International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

The adverse cardiovascular effects of aromatase inhibitors and its management in patients with breast cancer

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Summary

The purpose of this systematic review is to summarize adverse cardiovascular effects of aromatase inhibitors (AIs) in postmenopausal patients diagnosed with breast cancer (BC) and outline a management plan for these patients. Aromatase inhibitors are indicated as a first-line adjuvant endocrine therapy in postmenopausal women with estrogen-positive BC. Although AIs have better efficacy and toxicity profiles compared to tamoxifen, adverse cardiac events are important considerations due to estrogen deprivation and the probability of worse lipid profile outcomes. A systematic PubMed literature search through April 2011 was conducted. Studies comparing adverse cardiovascular events from AIs with tamoxifen as primary or secondary outcomes and published as a full text manuscript in English were included. Many trials that prospectively analyzed the effects of AIs on the cardiovascular system were found. When compared with tamoxifen, AIs had worse outcomes in short-term follow-up, but had similar outcomes in long-term follow-up. Several trials suggested that regular assessment of serum lipids, cardiac parameters which might be effected by adjuvant therapy, and management of hypertension and weight control are important to minimize cardiovascular risks, especially in women aged >65 years, who constitute >50% of the BC population. In conclusion, we found no direct comparison between the AIs in adjuvant therapy, but the decision to use one specific AI should depend on its toxicity and efficacy profile. Reducing the severity and frequency of adverse cardiac events may improve quality of life for patients taking AIs and yield continuation of this well-documented and beneficial therapy.

Review criteria

Information on adverse cardiac events from AIs was collected via a search for primary trials comparing AIs with tamoxifen and review literature in PubMed using the terms «AIs», «adverse cardiovascular events», «breast cancer» and «cardiac management of adverse cardiac events». This data was then gathered with other relevant articles such as those comparing AIs and placebos.

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Message for Clinic

AIs are one of the best options for adjuvant treatment in patients with BC; however concerns about their cardiac effects should be taken into account in management strategies. Recently, published data on cardiac events implied that AIs can be selected as a first-line therapy or switched therapy based on the patient's tolerance. Cancer patients are vulnerable to many conditions; they can be protected from adverse events with better therapy regimens and regular assessment.

Keywords

Aromatase inhibitors, breast cancer, adverse cardiovascular effects

Introduction

BC is the most often diagnosed cancer, the second cause of cancer mortality following lung cancer, and a common health problem in the Western world comprising about one to third of all cancers in women [1]. BC incidence increased about 0.2% annually between 1997 and 2000; during the same time, incidence of mortality due to BC reduced 2.3% per year. Endocrine treatment remains the mainstay of adjuvant therapy for postmenopausal women with hormone-responsive BC. Women with early stage BC are now surviving longer by means of improved outcomes with chemo and hormone therapy; one disadvantage of this improvement is the risk of long-term adverse cardiovascular effects from BC therapy.

Cardiovascular disease is one of the most major health problems in many developed countries, with a prevalence of 42.7 million in 2005 and mortality of 459,000 in 2004 in the United States [2]. In addition, cardiovascular disease constitutes an important health concern in older, postmenopausal women independent of BC [2,3].

For a long time, tamoxifen was the standard adjuvant endocrine therapy for postmenopausal women with BC, resulting in a reduction of the odds of recurrence of BC by 40% and death by 26% after five years [4]. In women with estrogen-receptor (ER) — positive (or ER unknown) disease, five years of treatment with tamoxifen after definitive surgery reduces the annual recurrence rate by 41% and BC mortality by 34%, translating into an absolute reduction of 9.2% in patients dying from BC by 15 years [5]. Results from meta-analyses showed that tamoxifen had lipid lowering effects; a potential cardio-protective effect of the drug was observed in which the rate of death from serious cardiovascular events such as myocardial infarction (MI) was reduced during active treatment [5–8]. However, tamoxifen was associated with some potential and sometimes life-threatening side effects because of its partial estrogen agonist activity. These side effects include an increased incidence of endometrial cancer [5,9] and thromboembolic events [10] related to duration of drug exposure. *Cancer Research Network* results have demonstrated that the third generation AIs have been replacing tamoxifen as adjuvant endocrine therapy for postmenopausal women with early BC since 2000 [11].

Third generation AIs are highly selective for the aromatase enzyme and substantially well tolerated. Currently, three third-generation AIs are being used clinically in the U.S. All third-generation AIs reduce systemic estrogen levels by 98% [12]. A review of 25 studies reported that AIs showed a significant survival benefit in the treatment of metastatic BC compared to other endocrine therapies [13]. The AIs have proven between 15% and 25% more effective than tamoxifen in reducing the relative risk of recurrence [14–16]. Both anastrozole and letrozole improved disease-free survival (DFS), but not overall survival (OS), compared to tamoxifen for five years. A meta-analysis [17] of first line and sequential strategies endorsed the recommendation in guidelines that AIs should be included in adjuvant therapy for postmenopausal women with endocrine-responsive BC [18,19].

Women with BC live longer due to effective therapies; most may not suffer recurrence of BC despite the fact that they are all vulnerable to toxicities. Therefore, there are at higher risk of both cardiovascular disease [20] and the cardiovascular side effects of BC treatments [21]. Cardiovascular disease will remain as a cause of death in these patients. It has been reported that in the U.S. as high as 2.3 million women live with such risk [20].

The risk of cardiovascular disease increases after menopause and is the greatest cause of morbidity and mortality in postmenopausal women. Estrogen deprivation has been demonstrated to be an independent risk factor for coronary heart disease in symptomatic women [22]. The effects of estrogen in cardiovascular disease are still being investigated, but it has been concluded that estrogen contributes to the cardiovascular system in many ways, affecting endothelial

integrity, inflammation, thrombosis [23], and lipids. It is still being investigated whether the increasing rate of cardiovascular events seen with AIs compared to tamoxifen results from direct AI cardiac toxicity, or is due to the cardio-protective effect of tamoxifen.

Considering the incidence of cardiovascular disease that is mostly unrecognized in women and the potential BC therapy-related adverse effects of cardiovascular disease, it is important to assess the cardiovascular risk factors in postmenopausal women who are receiving adjuvant treatment for BC. An updated analysis of the Breast International Group (BIG) 1–98 trial demonstrated higher rates of cardiac events in a letrozole treated arm than a tamoxifen treated arm, particularly for women between 65 and 74 years old [24]. Recent data suggest that women with early BC are more likely to die of heart disease than recurrent cancer [25].

The aim of this review is to summarize the adverse cardiovascular effects of AIs in postmenopausal patients diagnosed with BC and outline a management plan for these patients.

The effect of estrogen in cardiovascular disease

Estrogen protects against cardiovascular disease in premenopausal women compared to age-matched men, but these advantages in women disappear with increasing age and decreasing estrogen levels with menopause. The two classical estrogen receptors, ER-α, and ER-β, effect the cardiovascular system via intracellular interactions. Estrogen has been shown to promote endothelial progenitor cell mobilization [26], increase mesenchymal stem cell-mediated vascular endothelial growth factor (VEGF) release [27,28], and improve endothelial and myocardial function after ischemia. Lately, a new membrane-bound and G protein-coupled estrogen receptor 30 (GPR30) has been described. Ischemic reperfusion injury was reduced and cardiac function was preserved via activation of the GPR30 receptor in the heart. The decreasing effect of estrogen is related to the increase in methylation of the promoter region of the estrogen receptor with age in menopausal women. Estrogen receptors expression in the arterial wall diminishes sharply with menopause [29,30].

Clinical studies with tamoxifen and aromatase inhibitors

There are two approaches used for the treatment of hormone receptor positive BC through blocking of estrogen synthesis or its action. Several prospective studies compared the effects of various AIs (anastrozole, exemestane, and letrozole) with tamoxifen. These studies examined the effects of these approaches on behalf of their therapeutic effects in postmenopausal women with hormone receptor positive BC. The third generation AIs showed better efficacy than tamoxifen in regards to improvement in disease-free survival and possibly overall survival rate in women with BC [16,31–33].

Nonsteroidal aromatase inhibitors

Anastrozole

Anastrozole, a nonsteroidal AI, binds reversibly to the heme group of the aromatase enzyme. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared the efficacy and safety of one of the third generation AIs, anastrozole (1 mg), with tamoxifen (20 mg), both given orally every day for five years as first line adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive early BC. This trial compared anastrozole with tamoxifen in 9,366 women with newly diagnosed early stage BC, and 84% of whom hormone-receptor positive. This trial failed to point out statistically significant differences in cardiac events between anastrozole and tamoxifen therapies; also the trial's definition of cardiovascular events was limited to ischemic heart disease (IHD). The event rate was 4.1% and 3.4% in the anastrozole and tamoxifen groups, respectively (P = 0.1) [15]. ATAC was the first trial to reveal that an AI is more effective and has fewer serious adverse effects than tamoxifen in adjuvant treatment.

A 120 months follow up of the ATAC trial was recently published [34]. The highest relative reduction in time to recurrence, contralateral BC, and disease-free survival was observed in the anastrozole group compared to the tamoxifen group in the first two years of the active treatment and these differences were maintained all through the entire follow-up period, including after treatment completion of between treatment groups. An absolute reduction of recurrence for the anastrozole group was 2.7% at five years and 4.3% at 10 years follow-up compared to tamoxifen in the hormone receptor-positive BC patients [34]. Tamoxifen has shown a carryover benefit for recurrence in the first five years after treatment, but not after that [5]. The carryover effect for recurrence was more prolonged for anastrozole than for tamoxifen in the present study and remained statistically significant for the 10 year follow up period.

Generally, treatment-related serious adverse events were lower in the anastrozole group than in the

tamoxifen group (OR 0.84, 95% CI 0.60-1.19; *P* = 0.3), but were similar after completion of treatment (OR 0.84, 95% CI 0.60-1.19; *P* = 0.3) [34]. Of note, the increased fracture rate with anastrozole during treatment did not continue after treatment, assuming that this short-term effect could be managed with dual energy x-ray absorptiometry scans and bisphosphonates when needed [15,35,36]. Since the study's definition of cardiovascular events was limited to IHD the 68 month follow-up did not provide safety data on all cardiovascular diseases. At the 68 month follow-up, the incidence of IHD was not significantly higher with anastrozole compared to tamoxifen (4.1% vs. 3.4%, *P* = 0.10) (Table 1). Angina pectoris was a little higher in the anastrozole treated group than in the tamoxifen treated group, but the difference was not statistically significant (2% vs. 1.5%, *P* = 0.07). The myocardial infarctions rate was similar (1%) in both treatment arms, both during treatment and after its completion; when they were only captured as serious events at 68 months, 34 (0.27) and 33 (0.27) on treatment, 26 (0.28) and 28 (0.30) off treatment until 100 months follow-up. The incidence of both vascular and thrombotic events reduced significantly with anastrozole versus tamoxifen overall (2.8% vs. 4.5%, *P* = 0.0004) [15] and the incidence of thromboembolic events at 100 months was similar to that at 68 months [20]. Cerebrovascular events were less common in patients receiving anastrozole during treatment (OR 0.59 [0.32–1.05], *P* = 0.056), but not afterwards (OR 1.10 [0.57–2.13], *P* = 0.75) for those events defined as serious [36]. Additionally, the number of cardiovascular deaths was similar between the anastrozole and tamoxifen (49 vs. 46 at 68 months follow-up, 2% vs. 2% at 100 months follow-up, 2.9% vs. 3.0% at 120 months follow-up). It can be assumed that the prevalence of cardiovascular death is less in the anastrozole treated group. This has been verified in several studies with AIs [17,37].

Also, trials in which tamoxifen was switched to anastrozole in women with BC have been conducted. In the Arimidex-Nolvadex (ARNO) —95 / Austrian Breast and Colorectal Cancer Study Group (ABCSG) — 8 trials (in which patients were switched to anastrozole after two-three years of tamoxifen), the incidence of MI was low in both the anastrozole and the tamoxifen groups (Table 1). The Italian Tamoxifen Arimidex (ITA) trial compared continued tamoxifen therapy to switching to anastrozole after two-three years. Overall, the serious adverse event rate was similar (40 vs. 37 *P* = 0.7); additionally there was no difference in cardiovascular event rates between the two arms (14 vs. 16 *P* = 0.4 at preliminary and 14 vs. 17 *P* = 0.6 at update).

Letrozole

Another nonsteroidal AI is letrozole, which binds reversibly to the heme group of the aromatase enzyme and has a longer half-life at 96 hours. The Breast International Group (BIG) 1–98 trial is the only study with a four-arm design comparing the five-year sequence of either tamoxifen followed by letrozole or the inverse (letrozole followed by tamoxifen) head to head over five years. The BIG 1–98 trial was designed to gather the potential effects of letrozole on cardiac risk. These included any cardiac adverse effects, IHD, cardiac failure, hypertension, peripheral atherosclerosis, thromboembolic events, and other cardiovascular adverse effects. Specific adverse events were graded according to the Common Toxicity Criteria of the *National Cancer Institute* (version 2) at each study visit during treatment [38]. All data were collected separately on adverse effects of any grade and especially for grade 3 to 5 only. The safety data at median 30.1 months follow-up showed that the incidence of cardiovascular events was similar and low in both the letrozole and tamoxifen treated arms [38], meanwhile, letrozole was related to significantly more peripheral atherosclerosis and other cardiovascular events of any grade. When all events were reassessed for grade 3 to 5 adverse effects, it was concluded that tamoxifen resulted in more grade 3 to 5 thromboembolic events and letrozole resulted in significantly more grade 3 to 5 cardiac events of any type, especially cardiac failure (2.4% vs. 1.4%, *P* = 0.001), whereas the events rate was relatively low in both arms [38].

The incidence of ischemic heart disease was higher with letrozole than tamoxifen but results did not reach statistical significance ([1.1%] vs. [0.7%], *P* = 0.06) [38]. The fifty-one months follow-up showed that despite letrozole being associated with higher cardiac events in each grade than tamoxifen, there was no statistically significant difference in cardiac events overall (5.5% vs. 5.0%), IHD (2.2% vs. 1.7%), and cardiac failure (1% vs. 0.6%) between the letrozole and tamoxifen monotherapy groups [39] (Table 2). Although the number of events was small in each arm, there was an increase in the incidence of grade 3 to 5 cardiac events with letrozole (Fisher exact test, *P* < 0.001) [39]. At a median follow-up of 71 months after randomization, the incidence of any type or grade cardiac events was similar between women who were treated with one of the regimens that included letrozole and women who were treated

TABLE 1 **Anastrozole: rever sibl, third-generati on nonsteroidal aromatase inhibitor**	**ATAC (Arimidex, Tamoxifen, alone or in Combination)**									**ITA (The Italian Tamoxifen Anastrozole Trial)**			**ABCSG8/ARNO 95 (The Austrian Breast and Colorectal Study Group / Arimidex - Nolvadex 95)**		
	Tamoxifen for 5 years vs Anastrozole for 5 years (Tamoxifen + Anastrozole arm was discontinued at 47 months)									**Tamoxifen for 5 years vs Tamoxifen for 2-3 years followed by Anastrozole**			**Tamoxifen for 5 years vs Tamoxifen for 2-3 years followed by Anastrozole**		
Design	First line adjuvant									Combined adjuvant			Combined adjuvant		
Median Follow-up	68 months			100 months			120 months(overall)			64 months			28 months		
	ANA	TAM	P value	ANA	TAM	P value	ANA	TAM	P value	ANA	TAM	P value	ANA	TAM	P value
Number of patients	3125	3116								223	225		1618	1606	
Median age	64.1 years(+5.7 years)			72 years			+13 months			63 years			62 years		
Disease free-survival	HR: 0.83(0.73-0.94)		P=0.005	HR: 0.85(0.76-0.94)		P=0.003	HR: 0.86(0.78-0.95)		P= 0.003	**HR: 0.42(A>T)		P=0.001	HR: 0.42(A>T)		P=.0001
Time to distant recurrence	HR: 0.84(0.70-1.00)		P=0.06	HR: 0.84(0.72-0.97)		P= 0.022	HR: 0.85(0.73-0.98)		P=0.02						
Time to recurrence	HR: 0.74(0.64-0.87)		P=0.0002	HR: 0.76(0.67-0.87)		P=0.0001	HR: 0.79(0.70-0.89)		P=0.0002	NA			NA		
Overall survival	HR: 0.97(0.85-1.12)		P= 0.7	HR: 0.97 (0.86-1.11)		P=0.7	HR: 0.95(0.84-1.06)		P=0.4	HR: 0.56(0.28-1.15)		P=0.1	HR: 0.7 (A>T)		P= 0.038
Ischemic cardiovascular events	127(4.1%)	104(3.4%)	P= 0.10	NA			NA			NA					
Myocardial infarction	37(1.0%)	34(1.0%)	P= 0.5	60(1.9%)	61(1.9%)		NA			NA			3(<1%)	2(<1%)	P= 1
Angina	71(2.0%)	51(1.5%)	P=0.07	NA			NA			NA					
Cerebrovascular events	62(2.0%)	88(3.0%)	P= 0.03	64	91	P= 0.03	NA			NA			2(<1%)	9(<1%)	P= 0.064
Thromboembolic Disease	87(2.8%)	140(4.5%)	P= .0004	NA			NA			NA			3(<1%)	12(<1%)	P= 0.034
All cardiac events	NA	NA		NA			NA			All cardiovascular diseaseA: 7.6%,T:6.2%		P= 0.6	NA		
Cardiovascular deaths	49(2%)	46(1%)		67(2%)	66(2%)		91(2.9%)	95(3.0%)							
Cerebrovascular deaths	14(<1%)	22(1%)	P= NS	25(0.8)	29(0.9)		33(1.1%)	36(1.2%)							

ATAC: Results from ATAC study were from HR+ group,
NA: Not available, HR: Hazard ratio,
** 36 Months follow-up

TABLE 2
Letrozole: reversible, third-generation nonsteroidal aromatase inhibitor

	BIG 1-98												MA.17		
	Adjuvant Endocrine Therapy for Early Breast Cancer Using Letrozole of Tamoxifen (four-arm trial comparing 5 years of monotherapy with tamoxifen or with letrozole with sequences of 2 years of one of these agents followed by 3 years of the other)												Letrozole vs placebo after 5 years tamoxifen treatment		
Design	First line adjuvant												Extended adjuvant		
Median follow-up	25.8 months			30.1 months			51 months**			74 months**			30 months		
	LET	TAM	P value	LET	TAM	P value	LET	TAM	P value	LET	TAM	P value	LET	TAM	P value
Number of patients	4003	4007		3975	3988		2448	2447		2448	2447		2583	2587	
Median age	61 years			61 years			61 years			61 years			62 years		
Disease free survival	HR:0.81(0.70-0.93)		P=0.003	NA			HR: 0.88(0.71-0.95)		P=0.007	HR:0.83(0.74-0.94)		P=0.03	HR: 0.58(0.45-0.76)		P<0.01
TTR	HR:0.72(0.61-0.86)		P<0.001	NA			231(0.65)	291(0.92)	P=0.004	NA			NA		
TTDR	HR:0.73(0.60-0.88)		P=0.001	NA			HR: 0.81(0.67-0.98)		P=0.03	HR:0.80(0.67-0.94)		P=0.05	HR: 0.60(0.43-0.84)		P=0.002
Overall survival	HR:0.86(0.70-1.06)		P=0.16	NA			HR: 091(0.75-1.11)		P=0.35	HR: 0.82(0.70-0.95)		P=0.08	HR: 0.82(0.57-1.19)		P=0.3
Cardiac events	162(4.1)	153(3.8)	P=0.61	191(4.8)	188(4.7)	P=0.87	134(5.5)	122(5.0)	P=0.48	169(6.9)	152(6.2)	P=0.36	NA		
Grade 3-5	85(2.1)	44(1.1)	P<0.001	96(2.4)	57(1.4)	P=0.001	74(3.0)	45(1.8)	P<0.001	93(3.8)	51(2.1)		NA		
Ischemic heart disease	57(1.4)	46(1.2)	P=0.28	68(1.7)	60(1.5)	P=0.48	54(2.2)	41(1.7)	P=0.21	69(2.8)	49(2.0)	P=0.08	NA		
Myocardial infarction	NA			NA			NA			NA			9(0.3)	11(0.4)	NS
Angina	NA			NA			NA			NA			31(1.2)	23(0.9)	NS
Cardiac failure	31(0.8)	14(0.4)	P=0.01	40(1.0)	29(0.7)	P=0.19	24(1.0)	14(0.6)	P=0.14	30(1.2)	25(1.0)	P=0.59			
Other cardiovascular events	19(0.5)	8(0.2)	P=0.04	26(0.7)	11(0.3)	P=0.01	19(0.8)	6(0.2)	P=0.014	24(1.0)	13(0.5)	P=0.10	100(3.9)	95(3.7)	NS
CVA/TIA	39(1.0)	41(1.0)	P=0.91	47(1.2)	49(1.2)	P=0.92	34(1.4)	35(1.4)	P=0.90	45(1.8)	38(1.6)	P=0.51	17(0.7)	15(0.6)	NS
Thromboembolic	61(1.5)	140(3.5)	P<0.001	68(1.7)	154(3.9)	P<0.001	50(2.0)	94(3.8)	P<0.001	63(2.6)	104(4.3)	P<0.001	11(0.4)	6(0.2)	NS
Cardiac death	13(0.3)	6(0.2)		NA			12(0.5)	7(0.3)		NA			5*	5*	
Cerebrovascular death	7(0.2)	1(0.03)		NA			8(0.3)	3(0.1)		NA			2*	1*	

TTDR: Time to distant recurrence, TTR: Time to recurrence, NA: Not available, NS: Not significance, HR: Hazard ratio,
*Lymph node-negative patients,
** Results from monotherapy arms.

with tamoxifen monotherapy (6.1 to 7.0% and 5.7%, respectively; $P = 0.45$)[37]. The incidence of thromboembolic events was significantly lower with letrozole than tamoxifen before switching tamoxifen to letrozole or inverse (1.5% vs. 3.5%, $P<0.001$, 1.7% vs. 3.9%, $P<0.001$ at 25.8 months) [14] (Table 2). Furthermore, the reduction in thromboembolic event with letrozole remained significant after switching analysis of the monotherapy arms at 51 months and 74 months (2% vs. 3.8%, $P<0.001$ at 51 months, 2.6% vs. 4.3%, $P<0.001$ at 74 months follow-up) [39,40]. Hence, the reduction in letrozole monotherapy remained significant comparing one of the regimens that included tamoxifen at a median follow-up of 71 months ($P<0.001$) [37].

Letrozole has a similar incidence of cerebrovascular accidents / transient ischemic attacks (CVA / TIA) as tamoxifen before switching tamoxifen to letrozole or inverse (Table 2) [38]. Also, the incidence of CVA / TIA remained similar after 51 months and 74 months follow-up (1.8% 1.6%). Furthermore, there were similar rates of CVA / TIA patients who were assigned to one of the regimens that included tamoxifen and those who were assigned letrozole monotherapy [37].

The MA.17 trial was designed to evaluate the impact of letrozole on lipid parameters compared to placebo in postmenopausal women who had already taken five years adjuvant tamoxifen treatment for early stage BC [41]. The incidence of cardiovascular disease was similar between the letrozole group and the placebo group at 2.5 years follow-up [41]. MI was occurred in only in <1% of both groups.

Steroidal aromatase inhibitor
Exemestane

Exemestane is a third-generation steroidal AI which is orally active and binds irreversibly to the substrate-binding pocket of the aromatase enzyme. Exemestane is indicated as an adjuvant treatment for hormone-receptor positive early stage BC after two-three years of tamoxifen treatment in postmenopausal women. When exemestane is used as a first line adjuvant treatment in patients not previously exposed to AIs, there was an increased response rate (from 31% to 46%) and progression-free survival (from 5.8 to 9.9 months) compared to tamoxifen [42]. There are three trials evaluating the use of exemestane as an adjuvant treatment in postmenopausal women with early stage BC; IES (Intergroup Exemestane Study), TEAM (Tamoxifen Exemestane Adjuvant Multinational) and NSABP (National Surgical Adjuvant Breast and Bowel Project) B-33 [43].

The IES study randomized 4,724 postmenopausal patients with unilateral invasive, estrogen-receptor-positive (or unknown) BC who were disease free after two-three years of tamoxifen treatment to switch to exemestane (n = 2,352) or to continue tamoxifen (n = 2,372). At a median follow-up of 55.7 months, exemestane had a 3.3% absolute benefit by the end of the treatment. When the estrogen receptor negative patients were excluded, the hazard ratio (HR) emerged as 0.75 (0.65–0.87; $P = 0.0001$) and the absolute benefit as 3.5%; furthermore, there was a plausible difference in overall survival reaching statistical significance with an HR of 0.83 (0.69–1.00) [16]. An updated analysis was reported at the 2009 San Antonio Cancer Symposium [44] verifying the statistically significant improvement in overall survival with an HR of 0.86 (0.75 – 0.99, $P = 0.04$) translating into an absolute survival benefit of 2.4% after eight years of randomization.

The IES trial compared the toxicity profile of exemestane with tamoxifen in patients who had already received adjuvant tamoxifen for two-three years before randomization in women with early stage BC. Cardiac events were defined as ischemic and others. Results from the trial shows the overall rates of ischemic events were 9.9% in the exemestane group and 8.6% in the tamoxifen group, the rates of MI were 1.3% for exemestane and 0.8% for tamoxifen, and angina rates were 7.1% for exemestane and 6.5% for tamoxifen; even though overall rates were higher in exemestane group compared with tamoxifen group, none of these became statistically significant [45]. At 55.7 months follow-up, the incidence of cardiovascular events was not statistically significance different between the exemestane and tamoxifen groups either during treatment (16.5%, 15%, respectively) or post-treatment [16]. The incidence of ischemic cardiovascular disease was comparable between the two arms; 8% for the exemestane group and 6.9% for the tamoxifen group ($P = 0.17$) and there was no statistical significance in terms of MI (1.3% vs. 0.8%, respectively; $P = 0.08$). But, in the exemestane arm, patients who experienced an MI had higher histories of hypertension compared to tamoxifen (71.1% vs. 31.6%, respectively). These findings emphasize that blood pressure monitoring for patients who are receiving adjuvant exemestane is crucial [16]. The incidence of venous thromboembolic events was 1.2% in patients who switched to exemestane and 2.3% in patients who stayed on tamoxifen ($P = 0.004$) and similar results were observed in the overall study ($P = 0.01$) (Table 3). The incidence of cerebrovascular events occurred in similar proportion between exemestane and tamoxifen in the IES (2.5% vs. 2.4%, $P = 0.89$). Consequently, the number of cardiovascular deaths was very low in both treatment groups.

TABLE 3 Exemestane: irreversibl, third generation steroidal aromatase inhbitor	**IES (Intergroup Exemestane Study)**			**TEAM (The Tamoxifen Exemestane Adjuvant Multicenter)**		
	Tamoxifen vs Exemestane after 2-3 years Tamoxifen(total of 5 years)			**Exemestane vs Exemestane after 2-3 years Tamoxifen(total of 5 years)**		
Design	Combined adjuvant			First line adjuvant		
Median follow-up	55.7 months			5.1 years		
	TAM--EXE	TAM	P Value	TAM--EXE	EXE	P Value
Number of patients	2352	2372		4868	4898	
Median age	<60: 32.4%, 60–69: 42.7%	<60: 32.0%, 60–69: 42.8%		64 years		
Disease free survival	HR: 0.75(0.64-0.88)		P=0.0003	HR: 0.97(0.88-1.08)		P= 0.60
TTDR	HR:0.83(0.70-0.98)		P=0.03	HR: 0.93(0.81-1.07)		P=0.30
Overall survival	HR:0.83(0.69-0.99)		P=0.04	HR: 1.00(0.89-1.14)		P>0.99
All cardiac events	483(20.8)	441(18.9)	P=0.09	NA		
Cardiac events	NA	NA		NA		
Ischemic heart disease	229(9.9)	200(8.6)	P=0.12	NA		
MI or ischemia	31(1.3)	19(0.8)	P=0.08	64(1%)	82(2%)	P=0.171
Angina	7.1%	6.5%	P=0.44	NA		
Cardiac failure	1.8%	1.8%	P=0.94	26(<1%)	50(1%)	
Other cardiovascular events	261(11.3)	262(11.2)	P= 0.96	73(2%)	77(2%)	P=0.843
CVA/TIA	2.5%	2.4%	P=0.89	60(1%)	87(2%)	P=0.035
Thromboembolic	45(1.9)	572(3.1)	P=0.01			
Venous thrombosis				99(2%)	47(<1%)	P=0.0001
Cardiac death	14	13		28(<1%)	43(<1%)	P=0.11
Cerebral related	17	11		14(<1%)	19(<1%)	
Vascular related				3(<1%))	4(<1%)	

IES: HR+ group, TEAM: Phase 3, HR+ group. MI: myocardial infarction, NA: Not available, HR: Hazard ratio, TTDR: Time to distant recurrence.

The TEAM phase 3 trial was primarily designed to evaluate the efficacy and safety of five years of adjuvant exemestane against five years of tamoxifen in postmenopausal women with early stage BC. Albeit during that period results were in favor of the exemestane group, a recent update analyzing five years of disease free survival showed similar rates between the groups (85.7% vs. 85.4%) randomized to upfront exemestane or sequential treatment with tamoxifen followed by exemestane, with no differences in time to recurrence or overall survival [46]. The incidence of hypertension was higher in the exemestane arm than in the sequential arm, but not significantly important (4% vs. 3%, respectively; P = 0.38). The frequency of arrhythmia was 4% vs. 3% for the exemestane arm vs. the sequential arm, respectively (P=0.038); the frequency of myocardial ischemia or infarction was 2% vs. 1%, respectively (P = 0.171); and the frequency of cardiac failure was 1% vs. <1%, respectively (P = 0.009). Although the overall incidence of cardiovascular events was higher in the exemestane group than in the sequential arm, none of these reached statistical significance. The benefit of AI on tamoxifen in terms of reducing vascular thrombotic events was evident in women with previous exposure to tamoxifen. In the TEAM study, vascular thrombotic events occurred in 2% of patients who switched to exemestane, compared to <1% of patients exposed only to exemestane (P = 0.0001).

Cardiovascular deaths were numerically higher with exemestane than with sequential treatment; however, this difference was not statistically significant (<1%). Depending on the differences between exemestane monotherapy and sequential treatment in terms of adverse events, the safety of these treatment strategies might play an important role in treatment decisions.

It is important to consider the impact of patient age on cardiovascular health, as demonstrated by the prevalence of comorbid illness among patients increased with age in newly diagnosed BC, the most common comorbid illness being cardiovascular disease. History of hypertension was a significant predictor of IHD, CVA / TIA, and thromboembolism. Hypercholesterolemia was associated with any adverse cardiac events, especially IHD.

Discussion

Current treatments for BC, which is the most common malignancy among women, involve the adjuvant use of endocrine therapy for hormone receptor positive BC after surgery [47,48]. AIs have been shown to be more effective and safer than tamoxifen for adjuvant endocrine strategy for either early or advanced

stage hormone receptor positive BC in postmenopausal women [13,49–54]. As an endocrine therapy, increasing use of AIs either sequentially or instead of tamoxifen seems to provide benefit in lowering the incidence of common serious events, such as thromboembolism and stroke, which are increased with tamoxifen treatment. The molecular differences between third-generation AIs might effects not only selectivity for aromatase binding but also adverse cardiovascular events via upon cardiovascular receptors or small alterations in serum lipid levels. However, the weight of evidence from large clinical trials shows no major differences with respect to overall cardiovascular safety between AIs [21,55]. Anastrozole is mostly specific to the aromatase enzyme and has fewer interactions with other enzymes. Hence, anastrozole is emerging as one plausible standard adjuvant treatment for hormone sensitive early BC [56]. A recently published 10 year analysis of the ATAC trial confirmed the previously reported efficacy and tolerability benefits of anastrozole as an initial adjuvant therapy for hormone sensitive BC. Treatment-related serious adverse events were fewer in the anastrozole arm than the tamoxifen arm ($P<0.0001$); however, rates were similar in the post treatment period ($P = 0.3$) [34]. Although deaths without recurrence were higher with anastrozole (10.8% vs. 9.8%; P = NS), cardiovascular deaths were less common with anastrozole than tamoxifen (2.9% vs. 3.0%). Also, it can be assumed that the incidence of cardiovascular deaths is decreasing with anastrozole in the off-treatment period comparing to tamoxifen (Table 1). Even though median age was 72 years and having cardioprotective effect of tamoxifen, decreasing with anastrozole can be thought remarkable. Regard to reduction in distant recurrence, it assumed that decreasing with anastrozole on behalf of cardiovascular mortality might become significantly lower than tamoxifen in the future. At the 100 month follow-up, fewer cerebrovascular accidents were reported in patients receiving anastrozole ($P = 0.056$), but not in the off-treatment period ($P = 0.75$) [36]. After publishing 74 months of BIG 1–98 follow-up data, the incidence of cardiac and thromboembolic events were proportionately consistent during follow-up. Incidence of IHD was higher in the letrozole arm than in the tamoxifen arm, despite overall similar cardiac events (Table 2). An increase in the incidence of grade 3 to 5 cardiac events with letrozole carried on with 74 months follow-up; even though the number of events was small in each arm (3.8% vs. 2.1%, respectively). In the BIG 1–98 trial, the incidence of heart failure was similar at 74 months median follow-up between monotherapy groups of letrozole and tamoxifen (1.2% vs. 1.0%), even though it was statistically different at 25.8 months follow-up (0.8% vs. 0.4%, $P = 0.01$). It can be assumed that incidence of heart failure was lower after cessation of treatment with letrozole than active treatment period.

In the IES, at 55.7 months follow-up, the frequency myocardial infarction was very low in both treatment groups, despite the fact that the patients consisted of a population at risk for adverse cardiac events because of their age [16]. Mostly, patients who experienced MI in the exemestane group had a history of hypertension (71.1%) compared to the tamoxifen group (31.6%). The importance of monitoring blood pressure should be stressed [16]. Disregarding the other cardiovascular risk factors, advanced age and uncontrolled blood pressure may be related to these cardiac events. In the TEAM trial, at a median 5.1 years follow-up, no significant differences were reported between the exemestane and sequential groups in terms of disease free survival ($P = 0.60$) and overall survival ($P>0.99$) [4]. Data on disease free survival was consistent with that from the BIG 1–98 trial, in which tamoxifen followed by letrozole or the reverse sequence versus letrozole alone were not associated with statistically significant differences in efficacy after a median 71 month follow-up [37]. Cardiac-related deaths were not significantly different, even though they were higher with exemestane than the sequential group ($P = 0.11$). The incidence of cardiac failure was significantly higher in the exemestane monotherapy group than in the sequential group ($P = 0.009$). This result did not emerge previously in AI monotherapy trials. However, it is plausible to see the result from next follow-up because about 20% of patients were still on trial treatment. Consequently, treatment compliance appears suboptimum, particularly in the sequence group (47% of patients in the sequence and 19% of patients in the exemestane group discontinued before five years for reasons other than disease free survival).

The lipid-lowering effect of tamoxifen may clarify the reason for increasing lipid levels with AIs versus tamoxifen [57]. Whether AIs had long-term detrimental effect on lipids is not known, despite the findings that significantly more patients had hypercholesterolemia in the aromatase group than in the tamoxifen group in the ATAC and BIG 1–98 trials [14,15]. Although it has been thought that a steroidal AI (exemestane) may have beneficial effects on lipid metabolism [58], all third-generation AIs have similar effects on lipids [59]. Also, cardiovascular events were similar between

the letrozole and placebo groups after five years of tamoxifen treatment in the MA.17 trial. All studies comparing safety of AIs against tamoxifen have shown an overall decreased risk of thromboembolic events in patients taking AIs versus those taking tamoxifen [5]; however, postmenopausal women who are taking endocrine therapy for BC live longer with their disease, and remain at risk for such adverse events. Since receiving AIs carry risk for cardiovascular events; these patients should be evaluated more carefully than age-matched individuals to minimize cardiovascular events during therapy.

Management

Recent advancements in curative-intent therapies have led to significant improvements in BC survival, but at the direct expense of increased risk of cardiovascular event or injury. It is important to recognize cardiac toxicity and to attempt to mitigate its onset; not only by selecting appropriate patients for adjuvant therapy, but also selecting appropriate therapy based on patient risk factors and risk of recurrence. Increasing awareness and educating patients about cardiac toxicity is crucial. Overall, women with BC had a notably worse cardiovascular risk profile in comparison to age-matched controls [60,61]. Adjuvant therapies are selected on the basis of a complex schema, including patient factors (age, comorbid illness, and patient preference) and tumor factors (grade, size, lymph node involvement, estrogen receptor [ER] and human epidermal growth factor receptor 2 [HER2]) [62].

Women diagnosed with BC are already at risk for cardiovascular disease, and practically all adjuvant therapies are associated with unique and varying degrees of cardiovascular injury. When selected for a treatment regimen, they will be subjected to a series of sequential cardiovascular injury risks coupled with lifestyle perturbations that leave patients with obvious or sub-clinical cardiovascular disease. Unfortunately, each of the chemotherapeutic agents used in BC treatment has identically unique acute and long-term cardiac complications. IHD (MI, angina pectoris), cardiac failure, hypertension, peripheral atherosclerosis, and thromboembolic events are the major complaints of these agents. The mechanism of chemotherapy-associated cardiac dysfunction or injury remains to be elucidated.

Measurement of left ventricular ejection fraction (LVEF) by echocardiography is a frequently used effective approach to monitor cardiac function and its impairment by chemotherapy. LVEF is one of most important predictors of prognosis while patients with significantly reduced ejection fraction usually have poorer prognosis. However, current imaging techniques (echocardiography, coronary angiography etc.) have limited ability to detect early cardiac damage [63]. It has been proven that the use of sensitive monitoring modalities (magnetic resonance imaging, exercise or dobutamine stress testing, etc.) and biochemical markers (troponin I, brain natriuretic peptide) permit more accurate detection and quantification of subclinical cardiac damage. It has been reported that increase in troponin I level was a significant predictor of left ventricular dysfunction after chemotherapy among cancer patients [64].

Decreases in physical activity with diagnosis of BC may trigger increases in body weight and body fat which may lead to a worse cancer prognosis [65,66]. It was reported that a greater decrease in physical activity was observed among obese BC patients than normal weight and overweight patients (P<0.05) suggesting a potential weight gain among already obese women [65,66]. Furthermore, obesity is significantly associated with increased recurrence risk in BC patients without any connection to age or menopausal status [67,68]. Results from one weight gain study reported that 84% of 535 BC patients gained weight (mean 1.6 kg) in the first year after diagnosis [69], and the Women's Healthy Eating and Living (WHEL) study reported that 60% of 1,116 women gained weight (mean 2.7 kg) from one year before diagnosis to up to four years after diagnosis [70]. The effects of weight gain on BC are unclear. Although some studies have associated weight gain with an earlier disease recurrence [71–73], others have failed to show similar results [69,74–77]. One study in which 646 patients were followed for a median of 6.6 years found that premenopausal women who gained more than 5.9 kg were 1.5 times more likely to relapse and 1.6 times more likely to die from BC than those were gaining less weight [72]. While it remains to be elucidated whether post-diagnosis weight gain influences risk for progressive disease, it is known that weight gain unfavorably affects risk for cardiovascular disease, hypertension, and diabetes [78–80].

Several strategies have been advised to prevent or to reduce cardiac toxicity. One of them is angiotensin converting enzyme inhibition (ACEI), which has shown a significant reduction in left ventricular dysfunction in patients with increased troponin I soon after chemotherapy [81]. The management of risk factors in patients with BC is crucial. Recommendations for the treatment of these risk

factors include either pharmacotherapy or lifestyle modification. Mostly, beta-blockers and/or ACEI are suggested as the initial therapies for hypertension, with the addition of other agents (thiazides, etc.). In case of hypercholesterolemia, statins are recommended to reduce low-density lipoprotein cholesterol under 100 mg/dL. Furthermore, statins have been associated with reduced incidence of thromboembolism in patients with cancer [82]. Also, management of diabetes mellitus is related to cardiovascular disease, considering utility of using biguanides or sulfonylurea for women with type II diabetes to achieve a 7% glycosylated hemoglobin (HbA1c) [83]. Exercise training may be favorable with regard to its demonstrated effects on cardiovascular reserve, individual risk factors, and overall reductions in cardiovascular mortality [84,85]. A meta-analysis reported that exercise training resulted in a significant increase in exercise capacity among women with early BC while epidemiologic data recommended that greater physical activity after therapy was related to a reduction in all causes of mortality, including BC-specific causes [86].

Of note, data on adverse cardiovascular effects of AIs must be interpreted with caution in conjunction with baseline cardiovascular disease, LVEF, and cardiac risk factors. All the safety analyses have been conducted by comparing tamoxifen, whereas the mechanisms of cardiovascular events have not been clearly elucidated. It is difficult to know how to apply the results of these safety analyses to patients with an elevated risk of cardiovascular disease without analyzing baseline cardiovascular risk factors. Because of this weak evidence regarding to cardiovascular toxicity and short-term follow-up, there is no consensus about management of cardiovascular toxicity and its consequences.

Further research is required to anticipate the relative portion of cardiovascular morbidity and mortality attributable to either lifestyle modification or an adjuvant therapy among women with BC.

Conclusion

Cardiotoxicity is one of the most serious complications of endocrine therapy and/or cancer chemoprevention. AIs produce some cardiovascular adverse events, including IHD, heart failure, etc.; however, their toxicity mechanisms on the heart are not well-known. While women with BC live longer due to these effective therapies, most of them may not suffer recurrence of BC despite the fact that they are all vulnerable to toxicities. Patients at higher risk are mre susceptible to these detrimental effects. Since, cardiac morbidity and mortality can be reduced by detecting patients who are at higher risk, several different strategies have been advised in an attempt to prevent or to reduce cardiac toxicity. Regular assessment of serum lipids and management of hypertension and weight control are important to minimize cardiovascular risks, especially in women over 65 years old, who constitute more than 50% of BC population [87]. Also, switching to other therapies and regular assessment of patients on AI therapy may reduce and prevent adverse cardiovascular event. Even considering adverse cardiac events of AIs compared to tamoxifen, further evaluation is needed for long term results and assessment of novel adverse events which may be attributable to AIs.

Reducing the severity and frequency of adverse cardiac events may improve quality of life for patients taking AIs and yield continuation of this well-documented and beneficial therapy.

Conflict of interest: None declared

References

1. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics. 2002. CA Cancer J Clin. 2002;52:23-47.
2. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117:e25-146.
3. British Heart Foundation. European Cardiovascular Disease Statistics. London (UK): British Heart Foundation; 2005.
4. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet. 2011;377:321-31.
5. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687-717.
6. Braithwaite RS, Chlebowski RT, Lau J, et al. Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med. 2003;18:937-47.
7. McDonald CC, Alexander FE, Whyte BW, et al. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. The Scottish Cancer Trials Breast Group. BMJ. 1995;311:977-80.
8. Herrington DM, Klein KP. Cardiovascular trials of estrogen replacement therapy. Ann N Y Acad Sci. 2001;949:153-62.
9. Wysowski DK, Honig SF, Beitz J. Uterine sarcoma associated with tamoxifen use. N Engl J Med. 2002;346:1832-3.
10. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst. 1996;88:1529-42.

11. Aiello EJ, Buist DS, Wagner EH, et al. Diffusion of AIs for breast cancer therapy between 1996 and 2003 in the Cancer Research Network. Breast Cancer Res Treat. 2008;107:397-403.
12. Janicke F. Are all AIs the same? A review of the current evidence. Breast. 2004;13 Suppl 1:S10-8.
13. Gibson LJ, Dawson CK, Lawrence DH, Bliss JM. AIs for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2009;(4):CD003370.
14. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005;353:2747-57.
15. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005;365:60-2.
16. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007;369:559-70.
17. Dowsett M, Cuzick J, Ingle J et al. Meta-analysis of breast cancer outcomes in adjuvant trials of AIs versus tamoxifen. J Clin Oncol. 2010;28:509-18.
18. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of AIs as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol. 2005;23:619-29.
19. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007;18:1133-44.
20. Jones LW, Haykowsky MJ, Swartz JJ, et al. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007; 50:1435-41.
21. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res. 2008;14:14-24.
22. Esteva FJ, Hortobagyi GN. Comparative assessment of lipid effects of endocrine therapy for breast cancer: implications for cardiovascular disease prevention in postmenopausal women. Breast. 2006;15:301-12.
23. Walsh BW, Schiff I, Rosner B et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med. 1991;325:1196-204.
24. Crivellari D, Sun Z, Coates AS, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: the BIG 1–98 trial. J Clin Oncol 2008;26:1972-9.
25. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, et al. Overall survival and cause-specific mortality of patients with stage T1a,bN0M0 breast carcinoma. J Clin Oncol. 2007;25:4952-60.
26. Erwin GS, Crisostomo PR, Wang Y et al. Estradiol-treated mesenchymal stem cells improve myocardial recovery after ischemia. J Surg Res. 2009;152:319-24.
27. Bolego C, Rossoni G, Fadini GP, et al. Selective estrogen receptor-alpha agonist provides widespread heart and vascular protection with enhanced endothelial progenitor cell mobilization in the absence of uterotrophic action. FASEB J. 2010;24:2262-72.
28. Baruscotti I, Barchiesi F, Jackson EK, et al. Estradiol stimulates capillary formation by human endothelial progenitor cells: role of estrogen receptor-{alpha}/{beta}, heme oxygenase 1, and tyrosine kinase. Hypertension. 2010;56:397-404.
29. Post WS, Goldschmidt-Clermont PJ, Wilhide CC, et al. Methylation of the estrogen receptor gene is associated with aging and atherosclerosis in the cardiovascular system. Cardiovasc Res. 1999;43(4):985-91.
30. Kim J, Kim JY, Song KS, et al. Epigenetic changes in estrogen receptor beta gene in atherosclerotic cardiovascular tissues and in-vitro vascular senescence. Biochim Biophys Acta. 2007;1772(1):72-80.
31. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of AI-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. Oncologist. 2008;13:503-14.
32. Boccardo F, Rubagotti A, Aldrighetti D, et al. Switching to an AI provides mortality benefit in early breast carcinoma: pooled analysis of 2 consecutive trials. Cancer. 2007;109:1060-7.
33. Brown SA, Guise TA. Cancer treatment-related bone disease. Crit Rev Eukaryot Gene Expr. 2009;19(1):47-60.
34. Cuzick J, Sestak I, Baum M et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11:1135-41.
35. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer. 2003;98:1802-10.
36. Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 2008;9:45-53.
37. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med. 2009;361:766-76.
38. Mouridsen H, Keshaviah A, Coates AS et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1–98 trial. J Clin Oncol. 2007;25:5715-22.
39. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007;25:486-92.
40. Colleoni M, Giobbie-Hurder A, Regan MM, et al. Analyses adjusting for selective crossover show improved overall survival

with adjuvant letrozole compared with tamoxifen in the BIG 1–98 study. J Clin Oncol. 2011;29:1117-24.

41. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005;97:1262-71.
42. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol. 2008;26:4883-90.
43. Robinson A. A review of the use of exemestane in early breast cancer. Ther Clin Risk Manag. 2009;5:91-8.
44. Bliss JM, Kilburn LS, Coleman RE, at al. Disease related outcome with long term follow-up: an updated analysis of the Intergroup Exemestane Study (IES) [abstract]. Cancer Res. 2009;69 (24 Suppl). Abstract 12.
45. Coombes RC PR, Jassem J, et al. First mature analysis of the Intergroup Exemestane Study. J Clin Oncol. 2006;24.
46. Rea D HA, Seynaeve C, et al. Five years of exemestane as initial therapy compared to 5 years of tamoxifen followed by exemestane: the TEAM trial, a prospective, randomized, phase III trial in postmenopausal women with hormone-sensitive early breast cancer. Cancer Res. 2009;69.
47. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
48. Ingle JN. Adjuvant endocrine therapy for postmenopausal women with early breast cancer. Clin Cancer Res. 2006; 12:1031s-6s.
49. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with AIs and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst. 2006;98:1285-91.
50. Mouridsen HT, Robert NJ. The role of AIs as adjuvant therapy for early breast cancer in postmenopausal women. Eur J Cancer 2005;41:1678-89.
51. Morandi P, Rouzier R, Altundag K et al. The role of AIs in the adjuvant treatment of breast carcinoma: the M. D. Anderson Cancer Center evidence-based approach. Cancer. 2004;101:1482-9.
52. Henderson IC, Piccart-Gebhart MJ. The evolving role of AIs in adjuvant breast cancer therapy. Clin Breast Cancer. 2005;6:206-15.
53. Goss PE. Emerging role of AIs in the adjuvant setting. Am J Clin Oncol. 2003;26:S27-33.
54. Buzdar A, Chlebowski R, Cuzick J, et al. Defining the role of AIs in the adjuvant endocrine treatment of early breast cancer. Curr Med Res Opin. 2006;22:1575-85.
55. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol. 2006;17 Suppl 7:vii10-4.
56. Buzdar A. Anastrozole as adjuvant therapy for early-stage breast cancer: implications of the ATAC trial. Clin Breast Cancer. 2003;4 Suppl 1:S42-8.
57. Wasan KM, Goss PE, Pritchard PH, et al. The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA.17L). Ann Oncol. 2005;16:707-15.
58. Gandhi S, Verma S. AIs and cardiac toxicity: getting to the heart of the matter. Breast Cancer Res Treat. 2007;106:1–9.
59. McCloskey EV, Hannon RA, Lakner G, et al. Effects of third generation AIs on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. Eur J Cancer. 2007;43:2523-31.
60. Jones LW, Haykowsky M, Peddle CJ, et al. Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. Cancer Epidemiol Biomarkers Prev. 2007;16:1026-31.
61. Jones LW, Haykowsky M, Pituskin EN, et al. Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor–positive operable breast cancer. Oncologist. 2007;12:1156-64.
62. Carlson RW, Hudis CA, Pritchard KI. Adjuvant endocrine therapy in hormone receptor-positive postmenopausal breast cancer: evolution of NCCN, ASCO, and St Gallen recommendations. J Natl Compr Canc Netw. 2006;4:971-9.
63. McCrohon JA, Moon JC, Prasad SK, et al. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. Circulation. 2003;108:54-9.
64. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109:2749-54.
65. Demark-Wahnefried W, Rimer BK, Winer EP. Weight gain in women diagnosed with breast cancer. J Am Diet Assoc. 1997;97 (5):519-26,29; quiz 527-8.
66. Goodwin P, Esplen MJ, Butler K, et al. Multidisciplinary weight management in locoregional breast cancer: results of a phase II study. Breast Cancer Res Treat. 1998;48:53-64.
67. Holmberg L, Lund E, Bergstrom R, et al. Oral contraceptives and prognosis in breast cancer: effects of duration, latency, recency, age at first use and relation to parity and body mass index in young women with breast cancer. Eur J Cancer. 1994;30A:351-4.
68. Lethaby AE, Mason BH, Harvey VJ, Holdaway IM. Survival of women with node negative breast cancer in the Auckland region. N Z Med J. 1996;109:330-3.
69. Goodwin PJ, Ennis M, Pritchard KI, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol. 1999;17:120-9.

70. Rock CL, Flatt SW, Newman V, et al. Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. J Am Diet Assoc. 1999;99:1212-21.
71. Chlebowski RT, Weiner JM, Reynolds R, et al. Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Res Treat. 1986;7:23-30.
72. Camoriano JK, Loprinzi CL, Ingle JN, et al. Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. J Clin Oncol. 1990;8:1327-34.
73. Bonomi P, Bunting N, Fishman D, et al. Weight gain during adjuvant chemotherapy or hormone-chemotherapy for stage II breast cancer evaluated in relation to disease free survival (DFS) [Abstract]. Breast Cancer Res Treat. 1984;4:339. Abstract.
74. Levine EG, Raczynski JM, Carpenter JT. Weight gain with breast cancer adjuvant treatment. Cancer. 1991;67:1954-9.
75. Heasman KZ, Sutherland HJ, Campbell JA, et al. Weight gain during adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat. 1985;5:195-200.
76. Goodwin PJ, Panzarella T, Boyd NF. Weight gain in women with localized breast cancer–a descriptive study. Breast Cancer Res Treat. 1988;11:59-66.
77. Costa LJ, Varella PC, del Giglio A. Weight changes during chemotherapy for breast cancer. Sao Paulo Med J. 2002;120:113-7.
78. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. JAMA 1995;273(6):461-5.
79. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999;341:1097-105.
80. Kopelman PG. Obesity as a medical problem. Nature. 2000;404:635-43.
81. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114:2474-81.
82. Khemasuwan D, Divietro ML, Tangdhanakanond K, et al. Statins decrease the occurrence of venous thromboembolism in patients with cancer. Am J Med. 2010;123:60-5.
83. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. J Am Coll Cardiol. 2007;49:1230-50.
84. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003;108:1554-9.
85. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Eng J Med. 2002;347:716-25.
86. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. JAMA. 2005;293:2479-86.
87. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39.