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Cardiovascular Health and Aromatase Inhibitors

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Abstract

Cardiovascular disease is the most frequent cause of death in North American women, and so death resulting from cardiovascular disease, rather than from malignancy, is not uncommon in breast cancer patients. This may be a consequence of the shared risk factors for developing breast cancer and cardiovascular disease, as well as the difficulty of managing cancer patients at higher risk for developing cardiovascular disease. Recently, much attention has focused on understanding the cardiovascular risk factors associated with breast cancer therapies. Tamoxifen has a lowering effect on serum lipids and is reported to decrease the risk of myocardial infarction but to increase the risk of thromboembolic events. Current data indicate that aromatase inhibitors (AIs) are not associated with an increased risk of thromboembolic or cerebrovascular events. Reports of a greater incidence of hypercholesterolaemia when AIs are compared head-to-head with tamoxifen may be a result of the intrinsic lipid-lowering effects of tamoxifen therapy and may be confounded by differences in data collection among trials. The incidence of cardiovascular events associated with AIs in large trials has been reported to be higher in trials comparing AIs with tamoxifen; comparisons within

the MA.17 trial, which evaluated an AI versus placebo, did not show increases in hypercholesterolaemia or in cardiovascular events with the AI.

When treating breast cancer patients, oncologists should consider the same positive lifestyle changes that are proposed to lower the risk of cardiovascular disease in patients who do not have breast cancer. Moreover, physicians should assess cardiovascular risk, and monitor and treat patients already diagnosed with or at risk for coronary heart disease, according to established guidelines.

Cardiovascular disease (CVD) is the most common cause of death in women in North America. Therefore, it is not surprising that a range of CVDs develop or are present independent of malignant disease in patients undergoing treatment for breast cancer.[1,2] However, concern exists regarding the possibility that cancer therapies may themselves promote the occurrence of CVD. Possible links between chemotherapy and radiation therapy for breast cancer and a variety of CVDs have been reported in the literature. Meta-analyses have shown an excess of vascular deaths in women receiving radiotherapy for breast cancer,[3,4] and adjuvant chemotherapy (e.g. anthracyclines) has also been associated with increased cardiotoxicity, especially in older patients with breast cancer.[5-7] Even a biological, targeted therapy (trastuzumab) has been associated with cardiotoxicity.[8-10] In contrast, a meta-analysis of both prevention and treatment trials with a maximum follow-up of 6.7 years has revealed that tamoxifen significantly reduces deaths resulting from myocardial infarction (MI) [relative risk (RR) 0.62; 95% CI 0.41, 0.93].[11] A report of the 2000 Oxford Overview of randomised trials[12] using 5 years of tamoxifen found that mortality from heart disease was slightly but not significantly lower with tamoxifen therapy than with controls (either placebo or no treatment) [p = 0.06]. More recently published data from a randomised trial of 2 versus 5 years of tamoxifen also reported reduced cardiac events and mortality in the 5-year tamoxifen arm.[13]

The aromatase inhibitors (AIs) anastrozole, letrozole and exemestane have been shown to be superior to tamoxifen in preventing breast cancer recurrence when given either as first-line adjuvant endocrine therapy (anastrozole or letrozole) or after 2 years of tamoxifen (exemestane or anastrozole), and superior to placebo when given after 5 years of tamoxifen (letrozole). A current American Society of Clinical Oncology (ASCO) technology assessment recommends the use of an AI as part of the adjuvant treatment of all women with hormone receptor-positive breast cancer.[14] Thus, these third-generation AIs are rapidly replacing tamoxifen as the gold standard adjuvant hormonal therapy in postmenopausal women with early breast cancer. Establishing the safety profile of these agents is becoming increasingly important as efficacy data and models emerge supporting their more extensive use.[15-18] To date, data from eight AI clinical trials,[16,17,19-24] which have enrolled a total of >25 000 women, indicate a small increase in the incidence of cardiovascular adverse events. However, such reports arise from trials comparing AIs (anastrozole, exemestane and letrozole) with tamoxifen, and consequently, the lipid-lowering and cardioprotective effects of tamoxifen may be driving these results. This review examines the incidence of CVD in the general population, the incidence of CVD among breast cancer patients and the cardiovascular safety profiles of the AIs.

The search terms 'menopause', 'cholesterol', 'breast cancer', 'tamoxifen', 'cardiovascular', 'anastrazole', 'exemestane' and 'letrozole' were used to search MEDLINE for English-language studies published from 1990 to 2006. Abstracts were also searched for from the proceedings of several oncology meetings between 2001 and 2006 to capture emerging data.

1. Cardiovascular Disease

1.1 Prevalence

In the US, one in four people aged ≥20 years has some form of CVD (high blood pressure, coronary heart disease, congestive heart failure, stroke or congenital cardiovascular defects). In both sexes,

the risk of CVD increases with age; in women, the risk increases substantially and progressively at or after the age of 55 years.[1] The risk for cardiovascular morbidity also increases progressively after menopause.[25] These increasing CVD rates in women lag about 10 years behind those of men; however, this gap narrows with advancing age.[1] Although breast cancer is a common cause of death up to the age of 55 years, women overall experience greater mortality from CVD than from breast cancer. During 2001, 1 in 2.5 women died from CVD, whereas 1 in 30 women died from breast cancer.[1] CVD (heart disease and stroke) is also the leading cause of death in Canada (36%).[26] When looking at causes of death in Canadian women only, ischaemic heart disease and cerebrovascular disease (mainly stroke) accounted for 49.7% and 9.0% of deaths, respectively, in 1997.[26] Projections to 2016 suggest that the number of women who will die from CVD will increase by 28% between 1995 and 2016 and will likely surpass deaths among men in the near future.[26] Similar morbidity from CVD is observed in Europe, where CVD is also the most common cause of death among women.[27]

1.2 Risk Factors

There are well established risk factors for CVD. These include hypertension, diabetes mellitus, cigarette smoking, adverse lipid profile, family history, abdominal obesity and physical inactivity (table I).[1,28] Any combination of two or more risk factors increases the overall risk for the occurrence of a cardiovascular event. Normal changes associated with aging also play a role in the development of CVD.[29] Breast cancer and CVD share several risk factors, including age, obesity and inactivity.[30,31] The sedentary obese individual is also at risk for developing other risk factors, such as high lipid levels, hypertension and diabetes. Postmenopausal breast cancer patients may also be susceptible to particular co-morbidities associated with CVD, including diabetes and hypertension.[32-34] The prevalence of hypertension appears to be slightly elevated in women with breast cancer (compared with other tumour sites),[35] and an increased incidence of stroke (specifically cerebral infarction) has also been noted in women who were ≥55 years of age when their breast cancer was diagnosed.[3] The prevalence of a co-morbidity at the time of breast cancer diagnosis has been found to increase from 9% for patients aged <50 years to 55% for those aged ≥80 years. The most frequently encountered co-morbidities were CVD (7%) and diabetes (7%).[32]

Table I. Risk factors for coronary heart disease and stroke

Coronary heart disease[1,28]	Stroke[1,28]
Hypertension	Age >75 years
Hyperlipidaemia	Black race
Cigarette smoking	Male sex
Diabetes mellitus	Diabetes mellitus
Abdominal obesity	Heavy smoker
Physical inactivity	Atrial fibrillation
Low daily fruit and vegetable consumption	Hypertension
	Physical inactivity
Alcohol overuse	
Male sex	
Increasing age	
Family history	

A current approach to cardiac risk assessment is to add lipid values to blood pressure, age, smoking status and family history. Elevated low-density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC), as well as these other factors, are predictive of future coronary heart disease.[36,37] Studies have suggested that apolipoprotein (Apo) B levels or the ratio of Apo B to Apo A-1 is a superior indicator in determining the risk of coronary heart disease, compared with TC or LDL-C levels, or the ratio of TC to high-density lipoprotein-cholesterol (HDL-C).[38] Irrespective of the method used to measure risk, many patients do not achieve optimal control of blood pressure and cholesterol levels and are likely to miss the maximum benefit associated with improving the risk-factor profile and lowering the risk of CVD.[39]

2. Tamoxifen and Aromatase Inhibitor (AI) Therapy and Serum Lipids

2.1 Tamoxifen

Selective estrogen-receptor modulators (SERMs) prevent the mitogenic effects of estrogen by competitively binding to estrogen receptors. SERMS, including tamoxifen, have consistently shown a modest LDL-C-lowering effect (6–28% reduction), although the effects on HDL-C have been more variable.[40-42] Tamoxifen can also be associated with elevated triglyceride (TG) levels, which can be

quite marked in some patients.[43] The generally favourable impact of tamoxifen on lipid profiles has been widely reported, and investigations have provided some insight into how tamoxifen is able to elicit such beneficial effects (table II).[43-51] However, trials of hormone replacement therapy (HRT), which have shown benefit in lipid profiles, have not shown the expected cardiovascular protection in the women studied.[52-54] The ongoing RUTH (Raloxifene Use for The Heart) trial, which compared raloxifene with placebo in women at higher risk of major coronary events, will soon provide further data regarding the effect of antiestrogens on CVD.[55] Preliminary analyses suggest that, compared with placebo, raloxifene reduces the incidence of breast cancer but also tends to increase the risk of stroke and has no cardiovascular benefit.[56] However, a recent publication of data from STAR (Study of Tamoxifen And Raloxifene for prevention of breast cancer) showed no difference in cardiovascular events between tamoxifen and raloxifene, although fewer thromboembolic events were seen with raloxifene.[57,58] The lack of benefit seen with estrogen replacement therapy/HRT and the minor benefit seen with tamoxifen may be partly related to inflammatory and prothrombotic effects countering the positive lipid results.

2.2 Early Studies with AIs

AIs block peripheral aromatase, with a resultant decrease in estradiol to prevent estrogen receptor activation. Unlike tamoxifen, AIs lack partial estrogen agonist activity and, therefore, lack the positive lipid-lowering effects seen with tamoxifen. When assessing the available data regarding AI therapy and lipid profiles, it is important to consider the trial design (whether patients received prior treatment with tamoxifen), treatment setting, duration of therapy and how the lipid data were collected.

Preclinical studies in ovariectomised rats have not demonstrated an adverse impact of any AI on serum lipids (table III).[59-70] In the advanced breast cancer setting, one study (n = 72) reported a significant reduction in TG in patients receiving exemestane but found no significant changes in TC, HDL-C, Apo A-1, or Apo B.[64] A second study (n = 23) reported significant reductions in TG, but also noted a significant reduction in TC, as well as an unfavourable reduction in mean HDL-C with exemestane therapy.[63] In one study of patients with advanced breast cancer, letrozole therapy was associated with significant increases in TC and LDL-C (table III).[62] However, these results must be considered carefully because the letrozole study was also small in size (n = 20), investigated a short treatment duration (8–16 weeks), and approximately one-half of the patients had previously been treated with tamoxifen.[62] Generally speaking, the effects seen in all of these studies of advanced breast cancer may be confounded by previous treatment with tamoxifen, making it difficult to separate the effect of AIs from the effect of tamoxifen and/or its withdrawal on serum lipids.

A better evaluation of the impact of AIs on lipid profiles comes from studies in earlier stages of breast cancer. Two early breast cancer studies with anastrozole (n = approximately 40 each) that involved mostly patients who did not have prior tamoxifen exposure showed that anastrozole did not

Table II. Effects of tamoxifen on serum lipids

Postmenopausal primary breast cancer patients (n = 197) with node-negative, hormone receptor-positive tumours receiving adjuvant tamoxifen therapy experienced significant reductions in HDL-C[44]
Healthy young men (n = 15) taking tamoxifen experienced significant decreases in TC and Apo A levels from baseline but had non-significant decreases in LDL-C, HDL-C, triglycerides, and Apo B levels[45]
Potently inhibited acyl-coenzyme A: cholesterol acyltransferase 1 and 2, which decreased cholesterol absorption, plasma cholesterol and aortic cholesterol esterification in the aorta[46]
Adjuvant tamoxifen therapy lowered TC by 4.6% and LDL-C by 8.3% below the baseline levels in postmenopausal women with early breast cancer (n = 146)[47]
Has antioxidant properties and protects cell membranes and LDL-C particles against oxidative damage[48,49]
Can be associated with hypertriglyceridaemia[43]
Can be modified by Apo E polymorphisms[50,51]

Apo = apolipoprotein; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **TC** = total cholesterol.

Table III. Early studies evaluating the effects of aromatase inhibitors (AIs) on lipid profiles

Study	Patient group	AI	Comparator(s)	No. of subjects	Results
Hozumi et al.[59]	Preclinical (OVX rats)	Anastrozole	Tamoxifen	NR	No effect of anastrozole on lipids and LPL. TC and LPL reduced by tamoxifen
Goss et al.[60]	Preclinical (OVX rats)	Letrozole	Atamestane, toremifene, control rats	NR	No significant effect of letrozole or atamestane on serum lipids. Toremifene and toremifene + atamestane significantly reduced both serum TC and LDL-C
Goss et al.[61]	Preclinical (OVX rats)	Exemestane	OVX control rats	108	Exemestane reduced TC by up to 42% and LDL by >68%
Elisaf et al.[62]	Advanced breast cancer	Letrozole	Baseline values before letrozole treatment	20	Significant increases in TC, LDL-C, Apo B and atherogenic risk ratios observed with letrozole
Engen et al.[63]	Metastatic breast cancer	Exemestane	Tamoxifen	23	Significant reduction in TC, TG and mean HDL-C observed with exemestane
Atalay et al.[64]	Metastatic breast cancer	Exemestane	Tamoxifen	72	No significant effect of exemestane on TC, HDL-C, Apo A-1, Apo B, lipoprotein a, or the TC : HDL-C ratio, but significant reduction in TG observed
Sawada and Sato[65] & Sawada et al.[66]	Early breast cancer (phase II)	Anastrozole	Tamoxifen	44	No significant negative impact of anastrozole on lipids or atherogenic risk ratios
Wojtaki et al.[67]	Early breast cancer (phase II)	Anastrozole	Tamoxifen	43	Anastrozole did not reverse the favourable effects of tamoxifen on lipid metabolism
Harper-Wynne et al.[68]	Healthy postmenopausal women	Letrozole	Baseline values before letrozole treatment	32	No significant effect of letrozole on TC, HDL-C or LDL-C
McCloskey et al.[69]	Healthy postmenopausal women	Letrozole, anastrozole, exemestane	Baseline values before treatment	90	No significant differences in TC, TG, LDL-C/HDL-C ratios, and non-HDL-C were observed between the AIs A significant difference in Apo B/Apo A-1 ratios was observed between anastrozole and exemestane
Heshmati et al.[70]	Healthy postmenopausal women	Letrozole	Placebo	42	No significant effect of letrozole on TC, HDL-C, LDL-C or TG

Apo = apolipoprotein; **HDL-C** = high-density lipoprotein-cholesterol; **LPL** = lipoprotein lipase level; **LDL-C** = low-density lipoprotein-cholesterol; **NR** = not reported; **OVX** = ovariectomised; **TC** = total cholesterol; **TG** = triglycerides.

have a negative impact on lipid profiles.[65-67] Similarly, short courses of letrozole (3 and 6 months) have shown no significant effects on serum lipids (TC, HDL-C or LDL-C) in studies of postmenopausal women with either no active breast disease or normal breast tissue (table III).[68,70]

2.3 AIs versus Placebo

A randomised, double-blind trial comparing exemestane with placebo in postmenopausal women with early breast cancer (n = 147) showed no significant differences in TC between the treatment arms, but 2 years of exemestane treatment resulted in a modest but significant drop in HDL-C (range 6–9%)

compared with placebo (1–2% increase; $p < 0.001$). Exemestane also significantly reduced Apo A-1 compared with placebo (5–6% vs 0–2%; $p = 0.004$).[71]

In the open-label, companion subprotocol to the ATENA (Adjuvant post-Tamoxifen Exemestane versus Nothing Applied) trial (n = 340), the effects of extended adjuvant exemestane therapy on the lipid profile, compared with an observational arm, were followed at 6 and 12 months of treatment in patients who were recruited from study sites in the Hellenic Breast Surgeons Society and had previously received 5–7 years of tamoxifen therapy.[19] A significant increase in TC and LDL from baseline was seen in both the exemestane and observational arms at 6 months and was stable through to 12 months, but there were no significant differences between the treatment arms. HDL-C was significantly decreased only at 12 months in the exemestane arm compared with the observational arm.[19] Although the ABCSG (Austrian Breast and Colorectal cancer Study Group) 6a trial, comparing extended adjuvant therapy with anastrozole and placebo, has reported efficacy data, the safety information is not yet available.[72]

The NCIC CTG (National Cancer Institute of Canada Clinical Trials Group) MA.17 (Mammary 17) trial (n = 5187) was the first to show a survival advantage for a subgroup of patients with early breast cancer receiving extended adjuvant letrozole therapy compared with placebo.[20] Hypercholesterolaemia occurred with the same frequency in the placebo and letrozole groups (16% in each).[20] In the MA.17 lipid substudy, plasma samples from 347 patients were drawn under fasting conditions, and TC, LDL-C, HDL-C, TG and Apo A levels were measured.[73] As was observed in the ATENA trial, possibly as a consequence of tamoxifen discontinuation, an increase in TC was seen in both arms at 6 months and then the levels remained stable, with no differences between letrozole and placebo up to 36 months.[73] Marginally significant differences in the percentage change from baseline in HDL-C at 6 months ($p = 0.049$) and in LDL-C at 12 months were observed between the letrozole and placebo arms.[73] However, all comparisons of lipid parameters at other timepoints were not significantly different between the two treatment arms, indicating that the lipid profile in postmenopausal women with primary breast cancer who were treated with letrozole was not significantly altered for up to 36 months in the extended adjuvant setting.[73]

2.4 Als versus Tamoxifen

In a substudy of the neoadjuvant IMPACT (IMmediate Preoperative Arimidex, tamoxifen, or Combined with Tamoxifen) trial (n = 176), 3 months of therapy with anastrozole resulted in no detrimental effects on lipid profiles in postmenopausal women. Both anastrozole and tamoxifen treatment resulted in significant increases in HDL-C (11.2% and 26.5%, respectively). Anastrozole was associated with nonsignificant increases in non-HDL-C (3.4%) and TC (2.9%), while tamoxifen significantly decreased TC by 6.5% and non-HDL-C by 12.3%.[74] The small, open-label ITA (Italian Tamoxifen Anastrozole) trial compared a 2- to 3-year regimen of tamoxifen with a subsequent switch to anastrozole with 5 years of tamoxifen therapy in 448 patients. There was a significant increase in lipid metabolism disorders in the anastrozole arm compared with the tamoxifen monotherapy arm (9.3% vs 4.0%; $p = 0.04$).[21]

In the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial, investigating anastrozole in the initial adjuvant setting (n = 9366), hypercholesterolaemia occurred more frequently in anastrozole-treated patients than in tamoxifen-treated patients (9% vs 3.5%).[75] However, these results are difficult to interpret for three reasons. Firstly, TC data was collected irregularly; the visit forms did not specifically request this information and hypercholesterolaemia was only reported under "any other relevant medical history". Secondly, about 65% of patients with hypercholesterolaemia were started on a lipid-lowering medication while receiving treatment, but no information was provided regarding lipid-lowering success and concomitant use of breast cancer hormonal agents. Thirdly, patients who discontinued anastrozole, tamoxifen or combined treatment were not followed beyond 14 days for adverse events unless the adverse events were determined to be serious.[76]

In the BIG (Breast International Group) 1-98 trial comparing letrozole with tamoxifen in 8010 patients, TC was stable in the letrozole group, while

there was a 12.1% decrease in TC in the tamoxifen group over 60 months.[22] As a check-listed adverse event recorded at each regular patient visit, hypercholesterolaemia was noted in 43% of letrozole patients and 19% of tamoxifen patients. However, >80% of the patients experienced no more than grade 1 hypercholesterolaemia. Also, the majority of data were collected in nonfasting patients, so its interpretation is also difficult. Data from the switching arms of the BIG 1-98 trial should be available in 2008.

The TEAM (Tamoxifen Exemestane Adjuvant Multicenter) trial compared exemestane with tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer for a total of 5 years.[23] The trial began in 2001 and has been amended to investigate the efficacy of switching from tamoxifen to exemestane. Interim results from the TEAM Greek substudy (n = 176) reported that exemestane had a neutral effect on TC and HDL-C, and that LDL-C increased at 3 and 6 months but not at later timepoints. Exemestane significantly decreased TG levels.[23,77] The IES (Intergroup Exemestane Study; n = 4742), which investigated exemestane in the sequential setting, did not report any data on the effect of exemestane on lipid profiles.[17]

Together, the data regarding the AIs indicate that while these newer therapies lack the beneficial effects on lipid profiles observed with tamoxifen, they demonstrate a neutral rather than a negative impact on serum lipid levels.[78]

3. AIs and Cardiovascular Health

The reported impact of AIs on cardiovascular health is inconsistent in the published data across trials of adjuvant endocrine therapy. This inconsistency may be a reflection of different study populations, differences in study endpoints and/or data collection (i.e. systematic data collections versus irregular collections; use of check-listed report forms versus open non-prompted reporting), and other aspects/reporting methodology. A variety of cardiovascular endpoints or predefined parameters have been used in the major AI therapy trials and are shown in table IV.[17,20,22,24,73,79] Not only do the endpoints differ, but there are differences in how they were reported. The ATAC trial predefined certain cardiovascular and cerebrovascular adverse events for data collection; venous thrombolic events

Table IV. Cardiovascular endpoints from aromatase inhibitor trials

Study	Protocol-defined cardiovascular end points or predefined events	Reported cardiovascular events
ABCSG 8/ARNO 95[24]	Monitored for any adverse event	MI, thromboses, embolism
ATAC[79]	Monitored for any adverse event	Ischaemic cardiovascular disease, ischaemic cerebrovascular event, any venous thromboembolic event, DVT
BIG 1-98[22]	Monitored for any adverse event using check list collection	Thrombolic events, cerebrovascular accident/TIA, cardiac events including ischaemic heart disease and cardiac failure
IES[17]	Monitored for any adverse event	Death resulting from cardiac or vascular causes; thromboembolic events
MA.17[20]	Monitored for any adverse event using check list collection	Hypercholesterolaemia and cardiovascular disease including MI, stroke/TIA, angina requiring PTCA, angina requiring CABG, thromboembolic events and other
MA.17L[73]	Serum lipid levels (TC, LDL-C, HDL-C, TG, Apo A) at baseline, 6 and 12 months, and then yearly until study completion; monitored for any adverse event	MI, stroke/TIA, angina ± PTCA or CABG, thrombolic events, other

ABCSG 8/ARNO 95 = Austrian Breast and Colorectal cancer Study Group and ARimidex-NOlvadex trials; **Apo** = apolipoprotein; **ATAC** = Arimidex, Tamoxifen Alone or in Combination trial; **BIG** = Breast International Group; **CABG** = coronary artery bypass grafting; **DVT** = deep vein thrombosis; **HDL-C** = high-density lipoprotein-cholesterol; **IES** = Intergroup Exemestane Study; **L** = lipid; **LDL-C** = low-density lipoprotein-cholesterol; **MA.17** = Mammary 17 trial; **MI** = myocardial infarction; **PTCA** = percutaneous transluminal coronary angioplasty; **TC** = total cholesterol; **TG** = triglycerides; **TIA** = transient ischaemic attack.

and ischaemic CVD were predefined adverse events, and prior to unblinding, the Steering Committee requested that ischaemic cerebrovascular events and deep venous thromboembolism be formally analysed as well.[75,76] However, it is important to note that the case report forms in the ATAC trial had nonspecific requests to report adverse events. Specifically, each form had a separate line for the physician to describe an adverse event, and such a format may be tedious and lead to underreporting when compared with using one case report form with check boxes for all adverse events, as was done in the BIG 1-98 trial.[22,76] Several other trials (ABCSG 8/ARNO 95 [Austrian Breast and Colorectal cancer Study Group 8 and ARimidex-NOlvadex 95; n = 3224],[24] BIG 1-98[22] and IES[17]) monitored patients for any adverse events and then reported cardiac events in varying levels of detail (i.e. some reported rates of CVD while others reported rates of MI, specifically) [table III]. Understanding the effect of AIs on the cardiovascular system would be improved by consistent use of predetermined end points and consistent data collection across all trials.

3.1 Coronary Artery Disease

3.1.1 Tamoxifen versus Placebo

Although a positive cardiac effect of tamoxifen has not been described in all trials, many indicate that tamoxifen has a beneficial impact on cardiac health (table V).[12,13,80-86] The best way to further examine the issue is to look at more comprehensive trial reviews. A meta-analysis of 32 trials involving 52 929 patients attempted to estimate the effects of tamoxifen on vascular and neoplastic events.[11] Twelve of the 32 trials (n = 27 790) reported death from MI. The data showed that tamoxifen significantly decreased MI deaths compared with no-treatment controls (RR 0.62; 95% CI 0.41, 0.93) and was associated with a non-significant decrease in MI incidence (RR 0.90; 95% CI 0.66, 1.23).[11] Few trials attributed death to any outcome other than MI, so this outcome was used for analysis. In the 15-year survival update from the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis, involving around 15 000 women treated with approximately 5 years of tamoxifen versus no-treatment control, overall mortality from heart disease was slightly lower in the tamoxifen arm than in the control arm (120 vs 132 events; p = 0.06).[12]

3.1.2 AIs versus Placebo

The extended adjuvant MA.17 trial reported that cardiac events occurred with a similar frequency in the letrozole and placebo arms (5.8% and 5.6%, respectively).[20] Of the cardiac events that were not included in the unspecified other category (letrozole 3.9%; placebo 3.7%), new or worsening angina pectoris was the most frequent, with 1.2% of letrozole and 0.9% of placebo recipients reporting this event. Combined, angina alone or angina requiring percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery was reported by 1.4% and 1.7% of letrozole and placebo recipients, respectively.[20,87] Thus, in this large study comparing an AI (letrozole) with placebo, the AI decreased the risk of breast cancer recurrence without increasing the risk of a cardiac event.

3.1.3 AIs versus Tamoxifen

In the adjuvant ATAC trial, ischaemic cardiac disease was observed in 4.1% of patients treated with anastrozole and 3.4% of those treated with tamoxifen at a median 68 months of follow-up; however, the details and outcomes of these events were not specifically reported.[16] Angina pectoris was reported more frequently in anastrozole-treated patients (2.3%) than in tamoxifen-treated patients (1.6%), but the occurrence of MI was similar between groups (1.2% and 1.1%, respectively).[75] These rates are actually quite low in both arms in comparison to an age-matched general population. In the IES, the rate of cardiac disease (excluding MI) was similar between groups, with a reported 42.6% in exemestane patients compared with 39.2% in tamoxifen patients (p = 0.11).[17] These strikingly high incidences of cardiac disease are higher than those seen in other trials because the definition of cardiac disease in this trial encompassed adverse events of limited clinical importance as well. The occurrence of fatal or nonfatal MI during IES was significantly greater in the exemestane group than in the tamoxifen group (0.9% vs 0.4%, respectively; p = 0.02).[88] In the BIG 1-98 trial, the overall incidence of cardiac events (grades 1–5) was similar between treatment arms (letrozole 4.1% vs tamox-

Table V. Effects of tamoxifen on cardiac health

Study	Study population	No. of patients	Effects of tamoxifen
Rutqvist and Mattsson[80]	Postmenopausal women, early breast cancer	2 356	Significant reduction in hospital admissions for any cardiac disease (HR = 0.68; 95% CI 0.48, 0.97; p = 0.03)
McDonald et al.[81]	Pre- and postmenopausal women with primary operable breast cancer	1 312	Significantly fewer hospital admissions for fatal and non-fatal MI and the incidence of MI (HR = 1.92[a]; 95% CI 0.99, 3.73; p = 0.051) and of death from acute MI (HR = 0.37; 95% CI 0.18, 0.77)
Costantino et al.[82]	Pre- and postmenopausal women with node-negative breast cancer	2 885	Lower death rates from fatal MI, coronary heart disease and possible MI (HR = 0.85; 95% CI 0.46, 1.58)
Stamatelopoulos et al.[83]	Postmenopausal women, early breast cancer (n = 14) and healthy postmenopausal women (n = 13)	27	Improved brachial artery flow-mediated dilatation (2.2% ± 0.9% tamoxifen vs 0.85% ± 1.0% control; p = 0.012) and carotid intima-media thickness (−0.088 ± 0.03mm tamoxifen vs 0.04 ± 0.03mm control; p = 0.018)
Bradbury et al.[84]	Pre- and postmenopausal women at first diagnosis of breast cancer	7 263	Reduced risk of acute MI or angina during 5-year study (adjusted OR = 0.4; 95% CI 0.2, 0.7)
Fisher et al.[85]	Pre- and postmenopausal women at increased risk for breast cancer	13 388	No reduction in the risk of or mortality from ischaemic heart disease, including MI (RR = 1.11; 95% CI 0.65, 1.92) or angina requiring coronary artery bypass grafting or angioplasty (RR = 0.93; 95% CI 0.40, 2.14) Younger patients had fewer ischaemic heart disease events and may be at lower risk (RR = 0.76; 95% CI 0.11, 4.49)
Fisher et al.[86]	Pre- and postmenopausal women with operable breast cancer who were disease-free after completing 5 years of standard adjuvant tamoxifen therapy	1 172	No statistically significant reduction in fatal cardiac first events (3 placebo vs 6 tamoxifen)
Nordenskjold et al.[13]	Postmenopausal women <75 years of age who had early stage breast cancer	4 610	Mortality from coronary heart disease was significantly reduced in patients randomised to 5 years of tamoxifen treatment compared with those in the 2-year group (RR = 0.67; 95% CI 0.47, 0.94; p = 0.02)
Early Breast Cancer Trialists' Collaborative Group[12]	Overview of randomised trials involving pre- and postmenopausal women	15 017	Fewer deaths from heart disease observed when compared with no-treatment control (120 vs 132; p = 0.06)

a HR expressed as controls (no treatment) divided by tamxifen treatment.

HR = hazard ratio; **MI** = myocardial infarction; **OR** = odds ratio; **RR** = risk ratio.

ifen 3.8%; p = 0.61). However, the incidence of grade 3–5 cardiac adverse events, although very small in each arm, was significantly higher in the letrozole compared with the tamoxifen arm (2.1% vs 1.1%), with patients in the letrozole arm experiencing a higher incidence of ischaemic heart disease (1.1% vs 0.6%) and of cardiac failure (0.5% vs 0.1%).[22]

A community-based prospective cohort study of 7944 women born between 1923 and 1930, and who participated in mammography screening for breast cancer, reported the risk ratios for CVD, coronary artery disease and deaths from acute MI.[2] The frequency of fatal cardiovascular events (including death from coronary artery disease) in the adjuvant AI trials is quite comparable to that found in this age-matched population of postmenopausal women without breast cancer, suggesting that treatment with AIs does not increase the incidence of fatal cardiovascular complications.[2] Information from other databases (UK General Practice Research Database and Swedish Myocardial Infarction Register) has led to similar conclusions.[89]

4. AIs and Thromboembolic and Cerebrovascular Events

The annual incidence of deep venous thrombosis (DVT) and pulmonary embolism increases expo-

nentially with age,[90-92] from approximately 1 in 1000 for persons aged 40–75 years to 1 in 100 for those aged >75 years.[93] While the incidence of both DVT and pulmonary embolism are significantly greater in men than in women,[90] the incidence rates increase markedly in women aged >60 years.[91] Additionally, hormone and estrogen replacement trials show that estrogen increases the risk for stroke in women treated with these drugs compared with placebo.[94] In contrast, AIs may afford protection from stroke by decreasing the availability of estrogen.[95]

4.1 Tamoxifen versus Placebo

In early breast cancer, the risk of venous thromboembolic events is usually increased with tamoxifen compared with placebo. In a study evaluating tamoxifen treatment in patients with node-negative breast cancer (n = 2644), phlebitis was reported in 2 patients receiving placebo and in 12 patients receiving tamoxifen.[96] A meta-analysis also confirmed the elevated risk of thromboembolic events, finding that tamoxifen was associated with a statistically significant increase in pulmonary emboli (RR 1.88; 95% CI 1.17, 3.01) and DVT (RR 1.87; 95% CI 1.33, 2.64).[11] Finally, the 15-year survival update from the EBCTCG data also show a slightly increased incidence of mortality resulting from thromboembolic events (15 vs 8; p-value not stated) and stroke (54 vs 29; p = 0.07) in patients receiving tamoxifen when compared with receiving no treatment.[12]

4.2 AIs versus Placebo

In the MA.17 trial, thromboembolic events were low in both arms; they were reported in 11 patients (0.4%) in the letrozole arm and 6 patients (0.2%) in the placebo arm (p-value not stated).[20] The trials also showed that the incidence of stroke and/or transient ischaemic attacks was low and similar between the two groups (letrozole 0.7%; placebo 0.6%).[20]

4.3 AIs versus Tamoxifen

In trials that compared AIs with tamoxifen, thromboembolic events occurred more frequently in tamoxifen-treated patients. The ATAC trial reported significantly more venous thromboembolic events in the tamoxifen group compared with the anastrozole group (4.5% vs 2.8%; p = 0.0004). Patients receiving tamoxifen also had significantly more DVT (2.4% vs 1.6%; p = 0.02) and cerebrovascular events (2.8% vs 2.0%; p = 0.03) than anastrozole-treated patients.[16] In the IES, 2.4% of tamoxifen-treated patients and 1.3% of those receiving exemestane experienced a thromboembolic event during the trial (p = 0.007), but the trial did not report the incidence of cerebrovascular events.[17] In the BIG 1-98 trial, fewer thromboembolic adverse events were reported in the letrozole arm compared with the tamoxifen arm (letrozole 1.5% vs tamoxifen 3.5%), and patients receiving tamoxifen had significantly more grade 3–5 thromboembolic events than patients receiving letrozole (overall risk 0.38; p < 0.0001).[15,22]

5. Successful Patient Management

Physicians should suggest options that would help improve their patients' cardiovascular risk, including assessing and treating blood pressure, lipids and overall cardiovascular risk during adjuvant endocrine therapy. As for healthy women, women with breast cancer should be encouraged to make lifestyle changes (e.g. smoking cessation, regular exercise and maintenance of a healthy diet and weight) that are likely to decrease their risk for CVD. A risk assessment should be performed intermittently for all women, whether or not they have pre-existing risk factors for coronary heart disease, and these risk factors should be monitored and treated according to current guidelines.

6. Conclusions

Because of the differences in patient populations, trial endpoints, data collection and reporting of adverse events among the trials, the risk of coronary artery disease in patients receiving adjuvant AI therapy has not been completely elucidated. Trials to date have reported greater incidences of ischaemic cardiac disease, MI and angina pectoris in patients receiving AIs than in those receiving tamoxifen. Although this requires further exploration, these data may be related to a cardioprotective effect of tamoxifen rather than to a deleterious effect of AIs

on cardiac health. In fact, cardiac event rates associated with AIs are similar in direct comparisons with placebo and appear similar to those encountered in the general population. Similarly, reports of a greater incidence of hypercholesterolaemia in patients receiving an AI compared with those receiving tamoxifen are likely to be a confirmation of the lipid-lowering effects of tamoxifen rather than an indication of any true hyperlipidaemic effect from AI therapy, since no significant differences in serum lipids have been observed in studies comparing AIs with placebo.

Placebo-controlled trials in the prevention setting will shed further light on the safety profile of AIs, as the results will not be biased by confounding factors related to breast cancer itself or by other treatment modalities for breast cancer. Two major AI trials investigating the efficacy of AIs as preventive therapy are underway. The IBIS 2 (International Breast cancer Intervention Study) prevention trial is randomising women to receive anastrozole or placebo, and the NCIC CTG MAP.3 (Mammary Prevention) is randomising women to receive exemestane or placebo. The inclusion of a placebo arm is expected to provide more insights into the risk of cardiac, cerebrovascular and thromboembolic events during AI treatment.[97]

Head-to-head, suitably powered trials involving a large number of participants would be helpful in assessing the impact of AIs on lipid metabolism and long-term cardiovascular health in a comparative manner.[98] For instance, the FACE (Femara Anastrozole Clinical Evaluation) trial, which is directly comparing adjuvant letrozole with adjuvant anastrozole in node-positive patients, and the NCIC CTG MA.27 trial, which is directly comparing anastrozole with exemestane in node-positive and node-negative women, should provide important information regarding the comparative efficacy and safety of adjuvant AI therapy. However, the available data from adjuvant AI trials involving >25 000 women indicate that AIs are not associated with an increased risk of thromboembolic or cerebrovascular events. Although the data suggest that AIs do not adversely alter lipid levels in a clinically relevant manner or have a detrimental impact on cardiac health, clinicians should proceed with caution. Cardiac risks and events need to be evaluated on an ongoing basis in women taking these drugs for breast cancer. Women with breast cancer have the same cardiovascular risk factors as women in the general population. Consequently, it is prudent to assess risk and periodically monitor serum lipid levels and overall cardiac risk for women with breast cancer as well as for the general population.

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