REVIEW ARTICLE

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Putting the Cardiovascular Safety of Aromatase Inhibitors in Patients with Early Breast Cancer into Perspective

A Systematic Review of the Literature

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Contents

Abstract

In the adjuvant setting, the third-generation aromatase inhibitors (AIs) anastrozole, letrozole and exemestane are recommended at some point during treatment, either in the upfront, switch after tamoxifen or extended treatment setting after tamoxifen in postmenopausal patients with hormone receptor-positive early breast cancer. AIs have demonstrated superior disease-free survival and overall benefit-to-risk profiles compared with tamoxifen. Potential adverse events, including cardiovascular (CV) side effects, should be considered in the long-term management of patients undergoing treatment with AIs. AIs reduce estrogen levels by inhibiting the aromatase enzyme, thus

1 Although now at a new address, author was employed by Pfizer throughout the conduct of this study and its analysis.

reducing the levels of circulating estrogen. This further reduction in estrogen levels may potentially increase the risk of developing CV disease.

This systematic review evaluated published clinical data for changes in plasma lipoproteins and ischaemic CV events during adjuvant therapy with AIs in patients with hormone receptor-positive early breast cancer. The electronic databases MEDLINE, EMBASE, Derwent Drug File and BIOSIS were searched to identify English-language articles published from January 1998 to 15 April 2011 that reported data on AIs and plasma lipoproteins and/or ischaemic CV events. Overall, available data did not show any definitive patterns or suggest an unfavourable effect of AIs on plasma lipoproteins from baseline to follow-up assessment in patients with hormone receptor-positive early breast cancer. Changes that occurred in plasma lipoproteins were observed soon after initiation of AI therapy and generally remained stable throughout the studies. Available data do not support a substantial risk of ischaemic CV events associated with adjuvant AI therapy; however, studies with longer follow-up are required to better characterize the CV profile of AIs.

1. Introduction

Historically, tamoxifen, an oral selective estrogen receptor modulator, has been the standard adjuvant endocrine therapy for patients with hormone-receptor-positive (HR-positive) breast cancer.[1-3] However, the third-generation aromatase inhibitors (AIs) anastrozole, letrozole and exemestane are options included in treatment guidelines (American Society of Clinical Oncology guidelines,[4] National Cancer Care Network Guidelines[5] and St Gallen guidelines[6]) and are recommended at some point during adjuvant treatment in postmenopausal patients with HR-positive breast cancer, based on their overall superior benefit-to-risk profile and disease-free survival compared with tamoxifen.[7-9] Several large, randomized controlled trials (RCTs) have demonstrated the superiority of AIs plus tamoxifen over tamoxifen alone or placebo in various adjuvant treatment settings: upfront (initial adjuvant treatment with an AI),[10-13] switch (2–3 years of treatment with tamoxifen followed by an AI)[9,14-16] or extended therapy (initial 5 years of treatment with tamoxifen followed by an AI).[17-20]

In postmenopausal women with HR-positive breast cancer, the potential cardiovascular (CV) risk associated with AI therapy is an important consideration. It is well established that postmenopausal women are at increased risk of CV disease compared with women of premenopausal status, both in overall and age-matched comparative analyses.[21,22] After menopause, significant changes in levels of plasma lipoproteins, including a reduction in plasma high-density lipoprotein cholesterol (HDL-C) and an elevation of plasma low-density lipoprotein cholesterol (LDL-C), due in part to the reduction in estrogen production, are thought to increase the risk of CV disease.[23] In postmenopausal women, estrogen is mainly produced in the adrenal gland from the conversion of androgens by the enzyme aromatase and, to a lesser extent, by conversion via the same mechanism occurring in adipocytes.[24] Inhibiting the aromatase enzyme during treatment with AIs further reduces the levels of circulating estrogen in postmenopausal women who already have low levels of estrogen.[25] This additional decrease in estrogen could have an unfavourable effect on plasma lipoproteins by compounding the effects naturally observed after menopause and may contribute to an increase in the risk for CV events in patients undergoing treatment with AIs.[25]

Several recently published safety subgroup analyses and review articles based on data from RCTs have focused on CV safety in patients with breast cancer receiving hormonal adjuvant therapy with AIs.[25-29] Although informative, the majority of review articles examined studies conducted

in both early and metastatic breast cancer patients, and the data were generally interpreted together. Given the differences in chemotherapy regimens and duration of survival between patients with early breast cancer and those with metastatic breast cancer, interpretation of data on plasma lipoproteins and CV events in mixed patient groups may not be appropriate. Additionally, the majority of review articles included both ischaemic and non-ischaemic CV events in the CV endpoint analyses, thus adding further complexity to data interpretation because of differences in aetiology between ischaemic and non-ischaemic CV events.

This report systematically evaluates the effect of AIs on plasma lipoproteins and ischaemic CV events in postmenopausal women with HR-positive early breast cancer in all adjuvant treatment settings: upfront, switch and extended. This systematic review of the most recent data available in the literature will help healthcare professionals consider the CV safety of AIs and make informed decisions when treating patients with HR-positive early breast cancer.

2. Methodology

2.1 Literature Search Strategy

Electronic databases (MEDLINE, EMBASE, Derwent Drug File and BIOSIS) were searched to identify peer-reviewed articles published from January 1998 to 15 April 2011 that reported data on AIs and plasma lipoproteins and/or CV events. An experienced information analyst conducted the literature search, using keywords that three of the authors identified. A broad search string using Boolean terminology to combine aromatase inhibitor(s) or generic or brand names of AIs was used with expanded terms of 'cardiovascular safety' OR 'cardiovascular adverse' OR 'CV event' OR 'lipid parameter(s)'. *Ad hoc* literature searches were conducted by the authors to identify articles for development of the Introduction and Discussion sections. Initial screening of articles by title and abstract was conducted to identify relevant articles, and bibliographies cited by each identified paper were manually scrutinized to identify additional papers. The article selection process was carried out by one author, and a second and third author were consulted when a question arose as to whether an article met the inclusion criteria. Manuscripts were reviewed in full to confirm relevance to the search topic and application of appropriate study endpoints. Only ischaemic CV events (e.g. myocardial infarction [MI], angina) were included because changes in plasma lipoproteins may contribute to ischaemic CV disease. However, some articles reporting other CV endpoints (e.g. cardiac event, CV disease and death from cardiac events) were included because they encompassed ischaemic as well as non-ischaemic CV events. Non-English articles, reports that were not peer reviewed and conference abstracts were excluded. Studies in metastatic/advanced breast cancer populations or healthy volunteers were also excluded. Specific search terms used to identify relevant articles and results of the literature search are shown in figure 1.

2.2 Data Extraction and Presentation

For all potentially relevant papers, the full text was reviewed. When needed, authors of individual manuscripts included in this review were contacted to obtain additional data or clarification. Data extracted from identified papers are presented herein using a tabular format to facilitate reading and interpretation; separate tables summarize plasma lipoprotein and CV event data. For each article presented in the tables, publication references, study design, study population, sample size, follow-up time, plasma lipoprotein levels and incidence of CV events are reported.

All publications that reported data on total cholesterol (TC), LDL-C, HDL-C and triglycerides (TRG) were included, although ratios of plasma lipoproteins (e.g. HDL/LDL) were not specifically evaluated. When multiple publications from a single study were identified, data for all plasma lipoprotein follow-up assessments were included. The changes in plasma lipoprotein estimates from baseline to follow-up were presented as 'percentage change'. To ensure consistency, mean lipoprotein values were used to compute

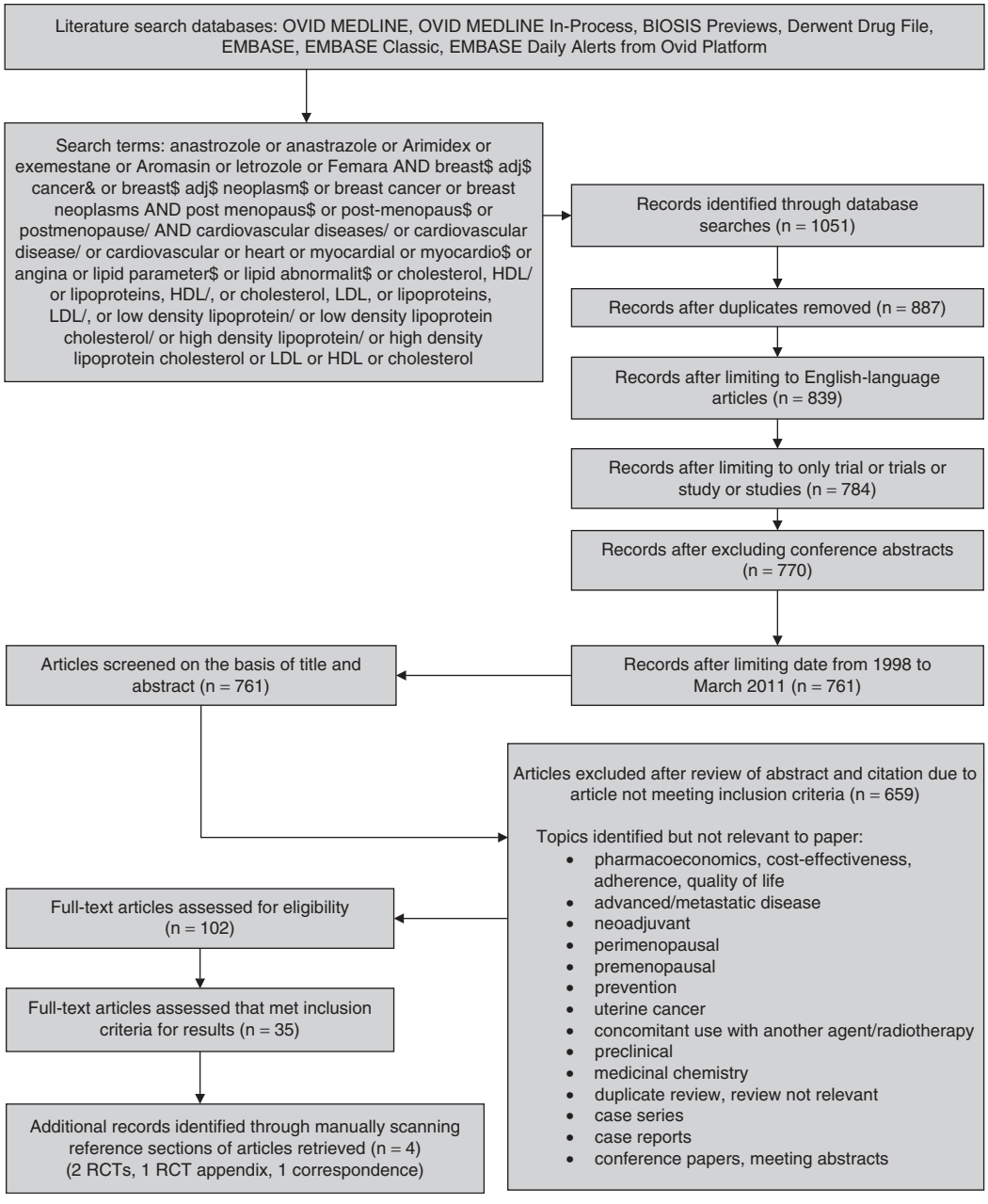

Fig. 1. Flow diagram for the literature search strategy. **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **RCT** = randomized controlled trial.

percentage changes from baseline to follow-up in studies where percentage-change estimates were not reported. p-Values for within-group changes from baseline to follow-up assessment for each treatment group (hereafter referred to as 'p_{within}') and differences between treatment groups (here-

after referred to as '$p_{between}$') were included, when available. Studies reporting data on the incidence of hypercholesterolaemia and associations between hypercholesterolaemia and CV events were summarized separately (although only incidence of hypercholesterolaemia reported in studies with the longest follow-up was discussed).

Data on ischaemic CV events from all publications are presented, although the publications with the longest follow-up are discussed in greater detail. Articles providing data on CV events, that encompass ischaemic events such as mortality from CV causes, are also presented. Non-ischaemic CV events, such as congestive heart disease or cardiac fibrillation, are not included in the tables. At least two authors and an independent analyst checked all data points for transcription errors.

3. Results

3.1 Overview of Studies

In total, 35 papers from 15 RCTs were identified that reported the effect of AIs on plasma lipoproteins and/or CV events. Table I provides a description of each study included in this systematic review.[7,9-18,30-44,46-54] The literature search identified one observational study examining the effect of an AI on CV events;[55] no observational studies evaluating AI effects on plasma lipoproteins were found.

Three trials investigated an AI as initial adjuvant therapy ('upfront' setting): Arimidex, Tamoxifen, Alone or in Combination (ATAC),[10,12,30,32] Tamoxifen Exemestane Adjuvant Multicenter (TEAM) Greek and Japanese substudies[39-41] and Breast cancer International study Group (BIG) 1-98.[11,13,35-37] In the ATAC study, patients (n = 9366) were randomized to receive anastrozole alone, tamoxifen alone, or anastrozole/tamoxifen combinations for 5 years.[10] The TEAM study (n = 9779) had nine participating countries, and substudies were planned. Although the study was initially designed to be an upfront study of 5 years of treatment with exemestane versus tamoxifen (as reported in the Greek and Japanese TEAM substudies),[39,41] it was amended to investigate sequential therapy with 2.5–3 years of tamoxifen followed by exemestane.[47] The BIG 1-98 study (n = 8010) evaluated four different treatment arms, two of which were upfront treatment arms: tamoxifen alone for 5 years and letrozole alone for 5 years.[13]

Seven trials investigated switch therapy with tamoxifen followed by an AI (switch regimen): Intergroup Exemestane Study (IES),[7,15] Austrian Breast and Colorectal cancer Study Group 8 (ABCSG 8),[16] ARimidex-NOlvadex 95 (ARNO 95),[9,16] Italian Tamoxifen Anastrozole (ITA),[14,44] National Surgical Adjuvant Study of Breast Cancer (N-SAS BC 03),[50] TEAM[47] and BIG 1-98.[11,13,35-37] In the IES study, patients (n = 4724) who remained disease-free after receiving adjuvant tamoxifen for 2–3 years received exemestane or tamoxifen for a total of 5 years of treatment.[7] Patients in ABCSG 8 (n = 3714)[45] had completed 2 years of adjuvant tamoxifen and either continued tamoxifen or switched to anastrozole for 3 years.[16] For ARNO 95 and ITA, patients (n = 979 and n = 448, respectively) had completed 2–3 years of adjuvant tamoxifen and either continued with tamoxifen or switched to anastrozole for 2 or 3 additional years (for a total of 5 years of treatment).[9,44] The BIG 1-98 study evaluated two switch treatment arms: tamoxifen for 3 years followed by letrozole for 2 years, or letrozole for 3 years followed by tamoxifen for 2 years.[13]

Two trials were in the extended adjuvant setting: the National Cancer Institute of Canada Clinical Trials Group trial MA.17[17,18,53,54] and Adjuvant post-Tamoxifen Exemestane vs Nothing Applied (ATENA).[51] Patients in the MA.17 study (n = 5187) received either letrozole or placebo after 5 years of tamoxifen,[17] and patients in the ATENA study (n = 411) received either exemestane or no treatment for 5 years after 5 years of tamoxifen.[51]

Thirteen studies compared AIs to either tamoxifen monotherapy or switch therapy with tamoxifen followed by an AI, and two studies used placebo (observation alone or no active therapy) as the comparator. Of the 15 RCTs, seven studied anastrozole, six studied exemestane and two studied letrozole.

Table I. Summary of aromatase inhibitor studies included in the review

Study	No. of patients	Study location	Patient age [y][a]	Study description
Upfront setting				
Arimidex, Tamoxifen, Alone or in Combination (ATAC)[10,12,30-33]	9366 (A: 3125; T: 3116; A+T: 3125)	Multinational	A: 64.1 (9.0)[b] T: 64.1 (9.0)[b] A+T: 64.3 (9.1)[b]	Postmenopausal women with histologically proven invasive breast cancer who had completed surgery and chemotherapy. Patients were randomized to receive anastrozole alone, tamoxifen alone or anastrozole/tamoxifen combination for 5 years
Sawada et al.[34]	44 (A: 22; T: 22)	Japan	A: 58.7 (5.4)[b] T: 59.3 (5.9)[b]	Postmenopausal Japanese women with HR-positive breast cancer who had undergone total mastectomy or a breast-conserving resection with axillary evacuation. Patients received no prior radiation, chemotherapy or drugs known to affect the lipid profile. Patients were randomized to receive either tamoxifen or anastrozole for 12 weeks
Breast cancer International study Group (BIG 1-98)[11,13,35-38]	8010 (upfront approach, L: 2463; T: 2459)[36]	Multinational	L: 61 (38–89) T: 61 (39–90)	Postmenopausal women with ER-positive, PgR-positive or ER/PgR-positive, operable, invasive breast cancer aged ≥30 years. Patients (n = 8010) were randomized into four treatment arms: 1) tamoxifen alone for 5 years (upfront, n = 2459); 2) letrozole alone for 5 years (upfront, n = 2463), and patients in groups 3 and 4 received switch therapy and are described further in this table, below
Tamoxifen Exemestane Adjuvant Multicenter (TEAM) Greek substudy[39,40]	142 (E: 77; T: 65)	Greece	E: 65 (43–87) T: 63 (40–82)	The study was originally designed as an *upfront* treatment strategy study comparing 5 years of adjuvant exemestane vs 5 years of tamoxifen. However, the study protocol was amended to evaluate sequential therapy with 2.5–3 years of tamoxifen followed by exemestane for a total of 5 years compared with exemestane for 5 years. These results report data from the upfront setting
Tamoxifen Exemestane Adjuvant Multicenter (TEAM) Japanese substudy[41]	154 (E: 52; T: 52; A: 50)	Japan	E: 64 (51–83) T: 61 (50–88) A: 63 (49–81)	Postmenopausal women with HR-positive early breast cancer. This substudy was designed as an *upfront* treatment strategy study comparing adjuvant exemestane vs tamoxifen or anastrozole for 1 year
Lonning et al.,[42] Geisler et al.[43]	147 (E: 73; P: 74)	Norway	E: 60 (46–73) P: 59 (51–74)	Postmenopausal women with low-risk, surgically treated early breast cancer or ductal carcinoma *in situ*. This study used an *upfront* approach. Patients were randomized to either exemestane or placebo for 2 years
Switch setting				
Italian Tamoxifen Anastrozole (ITA)[14,44]	448 (T: 225; T/A: 223)	Italy	T: 63 (43–77) T/A: 63 (38–76)	Postmenopausal women or women aged >50 years who had undergone hysterectomy and who had histologically confirmed HR-positive breast cancer and no evidence of recurrent or metastatic disease. Patients were randomized following completion of 2–3 years of adjuvant tamoxifen to either continue tamoxifen or switch to anastrozole to complete 5 years of treatment
Austrian Breast and Colorectal cancer Study Group 8 (ABCSG 8)[16,45]	3714 (T: 1849; T/A: 1865)[45][c]	Austria	T: 64.0 (41.4–80.0) T/A: 63.6 (44.1–80.5)	Postmenopausal women aged ≤80 years with invasive/minimally invasive HR-positive early breast cancer. Patients received no prior chemotherapy, radiotherapy or hormonal therapy. Patients were randomized following completion of 2 years of adjuvant tamoxifen to either continue tamoxifen or switch to anastrozole for 3 years

Continued next page

Table I. Contd

Study	No. of patients	Study location	Patient age [y][a]	Study description
ARimidex-NOlvadex 95 (ARNO 95)[9,16]	979 (T: 490; T/A: 489)	Germany	T/A: 60.9 (46–74) T: 60.5 (47–73)	Postmenopausal women aged ≤75 years with histologically confirmed HR-positive early breast cancer. Patients were randomized following completion of 2 years of adjuvant tamoxifen to either continue tamoxifen or switch to anastrozole for an additional 3 years
Wojtacki et al.[46]	44	Poland	61.6[d] 64.5[e] 47–75[f]	Postmenopausal women with breast cancer who received tamoxifen (median 15 months) and experienced disease progression. All patients received anastrozole for up to 32 weeks
Breast cancer International study Group (BIG 1-98)[11,13,35-38]	8010 (T/L: 1548; L/T: 1540)[36]	Multinational	T/L and L/T: 61 (38–89)	Postmenopausal women with ER-positive, PgR-positive or ER/PgR-positive, operable, invasive breast cancer aged ≥30 years. Patients (n = 8010) were randomized into four treatment arms: Patients in groups 1 and 2 received upfront therapy and are described above in this table; 3) tamoxifen for 3 years followed by letrozole for 2 years (switch, n = 1548); 4) letrozole for 3 years followed by tamoxifen for 2 years (switch, n = 1540)
Intergroup Exemestane Study (IES)[7,15]	4742 (T: 2380; T/E: 2362)	Multinational	T: 64.2 (8.2)[b] T/E: 64.3 (8.1)[b]	Postmenopausal women with early breast cancer. Patients who remained disease-free after receiving adjuvant tamoxifen therapy for 2–3 years were randomized to receive exemestane or tamoxifen to complete a total of 5 years of treatment
Tamoxifen Exemestane Adjuvant Multicenter (TEAM)[47]	9779 (E: 4904; T/E: 4875)	Multinational	E and T/E: 64 (35–96)	Postmenopausal women with HR-positive early breast cancer. The study was originally designed as an upfront treatment strategy study comparing 5 years of adjuvant exemestane vs 5 years of tamoxifen. However, the study protocol was amended to evaluate sequential therapy with 2.5–3 years of tamoxifen followed by exemestane for a total of 5 years compared with exemestane for 5 years. There were nine participating countries in this study and substudies were planned
Francini et al.[48]	55 (T: 27; T/E: 28)	Italy	T: 61.15 (2.74)[g] T/E: 61.89 (4.45)[g]	Postmenopausal women with HR-positive resected breast cancer aged <75 years who had a BMI of 25–35 kg/m^2 and received at least 2 years of adjuvant tamoxifen. Patients were randomized to receive exemestane or tamoxifen for 1 year
Montagnani et al.[49]	68 (T: 35; T/E: 33)	Italy	T: 62.2 (9.0)[b] T/E: 61.6 (7.2)[b]	Postmenopausal women with completely resected, unilateral, HR-positive breast cancer who had received 2–3 years of tamoxifen adjuvant treatment, were <75 years of age and had a BMI of 25–35. Patients were randomized to continue tamoxifen or switch to exemestane for a total of 5 years of adjuvant treatment
National Surgical Adjuvant Study of Breast Cancer (N-SAS BC 03)[50]	706 (T: 352; T/A: 354)	Japan	T: 60.2 (7.4)[b] T/A: 59.5 (7.4)[b]	Postmenopausal women with HR-positive resected breast cancer who were <75 years of age and had received postoperative tamoxifen for 1–4 years were included. Patients were randomized to continue tamoxifen or *switch* to anastrozole for a total of 5 years of adjuvant treatment

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Table I. Contd

Study	No. of patients	Study location	Patient age [y][a]	Study description
Extended setting				
Adjuvant post-Tamoxifen Exemestane vs Nothing Applied (ATENA)[51,52]	411 (E: 211; NT: 200)	Greece	E: 62.6 (40–81) NT: 61.8 (39–81)	Postmenopausal women with operable breast cancer who had received 5–7 years of adjuvant tamoxifen. Patients received either exemestane or no treatment for 5 years after tamoxifen. Study was discontinued after publication of the MA.17 results
National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17[17,18,53,54]	5187 (L: 2593; P: 2594)	Multinational	L: 62[d] P: 62[d]	Postmenopausal women with HR-positive or receptor-unknown early-stage breast cancer. After 5 years of receiving tamoxifen, patients either received letrozole or placebo

a Values presented as median (range) unless otherwise specified.
b Mean (SD).
c Patient numbers only were taken from Dubsky et al.;[45] no additional data from this presentation were used in this review.
d Mean.
e Median.
f Range.
g Not reported.
A=anastrozole; **BMI**=body mass index; **E**=exemestane; **ER**=estrogen receptor; **HR**=hormone receptor; **L**=letrozole; **NT**=no treatment; **P**=placebo; **PgR**=progesterone receptor; **T**=tamoxifen.

3.2 Effects of Aromatase Inhibitors (AIs) on Plasma Lipoproteins

The search identified 13 papers based on nine RCTs that reported data on plasma lipoproteins in both the AI and comparator arms (figure 2; table II).[13,34,37,39,41-43,46,48,49,51,52,54] Studies varied considerably in size, and data were not always available regarding the number of patients evaluable at the end of the treatment period. The majority of studies reported changes in plasma lipoproteins, including TC, LDL-C, HDL-C and TRG, as mean percentage change from baseline to a specific follow-up time within each treatment group.

Overall, the data showed that levels of plasma lipoproteins changed from baseline to follow-up assessments in all of the reported studies, irrespective of AI treatment assignment or setting. However, there was no consistent pattern in plasma lipoprotein variations. In many studies, increases or decreases from baseline in plasma lipoproteins were noted at the first assessment and often remained stable throughout the study. In the majority of studies in which statistical comparisons were made either between baseline and follow-up values within the AI group or between the AI and the comparator groups, statistical significance (defined as $p < 0.05$ unless otherwise indicated) was not achieved.[34,42,46,48,49,54]

3.2.1 Within-Group/Arm Effects of AIs on Plasma Lipoproteins from Baseline to Follow-Up

In the study of anastrozole in Japanese women in the upfront setting (n = 44), TC was increased by 0.9% and HDL-C increased by 10.2% from baseline to 12 weeks; LDL-C and TRG decreased by 3.1% and 20.1%, respectively, during the same time period.[34] The upfront letrozole and exemestane studies (BIG 1-98,[13] Greek TEAM substudy[39] and the study reported by Lonning et al.[42] and Geisler et al.[43]) reported unchanged or decreased TC from baseline, with assessments starting at 6 months. However, only the exemestane studies (Greek TEAM substudy[39] and the study reported by Lonning et al.[42] and Geisler et al.[43]) reported data on HDL-C, LDL-C and TRG. In the Greek TEAM substudy, although variable decreases in percentage change

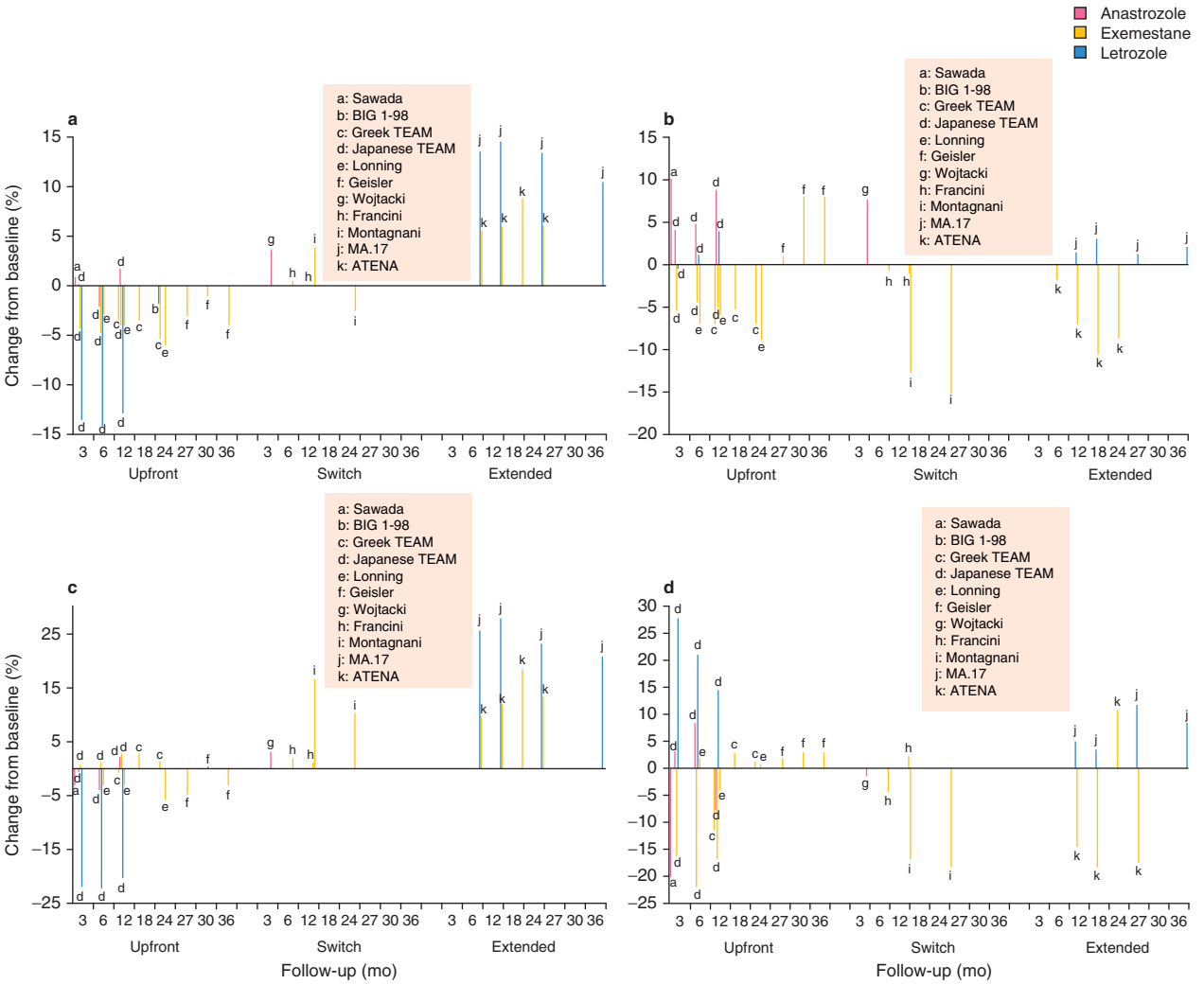

Fig. 2. Mean percentage changes from baseline in plasma lipoproteins assessed in clinical trials at specific follow-up times after treatment of patients with early breast cancer with the aromatase inhibitors anastrozole, exemestane and letrozole: (**a**) total cholesterol; (**b**) high-density lipoprotein cholesterol; (**c**) low-density lipoprotein cholesterol; (**d**) triglycerides. Data from Thürlimann et al.,[13] Francini et al.,[48] Geisler et al.,[43] Goss et al.,[53] Lonning et al.,[42] Markopoulos et al.,[39,51,52] Montagnani et al.,[49] Mouridsen et al.,[37] Sawada et al.,[34] Wasan et al.,[54] Wojtacki et al.[46] and Hozumi et al.[41] Results reported for the Japanese Tamoxifen Exemestane Adjuvant Multicenter (TEAM) study include unpublished data (Hozumi Y, personal communication).

Table II. Plasma lipoprotein changes from baseline in patients receiving aromatase inhibitors vs tamoxifen or placebo in randomized phase III studies

Study, follow-up[a]	No. of patients[b]	Treatment group	Plasma lipoproteins	Aromatase inhibitor (% change)	p-Value within group	Tamoxifen/ placebo (% change)	p-Value within group	p-Value between groups
Upfront treatment								
Sawada et al.[34]								
12 wk	A: 22 T: 22	A vs T	TC	+0.9[c]	0.498	−13.4	0.001	<0.001
			HDL	+10.2	0.358	+3.3[c]	<0.001	0.029
			LDL	−3.1[c]	<0.001	−23.5	0.367	<0.001
			TRG	−20.1	0.003	+21.7	0.005	<0.001
			RLP	−22.2	<0.001	+22.6	0.011	<0.001
Breast cancer International study Group (BIG 1-98)[13,37]								
6 mo	L: 4003 T: 4007	L vs T	TC	0.0	NS	−12.0	NR	NR
12 mo			TC	0.0	NS	−13.5	NR	NR
24 mo			TC	−1.8	NR	−14.1	NR	NR
Tamoxifen Exemestane Adjuvant Multicenter (TEAM)[39]								
12 mo[d]	E: NR T: NR	E vs T	TC	−3.5[c]	NR	−13.4[c]	NR	NR
			HDL	−7.1[c]	NR	0.0[c]	NR	NR
			LDL	−0.7[c]	NR	−15.9[c]	NR	NR
			TRG	−11.5[c]	NR	−6.0[c]	NR	NR
18 mo[d]	E: 51 T: 47		TC	−3.5[c]	NR	−9.0[c]	NR	NR
			HDL	−5.4[c]	NR	−5.2[c]	NR	NR
			LDL	+2.8[c]	NR	−17.9[c]	NR	NR
			TRG	−8.6[c]	NR	−3.7[c]	NR	NR
24 mo[d]	E: 39 T: 38		TC	−5.3[c]	NR	−14.2[c]	NR	NR
			HDL	−7.1[c]	NR	−1.7[c]	NR	NR
			LDL	+1.4[c]	NR	−20.0[c]	NR	NR
			TRG	−20.9[c]	NR	+9.7[c]	NR	NR
Japanese TEAM[41][e]								
3 mo	E: 50 T: 49	E vs T	TC	−4.4	NR	−13.5	NR	0.004
			HDL	−5.4	NR	−0.5	NR	NR
			LDL	0.8	NR	−22.0	NR	<0.001
			TRG	−16.2	NR	27.9	NR	<0.05

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Table II. Contd

Study, follow-up[a]	No. of patients[b]	Treatment group	Plasma lipoproteins	Aromatase inhibitor (% change)	p-Value within group	Tamoxifen/ placebo (% change)	p-Value within group	p-Value between groups
6 mo	E: 48 T: 50	E vs T	TC	−4.8	NR	−14.3	NR	0.001
			HDL	−4.4	NR	1.2	NR	NR
			LDL	1.0	NR	−22.3	NR	<0.001
			TRG	−22.1	NR	21.1	NR	<0.05
12 mo	E: 47 T: 49	E vs T	TC	−4.0	NR	−12.9	NR	0.003
			HDL	−5.1	NR	4.0	NR	NR
			LDL	2.9	NR	−20.4	NR	<0.001
			TRG	−16.8	NR	14.5	NR	<0.05
Lonning et al.[42]								
6 mo	E: 73 P: 74	E vs P	TC	−3.0	NR	0	NR	NS
			HDL	−7.0	NR	+1.0	NR	<0.001
			LDL	−3.0	NR	−2.0	NR	NS
			TRG	+2.0	NR	+7.0	NR	NS
			Lp(a)	−5.0	NR	+8.0	NR	0.004
12 mo			TC	−4.0	NR	−4.0	NR	NS
			HDL	−6.0	NR	+1.0	NR	<0.001
			LDL	−3.0	NR	−5.0	NR	NS
			TRG	−4.0	NR	+1.0	NR	NS
			Lp(a)	−5.0	NR	+7.0	NR	0.004
24 mo			TC	−6.0	NR	−5.0	NR	NS
			HDL	−9.0	NR	+2.0	NR	<0.001
			LDL	−6.0	NR	−6.0	NR	NS
			TRG	+1.0	NR	−3.0	NR	NS
			Lp(a)	+7.0	NR	+2.0	NR	0.004
Geisler et al.[43][f]								
27 mo	E: 73 P: 74	E vs P	TC	−3.0	NR	−4.0	NR	NR
			HDL	+1.0	NR	+5.0	NR	NR
			LDL	−5.0	NR	−6.0	NR	NR
			TRG	+2.0	NR	−3.0	NR	NR

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Table II. Contd

Study, follow-up[a]	No. of patients[b]	Treatment group	Plasma lipoproteins	Aromatase inhibitor (% change)	p-Value within group	Tamoxifen/ placebo (% change)	p-Value within group	p-Value between groups
30 mo			TC	−1.0	NR	−3.0	NR	NR
			HDL	+8.0	NR	+4.0	NR	NR
			LDL	−2.0	NR	−4.0	NR	NR
			TRG	+3.0	NR	−3.0	NR	NR
36 mo			TC	−1.0	NR	−5.0	NR	NR
			HDL	+8.0	NR	+7.0	NR	NR
			LDL	−3.0	NR	−7.0	NR	NR
			TRG	+3.0	NR	−4.0	NR	NR
Switch treatment								
Wojtacki et al.[46]								
13 wk	44	T→A[g]	TC	+3.7	0.50			
			HDL	+7.7	0.69			
			LDL	+2.9	0.51			
			TRG	−1.2	0.95			
Francini et al.[48]								
6 mo	E: 28 T: 27	T→E vs T	TC	+0.5[c]	NS	+4.0[c]	NS	NS
			HDL	−0.7[c]	NS	−8.0[c]	NS	NS
			LDL	+1.8[c]	<0.01	+14.4[c]	NS	NS
			TRG	−4.5[c]	<0.01	−13.6[c]	NS	NS
12 mo			TC	+0.1[c]	NS	+3.9[c]	NS	NS
			HDL	−1.1[c]	<0.05	−11.8[c]	NS	NS
			LDL	+0.9[c]	<0.01	+16.7[c]	NS	<0.05
			TRG	+2.2[c]	<0.01	−18.6[c]	NS	NS
Montagnani et al.[49]								
12 mo	E: 33 T: 35	T→E vs T	TC	+3.8[c]	NR	−0.4	NS	NS
			HDL	−12.7	<0.05	−2.1	NS	<0.05
			LDL	+16.5	<0.01	−1.1	NS	<0.05
			TRG	−16.9	<0.05	+2.5	NS	<0.05
24 mo			TC	−2.5[c]	NR	−0.5	NS	NR
			HDL	−15.2	<0.01	+2.4	NS	<0.05
			LDL	+10.1	<0.05	−0.5	NS	<0.05
			TRG	−18.1	<0.05	+4.1	NS	<0.05

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Table II. Contd

Study, follow-up[a]	No. of patients[b]	Treatment group	Plasma lipoproteins	Aromatase inhibitor (% change)	p-Value within group	Tamoxifen/ placebo (% change)	p-Value within group	p-Value between groups
Extended treatment								
MA.17[54]								
6 mo	L: 183 P: 164	L vs P	TC	+13.58	NR	+12.49	NR	0.32
			HDL	+1.46	NR	+4.31	NR	0.049
			LDL	+25.40	NR	+23.40	NR	0.48
			TRG	+5.13	NR	+1.87	NR	0.28
			Lp(a)	+89.01	NR	+92.02	NR	0.19
12 mo			TC	+14.55	NR	+11.15	NR	0.078
			HDL	+3.07	NR	+3.21	NR	0.91
			LDL	+27.65	NR	+21.49	NR	0.033
			TRG	+3.52	NR	+6.40	NR	0.37
			Lp(a)	+106.58	NR	+89.14	NR	0.25
24 mo			TC	+13.35	NR	+10.19	NR	0.34
			HDL	+1.22	NR	+6.53	NR	0.31
			LDL	+23.07	NR	+22.03	NR	0.89
			TRG	+11.87	NR	−1.33	NR	0.036
			Lp(a)	+108.22	NR	+113.22	NR	0.22
36 mo			TC	+10.53	NR	+8.36	NR	0.58
			HDL	+2.08	NR	+12.90	NR	0.33
			LDL	+20.72	NR	+18.19	NR	0.39
			TRG	+8.44	NR	+3.11	NR	0.94
			Lp(a)	+134.75	NR	+114.59	NR	0.11
Adjuvant post-Tamoxifen Exemestane vs Nothing Applied (ATENA)[51,52]								
6 mo[d]	E: 211 O: 200	E vs O	TC	+5.6[c]	NR	+4.2[c]	NR	NR
			HDL	−1.8[c]	NR	+5.3[c]	NR	NR
			LDL	+9.6[c]	NR	+7.5[c]	NR	NR
			TRG	−14.7[c]	NR	−5.9[c]	NR	NR
12 mo[d]			TC	+6.0[c]	NR	+6.5[c]	NR	NR
			HDL	−7.0[c]	NR	+5.3[c]	NR	NR
			LDL	+11.8[c]	NR	+9.0[c]	NR	NR
			TRG	−18.4[c]	NR	−13.3[c]	NR	NR
18 mo[d]			TC	+8.8[c]	NR	+5.1[c]	NR	NR

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Table II. Contd

Study, follow-up[a]	No. of patients[b]	Treatment group	Plasma lipoproteins	Aromatase inhibitor (% change)	p-Value within group	Tamoxifen/ placebo (% change)	p-Value within group	p-Value between groups
			HDL	−10.5[c]	NR	+5.3[c]	NR	NR
			LDL	+18.4[c]	NR	+9.0[c]	NR	NR
			TRG	−11.0[c]	NR	−17.8[c]	NR	NR
24 mo[d]			TC	+6.0[c]	NR	+6.0[c]	NR	NR
			HDL	−8.8[c]	NR	+8.8[c]	NR	NR
			LDL	+13.2[c]	NR	+2.3[c]	NR	NR
			TRG	−17.6[c]	NR	−12.6[c]	NR	NR

a Time of assessment.

b Patients analysed.

c Calculated values.

d Mean observed absolute values were used in the calculations; an earlier publication (Markopoulos et al.[52]) reported preliminary data.

e Includes unpublished data (Hozumi Y, personal communication).

f Includes data from Pfizer Inc., on file.

g Measuring only A treatment from switch.

A = anastrozole; **E** = exemestane; **HDL** = high-density lipoprotein; **L** = letrozole; **LDL** = low-density lipoprotein; **Lp(a)** = lipoprotein a; **NR** = not reported; **NS** = not significant; **O** = no treatment; **P** = placebo; **RLP** = remnant-like particle; **T** = tamoxifen; **TC** = total cholesterol; **TRG** = triglycerides; → indicates transition from one treatment to another in a switch study.

from baseline were observed in TRG at 12, 18 and 24 months (11.5%, 8.6% and 20.9%, respectively), no significant trend was observed.[39,40] In addition, an initial decrease in LDL-C at 12 months from baseline was followed by increases ranging from 1.4% to 2.8%.[39,40] At 24 months, the Lonning et al.[42] study reported decreased HDL-C levels and LDL-C levels from baseline by 9% ($p = 0.511$) and 6% ($p = 0.299$), respectively, and increased TRG levels from baseline by 1.0% ($p = 0.547$) with exemestane.[43] In the Japanese TEAM substudy, patients were randomized to exemestane, anastrozole or tamoxifen, and lipid parameters were assessed at baseline, 3 and 6 months, and 1 year.[41] In the exemestane group, TC levels decreased within 3 months; thereafter, they remained stable. Levels of TC fluctuated only slightly from baseline among patients receiving anastrozole therapy. During the first year of therapy, HDL-C levels did not change significantly from baseline in the anastrozole group. In the exemestane group, HDL-C levels decreased slightly at 3 months and remained decreased for the duration of the study. In both the exemestane and anastrozole groups, LDL-C levels remained essentially unchanged from baseline. There was a decrease in TRG levels during the first 6 months of therapy in the exemestane group, and a slight increase in the anastrozole group.

In the switch setting, TC generally increased from baseline by 0.1–4.0% at different follow-up times in AI groups, with the exception of the 24-month timepoint in one study reported by Montagnani et al.[49] (where TC decreased from baseline by 2.5%).[46,48] Among these studies, all reported HDL-C levels decreased by 0.7–15.2% from baseline and LDL-C levels increased by 0.9–16.7% at all timepoints, with one exception (reported by Wojtacki et al.[46]). However, all switch studies reported TRG levels decreased 1.2–18.1% from baseline except the 12-month timepoint in the study by Francini et al.[48] (who reported a 2.2% increase from baseline).[46,49,51,54]

In the extended adjuvant setting, TC increased from baseline for all evaluated AIs at the majority of timepoints evaluated.[51,54] Among these studies, MA.17 (letrozole vs placebo)

reported increased HDL-C levels from baseline with changes of 3.07%, 1.22% and 2.08% at 12, 24 and 36 months, respectively, while the ATENA study (exemestane vs no treatment) reported decreased HDL-C, with the largest change of 10.5% observed at 18 months. Both studies observed increased LDL-C levels from baseline, with changes from 9.6% to 27.65% at different timepoints.[51,54] The MA.17 study found increased TRG levels from baseline, with the largest increase (11.87%) observed at 24 months.[54]

3.2.2 Between-Group/Arm Differences in Plasma Lipoproteins: AIs versus Tamoxifen

In the majority of studies comparing AIs with tamoxifen, treatment with tamoxifen was associated with decreases in TC and LDL-C from baseline, whereas changes from baseline for HDL-C and TRG were inconsistent. Because of the differing pattern of lipoprotein changes with tamoxifen, comparison with AI therapy resulted in substantial between-group differences (tamoxifen vs AIs) in TC and LDL-C in some studies, but plasma lipoproteins were generally more favourable in the tamoxifen arm (three of five studies) regardless of treatment setting. However, substantial between-group differences were also observed with regard to declines in TRG that favoured treatment with AIs.[13,34,39,41,48,49]

3.2.3 AIs versus Placebo or No Treatment

Among the three studies that compared effects on plasma lipoproteins in patients treated with an AI versus placebo or observation only, in the upfront or extended adjuvant setting, only a decreased HDL-C level in one exemestane study (Lonning et al.[42]) and an increased LDL-C level at one timepoint in a letrozole study (MA.17)[54] showed a significant difference from placebo ($p_{between} \leq 0.03$ for both). There were no consistently significant alterations in the lipid profile when exemestane was compared with an observation-only arm.[51,54]

3.3 Incidence of Hypercholesterolaemia with AI Treatment

A number of studies also reported the incidence of hypercholesterolaemia in patients undergoing treatment with AIs. In the trials that evaluated AIs in the upfront setting, a higher incidence of hypercholesterolaemia was observed in the AI group. In the BIG 1-98 primary core analysis (median follow-up 25.8 months), a higher incidence of hypercholesterolaemia was reported in the letrozole arm compared with the tamoxifen arm (43.6% vs 19.2%, respectively); the majority of events were grade 1.[13] A higher incidence of hypercholesterolaemia was also observed in the letrozole arm in a subset analysis of the same study (BIG 1-98 at a median follow-up of 51 months) that included only data derived from patients in the letrozole arm compared with the tamoxifen arm (50.6% vs 24.6%, respectively; $p < 0.001$);[11] the majority of these events were grade 1. In the ATAC trial, at a median follow-up of 68 months, a significant increase in hypercholesterolaemia was observed in the anastrozole arm compared with the tamoxifen arm (9.0% vs 3.0%, respectively; $p < 0.0001$).[31]

In the switch setting (i.e. the IES,[7,15] BIG 1-98,[36] ARNO 95,[9,16] ABCSG 8[16] and ITA[14] studies), a higher proportion of patients receiving AI therapy had hypercholesterolaemia compared with patients receiving tamoxifen monotherapy. In IES, exemestane was associated with a higher incidence of hypercholesterolaemia compared with tamoxifen at 55.7 months' post-treatment follow-up (8.8% vs 7.6%, respectively; $p = 0.14$), although hypercholesterolaemia was not defined in this study.[15] In the BIG 1-98 switch analysis at a median follow-up of 71 months, a higher incidence of hypercholesterolaemia was observed in the switch cohorts (41.4% for tamoxifen followed by letrozole arm vs 44.5% for letrozole followed by tamoxifen) than the tamoxifen arm (29.9%).[36] In the ARNO 95 and ABCSG 8 trials, hypercholesterolaemia was not reported,[9,16] whereas the ITA trial reported a significantly higher incidence of lipid metabolism disorders in the anastrozole switch arm compared with the tamoxifen arm (8.1% vs 1.4%, respectively; $p = 0.01$).[14]

In the extended setting, a higher incidence of grade 1 or 2 hypercholesterolaemia was observed in the AI group, whereas the overall incidence was similar between groups (16% in each case; $p = 0.79$).[17]

3.4 Effects of AIs on Cardiovascular Events

The search identified 22 papers that reported data on the incidence of CV events in AI and comparator groups based on data from eight RCTs. These RCTs evaluated different ischaemic CV events: MI, ischaemic heart disease, angina pectoris (including those events requiring percutaneous transluminal coronary angioplasty or coronary artery bypass graft) or a combination of these events.

Table III presents the incidence of ischaemic CV events associated with AIs and comparators by treatment group at different follow-up times.[7,9-18,30,32,33,35-37,44,47,50,53,56] Overall, a low incidence of ischaemic CV events was reported in all reviewed studies. As expected, the incidence of CV events in all settings, irrespective of treatment group, increased with duration of follow-up. In the upfront and switch settings, a slightly higher incidence of ischaemic CV events with AIs was noted in some studies comparing AI therapy with tamoxifen, although none of the observed differences were reported to be statistically significant and the clinical relevance of these events is uncertain. For example, in the ATAC study, the incidence of ischaemic CV disease was slightly higher in patients receiving anastrozole compared with tamoxifen after 47 months (2.8% vs 2.2%; $p_{between} = 0.12$) and 68 months (4.1% vs 3.4%; $p_{between} = 0.10$) of therapy. The CV-related mortality rate at 100 months was the same for the anastrozole and tamoxifen groups (2.0%).[12,30,32] In the TEAM study, a non-significant increase was observed for myocardial ischaemia or infarction in the exemestane group compared with tamoxifen (2% vs 1%; $p_{between} = 0.17$).[47] Similar findings for ischaemic CV disease (all grades) were reported in the BIG 1-98 study in the upfront setting at 51 months (2.2% vs 1.7%; $p_{between} = 0.21$) and switch settings at 71 months (letrozole → tamoxifen 1.7%; tamoxifen → letrozole 2.3%; and tamoxifen 1.5%).[11,36] The results for grade 3–5 ischaemic CV events followed a similar pattern (letrozole → tamoxifen 0.9%; tamoxifen → letrozole 1.3%; and tamoxifen 0.8%). However, during years 1 and 2 before the switch, the incidence of grade 3–5 ischaemic CV events was the same (0.5% for both therapies).[36] In the IES study, the incidence of ischaemic CV disease at 55.7 months in patients receiving exemestane or tamoxifen was similar when post-treatment events were included (9.9% vs 8.6%; $p_{between} = 0.12$).[15] In BIG 1-98 at 25.8 months and 51 months, death from cardiac causes occurred in 13/4003 (0.32%) and 12/2463 (0.49%) letrozole patients versus 6/4007 (0.15%) and 7/2459 (0.28%) tamoxifen patients, respectively.[11,13] In the IES study, death from cardiac causes occurred in 14 patients (14/2352 [0.6%]) in the exemestane group versus 13 patients (13/2372 [0.5%]) in the tamoxifen group.[15] However, follow-up data for CV-related deaths beyond the 36-month data reported for the Norwegian Breast Cancer Group study[43] have not yet been reported.

The incidence of angina, although not consistently reported for all AIs, was slightly higher in the switch setting with AI therapy compared with tamoxifen (0.9% for anastrozole vs 0% for tamoxifen; $p_{between}$ value not reported, and 7.1% for exemestane vs 6.5% for tamoxifen; $p_{between} = 0.44$).[9,15] In the placebo-controlled, extended adjuvant trials with letrozole, new or worsening angina was reported more frequently with letrozole at 30 months (1.2% vs 0.9% for placebo; $p_{between}$ value not reported); however, stenting or grafting for the management of these events was required less frequently (≤0.2% vs ≥0.3% for placebo).[17,18] In addition, the rate of angina was similar with letrozole compared with placebo after a mean follow-up of 5.3 years (0.5% vs 0.6%, respectively).[18]

MI was reported for all three AIs in each treatment setting and varied based on treatment setting. In the upfront setting, the incidence of MI following treatment with anastrozole was similar to tamoxifen at 100 months (0.28% vs 0.30%, respectively).[32] In two switch-setting studies, patients who received anastrozole had a lower or similar rate of MI compared with those who received tamoxifen at approximately 30 months (0% vs 0.2%, respectively, and <1.0% for both; $p_{between} = 1.0$),[9,16] whereas exemestane-treated patients had a slightly higher, but not statistically significant, MI rate compared with tamoxifen-treated patients at 55.7 months (1.3% vs

Table III. Incidence of cardiovascular adverse events in patients receiving aromatase inhibitors vs tamoxifen or placebo in randomized controlled studies

Study, follow-up	No. of patients	Treatment group	CV event	Aromatase inhibitor patients (%)	Tamoxifen/placebo patients (%)	p-Value between groups
Upfront treatment						
Arimidex, Tamoxifen, Alone or in Combination (ATAC)						
33.3 mo[10,56]	6241 (A: 3092; T: 3094)[a]	A vs T	Ischaemic CV disease	2.5	1.9	0.14
			MI	0.8	0.8	NR
			Angina	1.7	1.0	NR
47 mo[30]			Ischaemic CV disease	2.8	2.2	0.121
68 mo[12]			Ischaemic CV disease	4.1	3.4	0.10
100 mo[32]			CV death	2.0	2.0	NR
			MI	0.28	0.30	NR
120 mo[33]			CV death	2.9	3.0	NR
Breast cancer International study Group (BIG 1-98)						
25.8 mo[13]	8028 (L: 3975; T: 3988)[a]	L vs T	Ischaemic heart disease	1.4	1.2	0.28
			Any cardiac event[b]	4.1	3.8	0.61
			Grade 5 cardiac event	0.4	0.1	0.61
			Other CV events	0.5	0.2	0.04
30.1 mo[37]	(L: 3975; T: 3998)[a]		Ischaemic heart disease	1.7	1.5	0.48
			Cardiac event	4.8	4.7	0.87
			Other CV events	0.7	0.3	0.01
40.4 mo[35]	(L: 2448; T: 2447)[a]		Ischaemic heart events	2.2	1.8	0.42
			Cardiac event	5.7	5.2	0.45
51 mo[11]	(L: 2448; T: 2447)[a]		Ischaemic heart disease	2.2	1.7	0.21
			Cardiac event	5.5	5.0	0.048
			Other CV events	0.8	0.2	0.014
74 mo[38]	(L: 2448; T: 2447)[a]		Ischaemic heart disease	2.8	2.0	0.08
			Cardiac event	6.9	6.2	0.36
			Other CV events	1.0	0.5	0.10
Switch treatment						
ARimidex-NOlvadex 95 (ARNO 95)[9]						
30.1 mo	979 (T/A: 445;T: 452)[a]	T/A vs T	Angina	0.9	0.0	NR

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Table III. Contd

Study, follow-up	No. of patients	Treatment group	CV event	Aromatase inhibitor patients (%)	Tamoxifen/placebo patients (%)	p-Value between groups
			Chest pain	0.9	0.7	NR
			MI	0.0	0.2	NR
			Myocardial ischaemia	0.2	0.0	NR
ARNO 95/Austrian Breast and Colorectal cancer Study Group 8 (ABCSG 8)[16]						
28 mo	4960 (T/A: 1602; T: 1597)[a]	T/A vs T	MI	<1.0	<1.0	1.0
Italian Tamoxifen Anastrozole (ITA)						
36 mo[44]	448 (T/A: 223; T: 225)[a]	T/A vs T	CV disease	7.9	9.3	0.4
64 mo[14]			CV disease	7.6	6.2	0.6
Intergroup Exemestane Study (IES)						
30.6 mo[7]	4724 (T/E: 2309; T: 2332)[a]	T/E vs T	CV disease (not MI)	42.6	39.2	0.11
55.7 mo[15]	(T/E: 2320; T: 2338)		Ischaemic CV disease	9.9	8.6	0.12
			Angina	7.1	6.5	0.44
			MI	1.3	0.8	0.08
			Other CV events	11.3	11.2	0.96
Tamoxifen Exemestane Adjuvant Multicenter (TEAM)[47]						
60 mo	(E: 4852; T/E: 4814)	E vs T/E	Myocardial ischaemia or infarction	2	1	0.17
BIG 1-98[36]						
71 mo	8028 (T/L: 1540; L/T: 1526; T: 1540)[a]	T/L vs L/T vs T	Ischaemic heart disease	L→T: 1.7 T→L: 2.3	1.5	NR
			Any CV event	L→T: 6.1 T→L: 7.0	5.7	NR
			All CV events (not hypertension)	L→T: 0.9 T→L: 0.5	0.9	NR
National Surgical Adjuvant Study of Breast Cancer (N-SAS BC 03)[50]						
60 mo	706 (T: 349; T/A: 347)[a]	T vs T/A	Grade 4 heart disease[c]	0.9	0.6	0.66
Extended treatment						
MA.17						
2.4 y[53]	5187 (L: 2154; P: 2145)[a]	L vs P	CV events	4.1	3.6	0.40

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Table III. Contd

Study, follow-up	No. of patients	Treatment group	CV event	Aromatase inhibitor patients (%)	Tamoxifen/placebo patients (%)	p-Value between groups
30 mo[17]	(L: 2572; P: 2577)[a]		CV disease	5.8	5.6	0.76
			MI	0.3	0.4	NR
			Angina	1.2	0.9	NR
			Angina requiring PTCA	0.1	0.3	NR
			Angina requiring CABG	0.2	0.5	NR
5.3 y[18]	(L: 1579; P: 804)[a]		CV disease	4.2	3.1	0.17
			MI	0.4	0.6	NR
			Angina	0.5	0.6	NR
			Angina requiring PTCA	0.1	0.2	NR
			Angina requiring CABG	0.1	0.1	NR

a Patients analysed.

b 'Any cardiac event' includes both ischaemic heart disease and cardiac failure.

c 'Heart disease' was not further defined.

A = anastrozole; **CABG** = coronary artery bypass graft surgery; **CV** = cardiovascular; **E** = exemestane; **L** = letrozole; **MI** = myocardial infarction; **NR** = not reported; **P** = placebo; **PTCA** = percutaneous transluminal coronary angioplasty; **T** = tamoxifen; → indicates transition from one treatment to another in a switch study.

0.8%; $p_{between} = 0.08$).[15] In the extended adjuvant setting, patients treated with letrozole had a similar MI rate compared with placebo patients at both 30 months (0.3% vs 0.4%, respectively) and 5.3 years (0.4% vs 0.6%, respectively).[17,18]

Additionally, the BIG 1-98 study reported an association between previous hypercholesterolaemia and grade 3–5 cardiac events, including ischaemic heart disease. Moreover, letrozole was associated with a slightly greater incidence of grade 1–5 vascular adverse events that were classified as peripheral atherosclerotic disease.[37]

4. Discussion

The risk of CV disease increases with age in women and is considerably higher after 60 years of age (during postmenopausal years).[57] The incidence of breast cancer in women also increases with age up to 70 years.[58] Therefore, in postmenopausal women, CV side effects from breast cancer treatments represent a considerable health concern. A recent literature review of CV risks in women receiving adjuvant endocrine therapy reported that with improved treatment for breast cancer, patients are living longer, with CV disease emerging as a competing cause of death.[59] Therefore, potential CV adverse events related to anticancer therapies have become worthy of increased attention. Plasma lipoproteins are considered important factors in assessing CV adverse event risk because long-term elevations of LDL-C and TRG levels are associated with an increased risk of CV events.[60,61] However, in patients with breast cancer undergoing endocrine treatment, the clinical relevance of changes in plasma lipid and lipoprotein levels to subsequent CV morbidity and mortality has not been established.

This literature review evaluated changes in plasma lipoproteins and the potential effect of AI therapy on ischaemic CV events in patients with HR-positive early breast cancer. Overall, the available data do not suggest an increased potential for ischaemic CV events in this patient population. The majority of RCTs studying the efficacy and/or safety associated with AIs (plus tamoxifen) used tamoxifen alone as a compara-

tor. Therefore, mechanisms of action and treatment setting must be considered when evaluating observed changes in plasma lipids or the incidence of ischaemic CV events in patients treated with AIs compared with tamoxifen.

Tamoxifen has a relatively complex mode of action, with estrogen-like (agonist) effects on some body tissues and an estrogen antagonist effect in others.[62] In patients with HR-positive breast cancer, tamoxifen competitively binds to estrogen receptors on breast cancer cells and antagonizes estrogen receptors for signalling, leading to cell-cycle arrest.[63] On the other hand, the mechanisms by which tamoxifen exerts an effect on serum lipids are uncertain. Studies suggest that tamoxifen may act on the liver and alter lipoprotein transport and metabolism, thereby affecting plasma lipoproteins such as TC, LDL-C and HDL-C.[64-66] Although controversial, in the literature some investigators have referred to tamoxifen as a cardioprotective agent because of its favourable effects on TC and LDL-C.[65,66] In contrast to tamoxifen, AIs block the enzyme aromatase, with a resultant decrease in circulating estradiol.[24] AIs lack any estrogen agonist activity and, therefore, do not have the favourable effect on plasma lipoproteins observed with tamoxifen. Considering the significant difference in mechanism of action and resulting effect on plasma lipoproteins, comparison of data on plasma lipoproteins between AIs and tamoxifen should be interpreted with caution. The lipid-lowering effect of tamoxifen makes between-group comparisons (i.e. AIs vs tamoxifen) difficult. However, within-group assessments of change from baseline during follow-up provide meaningful estimates of the effect of each treatment on plasma lipoproteins depending on treatment settings.

Overall, no consistent pattern of detrimental changes in plasma lipoproteins from baseline to follow-up assessment was observed during and after treatment with AIs in the studies reviewed. Any changes in plasma lipoproteins appeared to occur within 3 months after initiation of AI therapy and then remained stable until the end of the study follow-up. However, heterogeneity in the patient population and dissimilarities in data collection methods used for the assessments may explain some of the reported differences in plasma lipoproteins across the studies. Unlike studies using tamoxifen as a comparator, placebo-controlled or no-treatment AI studies such as ATENA or MA.17 provide a meaningful between-group comparison of the effect of AIs on plasma lipoproteins. Data from these studies did not show any significant or consistent differences in plasma lipoproteins between patients who received AIs and placebo or no treatment.[51,52,54] Although one study showed that upfront exemestane decreased HDL-C compared with placebo at 12 and 24 months after initiation of therapy, HDL-C returned to baseline within 3 months of treatment discontinuation.[42,43] In the ATENA study, patients treated with exemestane had increases in TC and LDL-C compared with baseline, but there were no significant between-group differences.[51] In the same study, mean HDL-C levels were consistently decreased in patients treated with exemestane, while an increase was detected over time in the observation arm ($p = 0.08$).[51] In a substudy of MA.17, MA.17L, patients treated with letrozole had marginally significant decreases in HDL-C at 6 months, and marginally significant increases in LDL-C and TRG at 12 and 24 months, respectively, compared with the placebo group, but not at other timepoints[54] (table II). Overall, the study concluded that letrozole does not significantly affect TC, HDL-C, LDL-C, TRG or lipoprotein a.[54]

It is also critical to consider the setting of the study when assessing data on plasma lipoproteins. Some studies investigating effects of AIs after a period of treatment with tamoxifen (2–5 years) showed a significant increase in LDL-C levels in the AI group.[48,49] This could potentially be attributed to withdrawal from tamoxifen's favourable effect on plasma lipoproteins, rather than an adverse effect associated with AIs as a class *per se*.[67] For example, all the assessments (12–36 months) in the MA.17 study showed an increase from baseline for each plasma lipoprotein in both the letrozole and placebo groups.[54] In a study in Japanese patients treated with anastrozole in the upfront setting, TC and HDL-C were increased slightly from baseline to

12 weeks, whereas LDL-C and TRG levels at 12 weeks had decreased from baseline values;[34] these effects may result in a decreased risk for CV events.

Consistent with the favourable effects of estrogen on TC, a number of studies reported higher rates of hypercholesterolaemia in patients undergoing treatment with AIs compared with patients receiving tamoxifen.[13-15,17,31,36] It is important to note that both the method of evaluation and the definition of hypercholesterolaemia varied in these studies. Most of these studies used similar National Cancer Institute Common Toxicity Criteria for evaluating adverse events; however, in some studies, hypercholesterolaemia was classified at the investigator's discretion or used a method not specified in the study. In some studies, hypercholesterolaemia was defined as 1.5×the upper limit of normal (ULN); in other studies, hypercholesterolaemia included any measurement above the ULN that occurred in at least one assessment; in other studies, there were no systematic assessments for hypercholesterolaemia.

Although data on plasma lipoproteins provide valuable information for understanding the potential risk of ischaemic CV disease, these values have limitations.[68] It has been suggested that residual risk for CV events exists despite an optimal LDL-C level, and focus has turned to the CV risk associated with abnormal HDL-C and TRG levels. However, the anti-atherogenic effects of HDL-C depend on its functionality and not the cholesterol content; therefore, an increase in HDL-C concentration may not result in a CV clinical benefit. Moreover, interpretation of changes in TRG levels remains difficult because of the substantial intra-individual variability of TRG values.

Assessment of ischaemic CV events (i.e. clinical endpoints such as MI) during or after AI treatment provides more compelling data on the potential ischaemic CV risk associated with AIs than surrogate markers such as plasma lipoprotein levels. Despite the favourable effect of tamoxifen on TC and LDL-C, no marked differences were observed in the incidence of ischaemic CV events in studies comparing AIs and tamoxifen in various adjuvant settings.[7,9-18,30,32,33,35-37,44,47,50,53,56] Overall, a low incidence of ischaemic CV events was observed in patients receiving treatment with AIs and tamoxifen in the studies reviewed. Similarly, a smaller, retrospective, single-arm study that evaluated adverse events in 656 Japanese women who received anastrozole reported no cases of MI at a median follow-up of 23 months.[55] In contrast, a meta-analysis of CV risk in postmenopausal women with early breast cancer reported a significant increase in grade 3 and 4 CV adverse events with AIs compared with tamoxifen ($p = 0.0038$).[69] However, these events included oedema, hypertension, left ventricular dysfunction and phlebitis, as well as ischaemic events, thus making it difficult to associate risk of ischaemic events alone. In addition, the absolute difference between tamoxifen and AIs was low, and translated to a 0.5% difference in CV risk. Furthermore, the inclusion of a study with a shorter median follow-up, which reported the highest risk, may have biased the results. However, studies with longer term follow-up may provide varied results. In the MA.17 study, which compared an AI with placebo, a similar incidence of ischaemic events was seen between the two groups.[17,18,53] However, data comparing ischaemic events in AIs and placebo are limited.

The data on plasma lipoproteins or CV events included in this review should be interpreted with caution. It is especially difficult to draw conclusions because no single agent has been evaluated across all settings and against the same comparator. Additionally, the majority of these studies examined efficacy-related outcomes (e.g. 5-year survival) as a primary endpoint, and the information on plasma lipoproteins and adverse events, including ischaemic CV events, was derived from substudies that had relatively small numbers of patients. Moreover, event rates were difficult to compare because of the differences in patient population, data collection methods, assessment and follow-up time, and adjudication and reporting of CV events that may substantially explain some of the differences in CV incidence across the studies.

For example, blood samples for serum lipid levels were primarily taken from non-fasting patients in BIG 1-98,[37] and the timepoints at which blood samples were drawn varied among stud-

ies.[34,39,42,43,46,48,49,54] In addition, the case report forms used for BIG 1-98 included a predefined checklist of CV events, in contrast to patient self-reported CV events in the ATAC study.[59] Therefore, care should be exercised when comparing various estimates on plasma lipoproteins and CV events across studies and between AIs. Although the reported analyses have evaluated within-trial differences between AIs and comparators for both plasma lipoproteins and CV events, the analyses may not have had sufficient power to detect statistically significant differences for some events because of small sample sizes. Nevertheless, the randomized design of these studies allows valid comparison within each study.[12,13,15,17]

No study was identified that provided data on plasma lipoproteins or ischaemic CV events where head-to-head comparisons of AIs were made in patients with early breast cancer, and because of differences in study design, such comparisons should not be made from these reports. However, 36-week follow-up data from the Letrozole, Exemestane, Anastrozole Pharmacodynamics (LEAP) study suggest some differences among the AIs in terms of their effects on plasma lipoproteins in healthy postmenopausal women.[70] In this study, there were few significant changes from baseline in plasma lipoproteins between individual AIs; however, exemestane significantly reduced HDL-C levels at 24 weeks (−13.9% vs +0.3%; $p < 0.001$) and had a higher LDL-C to HDL-C ratio at 24 weeks (17.0% vs 4.6%; $p < 0.05$) compared with anastrozole, whereas letrozole had a higher increase in TRG compared with anastrozole at 12 weeks (+9.6% vs −2.9%; $p < 0.05$). CV endpoints were not evaluated in this study.[70]

5. Conclusions

CV safety is an important consideration when deciding on a treatment strategy for postmenopausal patients with early breast cancer. Based on the available data, no major safety concerns for ischaemic CV events emerged with the use of AIs in patients with HR-positive early breast cancer in various adjuvant settings. However, it is important to consider the overall benefit-to-risk profile when considering treatment with an AI. Differences in plasma lipoprotein levels in patients treated with tamoxifen or an AI must be evaluated with caution because tamoxifen has estrogen-agonist activities that are lacking in AIs, including the ability to reduce levels of plasma lipoproteins. As such, the effect of AIs on plasma lipoproteins in studies comparing AIs with tamoxifen following initial treatment with tamoxifen (switch and extended adjuvant settings) may reflect loss of the beneficial effect of tamoxifen rather than any detrimental effect of AI therapy. No study to date has identified any correlation between changes in plasma lipoproteins and occurrence of ischaemic CV events in this patient population. Available data do not support a substantial risk of ischaemic CV events associated with adjuvant AI therapy; however, longer follow-up is required to better characterize the CV profile of AIs.

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