

REVIEW

Toxicity of Adjuvant Endocrine Therapy in Postmenopausal Breast Cancer Patients: A Systematic Review and Meta-analysis

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- Background** Aromatase inhibitors are associated with consistent improvements in disease-free survival but not in overall survival. We conducted a literature-based meta-analysis of randomized trials to examine whether the relative toxicity of aromatase inhibitors compared with tamoxifen may explain this finding.
- Methods** We conducted a systematic review to identify randomized controlled trials that compared aromatase inhibitors and tamoxifen as primary adjuvant endocrine therapy in postmenopausal women by searching MEDLINE, EMBASE, and databases of the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium. Odds ratios (ORs), 95% confidence intervals (CIs), absolute risks, and the number needed to harm associated with one adverse event were computed for prespecified serious adverse events including cardiovascular disease, cerebrovascular disease, bone fractures, thromboembolic events, endometrial carcinoma and other second cancers not including new breast cancer. All statistical tests were two-sided.
- Results** Seven trials enrolling 30023 patients met the inclusion criteria. Longer duration of aromatase inhibitor use was associated with increased odds of developing cardiovascular disease (OR = 1.26, 95% CI = 1.10 to 1.43, $P < .001$; number needed to harm = 132) and bone fractures (OR = 1.47, 95% CI = 1.34 to 1.61, $P < .001$; number needed to harm = 46), but a decreased odds of venous thrombosis (OR = 0.55, 95% CI = 0.46 to 0.64, $P < .001$; number needed to harm = 79) and endometrial carcinoma (OR = 0.34, 95% CI = 0.22 to 0.53, $P < .001$; number needed to harm = 258). Five years of aromatase inhibitors was associated with a non-statistically significant increased odds of death without recurrence compared with 5 years of tamoxifen alone or tamoxifen for 2–3 years followed by an aromatase inhibitor for 2–3 years (OR = 1.11, 95% CI = 0.98 to 1.26, $P = .09$).
- Conclusions** The cumulative toxicity of aromatase inhibitors when used as up-front treatment may explain the lack of overall survival benefit despite improvements in disease-free survival. Switching from tamoxifen to aromatase inhibitors reduces this toxicity and is likely the best balance between efficacy and toxicity.

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The development of aromatase inhibitors has provided an alternative form of adjuvant endocrine therapy for postmenopausal women with breast cancer (1). Several large randomized trials have assessed the benefit of the third-generation aromatase inhibitors anastrozole, letrozole, and exemestane compared with 5 years of tamoxifen (2–5). These trials have shown that aromatase inhibitors are associated with reduced recurrence rates and improved disease-free survival but have not demonstrated a statistically significant improvement in overall survival. Despite their large size, the individual trials had limited statistical power to detect small (but potentially important) differences in overall survival in the absence of extended follow-up. A meta-analysis of the randomized trials by the Oxford Early Breast Cancer Trialists' Collaborative Group that had greater statistical power confirmed that use of aromatase inhibitors was associated with improved disease-free survival and also showed a statistically significant albeit modest improvement in

overall survival only for patients who took aromatase inhibitors for 2–3 years after treatment with tamoxifen for 2–3 years (6). No overall survival benefit was seen in those who received aromatase inhibitors as initial (ie, up-front) therapy.

The lack of an overall survival benefit with aromatase inhibitors despite improvements in disease-free survival is unexpected. We therefore hypothesized that the relative toxicity of aromatase inhibitors compared with tamoxifen (7,8) may explain these findings. Some have suggested that aromatase inhibitors should be used for 2–3 years after or before tamoxifen (ie, in a switching strategy) to maximize benefits and offset the toxic effects (8,9). Unfortunately, most individual trials that have assessed aromatase inhibitors vs tamoxifen had suboptimal statistical power and/or duration of follow-up to detect differences in toxicities between these strategies. Furthermore, meta-analyses conducted by the Oxford Overview have tended to assess efficacy, not toxicity. This

CONTEXT AND CAVEATS

Prior knowledge

Large randomized trials comparing an aromatase inhibitor with 5 years of tamoxifen as adjuvant endocrine therapy for postmenopausal breast cancer have shown that aromatase inhibitors are associated with consistent improvements in disease-free survival but not in overall survival. Differences in the toxicity of aromatase inhibitors and tamoxifen may explain these findings.

Study design

Systematic review and literature-based meta-analysis of seven randomized controlled trials that compared aromatase inhibitors with tamoxifen as primary adjuvant endocrine therapy for early-stage postmenopausal breast cancer. Absolute risks of six adverse events were computed separately for patients who received aromatase inhibitors and tamoxifen.

Contribution

Compared with tamoxifen, the use of aromatase inhibitors in postmenopausal women with early-stage breast cancer increased the odds of developing cardiovascular disease and bone fractures and decreased the odds of developing venous thrombosis and endometrial carcinoma. There were no statistically significant differences in the odds of cerebrovascular disease, other second cancers, or death without breast cancer recurrence between treatment strategies. There were fewer deaths without recurrence in those treated with switching from tamoxifen to aromatase inhibitors compared with those treated with either tamoxifen alone or up-front aromatase inhibitors.

Implication

The cumulative toxicity of aromatase inhibitors when used as up-front treatment may explain the lack of overall survival benefit despite improvements in disease-free survival.

Limitations

The meta-analysis was based on study-level adverse events that were reported by the investigator, not on individual patient data. No data on adverse events after breast cancer recurrence were available nor was information on potentially confounding baseline host factors or the use of concurrent medications. All grades of toxicity were included in the analysis.

From the Editors

study was designed to evaluate and compare serious and/or life-threatening adverse events reported in randomized trials comparing different adjuvant endocrine therapy strategies in postmenopausal women with early-stage breast cancer by using a meta-analysis.

Methods

Search Strategy

Relevant trials were identified using a computerized search of the following databases: MEDLINE (host: OVID), 1996–April week 2, 2010; EMBASE (host: OVID), 1980–2010 week 16; American Society of Clinical Oncology Annual Meetings, 2000–2009; and San Antonio Breast Cancer Symposium Annual Meetings, 2000–2009. The search was restricted to English language articles. The terms “adjuvant,” “aromatase inhibitor,” and “tamoxifen” and

“breast cancer” and similar terms were cross-searched by using the following search algorithm: ((aromatase inhibitor OR anastrozole OR letrozole OR exemestane) AND (tamoxifen) AND (adjuvant) AND (Breast neoplasm MeSH OR ((breast OR mammary) AND (carcinoma OR malignan* OR neoplasm OR tumor)))) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trial [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial”) [tw] OR singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw] AND (mask* [tw] OR blind* [tw])) OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw] NOT (animals [mh] NOT humans [mh])). Included studies were randomized phase III clinical trials that compared aromatase inhibitors with tamoxifen as initial adjuvant therapy in postmenopausal women with early-stage breast cancer. Only trials that had treatment durations of 5 years in total were included. Trials that had treatment durations longer than 5 years (extended adjuvant) were excluded, as were trials conducted in pre- or perimenopausal women. Published articles and abstracts presented at annual meetings were included in a meta-analysis. All data were from intent-to-treat analyses. The primary objective of this study was to assess toxicity; therefore, we included data from all randomly assigned patients regardless of their hormone receptor status.

Data Extraction

Data on prespecified serious or potentially life-threatening adverse events of any grade as defined by the individual trials were extracted. In addition, we assessed information on deaths without breast cancer recurrence. Data on adverse events and death without recurrence were extracted from the primary publications and from any associated online appendices by two authors (EA and BS) using a standardized data extraction form. Discrepancies were resolved by consensus. Six adverse events were prespecified in this analysis as follows: cardiovascular disease (including myocardial infarction, angina, and cardiac failure), cerebrovascular disease (including cerebrovascular accident and transient ischemic attack), venous thrombosis (defined as any venous thromboembolic episode), bone fracture (any), endometrial carcinoma alone, and other secondary cancers (defined as any invasive cancer excluding endometrial carcinoma and contralateral breast cancer). Hypercholesterolemia was assessed in a preplanned exploratory analysis because it is a well-documented adverse effect of aromatase inhibitors and is associated with both cardiovascular and cerebrovascular disease. All grades of hypercholesterolemia were included in the meta-analysis. Adverse events such as hot flashes or arthralgia were excluded.

Data Synthesis

The meta-analysis was carried out in three treatment cohorts: 1) 5 years of an aromatase inhibitor vs 5 years of tamoxifen (ie, up-front treatment with aromatase inhibitor vs tamoxifen), 2) tamoxifen for 2–3 followed by an aromatase inhibitor for 2–3 years vs 5 years of tamoxifen (ie, switching vs tamoxifen), and 3) tamoxifen for 2–3 years followed by an aromatase inhibitor for 2–3 years vs 5 years of an aromatase inhibitor (ie, switching vs aromatase inhibitor). In general, the aromatase inhibitor group included trial arms that

received aromatase inhibitors alone or aromatase inhibitors for longer durations compared with the other intervention arm, and the tamoxifen group included trial arms that received tamoxifen alone or aromatase inhibitors for shorter durations compared with the other treatment arm.

Statistical Analysis

The relative frequency of an individual adverse event per person was expressed as an odds ratio (OR) and a 95% confidence interval (CI). Initial analyses were conducted separately for each treatment cohort described above. We also analyzed the pooled data for all three cohorts. All data were analyzed using RevMan 5 analysis software (The Cochrane Collaboration, Copenhagen, Denmark). Pooled estimates of odd ratios were computed using generic inverse variance (10) and a fixed-effects model (11). Studies were weighted by their individual SE, thereby accounting for differences in both sample size and intrastudy heterogeneity. Data were not adjusted for different durations of follow-up between studies. Differences between the three cohorts (subgroups) were assessed using methods described by Deeks et al. (12). Absolute risks of each adverse event were calculated as the number of events per person over the follow-up period of the individual trial. The difference in absolute risk between the aromatase inhibitor group and the tamoxifen group was also presented as the number needed to harm, which quantifies the number of patients who would need to be treated with a particular intervention to cause an adverse event in one patient who would not otherwise have experienced the adverse event. Positive values indicate higher absolute risks in the aromatase inhibitor group, whereas negative values indicate higher absolute risks in the tamoxifen group. We conducted a post hoc sensitivity analysis for the switching vs tamoxifen cohort to adjust for better survival in the aromatase inhibitor group vs tamoxifen group. We adjusted for an absolute difference in overall mortality of 2.2% (6). No such analyses were carried out for the other two cohorts because meta-analyses have not shown survival differences in the included trials (6). All statistical tests were two-sided, and statistical significance was defined as *P* less than .05.

Results

We identified 377 potentially relevant articles in the primary literature search, of which seven were reports of randomized phase III trials enrolling 30 023 patients who met the inclusion criteria. Articles were excluded if they did not compare aromatase inhibitors to tamoxifen (*n* = 172), were review articles (*n* = 169), were cost-effectiveness analyses (*n* = 18), or were early analyses of included trials (*n* = 9). Two trials contributed data to the analysis of up-front aromatase inhibitors vs up-front tamoxifen: Arimidex, Tamoxifen, Alone or in Combination (ATAC; *n* = 6241 patients) (5) and Breast International Group 01-98 (BIG 1-98; *n* = 4922 patients) (3). Four publications comprising five trials contributed data to the analysis of switching from tamoxifen to aromatase inhibitors vs tamoxifen: A combined analysis of the Austrian Breast and Colorectal Cancer Study Group trial 8 and the German Adjuvant Breast Cancer Group/Arimidex–Nolvadex (ABCSG8/ARNO 95; *n* = 3226 patients) (4), the Intergroup Exemestane Study (IES; *n* = 4724 patients) (13), the Italian Tamoxifen

Anastrozole trial (ITA; *n* = 448 patients) (2), and the National Surgical Adjuvant Study Breast Cancer 03 trial (N-SAS BC03; *n* = 696 patients) (14). The sequencing arms of BIG 1-98 were not included because there were different follow-up times for the different arms of the trial. One trial—the Tamoxifen Exemestane Adjuvant Multinational trial (TEAM, *n* = 9766 patients) (15)—provided data for the analysis of switching from tamoxifen to aromatase inhibitors vs aromatase inhibitors. The study designs and characteristics of the included studies are shown in Figure 1 and Table 1, respectively.

The numbers of adverse events, follow-up time, and the number of evaluable patients for each adverse event are shown in Supplementary Table 1 (available online). Table 2 presents the difference in absolute risk for each adverse event between the aromatase inhibitor group and the tamoxifen group and the number needed to harm.

Cardiovascular Disease

Longer durations of aromatase inhibitor use were associated with increased odds of cardiovascular disease compared with tamoxifen use. Combined analysis of the two trials that evaluated up-front aromatase inhibitors vs up-front tamoxifen (3,5) showed a statistically significant association between aromatase inhibitor use and cardiovascular disease (OR = 1.30, 95% CI = 1.06 to 1.61, *P* = .01) (Figure 2, A). Combined analysis of trials that evaluated switching vs up-front tamoxifen (2,4,13,14) showed a non-statistically significant association between aromatase inhibitor use and cardiovascular disease (OR = 1.15, 95% CI = 0.93 to 1.41, *P* = .20) (Figure 2, A). After adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group, the odds ratio was 1.12 (95% CI = 0.92 to 1.35, *P* = .26). Finally, the one trial (15) that evaluated switching vs up-front aromatase inhibitors showed a statistically significant association between aromatase inhibitor use and cardiovascular disease (OR = 1.37, 95% CI = 1.05 to 1.79, *P* = .02) (Figure 2, A). A pooled analysis of the data for all three cohorts showed that longer duration of aromatase inhibitor use was associated with a statistically significant increase in the odds of developing cardiovascular disease compared with tamoxifen alone or shorter duration of aromatase inhibitor use (OR = 1.26, 95% CI = 1.10 to 1.43, *P* < .001) (Figure 2, A). Adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group did not change the pooled odds ratio for all cohorts (data not shown). In absolute terms, 4.2% of patients in the aromatase inhibitor group and 3.4% of patients in the tamoxifen group suffered a cardiovascular event (difference in absolute risk = 0.8%, number needed to harm = 132) (Table 2 and Supplementary Table 1, available online). Increased odds of cardiovascular events in the aromatase inhibitor group vs tamoxifen group were seen in all treatment cohorts, although the magnitude was numerically, but not statistically significantly lower for the treatment cohort where aromatase inhibitors were administered after 2–3 years of treatment with tamoxifen (ORs of 1.15 vs 1.30 and 1.37, test of subgroup differences, *P* = .53).

Cerebrovascular Disease

Neither the individual studies nor the pooled data showed any statistically significant difference in the odds of cerebrovascular

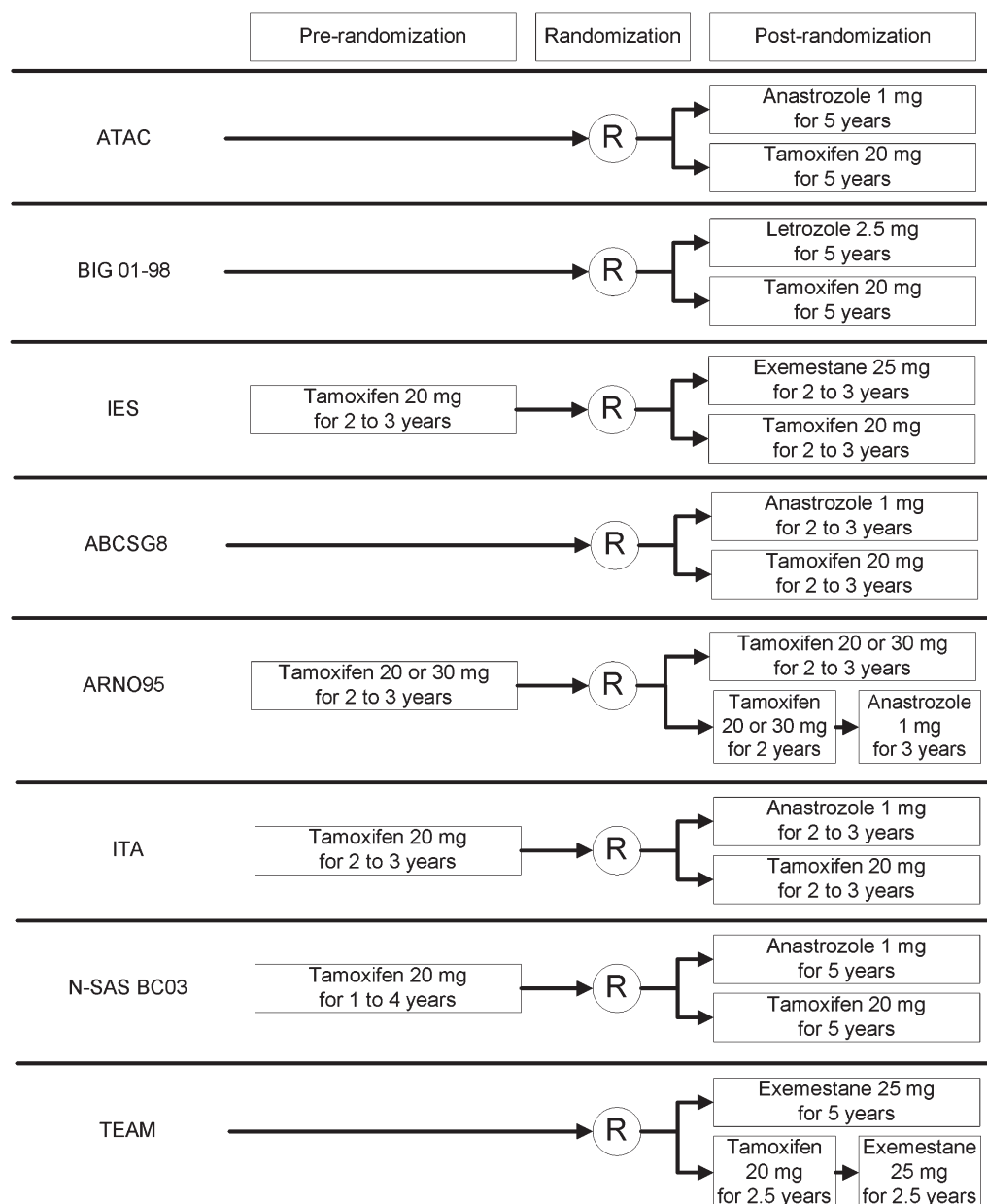


Figure 1. Designs of included studies. ATAC = Anastrozole, Tamoxifen alone or in combination (5); BIG 1-98 = Breast International Group 01-98 (3); ABCSG8 = Austrian Breast Cancer Study Group VIII (4); ARNO = German Adjuvant Breast Cancer Group/Arimidex–Nolvadex (4); ITA = Italian Tamoxifen Anastrozole Trial (2); N-SAS BC04 = National Surgical Adjuvant Breast Cancer 03 trial (14); TEAM = Tamoxifen Exemestane Adjuvant Multinational Trial (15); R = randomization.

disease between the two treatment groups (OR = 1.01, 95% CI = 0.81 to 1.26, $P = .93$) (Figure 2, B). Adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group did not change the pooled odds ratio for all cohorts (data not shown). Cerebrovascular disease was an uncommon adverse event: it occurred in 1.4% of patients in the aromatase inhibitor group and in 1.5% of patients in the tamoxifen group (difference in absolute risk = -0.1% , number needed to harm = -974) (Table 2 and Supplementary Table 1, available online).

Venous Thrombosis

Longer durations of aromatase inhibitor use were associated with decreased odds of venous thrombosis compared with tamoxifen. A pooled analysis of the data for all three cohorts revealed a 45% reduction in the relative odds of venous thrombosis for the aromatase inhibitor group compared with the tamoxifen group

(OR = 0.55, 95% CI = 0.46 to 0.64, $P < .001$) (Figure 2, C). Adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group did not change the pooled odds ratio for all cohorts (data not shown). The incidence of thrombosis was 1.6% and 2.8% in the aromatase inhibitor and tamoxifen groups, respectively (difference in absolute risk = -1.3% , number needed to harm = -79) (Table 2 and Supplementary Table 1, available online). The test of subgroup differences for up-front aromatase inhibitors vs switching from tamoxifen to aromatase inhibitors was not statistically significant ($P = .67$), suggesting that the relative harm of 2–3 years of tamoxifen was not reduced by switching to aromatase inhibitors.

Bone Fractures

Longer durations of aromatase inhibitor use were associated with increased odds of bone fractures compared with tamoxifen use.

Table 1. Characteristics of included studies*

Trial (reference)	Trial funding	Median follow-up, mo	Treatment arms	Sample size	Age of patients, y	Patients with tumor size >2 cm, %	Node-positive patients, %	Hormone receptor-positive patients, %	Other adjuvant therapy (%)
ATAC (5)	Industry	100	A; T	3125; 3116	Mean: 64.1	36	39	84	Radiotherapy: 63; chemotherapy: 20
BIG01-98 (3)	Industry	51	L; T	2463; 2459	Median: 61	38	43	100	Radiotherapy: 72; chemotherapy: 25
IES (13)	Industry	55.7	T→E; T	2352; 2372	Median: 63.9	52	48	98	Chemotherapy: 33
ABCSG8/ARNO 95 (4)	Industry/nonindustry†	28	T→A; T	1618; 1608	Median: 62	30	26	100	0‡
ITA (2)	Industry	64	T→A; T	225; 223	Median: 63	51	100	100	Radiotherapy: 49; chemotherapy: 67
N-SAS BC03 (14)	Nonindustry	42	T→A; T	347; 349	Mean: 59.9	22	40	93	Chemotherapy: 53
TEAM (15)	Industry	61	T→E; E	4868; 4898	Mean: 64.5	41	47	100	Radiotherapy: 70; chemotherapy: 36

* A = anastrozole; ABCSG = Austrian Breast Cancer Study Group VIII; ARNO = German Adjuvant Breast Cancer Group/Arimidex-Nolvadex; ATAC = Anastrozole, Tamoxifen Alone or in Combination; BIG = Breast International Group01-98/International Breast Cancer Study Group 18-98; E = exemestane; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Anastrozole Trial; L = letrozole; N-SAS BC03 = National Surgical Adjuvant Breast and Bowel Project Breast Cancer 03 trial; T = tamoxifen; TEAM = Tamoxifen Exemestane Adjuvant Multinational Trial.

† ABCSG8 was funded by industry and ARNO 95 was nonindustry funded.

‡ No previous radiotherapy or chemotherapy was allowed.

Table 2. Absolute differences and number needed to harm associated with one adverse event of each type*

Trial (reference)	Cardiovascular disease		Cerebrovascular disease		Venous thrombosis		Bone fractures		Endometrial Carcinoma		Other second cancers		Death without recurrence	
	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH
ATAC (5)	0.8	129	-0.8	-115	-1.8	-59	4.6	22	-0.6	-163	0.8	134	1.2	87
BIG01-98 (3)	0.9	107	0	∞	-1.8	-56	2.8	36	-0.5	-204	-0.3	-349	0	∞
IES (13)	1.3	79	0	∞	-1.2	-84	2.1	48	-0.2	-479	-1.1	-93	-1.0	-102
ABCSG8/ARNO (4)	<0.1†	1643†	NS	NS	-0.6	-179	1.1	91	-0.3	-268	NS	NS	-0.5	-225
ITA (2)	1.3	72	NS	NS	-2.3	-40	NS	NS	-2.2	-46	0.5	216	-0.4	-230
N-SAS BC03 (14)	-0.3	-354	NS	NS	0.3	347	-1.2	-85	-0.3	-349	0	∞	0.3	345
TEAM (15)	0.7	139	0.4	311	-1.1	-91	1.6	63	-0.2	-485	NS	NS	0.3	287
Pooled	0.8	132	-0.1	-974	-1.3	-79	2.2	46	-0.4	-258	-0.1	-1080	0.2	610

* Positive values indicate excess events with aromatase inhibitors and negative values indicate excess events with tamoxifen. NNH = number needed to harm; NS = not specified.

† Myocardial infarctions only.

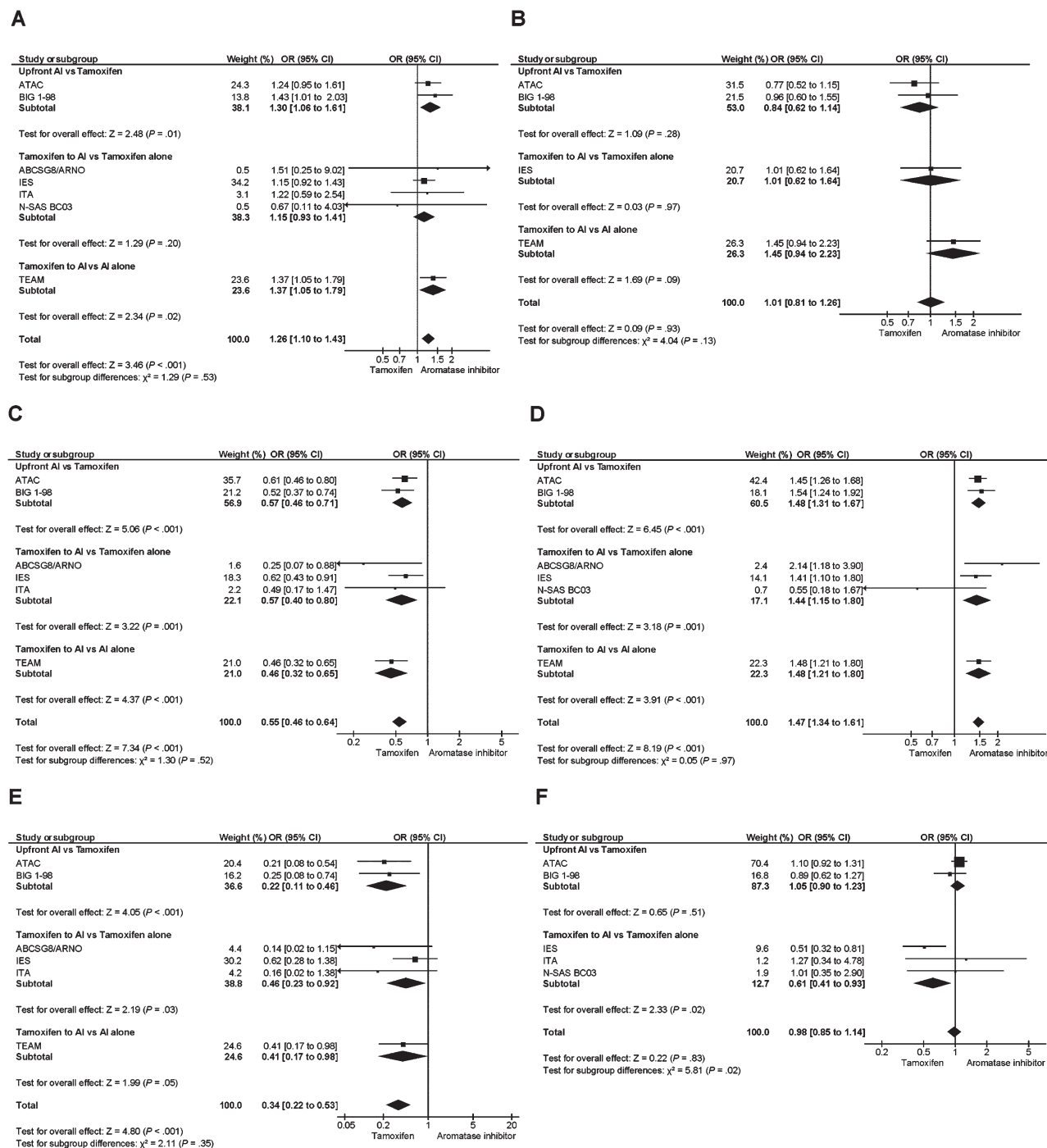


Figure 2. Forest plots of odds ratios for adverse events. **A)** Cardiovascular events. **B)** Cerebrovascular events. **C)** Venous thrombosis. **D)** Bone fractures. **E)** Endometrial carcinoma. **F)** Other second cancers. Odds ratios for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval. The diamonds represent the estimated pooled effect based for each cohort individually (labeled subtotal) and for all cohorts together (labeled total). Test of subgroup differences relates to the test of heterogeneity between the three treatment cohorts as defined by Deeks et al.

A pooled analysis of the data for all three cohorts showed that a longer duration of aromatase inhibitor use was associated with a 47% increase in the odds of bone fractures compared with tamoxifen (OR = 1.47, 95% CI = 1.34 to 1.61, $P < .001$) (Figure 2, D).

After adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group, the odds ratio decreased slightly to 1.45 (95% CI = 1.33 to 1.60) but remained statistically significant ($P < .001$). In absolute terms, fracture incidence was

7.5% and 5.2% in the aromatase inhibitor and tamoxifen groups, respectively (difference in absolute risk = 2.2%, number needed to harm = 46) (Table 2 and Supplementary Table 1, available online). The test of subgroup differences for up-front aromatase inhibitors vs switching from tamoxifen to aromatase inhibitors was not statistically significant ($P = .97$), suggesting that there was no difference in the relative harm of aromatase inhibitors between up-front use of aromatase inhibitors and use of aromatase inhibitors after switching from tamoxifen.

Endometrial Carcinoma

Analysis of the pooled data showed that longer duration of aromatase inhibitor use was associated with a 66% reduction in the relative odds of endometrial carcinoma compared with tamoxifen (OR = 0.34, 95% CI = 0.22 to 0.53, $P < .001$) (Figure 2, E). Adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group did not change the pooled odds ratio for any of the cohorts. Endometrial carcinoma was a very rare event: it occurred in 0.1% of the aromatase inhibitor group and in 0.5% of the tamoxifen group (difference in absolute risk = -0.4%, number needed to harm = -258) (Table 2 and Supplementary Table 1, available online). The test of subgroup differences for up-front aromatase inhibitors vs switching from tamoxifen to aromatase inhibitors was not statistically significant ($P = .35$).

Other Second Cancers

Analysis of the pooled data showed no statistically significant difference in the odds of developing other second cancers between the aromatase inhibitor group and the tamoxifen group (OR = 0.98, 95% CI = 0.85 to 1.14, $P = .83$), and adjustment for differential survival between the groups did not change the pooled odds ratio for any of the cohorts. The absolute rates of other cancers were 4.7% for aromatase inhibitor-treated patients and 4.8% for those receiving tamoxifen alone (Table 2). The test of subgroup difference for up-front aromatase inhibitors vs switching from tamoxifen to aromatase inhibitors was statistically significant ($P = .02$), suggesting that switching from tamoxifen to aromatase inhibitors may decrease the odds of second cancers.

Hypercholesterolemia

Hypercholesterolemia was assessed formally by only four studies (2,3,13,15) and was not graded consistently among those studies. Analysis of the pooled data showed that longer duration of aromatase inhibitor use was associated with a statistically significant increase in the odds of hypercholesterolemia compared with tamoxifen (OR = 2.36, 95% CI = 2.15 to 2.60, $P < .001$). This effect was most apparent when up-front aromatase inhibitor use was compared with tamoxifen alone (OR = 3.14, 95% CI = 2.78 to 3.55, $P < .001$) (3), less marked when up-front aromatase inhibitor use was compared with switching from tamoxifen to aromatase inhibitors (OR = 1.71, 95% CI = 1.38 to 2.13, $P < .001$) (15), and least evident when switching from tamoxifen to aromatase inhibitors was compared with tamoxifen alone (OR = 1.27, 95% CI = 1.01 to 1.59, $P = .04$) (2,13). The test of subgroup differences for up-front aromatase inhibitor use vs switching from tamoxifen to aromatase inhibitors was statistically significant ($P < .001$), suggesting that shorter

durations of aromatase inhibitors might reduce the odds of hypercholesterolemia.

Death Without Recurrence

In a pooled analysis, use of up-front aromatase inhibitors was associated with a non-statistically significant higher odds of death without recurrence compared with use of tamoxifen alone or switching from tamoxifen to aromatase inhibitors (OR = 1.11, 95% CI = 0.98 to 1.26, $P = .09$). Conversely, switching from tamoxifen to aromatase inhibitors was associated with decreased odds of death without recurrence compared with up-front tamoxifen for 5 years (OR = 0.75, 95% CI = 0.58 to 0.98, $P = .04$) (Figure 3). The test of subgroup differences for up-front aromatase inhibitor use vs switching from tamoxifen to aromatase inhibitors was statistically significant ($P = .03$), which suggests that switching to aromatase inhibitors after 2–3 years of tamoxifen may reduce the odds of death without recurrent breast cancer compared with the use of either tamoxifen or aromatase inhibitors alone. Analysis of all data combined revealed no association between longer duration of aromatase inhibitor use and the odds of death without recurrence (OR = 1.04, 95% CI = 0.93 to 1.16, $P = .51$) (Figure 3). Compared with those treated with 5 years of either tamoxifen or aromatase inhibitors, those treated with a switching strategy had statistically significant reduction in the odds of death without breast cancer recurrence (OR = 0.87, 95% CI = 0.77 to 0.99, $P = .03$). Adjustment for differential survival between the aromatase inhibitor group and the tamoxifen group did not change the pooled odds ratio. In absolute terms, 4.2% of patients who received longer durations of aromatase inhibitor died without breast cancer recurrence compared with 4.1% of patients treated predominantly with tamoxifen (difference in absolute risk = 0.2%, number needed to harm = 610) (Table 2 and Supplementary Table 1, available online).

Discussion

This systematic review and meta-analysis shows that, compared with tamoxifen, the use of aromatase inhibitors in postmenopausal women with early-stage breast cancer increases the odds of developing cardiovascular disease and bone fractures and decreases the odds of venous thrombosis and endometrial carcinoma. There were no differences in the odds of cerebrovascular disease, other second cancers, or death without breast cancer recurrence between treatment strategies.

Aromatase inhibitors can reduce recurrence of breast cancer, and pooled trial data show that they improve disease-free survival (6). However, in most trials, the improvement in breast cancer-specific outcomes has not resulted in subsequent improvement in overall survival. The lack of association between disease-free survival and overall survival requires careful evaluation of the toxicities of different endocrine therapy options. Tamoxifen and aromatase inhibitors have distinct toxicity profiles; however, individual trials have not shown a statistically significant difference in overall toxicity between patients treated with these therapies. Although randomized trials may have enough statistical power to detect differences in common toxicities between treatment groups, they typically lack statistical power to detect differences in rare but potentially serious adverse events (16). A previous attempt (17) to pool trial data to

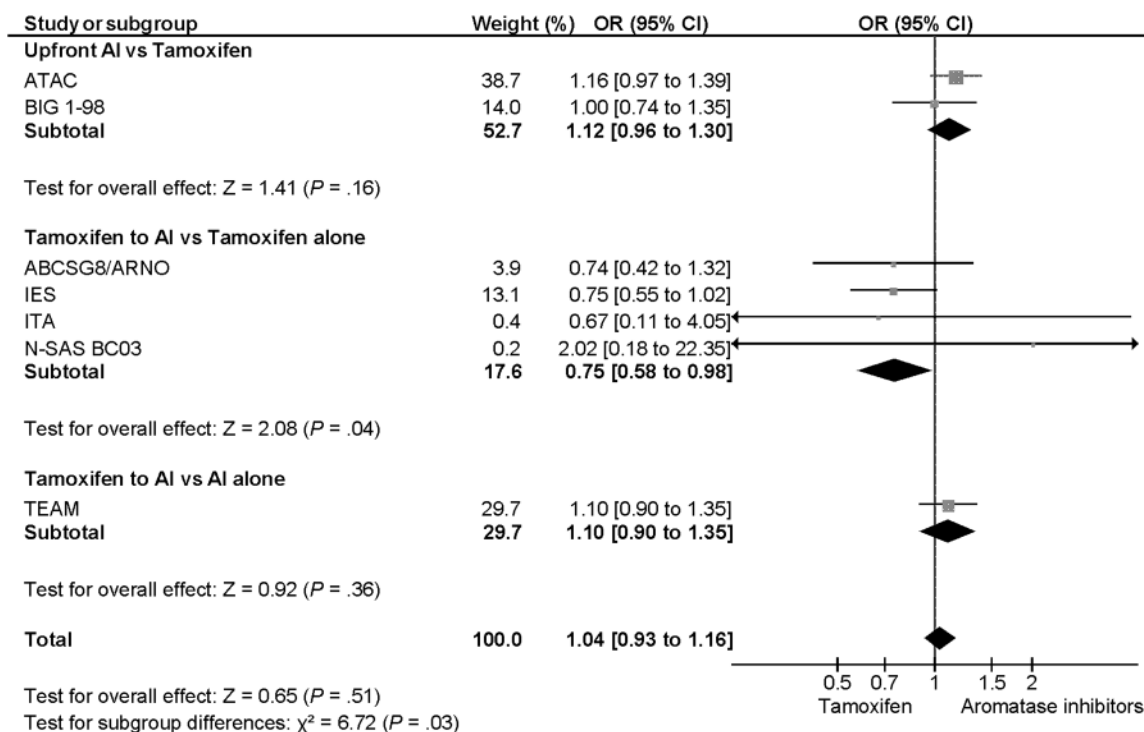


Figure 3. Forest plot of odds ratios for death without breast cancer recurrence. Odds ratios for each trial are represented by the **squares**, the **size of the square** represents the weight of the trial in the meta-analysis, and the **horizontal line** crossing the square represents the 95% confidence interval. The **diamonds** represent the estimated pooled effect based for each cohort individually (labeled subtotal) and for all cohorts together (labeled total). Test of subgroup differences relates to the test of heterogeneity between the three treatment cohorts as defined

by Deeks et al. (12). All P values are two-sided. ATAC = Anastrozole, Tamoxifen alone or in combination (5); BIG 1-98 = Breast International Group 01-98 (3); ABCSG8 = Austrian Breast Cancer Study Group VIII (4); ARNO = German Adjuvant Breast Cancer Group/Arimidex–Nolvadex (4); ITA = Italian Tamoxifen Anastrozole Trial (2); N-SAS BC04 = National Surgical Adjuvant Breast Cancer 03 trial (14); TEAM = Tamoxifen Exemestane Adjuvant Multinational Trial (15); AI = aromatase inhibitor; CI = confidence interval; OR = odds ratio.

assess the differential toxicity of aromatase inhibitors and tamoxifen was based on a limited number of studies with relatively short follow-up. These limitations have been addressed in this study.

Our data show that aromatase inhibitors and tamoxifen have different toxicity profiles (Figure 2 and Table 2). Many of the included adverse events were rare; therefore, if clinical decisions are made based on these data, they should be based on absolute risk (or number needed to harm) rather than relative risk, which can be confusing especially for endpoints of varying frequencies. Furthermore, because individual patients may have experienced more than one adverse event, absolute risks for the different adverse events should not be summed as this is not equivalent to the number of patients with one or more adverse event. For cardiovascular events, pooled data showed that longer durations of aromatase inhibitor use are associated with a statistically significantly higher odds of developing such events compared with tamoxifen alone or a shorter period of aromatase inhibitor use after an initial period of tamoxifen therapy ($OR = 1.26$, $P < .001$). The effect size demonstrated in individual trials was consistent among all included studies, and this finding was independent of whether patients received up-front aromatase inhibitors or whether aromatase inhibitors were given after 2–3 years of tamoxifen. Although the effect sizes corresponded to only a small increase in the absolute risk of cardiovascular disease in the overall population of women who received adjuvant hormonal therapy ($<1\%$, number needed to

harm = 132), it is possible that specific subpopulations of patients are at higher risk. For example, the US Food and Drug Administration–revised label for anastrozole (18) states that in women with preexisting heart disease in the ATAC trial (7.5% of the total trial population) (5), the incidence of cardiovascular events was 17% with anastrozole and 10% with tamoxifen and urges physicians to consider the risks and benefits of anastrozole therapy in such patients. To our knowledge, this important information has not been published in the scientific literature. Our data suggest that the increased risk of cardiovascular events in women with preexisting heart disease is not confined to anastrozole, but may be a class effect for aromatase inhibitors.

There are several possible explanations for the finding of an increased number of cardiovascular events with aromatase inhibitors compared with tamoxifen. First, data from male mice show that aromatase inhibitors may have a direct effect on endothelium that may predispose the mice to the development of atherosclerosis (19). Second, hypercholesterolemia is a well-known risk factor for the development of cardiovascular disease. Our pooled analysis showed that aromatase inhibitor use was associated with a statistically significantly increased odds of hypercholesterolemia compared with tamoxifen use ($OR = 2.36$, $P < .001$). This effect was most apparent with longer durations of aromatase inhibitor use, suggesting that it is the cumulative exposure to aromatase inhibitors that is important. However, we cannot exclude the

possible effect of interstudy differences in duration of follow-up, given that vascular events are likely to accumulate for an extended period after a rise in cholesterol. Increases in hypercholesterolemia and serious cardiovascular events with aromatase inhibitors compared with tamoxifen were also demonstrated in a combined analysis of the up-front and sequencing arms of the BIG 1-98 study (20). Finally, randomized and observational comparisons of tamoxifen vs placebo or no treatment have shown that tamoxifen is associated with a reduction in cardiovascular events (21–24). Therefore, any comparison with tamoxifen may be confounded. Unfortunately, data on the independent effect of aromatase inhibitors on cardiovascular events is unreliable as reporting of such events in women participating in trials of aromatase inhibitors or placebo is variable. For example, data from the National Cancer Institute of Canada MA.17 trial of letrozole vs placebo after an initial 5 years of tamoxifen showed little difference in cardiovascular events between the study arms (25). Moreover, cardiovascular adverse events were not reported at all in two other randomized trials also conducted in the extended adjuvant setting (26,27). The prolonged protective effect of tamoxifen in patients receiving aromatase inhibitors after 5 years of initial tamoxifen therapy cannot be excluded (28).

Oncologists should therefore consider carefully the risks and benefits of aromatase inhibitors in patients with preexisting heart disease or related risk factors. This is especially important in the extended adjuvant setting, where predictive factors for benefit remain scarce, and the potential harm from ongoing aromatase inhibitor therapy may outweigh any small reductions in the recurrence of breast cancer.

We found no statistically significant difference between aromatase inhibitors and tamoxifen in the odds of cerebrovascular disease. However, we cannot exclude the possibility that differences in the risk of cerebrovascular disease may become more apparent with longer follow-up of trial participants. The overlapping risk factors for the development of cardiovascular and cerebrovascular disease, including hypercholesterolemia, which is increased by aromatase inhibitors, might ultimately lead to an increase risk of cerebrovascular disease as well as of cardiovascular disease with aromatase inhibitors. Conversely, susceptibility to thrombosis is a recognized risk factor for cerebrovascular disease (29,30). The procoagulant effects of tamoxifen may offset any increase in risk of cerebrovascular events resulting from hypercholesterolemia with aromatase inhibitors.

Our data suggest that up-front use of aromatase inhibitors is associated with increased odds of death without breast cancer recurrence compared with the use of tamoxifen alone or a switch to aromatase inhibitors after 2–3 years of tamoxifen. This finding may explain why up-front use of aromatase inhibitors improves disease-free survival but not overall survival. Furthermore, our data suggest that switching to aromatase inhibitors after 2–3 years of tamoxifen is associated with a reduction in the number of deaths without breast cancer recurrence compared with the use of either tamoxifen or aromatase inhibitors alone. One explanation for this finding is a reduction in risk of cumulative toxicities brought about by switching from one agent to another. These hypothesis-generating data appear to support the use of switching strategies as a way to reduce cumulative toxicities and may be particularly

relevant among older women. For example, a secondary analysis of the ATAC trial showed that older age and increasing number of comorbidities were associated with a substantially increased risk of death without recurrence in women with lymph node-negative breast cancer (31).

From a clinical viewpoint, our data on cardiovascular adverse events suggest that the use of aromatase inhibitors for postmenopausal women with ischemic heart disease should be considered on an individual basis. In patients who are at a lower risk of breast cancer recurrence and for whom the absolute benefits of aromatase inhibitors are reduced, use of these agents should be avoided. In those who are at higher risk of breast cancer recurrence, the absolute benefit of aromatase inhibitors is greater and therefore these agents should be used in sequence with tamoxifen. Conversely, patients with a personal or family history of thromboembolic disease should probably avoid tamoxifen (32). These data may help physicians to better counsel patients with risk factors for toxicities from both treatments about their treatment options.

Our pooled data are consistent with data reported previously in the individual studies, which showed that compared with tamoxifen, aromatase inhibitors are associated with increased odds of bone fracture ($OR = 1.47, P < .001$) and reduced odds of venous thrombosis ($OR = 0.52, P < .001$) and endometrial carcinoma ($OR = 0.34, P < .001$). Switching from one agent to another did not appear to modify the relative risks of developing these adverse events. However, in most of the switching studies included in this meta-analysis, randomization to an aromatase inhibitor occurred after an initial 2–3 years of tamoxifen, and toxicities that occurred before randomization were not recorded. Furthermore, because our analysis was based on intention to treat, any patients who crossed over from the tamoxifen arms to aromatase inhibitors may have reduced protection from toxicity associated with switching strategies.

This study has several limitations. First, this is a meta-analysis of the literature rather than of individual patient data and is based on reports of trials with different durations of follow-up; we were not able to report actuarial rates of toxicity. Second, collection of data for the purpose of this meta-analysis was dependent on the rigorous collection and reporting of adverse events by the investigators, and the quality of such reporting is known to be variable (33). Furthermore, adverse events are usually collected in intervention trials only until an event of interest occurs, such as breast cancer recurrence (the primary endpoint in these trials). However, adverse events after breast cancer recurrence remain of interest because most women with hormone receptor-positive breast cancer survive for several years, even with metastatic disease. Such data were not available for the trials included in this meta-analysis. Third, information on the potentially confounding baseline host factors (eg, obesity, hypertension, diabetes, and family history of events of interest) or the use of concurrent medications was not available and therefore their effects on the odds of the adverse events could not be quantified. Finally, our analysis included all grades of toxicity. Higher-grade toxicities have more profound early implications; however, the influence of grading of toxicity on long-term health outcomes is unclear. In keeping with our objective to explore serious and/or potentially life-threatening toxicities, we felt that inclusion of all grades of toxicity was important.

Despite these limitations, this study demonstrates a statistically significant and consistent increase in cardiovascular risk associated with the use of aromatase inhibitors. Although the increase in absolute risk is small in the general population, it is likely to be higher in patients with preexisting cardiovascular disease or risk factors associated with it. Given our finding, that aromatase inhibitor use is associated with a greater than twofold increase in the odds of hypercholesterolemia, the risk of cardiovascular events may increase further with longer follow-up of patients on these trials. Furthermore, our data suggest an increase in the risk of death without breast cancer recurrence associated with the use of either tamoxifen or aromatase inhibitors alone compared with the use of aromatase inhibitors after 2–3 years of tamoxifen. Switching from tamoxifen to aromatase inhibitors appears to be the optimal strategy for offsetting serious adverse events of individual drugs.

In conclusion, we urge clinicians to consider carefully the toxicity profiles of different endocrine therapy options for breast cancer and choose those that best suit their patients' baseline health characteristics. Investigators participating in practice-changing clinical trials or in trial overviews should rigorously report not only efficacy data but also data on less common and potentially serious toxicities.

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