

# Cardiometabolic Effects of Endocrine Treatment of Estrogen Receptor–Positive Early Breast Cancer

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Estrogen receptor–positive early breast cancer is common and has a relatively good prognosis. It shares risk factors with cardiovascular disease, and cardiovascular disease is an important competing cause of mortality. Adjuvant endocrine therapy with aromatase inhibitors (requiring concomitant ovarian suppression in premenopausal women) or selective estrogen receptor modulators (usually tamoxifen) exert oncologic benefits by respectively inhibiting estradiol synthesis or breast estrogen receptor signaling. Aromatase inhibitors cause systemic estradiol depletion. Tamoxifen has mixed agonistic/antagonistic effects in a tissue-dependent fashion. Given that estrogens modulate cardiometabolic risk, a review of the effects of endocrine therapy on cardiometabolic outcomes is pertinent. The current, but limited, evidence suggests that tamoxifen treatment, although associated with increases in body fat, hepatic steatosis, serum triglycerides, and diabetes risk, modestly reduces low-density lipoprotein cholesterol and lipoprotein(a) and may have favorable effects on markers of subclinical atherosclerosis. Tamoxifen is associated with either no effect on, or a reduction in, cardiovascular events, and it is associated with an increase in venous thromboembolic events. Aromatase inhibitors, although fewer studies are available and often confounded by comparison with tamoxifen, have not been consistently associated with adverse changes in cardiometabolic risk factors or increases in cardiovascular events. Further clinical trials designed to evaluate cardiometabolic outcomes are needed to more accurately determine the effects of endocrine therapy on cardiovascular risks, to inform individualized decisions regarding choice and duration of endocrine therapy, and to implement evidence-based strategies to mitigate cardiometabolic risks. In the meantime, although breast cancer–specific evidence for benefit of lifestyle measures is available and recommended routinely, proactive monitoring and treatment of cardiovascular risk factors should follow general population recommendations.

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**Freeform/Key Words:** breast cancer, cardiovascular disease, aromatase inhibitor, selective estrogen receptor modulator

Breast cancer is the most common solid organ cancer diagnosed in women worldwide. In the United States, one in eight women will develop breast cancer in her lifetime, and, in 2018, there were 3.1 million breast cancer survivors living in the United States [1]. Approximately

Abbreviations: ASCO, American Society of Clinical Oncology; ATAC, Arimidex Tamoxifen Alone or in Combination; CV, cardiovascular; DXA, dual x-ray densitometry; ER, estrogen receptor; ER<sup>+</sup>, estrogen receptor-positive; estradiol, 17 $\beta$ -estradiol; HDL, high-density lipoprotein; HR, hazard ratio; IMT, intima–media thickness; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MHT, menopausal hormone therapy; RCT, randomized controlled trial; SERM, selective estrogen receptor modulator; TEAM, Tamoxifen Exemestane Adjuvant Multinational.

75% of women diagnosed with early stage breast cancer have estrogen receptor–positive (ER<sup>+</sup>) disease, and virtually all of these women will be offered adjuvant endocrine therapy to inhibit ER activation and prevent recurrence [2]. This can be accomplished either with aromatase inhibitors, which require concomitant ovarian suppression in premenopausal women, or with selective estrogen receptor modulators (SERMs, usually tamoxifen), which can be used as monotherapy irrespective of menopausal status. Given that women with ER<sup>+</sup> early breast cancer have a relatively good prognosis, with 5-year survival exceeding 90% [3], considering adverse effects of endocrine therapy is of prime importance.

Herein, we review the cardiometabolic effects of adjuvant endocrine therapy in women with ER<sup>+</sup> early breast cancer, including effects on body composition, hepatic lipid accumulation, glucose and lipid metabolism, arterial wall, and clinical cardiovascular events.

The material discussed is based on peer-reviewed journals within the PubMed database from January 1970 to 28 February 2018. The search terms “aromatase inhibitor,” “atherosclerosis,” “breast cancer,” “body composition,” “cardiovascular disease,” “cerebrovascular disease,” “diabetes,” “hypertension,” “lipids,” “metabolic syndrome,” “selective estrogen receptor modulators,” “steatosis,” and “tamoxifen” were used. We also searched the references listed in relevant publications. Original research articles, reviews, and societal guidelines were considered.

## 1. Background

### A. Cardiometabolic Effects of Estrogens in Women

Reflecting widespread expression of ERs, cardiometabolic effects of endogenous estrogens [mainly 17 $\beta$ -estradiol (estradiol), the major bioactive endogenous estrogen, and its metabolites estrone, and estriol] and of exogenous estrogens are operative in many somatic tissues [4]. These effects are complex and depend on age, comorbidities, genetic background, and, with respect to exogenous estrogens, on dose, route (oral vs transdermal), and timing (early vs late menopause) of administration, and on concomitant progestin treatment [5]. Observational studies suggest that endogenous estrogens have favorable associations with body composition, glucose and lipid metabolism, and endothelial function and atherosclerosis, especially in prematurely and early postmenopausal women [6]. Trials of estradiol treatment, administered in physiologic doses to women with premature menopause, have also reported improved cardiometabolic outcomes [7]. Effects of menopausal hormone therapy (MHT) are complex, with suggestions of some benefits in women with recent menopause (<6-10 years), but not in women who are >10 years postmenopausal [8, 9], the so-called “timing hypothesis” [10]. MHT is not recommended for prevention of cardiovascular disease [5]. Given evidence supporting cardiometabolic benefits of estrogens, especially in younger women (see further details on individual endpoints below), endocrine therapy that interferes with estrogenic signaling could increase cardiometabolic risks.

### B. Effects of Endocrine Therapy on Estrogen Receptor Signaling

In premenopausal women with an intact gonadal axis, aromatase inhibitors counteract estradiol-mediated negative hypothalamic–pituitary feedback and stimulate gonadotropin-mediated ovarian estradiol production. Aromatase inhibitors require concomitant ovarian suppression, either by GnRH analogs or bilateral ovariectomy. This causes rapid and profound reductions in circulating estradiol, from premenopausal concentrations to nearly zero.

In postmenopausal women, aromatase inhibitors profoundly (>95%) inhibit aromatase, the rate-limiting enzyme in the conversion of androgens to estradiol, causing “virtually complete” circulating estradiol deficiency, with reductions of plasma estradiol to  $\leq 3$  pmol/L (the detection limit of sensitive mass spectrometry–based assays), concentrations markedly below those measured in natural menopause, typically ranging from 20 to 50 pmol/L [11]. Improved oncologic outcomes [3] provide proof-of-principle data that residual postmenopausal estrogens are of biological significance.

Tamoxifen, the most commonly used SERM, acts as a pure ER antagonist in breast tissue [12], but as a partial ER agonist in other tissues such as the skeleton, liver, uterus, and the coagulation system [13, 14]. Although rigorous human data quantifying tissue-specific ER signaling potencies of tamoxifen are lacking, tamoxifen is considered to be a less potent ER agonist than native estradiol [12]. Therefore, clinical effects of tamoxifen on tissues other than breast depend on endogenous estradiol availability. In premenopausal women, tamoxifen competes with estradiol, a more potent ER ligand, to reduce net ER signaling. In postmenopausal women who have low estradiol, the partial agonistic tamoxifen activity may increase net ER signaling. This is true for the skeleton, based on data that tamoxifen treatment accelerates bone loss in premenopausal women, but mitigates bone loss in postmenopausal women [15].

Aromatase inhibitors, owing to global estradiol deprivation, could have adverse cardiometabolic effects, whereas the effects of tamoxifen should be favorable in tissues where it acts as an ER agonist. These effects are likely modified by age, time from menopause, and the degree of preexisting cardiovascular disease, and, for tamoxifen, endogenous estradiol availability.

### *C. Oncologic Benefits of Endocrine Therapy*

In postmenopausal women, aromatase inhibitors are superior to tamoxifen, with a modest improvement in 10-year breast cancer mortality (12.1% vs 14.2%, relative risk, 0.85; 95% CI, 0.75 to 0.96,  $P < 0.01$ ) [3]. Whereas initial studies used endocrine treatment for 5 years, in women with high-risk breast cancer, in particular those with node-positive disease [16], extending endocrine therapy to 10 years increases disease-free survival, which includes a reduction in local recurrences and new primary breast cancers [17].

In premenopausal women, more aggressive estradiol deprivation has been shown to be beneficial over tamoxifen monotherapy, especially in high-risk early breast cancer. The Tamoxifen and Exemestane Trial and Suppression of Ovarian Function Trial have reported improved disease-free survival with the combined use of aromatase inhibition and ovarian suppression compared with either tamoxifen monotherapy or the combined use of tamoxifen and ovarian function suppression [18–20].

If supported by further evidence, the use of more aggressive, longer duration endocrine therapy in many women may increase, potentially exposing more women to increased risks of adverse cardiometabolic outcomes. Of note, the US Preventive Services Task Force recently recommended aromatase inhibitors for breast cancer prevention in high-risk women, which could further increase the number of women exposed to potentially adverse cardiometabolic outcomes [21].

### *D. Cardiometabolic Disease in Women With Early Breast Cancer*

Breast cancer and cardiovascular disease share several risk factors, including postmenopausal obesity [22], hyperinsulinemia/diabetes [23], and physical inactivity [24]. In postmenopausal women with early breast cancer, cardiovascular disease risk may exceed breast cancer recurrence risk even prior to commencing endocrine therapy [25]. Women commonly receive nonendocrine therapies associated with cardiotoxicity, including radiotherapy, anthracycline-based chemotherapy, and targeted therapies such as trastuzumab [26]. Women with breast cancer have a higher risk of cardiovascular disease mortality than do women of the general population, and risk factors include older age, preexisting cardiovascular risk factors, and black ethnic origin [27]. Although breast cancer remains the most common cause of death in women with early breast cancer [28], cardiovascular death is a major cause of competing mortality. Cardiovascular disease becomes the leading cause of death in older women ( $\geq 70$  years of age) [29], especially in those surviving  $\geq 5$  or years after breast cancer diagnosis [28]. Even modest adverse effects of endocrine therapy on cardiovascular outcomes may be important.

TAMOXIFEN		CARDIOMETABOLIC EFFECTS OF ADJUVANT ENDOCRINE THERAPY		AROMATASE INHIBITORS	
Outcome	Evidence Source	Outcome	Evidence Source	Outcome	Evidence Source
<b>Body composition</b> ↑ body fat & visceral fat	<b>Study Type:</b> Observational <b>Size:</b> Small (n<100) <b>Population:</b> Women ≥ 40yrs, breast cancer, tamoxifen vs. unexposed, healthy or breast cancer controls <b>Imaging:</b> DXA or CT	<b>Body composition</b> ↓ fat mass & ↑ lean mass relative to tamoxifen	<b>Study Type:</b> Observational, convenience samples <b>Size:</b> Small (n<100) <b>Population:</b> Postmenopausal, breast cancer, aromatase inhibitors vs. tamoxifen <b>Imaging:</b> DXA or CT	<b>Hepatic fat accumulation</b> ↑ risk of hepatic steatosis	<b>Study Type:</b> Limited prospective <b>Population:</b> Women, breast cancer, aromatase inhibitors vs. tamoxifen <b>Imaging:</b> Ultrasound or CT
<b>Glucose metabolism</b> ↑ risk of diabetes	<b>Study Type:</b> Several large health database studies <b>Population:</b> Women, breast cancer, tamoxifen >2yrs vs. non-tamoxifen users	<b>Glucose metabolism</b> ? ↑ risk of diabetes	<b>Study Type:</b> Case-cohort <b>Population:</b> Postmenopausal women, breast cancer, aromatase inhibitor vs. no treatment	<b>Lipid metabolism</b> ↓ total cholesterol, LDL-C, Lp(a) ↑ triglycerides	<b>Study Type:</b> Mostly placebo-controlled, comparing oncological outcomes between aromatase inhibitors and tamoxifen. Lipid parameters collected largely in context of safety monitoring <b>Population:</b> Women, early breast cancer, aromatase inhibitors vs. tamoxifen
<b>Arterial wall</b> ↓ carotid intimal-media thickness, ↑ flow-mediated dilation	<b>Study Type:</b> Observational <b>Size:</b> n=51-410 <b>Population:</b> Postmenopausal, breast cancer, tamoxifen vs. unexposed, healthy or breast cancer controls	<b>Arterial wall</b> Adverse effects on measures of endothelial/vascular functions in most studies	<b>Study Type:</b> Observational <b>Size:</b> small (mostly n<100) <b>Population:</b> Postmenopausal, breast cancer aromatase inhibitors vs. unexposed, healthy or breast cancer controls	<b>Cardiovascular events</b> ↓ risk	<b>Study Type:</b> Observational, RCTs & meta-analyses <b>Population:</b> Tamoxifen vs. placebo or no treatment
		<b>Cardiovascular events</b> ↑ risk compared to tamoxifen	<b>Study Type:</b> Observational, RCTs & meta-analyses <b>Population:</b> Aromatase inhibitors vs. tamoxifen, or aromatase inhibitors (as extended therapy) vs. placebo		

**Figure 1.** Cardiometabolic effects of adjuvant endocrine therapy. Main outcomes and evidence sources for tamoxifen and aromatase inhibitors are presented. DXA, dual-energy X-ray absorptiometry; LDL, low density lipoprotein; Lp(a), lipoprotein(a); n, number; RCT, randomized control trial.

## 2. Effects of Endocrine Therapy on Cardiometabolic Outcomes

Herein, we discuss the effects of endocrine therapy on potential cardiac risk factors and clinical cardiovascular events. These are summarized in [Fig. 1](#).

### A. Body Composition

In women without breast cancer, both experimentally induced premature menopause [30] and natural menopause transition have been associated with increases in total and visceral adipose tissue [31], which, in most studies, is mitigated by estradiol add-back [30, 31]. Adiposity may be a proximate cause contributing to adverse cardiometabolic consequences of estradiol deprivation. In women with breast cancer, the postdiagnosis period is associated with weight gain, predominantly of body fat [32], and concomitant loss of muscle mass, in part due to chemotherapy-induced ovarian failure [33]. Effects of endocrine therapy on body composition are not well described. Current data are limited to observational studies of small ( $n < 100$ ) convenience samples, with limited confounder adjustments. In cross-sectional, case-control studies of women with early breast cancer  $\geq 40$  years of age, using dual-energy X-ray absorptiometry or CT scanning, tamoxifen use was associated with a higher amount of body fat, visceral adipose tissue, and liver fat, compared with age- and body mass index-matched women with [34] or without [35, 36] breast cancer not receiving tamoxifen. In a longitudinal study, postmenopausal women (mean age, 61 years) with prior tamoxifen treatment of 2 to 3 years were switched to the aromatase inhibitor exemestane ( $n = 28$ ) or continued on tamoxifen ( $n = 27$ ). After 12 months, total fat mass (by dual-energy X-ray absorptiometry) in the exemestane group decreased by 8% but remained stable in the tamoxifen group (between-group  $P < 0.01$ ), with no between-group difference in body weight, self-reported caloric intake, or physical activity [37]. In a secondary analysis of a 2-year randomized controlled trial (RCT) of 82 women with early breast cancer newly postmenopausal after chemotherapy (mean age, 51 years), women receiving aromatase inhibitors had an increase in lean mass (+1.2 kg) in conjunction with an increase in free testosterone,

whereas women not receiving aromatase inhibitors (comprising women receiving SERMs or no endocrine treatment) had increased total body fat (+1%), with between-group differences being significant [38]. In one uncontrolled study of 41 premenopausal women (mean age, 44 years), fat mass increased by 3 kg and lean mass decreased by  $-0.8$  kg 6 months after commencing tamoxifen plus ovarian suppression, and these changes were partially reversed by subsequent exercise [39]. However, given that ovarian suppression can cause changes in body composition, the extent to which reported effects were due to tamoxifen remains uncertain in this uncontrolled study [39]. Overall, the evidence suggests that tamoxifen treatment is associated with an increase in body fat. The few available studies have not demonstrated metabolically adverse changes in body composition with aromatase inhibitor treatment. More work is needed before firm conclusions can be drawn.

### B. Hepatic Fat Accumulation

Hepatic steatosis is closely associated with the metabolic syndrome and may be an independent factor of cardiovascular risk [40]. Estrogens protect against hepatic steatosis, in part mediated by hepatic ER $\alpha$  signaling [41]. Despite acting as a partial hepatic ER agonist [42], tamoxifen treatment is associated with an increased risk of hepatic steatosis in women with breast cancer [43]. Experimental data from healthy postmenopausal women have demonstrated that this is likely due to an indirect effect of tamoxifen on reducing GH-mediated hepatic lipoprotein export, an effect not observed with estradiol treatment [44]. Although an association between tamoxifen and hepatic steatosis is well documented [36, 41, 43], effects of aromatase inhibitor treatment on hepatic fat accumulation are less well described. In an observational study of 1203 Korean women without hepatic steatosis at baseline, hepatic steatosis incidence (diagnosed by ultrasound) was higher in tamoxifen-treated than in aromatase inhibitor-treated women (128.7 vs 81.1 per 1000 person-years,  $P = 0.021$ ) and associated with higher serum triglyceride and lower high-density lipoprotein (HDL) cholesterol concentrations [45]. Likewise, in a randomized 3-year prospective study of 353 Chinese women, the cumulative incidence of hepatic steatosis (diagnosed by CT) was lower in aromatase inhibitor-treated compared with tamoxifen-treated women (14.6% vs 41.1%,  $P < 0.0001$ ) [46]. In summary, whereas tamoxifen is associated with an increased risk of hepatic steatosis compared with aromatase inhibitor or no endocrine treatment, aromatase inhibitor-associated risks have not been adequately investigated.

### C. Glucose Metabolism

Most studies suggest that the menopausal transition [47] or premature menopause [48] is associated with increased risks of developing insulin resistance, the metabolic syndrome, and type 2 diabetes. This may be mediated by metabolically adverse changes in body composition and by the direct effect of estrogens on insulin sensitivity and pancreatic  $\beta$ -cells. Estrogens may also modulate glucose metabolism by effects on the central nervous system [49]. In clinical trials, MHT improves glucose homeostasis by insulin-dependent and insulin-independent mechanisms [47].

Female mice with a targeted deletion of the aromatase gene are at increased risk of diabetes, a phenotype prevented by estradiol treatment [50]. Tamoxifen promotes diabetes in female mice, and, *in vitro*, antagonizes estradiol-mediated protection against apoptosis in pancreatic  $\beta$ -cells [50]. Tamoxifen inhibits  $\beta$ -cell proliferation in an ER $\alpha$ -dependent fashion [51]. This suggests that tamoxifen has ER-antagonistic effects in pancreatic  $\beta$ -cells.

In an RCT of postmenopausal women at high risk of breast cancer, low-dose tamoxifen treatment (5 mg/d) decreased insulin sensitivity (estimated by the homeostasis model assessment: OR, 0.15; 95% CI, 0.03 to 0.88,  $P = 0.04$ ), compared with women not receiving tamoxifen, an effect, however, derived from a *post hoc* analysis restricted to trial participants who were overweight or obese [52]. In a nested case-control Canadian health database study of 14,360 breast cancer survivors  $\geq 65$  years of age followed for 5.8 years, tamoxifen treatment

was associated with a 24% increased risk of diabetes compared with no tamoxifen treatment (adjusted OR, 1.24; 95% CI, 1.08 to 1.42;  $P = 0.002$ ) [53]. A 31% increased diabetes risk in tamoxifen users, compared with non-tamoxifen users, was also reported in a Taiwanese database study involving 22,257 women with early breast cancer  $\geq 20$  years of age followed for up to 12 years [54]. These studies included too few women receiving aromatase inhibitor treatment to reliably estimate diabetes risk [53, 54]. In a more recent case-cohort study from Israel of 2246 postmenopausal women with early breast cancer followed for 5.9 years, aromatase inhibitor treatment was associated with a higher risk of incident diabetes [hazard ratio (HR), 4.27; 95% CI, 1.42 to 12.84;  $P = 0.010$  vs no endocrine treatment] than tamoxifen (HR, 2.25; 95% CI, 1.19 to 4.26;  $P = 0.013$  vs no endocrine treatment) [55]. A Surveillance Epidemiology and End Results database study of postmenopausal women reported no increased diabetes risk with either tamoxifen or aromatase inhibitor treatment within 2 years of endocrine treatment initiation, suggesting that longer follow-up is required [56]. Within the limitations inherent to observational studies (*e.g.*, residual confounding, nonrandomized treatment), the data suggest that both tamoxifen and aromatase inhibitor treatment, especially when used for  $>2$  years, is associated with an increased risk of developing diabetes.

#### D. Lipid Metabolism

In postmenopausal women, low-dose oral estradiol treatment reduces serum low-density lipoprotein (LDL) cholesterol, but increases HDL cholesterol and triglycerides, with treatment-associated changes in circulating lipid concentrations  $\sim 15\%$  to  $30\%$  [57]. This occurs, at least in part, via hepatic ER-mediated effects on the expression of hepatic genes involved in the regulation of lipid metabolism. Compared with oral estradiol treatment, effects are less marked with transdermal administration, due to lack of hepatic first pass effect [57].

In healthy postmenopausal women, tamoxifen decreases LDL cholesterol to similar degrees [58] as oral estradiol treatment, likely due to ER agonism at the liver. In a 2-year RCT designed to evaluate the effects of tamoxifen on serum lipids in 140 postmenopausal women (44 to 64 years of age) with early breast cancer, total cholesterol decreased by 12% and LDL by 20%, with no change in HDL, whereas triglycerides increased by 20% [59]. These changes were sustained in a subgroup of 62 women followed for 5 years [60]. At 5 years, a modest decrease in lipoprotein(a) [Lp(a)] was reported [60] and subsequently confirmed by a small meta-analysis of five RCTs with 215 participants (standardized mean difference,  $-0.41$ ; 95% CI,  $-0.68$  to  $-0.14$ ;  $P = 0.003$ ) [61]. Similar effects of tamoxifen on lipid parameters have been reported in smaller placebo-controlled studies in women with early breast cancer [62].

There is limited RCT evidence in women with breast cancer comparing the effects of aromatase inhibitor treatment on lipid parameters with placebo. In a 2-year placebo-controlled dedicated lipid endpoint RCT in 147 postmenopausal women with early breast cancer (mean age, 60 years), treatment with the aromatase inhibitor exemestane decreased HDL by 9% compared with a 2% increase with placebo ( $P < 0.001$ ), and marginally increased homocysteine ( $P = 0.018$ ) [63]. Between-group differences were no longer significant 12 months after cessation of aromatase inhibitor therapy [64]. In an breast cancer prevention RCT in 4560 postmenopausal women (mean age, 62.5 years) at high risk of breast cancer, after a median follow-up of 35 months, as part of safety monitoring, no significant differences with respect to hypercholesterolemia and hypertriglyceridemia were detected between aromatase inhibitor-treated and placebo-treated groups [65].

Several studies have reported less favorable lipid profiles in women receiving aromatase inhibitors compared with tamoxifen. Beneficial effects of tamoxifen may confound interpretation of RCTs where aromatase inhibitors were compared with, or sequenced after, tamoxifen. These RCTs were not designed as lipid endpoint trials, lipid parameters were collected in the context of adverse event monitoring, and between-group differences in confounding factors (*e.g.* differences in baseline lipid concentrations or in use of lipid lowering-medication) cannot be excluded. In the Breast International Group 1-98 RCT [66] of

8010 postmenopausal women (mean age, 61 years) after 23 months, total cholesterol was stable in the letrozole group but decreased by 14.1% in the tamoxifen group, and hypercholesterolemia (defined as above the assay reference) was higher in the letrozole arm compared with the tamoxifen arm (43.6% vs 19.2%). Total cholesterol >7.75 mmol/L was reported in 8.5% of letrozole-treated women and in 1.9% of tamoxifen-treated women [66]. Women receiving letrozole were threefold more likely to commence cholesterol lowering medications than women receiving tamoxifen [67].

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [68], an RCT of 6,186 postmenopausal women (mean age, 64 years) with early stage breast cancer reported, after a median follow up of 68 months, a higher prevalence of hypercholesterolemia in the anastrozole group compared with the tamoxifen group (9.0% vs 3.5%, respectively;  $P < 0.0001$ ). However, measurement of lipid levels was not protocolized, but it was left to the discretion of individual investigators [68].

Several RCTs have assessed the effects of aromatase inhibitors on serum lipids in women following primary adjuvant tamoxifen. In the Adjuvant post-Tamoxifen Exemestane Versus Nothing Applied lipid substudy [69], 411 postmenopausal women with early stage breast cancer who had received tamoxifen for at least 5 years were randomized to either an additional 5 years of exemestane or observation. In both study arms, total and LDL cholesterol increased, and triglycerides decreased. Changes were modest (<20%) compared with baseline levels, without between-group differences [69]. Likewise, in MA.17, a placebo-controlled RCT designed to assess the effects of letrozole on disease-free survival following 5 years of tamoxifen treatment, after a median follow-up of 30 months, there was no difference in the prevalence of hypercholesterolemia between letrozole-treated women ( $n = 2593$ ) and placebo-treated women ( $n = 2594$ ) treated women [70]. In MA.17L, an MA.17 lipid substudy involving 340 women with normal baseline serum lipid levels not receiving antilipid therapy, women treated with letrozole had marginal decreases in HDL at 6 months ( $P = 0.049$ ) and marginal increases in LDL ( $P = 0.033$ ) and triglycerides at 24 months ( $P = 0.036$ ), compared with placebo, but not at other time points [71]. In the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial [72] 9779 postmenopausal women were given exemestane either upfront or after tamoxifen. After a median follow-up of 5.1 years, hypercholesterolemia was reported more frequently in the exemestane monotherapy arm compared with the sequential arm [230 (5%) vs 136 (3%)  $P < 0.0001$ ] [72].

In summary, tamoxifen treatment is associated with modest decreases in LDL cholesterol and in Lp(a), but with increases in triglycerides that can occasionally be severe [73]. Aromatase inhibitor treatment does not appear to be associated with marked changes in lipid parameters. Changes reported with aromatase inhibitor treatment following tamoxifen appear to be due to tamoxifen washout rather than an aromatase inhibitor effect.

### *E. Arterial Wall*

Clinical studies generally demonstrate beneficial effects of estrogens on subclinical atherosclerosis [*e.g.*, coronary artery calcium scores, carotid intima–medial thickness (IMT)] in women with premature and early menopause, but potentially deleterious effects in late (>10 years) menopausal women [74, 75]. Several observational studies (including between 51 to 410 women) have reported associations of endocrine therapy with markers of atherosclerosis in postmenopausal women with early breast cancer. In a cross-sectional study, women ( $n = 67$ ; mean age, 61 years) receiving tamoxifen for a mean duration of 2.4 years had lower carotid IMT than did controls not receiving endocrine therapy, independent of adjustment for age and cardiovascular risk factors (610 vs 660 mm,  $P = 0.04$ ) [76]. In a 6-months prospective study ( $n = 27$ ; mean age, 63 years), tamoxifen treatment was likewise associated with decreased carotid IMT and an increase in flow-mediated dilation compared with untreated healthy controls [77].

Three studies have assessed markers of atherosclerosis and endothelial function in postmenopausal women receiving aromatase inhibitors. In a cross-sectional study, women

receiving aromatase inhibitors ( $n = 36$ ; mean age, 62 years) had reduced vascular relaxation and increased endothelial dysfunction assessed by several noninvasive measures, compared with age-, body mass index-, and cardiovascular risk factor burden-matched controls ( $n = 25$ ) [78]. In a prospective study, women ( $n = 97$ ; mean age, 66 years) initiating aromatase inhibitors were more likely to have a deterioration in their reactive hyperemia index at 12-month follow-up compared with matched controls (29% vs 11%,  $P = 0.04$ ), an effect more likely in women with at least three cardiovascular risk factors [79]. A large cross-sectional study reported no difference in carotid IMT between women treated with aromatase inhibitors ( $n = 410$ ; mean age, 71 years) for a median of 53 months and age-matched controls ( $n = 210$ ). However, women were older than in the other studies, and groups were not matched for cardiovascular risk [80]. Overall, the preliminary evidence, based largely on relatively small observational studies, suggests that aromatase inhibitors may have adverse effects on surrogate markers of atherosclerosis and vascular/endothelial function, whereas tamoxifen may have favorable effects. However, more definitive studies are needed.

## F. Cardiovascular Events

### F-1. Observational studies

Database studies including 5300 to 16,300 mostly postmenopausal women  $\geq 60$  years of age with early breast cancer from the United States [81, 82], United Kingdom [83], Denmark [84], and Taiwan [85] have assessed associations of tamoxifen with cardiovascular events, using a case-control design. These studies have reported either neutral effects or reductions in cardiovascular events with tamoxifen use. In a US database study of women with a mean age of 67 years, tamoxifen use, compared with nonusers, was not associated with risk of first stroke (OR, 1.0; 95% CI, 0.6 to 1.6) [81] or first acute myocardial infarction (AMI) (OR, 1.2; 95% CI, 0.7 to 1.9) [82], after adjustment for age and cardiovascular risk factors. Likewise, in Danish women, tamoxifen use was not associated with rates of a broad range of cardiovascular events after adjustment for age, cardiovascular risk, and nonendocrine therapy breast cancer treatments [84]. However, in studies from the United Kingdom and Taiwan, tamoxifen use was associated with a lower risk of AMI/angina (OR, 0.4; 95% CI, 0.2 to 0.7) [83], and of total cardiovascular events (HR, 0.5; 95% CI, 0.4 to 0.8) [85], after adjustment for comorbidities. Women in the Taiwanese cohort (mean age, 50 years) were younger than in other studies, and cardiovascular benefits are consistent with the timing hypothesis discussed above. Limitations include those inherent to database studies (*e.g.*, nonrandomized treatment, variable event adjudication, and residual confounding), and that numbers of events were generally low, ranging from 100 to 200 in each study.

Larger database studies ( $n = 5600$  to 44,000) from the United States [86–88] and Canada [89] with higher event rates (several thousands) comprising older women with breast cancer (mean age,  $>66$  years) have compared associations of tamoxifen with aromatase inhibitors on cardiovascular events. Three studies showed no difference in AMI or stroke rates between tamoxifen and aromatase inhibitor users after variable adjustments [86–88]. One study reported a higher risk of hospitalization for acute myocardial infarction (HR, 2.02; 95% CI, 1.16 to 3.53) in aromatase inhibitor-treated women [89].

### F-2. Randomized controlled clinical trials

Cardiovascular effects of adjuvant endocrine therapy have been analyzed in a large number of RCTs enrolling mostly postmenopausal women, and key RCTs [17, 66, 68, 70, 72, 90–92] are summarized in Table 1. Individual RCTs have been inconsistent, in part due to low event rates limiting statistical power. Therefore, several meta-analyses [93–100] have been conducted (Table 2). Of note, RCTs were designed to evaluate oncologic endpoints. Cardiovascular events were collected in the context of safety monitoring, with heterogeneity in definition, grading, and reporting of cardiovascular events. RCTs also differed



with respect to inclusion criteria, clinical characteristics of study populations, length of follow-up, and reporting on confounders (e.g., cardiovascular risk factors, comorbid burden, use of concurrent medications), limiting interpretation of these meta-analyses. Moreover, analyses were based on study-level, investigator-reported events rather than on individual patient data.

Meta-analyses comparing tamoxifen with placebo or no treatment consistently reported an increased risk of venous thromboembolism (including deep venous thrombosis and pulmonary embolism) but decreased cardiovascular events with tamoxifen [93, 98] (Table 2). Aromatase inhibitor treatment (either upfront or sequenced after tamoxifen) was consistently associated with an increased risk of cardiovascular events, but with a decreased risk of venous thromboembolism compared with tamoxifen treatment. In the extended setting (after initial endocrine therapy for 5 years), aromatase inhibitors were associated with an increased risk of cardiovascular events also when compared with placebo, although comparatively less data are available in this setting [99]. Associations with cerebrovascular events are less clear, in part due to lower event rates (Table 2). With respect to vascular mortality, a patient-level efficacy meta-analysis of 31,920 postmenopausal women [3] reported no differences in thromboembolic, cerebrovascular, or cardiac mortality between tamoxifen- and aromatase inhibitor-treated women (including upfront and sequenced therapy) within 5 years of follow-up, but vascular mortality was low [ $n = 394$  (1.2%)] during this period.

Profound estradiol deprivation in premenopausal women could be expected to increase long-term cardiovascular risk. However, no data are available to support this hypothesis. Among Suppression of Ovarian Function Trial/Tamoxifen and Exemestane Trial participants ( $n = 5648$ , aged 40 to 46 years at randomization) with low baseline cardiovascular risk, at 8 year follow-up, <50 cardiac ischemia/infarction events (<1%) were reported [20].

In summary, tamoxifen use in postmenopausal women is associated with an increase in venous thromboembolic risk, but with either no effect on, or reduction in, cardiovascular events. Whether aromatase inhibitors have cardiovascular toxicity remains unclear, as comparisons to placebo or no treatment are limited, and increased risks relative to current or previous use of tamoxifen may be explained by a protective effect of tamoxifen. Overall, reported effect sizes for cardiovascular events were modest (relative risks <30%, absolute risks <2%). However, true risks could be underestimated because first, most observational studies excluded women with preexisting cardiovascular disease, and RCT participants were often healthier than women receiving endocrine therapy outside of clinical trials; second, follow-up was relatively short; and third, adverse event reporting in oncologic endpoint RCTs may be incomplete; for example, aromatase inhibitor treatment-associated osteoporotic fracture rates were considerably higher in a dedicated fracture endpoint trial [101] compared with rates reported as adverse events in oncologic endpoint RCTs [15]. Finally, adverse events are only collected until an efficacy outcome occurs, yet adverse cardiovascular events can continue to accumulate thereafter. In older women with early breast cancer, cardiovascular disease exceeds breast cancer as the leading cause of death 6 to 10 years after diagnosis [28, 29], emphasizing the importance of cardiovascular death as a competing cause of mortality in long-term breast cancer survivors.

### 3. Implications for Clinical Practice

Proactive assessment and optimization of cardiovascular risk is an important component of survivorship breast cancer care. Almost two-thirds of US women with breast cancer are overweight and obese, and obesity is a risk factor not only for adverse cardiometabolic outcomes, but also for breast cancer recurrence [102]. American Cancer Society/American Society of Clinical Oncology (ASCO) guidelines emphasize the importance of educating breast cancer survivors about lifestyle modifications [102]. ASCO recommendations for smoking cessation, nutrition (a diet high in vegetables, fruits, whole grains, and legumes but low in saturated fats), and exercise (at least 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week, including strength training exercises at least 2 days per week) are

Table 1. Selected Trials Reporting Cardiovascular Risk Associated With Adjuvant Endocrine Therapies

Trial	Study Population	Design	Outcomes, % or RR/HR (95% CI)	Other Cardiometabolic Outcomes
Scottish Cancer Trials [91]	N = 1323; tamoxifen vs none (CTx, RT status unknown)	RCT: aims to assess the effect of tamoxifen given to patients with breast cancer immediately after mastectomy (or mastectomy plus RT) (adjuvant arm) or only after the patients had had a relapse	<i>Cardiovascular event</i> RR, 0.67; 95% CI, 0.43–1.04 <i>Cerebrovascular event</i> RR, 1.23; 95% CI, 0.69–2.19	
Rosell <i>et al.</i> , Swedish Breast Cancer Cooperative Group [92]	N = 4150; tamoxifen 2 vs 5 y (with/without prior CTx, RT)	RCT: aims to determine the morbidity and mortality from cardiac diseases during treatment and long term after treatment with tamoxifen	<i>Coronary heart disease</i> HR, 0.83; 95% CI, 0.70–1.00; <b>P = 0.048</b> <i>Myocardial infarction</i> HR, 0.75; 95% CI, 0.60–0.95; <b>P = 0.019</b> <i>Coronary heart disease mortality</i> HR, 0.72; 95% CI, 0.53–0.97, <b>P = 0.029</b> <i>Myocardial infarction mortality</i> HR, 0.68, 95% CI, 0.47–1.00; <b>P = 0.051</b>	<i>Hypercholesterolemia</i> Anastrozole 278 (9%) vs tamoxifen 108 (3.5%); <b>P ≤ 0.0001</b> <i>Hypertension</i> Anastrozole 402 (13%) vs tamoxifen 349 (11%); <b>P = 0.04</b> <i>Hypercholesterolemia</i> Letrozole (43.6%) vs tamoxifen (19.2%)
ATAC Trialists' Group [68]	N = 9366; anastrozole vs tamoxifen vs combination (with/without prior CTx, RT); median follow-up 68 mo	RCT: aims to assess the safety tolerability and risk/benefit of extended therapy beyond 5 y; lipids were not routinely assessed	<i>Cardiovascular event</i> Anastrozole 73 (2%) vs tamoxifen 66 (2%); <b>P = 0.5</b> <i>Cerebrovascular event</i> Anastrozole 62 (2%) vs tamoxifen 88 (3%); <b>P = 0.03</b>	
The Breast International Group 1-98 Collaborative Group [66]	N = 8010; letrozole vs tamoxifen; median follow-up 26 mo (with/without prior CTx, RT)	RCT: aimed to compare Letrozole with tamoxifen as adjuvant treatment of steroid hormone receptor–positive Breast cancer in postmenopausal women 90.8% of the cholesterol values were not obtained after an overnight fast	<i>Cardiovascular event</i> Letrozole 162 (4.1%) vs tamoxifen 153 (3.8%); <b>P = 0.61</b> <i>Cerebrovascular event</i> Letrozole 39 (1%) vs tamoxifen 41 (1%); <b>P = 0.91</b> More women in the letrozole group had grade 3, 4, or 5 cardiac events (2.1% vs 1.1%, <b>P &lt; 0.001</b> )	

(Continued)

Table 1. Selected Trials Reporting Cardiovascular Risk Associated With Adjuvant Endocrine Therapies (Continued)

Trial	Study Population	Design	Outcomes, % or RR/HR (95% CI)	Other Cardiometabolic Outcomes
Coombes <i>et al.</i> , Intergroup Exemestane Study [90]	N = 4742; tamoxifen vs tamoxifen switch to exemestane; median follow-up 55 mo; prior CTx	RCT: to determine whether after 2 to 3 y of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the 5 y of treatment RCT: aims to determine the effects of aromatase inhibitor letrozole on cancer outcomes after the discontinuation of 5 y of tamoxifen therapy	<i>Cardiovascular disease</i> Exemestane 984 (43%) vs tamoxifen 913 (39%); <b>P = 0.016</b>	<i>Hypercholesterolemia</i> Letrozole 257 (11.9%) vs placebo 247 (11.5%); <b>P = 0.67</b>
Goss <i>et al.</i> , MA 17 [70]	N = 5187; letrozole vs placebo after initial tamoxifen; median follow-up 2.4 y (with/without prior CTx, RT)	RCT: aims to determine whether extending treatment with an aromatase inhibitor to 10 y may further reduce the risk of breast cancer recurrence; secondary endpoints included long-term safety	<i>Cardiovascular event</i> Letrozole 88 (4.1%) vs 77 (3.6%); <b>P = 0.40</b> <i>Cerebrovascular</i> RR, 1.14; 95% CI, 0.57–2.27 <i>Cardiovascular events</i> Letrozole 116 (12%) vs 98 (10%); <b>P = 0.21</b> <i>Cerebrovascular events</i> RR, 1.1; 95% CI, 0.63–2.07	<i>Hypercholesterolemia</i> Letrozole 203 (21%) vs Placebo 184 (19%); <b>P = 0.31</b> <i>Hypertension</i> Letrozole 158 (16%) vs 145 (15%); <b>P = 0.48</b>
Goss <i>et al.</i> , MA 17R [17]	N = 1918; letrozole vs placebo after AI; median follow-up of 6.3 y	RCT: aims to compare the long-term effects of exemestane monotherapy with sequential treatment (tamoxifen followed by exemestane)	<i>Cardiac-related deaths</i> Exemestane 43 (<1%) vs sequential 28 (<1%); <b>P = 0.11</b> <i>Cardiac failure</i> Exemestane 50 (1%) vs sequential 26 (<1%); <b>P = 0.009</b>	<i>Hypertension</i> Exemestane 303 (6%) vs sequential 219 (5%); <b>P = 0.0003</b> <i>Hypercholesterolemia</i> Exemestane 230 (5%) vs sequential 136 (3%); <b>P ≤ 0.0001</b>
Van de Velde <i>et al.</i> , TEAM [72]	N = 9779; sequential = 4875 tamoxifen-exemestane vs exemestane; median follow-up 5 y (with/without prior CTx, RT); patients with substantial cardiac disease were excluded			

Bold text signifies statistical significance.

Abbreviations: ATAC, Arimidex, Tamoxifen Alone or in Combination; ATENA, Adjuvant Post-Tamoxifen Exemestane Versus Nothing Applied; CTx, chemotherapy; N, number; RR, relative risk; RT, radiotherapy; TEAM, Tamoxifen Exemestane Adjuvant Multinational.

**Table 2. Meta-Analyses Reporting Cardiovascular Risk Associated With Adjuvant Endocrine Therapies**

Study	Inclusion Criteria	Study Population	Comparison	Results, RR or OR <sup>a</sup> [95% CI]	Comments
Braithwaite <i>et al.</i> , 2003 [93]	Breast cancer RCTs comparing TAM to placebo/no treatment	32 RCTs; 52,529 women; average age 55 y	TAM vs placebo/no treatment	Stroke 1.49 [1.16–1.90] AMI 0.62 [0.41–0.93] AMI incidence 0.90 [0.66–1.23] PE 1.88 [1.17–3.01] DVT 1.87 [1.33–2.64] CV events 1.31 [1.07–1.60] Thromboembolic events 0.53 [0.42–0.65] Cerebrovascular events 0.76 [0.58–1.003] CV events 1.26 <sup>a</sup> [1.10–1.43] Venous thrombosis 0.55 <sup>a</sup> [0.46–0.64] Cerebrovascular events 1.01 [0.81–1.26] Total CV events 1.20 <sup>a</sup> [1.02–1.42] Thromboembolic events 0.61 <sup>a</sup> [0.50–0.75] Total CV events 1.13 [0.96–1.33]	Stroke AMI AMI incidence PE DVT CV events Thromboembolic events Cerebrovascular events CV events Venous thrombosis Cerebrovascular events ORs refer to primary AI therapy; ORs for CV events were similar for sequenced therapy, but not significant for extended therapy RR refers to primary AI therapy; RRs for sequenced and extended therapy were also not significant Similar CV event results reported with sequential AI treatment; no difference in cerebrovascular events between treatments AD 0.5% (NNH = 189) AD –1.2% (NNH = –85) RR combine upfront and sequential treatment AD 0.8% (NNH = 132) AD –1.3% (NNH = –79)
Cuppone <i>et al.</i> , 2007 [94]	Phase III RCTs comparing AIs (either upfront or sequential after 2 to 3 y of TAM) with TAM	7 RCTs; 19,818 postmenopausal women	AI vs TAM		
Amir <i>et al.</i> , 2011 [95]	Phase III RCTs >5 y in duration comparing AIs with TAM as primary endocrine therapy	7 RCTs; 30,032 postmenopausal women	AI vs TAM		
Aydiner 2013 [96]	RCTs comparing AIs with TAM as primary, sequential, or extended therapy (after 5 y of initial adjuvant endocrine therapy)	11 RCTs; 34,070 postmenopausal women	AI vs TAM		
Ryden 2016 [97]	RCTs comparing AIs with TAM as primary, sequential, or extended therapy with at least 5-year follow-up	8 RCTs; 34,489 postmenopausal women	AI vs TAM		
Khosrow-Khavar <i>et al.</i> , 2016 [98]	Phase III RCTs comparing AIs with TAM, AIs to placebo/no treatment, and TAM to placebo/no treatment	19 RCTs; 62,345 women	AI vs TAM TAM vs placebo/no treatment AI vs TAM TAM vs placebo/no treatment	<i>Total CV events</i> Primary AI vs TAM 1.19 [1.07–1.34] TAM vs placebo/no treatment 0.67 [0.45–0.98] Total CV events 1.18 <sup>a</sup> [1.00–1.40]	
Goldvaser <i>et al.</i> , 2017 [99]	Phase III RCTs comparing extended AIs with placebo/no treatment	7 RCTs; 16,3499 postmenopausal women	AI vs placebo/no treatment		AD 0.8% (NNH = 1 22) No association between AIs and hypertension
Mathews <i>et al.</i> , 2018 [100]	Studies investigating risk of CV outcomes with use of either TAM or AI or comparing the two treatments	15 RCTs; 11 observational studies	AI vs TAM TAM vs placebo/no treatment AI vs TAM TAM vs placebo/no treatment	<i>Thromboembolic events</i> Primary AI vs TAM 0.61 [0.58–0.63] <i>Heart failure</i> Tamoxifen vs placebo/no treatment 0.84 [0.56–1.07]	No meta-analyses conducted for other outcomes

Adapted and updated from Matthews *et al.* [100].

Cerebrovascular events included stroke and transient ischemic attack.

Abbreviations: AD, absolute difference; AI, aromatase inhibitor; AMI, acute myocardial infarction; CV, cardiovascular; DVT, deep venous thrombosis; NNH, number needed to harm; PE, pulmonary embolism; RR, relative risk; TAM, tamoxifen.

<sup>a</sup>CV events included AMI, angina, and cardiac failure. Refers to OR being used rather than RR.

based on evidence from RCTs conducted in breast cancer survivors [102]. RCT evidence regarding efficacy of pharmacotherapy to reduce cardiometabolic risk specific to breast cancer survivors is currently not available. The ASCO guidelines recommend cardiovascular monitoring consistent with clinical standards for other high-risk populations, and pharmacological management should follow recommendations for the general population [102].

#### 4. Conclusions

Adjuvant endocrine therapy may modulate cardiometabolic risk by several potential mechanisms (Fig. 1). Despite potential adverse effects on body and hepatic fat accumulation and on serum triglycerides, tamoxifen can reduce LDL cholesterol and Lp(a), and it may have beneficial effects on the arterial wall, effects that could contribute to tamoxifen-associated reductions in cardiovascular events. Aromatase inhibitors are associated with higher cardiovascular risks compared with tamoxifen, but whether this reflects aromatase inhibitor-related toxicity or a protective effect of tamoxifen remains uncertain.

Existing evidence regarding endocrine therapy-associated cardiometabolic risks remains incomplete owing to the scarcity of high-quality studies examining cardiometabolic risk factors, the low number of cardiovascular events reported in clinical trials, the relatively short follow-up, inconsistent adjudication of adverse events, and the predominant enrollment of women with relatively low cardiovascular risk. Even when cardiovascular data were collected in the context of an RCT, outcomes are primarily observational, given that to date no RCT has been designed to specifically evaluate cardiovascular risk. Cardiovascular disease is a major cause of mortality in older breast cancer survivors, and even minor increases in cardiovascular risks could have a significant impact. Although premenopausal women may be particularly susceptible to adverse cardiometabolic effects of estradiol depletion, their baseline risk for cardiovascular events is low, the existing studies are too small, and the follow-up is too short to estimate long-term risks. Evidence from larger studies examining the metabolic and cardiovascular consequences of endocrine therapy, including effects on body composition, glucose metabolism, and markers of atherosclerosis, are required to better define the cardiometabolic risks and to guide the clinical care of women with breast cancer to optimize long-term health outcomes. Proactive management of modifiable cardiovascular risk factors and pharmacotherapy to reduce cardiometabolic risk based on general population evidence should be an integral part of breast cancer survivorship care.

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