; ↓, decrease; –, no change; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, lipid parameter not measured. [a] $P = 0.05$. [b] $P < 0.05$. [c] $P < 0.005$. [d] $P = 0.005$.Modified from [53–56].

In a retrospective study, Ewer *et al.* [27] showed that ACE inhibitors and β-blockers, used at maximum tolerated doses, resulted in a return of LVEF to baseline in patients who interrupted trastuzumab for cardiac insufficiency, and patients were able to resume treatment with trastuzumab while continuing cardiologic drugs for heart failure.

Women diagnosed with breast cancer should be evaluated for cardiovascular risk before undergoing treatment with antineoplastic drugs [3]. Depending on the type of risk factor, patients should be advised as regards lifestyle

Fig. 3



'Multiple-hit' hypothesis. CVD, cardiovascular disease. Adapted from [3].

changes, and, in some cases, their drug regimen may have to be changed. Physical exercise is known to have positive effects on cardiovascular reserve, risk factors and total mortality [6]. β-blockers and ACE inhibitors are recommended for initial hypertension therapy. Statins are recommended to maintain LDL-C less than 100 mg/ml. Sulphonylureas and biguanids are recommended to maintain glycosylated hemoglobin less than 7% [31].

The treatment of breast cancer patients who begin to receive antineoplastic drugs should involve a new approach by the oncologist and the cardiologist. The oncologist must cooperate with the cardiologist, and the cardiologist must be aware of the cardiovascular effects of new biological therapies. Scientific associations together with schools of specialization should promote the education of cardiologists and oncologists in this field. Cardiologists and oncologists should be well aware of the multiple-hit hypothesis and the fact that these diagnostic and therapeutic problems will increasingly affect the treatment of women with early breast cancer. Cardiologists will be increasingly involved in the diagnosis and treatment of women affected by early breast cancer and should therefore be well versed in all aspects of this neoplasia.

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