REVIEW ARTICLE

Drug Safety 2006; 29 (9): 785-801
0114-5916/06/0009-0785/$39.95/0

Cardiovascular Safety Profiles of Aromatase Inhibitors

A Comparative Review

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Abstract

Third-generation aromatase inhibitors (AIs) are now being used for the adjuvant treatment of postmenopausal women with breast cancer, and are challenging tamoxifen, the previous 'gold standard' of care, in this setting. This review evaluates the potential clinical impact of anastrozole, letrozole and exemestane on the cardiovascular (CV) system of postmenopausal women with breast cancer. Some data for CV safety are available for AIs from the advanced disease setting; however, most derive from patients being treated for early disease. CV data on anastrozole for the treatment of early breast cancer were taken from the ATAC trial, in which anastrozole was compared with tamoxifen in the primary adjuvant setting, and the ABCSG trial 8/ARNO 95 combined analysis, in which switching to 3 years of anastrozole after 2 years of tamoxifen was compared with the standard 5 years of tamoxifen adjuvant therapy. Letrozole has been studied in the

primary adjuvant setting and the adjuvant sequencing setting in the BIG 1–98 study, as well as in extended adjuvant endocrine therapy after 5 years of tamoxifen in the MA-17 trial. For exemestane, results were reviewed from the IES trial, in which switching to exemestane following 2–3 years of adjuvant tamoxifen was compared with continued tamoxifen treatment.

All these trials clearly confirmed that all three AIs significantly reduce the risk of thromboembolic events compared with tamoxifen. Data on anastrozole versus tamoxifen from the ATAC trial (68 months' follow-up) showed a similar incidence of myocardial infarctions (MIs), CV deaths and overall deaths for both therapies; however, anastrozole appeared to be associated with a lower incidence of cerebrovascular events compared with tamoxifen. In addition, the ABCSG trial 8/ARNO 95 study reported no difference in terms of MIs for patients switching to anastrozole compared with patients continuing tamoxifen treatment.

Data from BIG 1–98 (26 months' follow-up) suggested that primary adjuvant treatment with letrozole may be associated with a significantly greater incidence of CV events and a numerical increase of cerebrovascular and cardiac deaths compared with tamoxifen. However, no increase in CV events with letrozole was reported from the MA-17 trial.

In the IES, updated data at 55 months' median follow up showed no significant difference in the incidence of MIs and cardiac deaths between patients who switched to exemestane compared with those who continued tamoxifen.

In conclusion, a significantly reduced risk of thromboembolic disease was observed for all three AIs compared with tamoxifen. Anastrozole is, at this point, the only AI with a detailed benefit-risk profile from over 5 years' follow-up in the adjuvant setting. Thus far, no apparent CV-safety concerns have emerged. Preliminary data on letrozole and exemestane suggest that longer follow-up is needed for these two AIs before being able to fully assess their respective long-term CV toxicity profile. The present differences in CV-safety profiles suggest that third-generation AIs should not be considered as equivalents in clinical practice.

The third-generation nonsteroidal aromatase inhibitors (AIs), anastrozole and letrozole, are now widely accepted as alternatives to tamoxifen as first-line therapy in postmenopausal women with hormone receptor (HR)-positive advanced breast cancer because of their improved clinical effectiveness.[1-3] AIs have also demonstrated additional advantages over tamoxifen in terms of tolerability.[1,2] This favourable efficacy and safety profile over tamoxifen in the advanced setting has encouraged the ongoing evaluation of third-generation AIs in the adjuvant setting.

The American Society of Clinical Oncology (ASCO) Technology Assessment Panel has recently evaluated available data from multiple large, randomised adjuvant trials in early breast cancer. The report recommended that the optimal adjuvant treatment for postmenopausal women with early breast cancer should now include an AI as either initial therapy or following tamoxifen to lower the risk of tumour recurrence.[4] The shift from tamoxifen to an AI in both the advanced and adjuvant setting has challenged the status of tamoxifen as the 'gold standard' treatment for postmenopausal women with HR-positive breast cancer. The use of AIs in the treatment of early breast cancer means that individual patients will be exposed to these agents for longer durations, making it increasingly important to establish their long-term safety.

AIs have demonstrated a reduction in the risk of thromboembolic events and uterine abnormalities compared with tamoxifen;[1] however, until recently, there has been insufficient evidence to determine the effects of AIs on cardiovascular (CV) disease and, in particular, on coronary heart disease risk.[4] Preliminary data from adjuvant trials have raised concerns that long-term use of letrozole and exemestane may increase the risk of CV events.[5-7] However, it remains unclear whether molecular differences between the AIs may account for potential differential effects on the CV system.

We have reviewed all available data on the CV events reported for anastrozole, letrozole and exemestane in order to evaluate the potential clinical impact of long-term use of AIs in the adjuvant setting. Data were compiled by searching the PubMed databases and recent meeting abstracts (San Antonio Breast Cancer Conference, ASCO, European Cancer Conference and European Society for Therapeutic Radiology and Oncology) up to July 2006. The search terms used were 'cardiovascular events/aromatase inhibitors'.

1. Cardiovascular (CV) Risk in Postmenopausal Women

The leading cause of morbidity and mortality worldwide is CV disease, particularly coronary artery disease.[8,9] The incidence of CV disease is low in premenopausal women, but it increases after the onset of the menopause. Menopause in women aged 45–55 years increases the risk of atherosclerosis by a factor of three; bilateral ovariectomy increases the risk of atherosclerosis by a factor of six.[10]

The rapid increase in CV risk after spontaneous or medically-induced menopause is believed to result, in part, from the loss of endogenous estrogen. The cardioprotective effects of estrogen were initially attributed to its favourable effects on cholesterol and lipid metabolism;[11] however, more recent studies suggest that estrogen deprivation has a more widespread impact on the CV system, with direct harmful effects on vessel-wall physiology as well as alterations in glucose metabolism and haemostatic variables.[12-15]

2. Thromboembolic Risk in Patients with Cancer

The increased risk of CV events in postmenopausal women is further amplified in oncology patients.[16] Patients with cancer may develop thromboembolic complications when physiological antithrombotic systems are defective or when prothrombotic activities overcome the normal physiological antithrombotic mechanisms.[17] For instance, tumour cells are able to activate the thrombotic system either directly to generate thrombin or indirectly by stimulating mononuclear cells to synthesise and express various procoagulants, leading to prothrombin activation, fibrin formation and generation of a thrombus.[18] Venous thromboembolism may be the first clinical manifestation of an occult cancer and in patients with clinically overt cancer a venous thromboembolic complication may develop at any stage of their disease.[19]

Treatments such as chemotherapy and certain endocrine therapies have been shown to further compound the risk of thromboembolic complications in patients with cancer. Chemotherapy can affect the synthesis or reactivity of blood-clotting factors through damage to endothelial cells, thereby intensifying coagulation and increasing the risk of thromboembolism.[17] In patients with breast cancer undergoing chemotherapy, the incidence of thrombosis has been reported to range from 1.3% (stages I–III) to 17.6% (stage IV), with the highest risk observed in postmenopausal patients.[16] Tamoxifen has also been associated with a small but significant increased risk of venous thromboembolism, which is further worsened by the addition of chemotherapy.[16] This increase in thromboembolic disease seen with tamoxifen is considered to be a consequence of its partial estrogen receptor-agonist activity in certain tissues.[16,17] Third-generation AIs, however, are potent inhibitors of estrogen synthesis and have been shown to significantly reduce the risk of thromboembolism compared with tamoxifen treatment in postmenopausal women with breast cancer.[1,2,7,20]

3. Estrogen as a Cardioprotective?

Initial observational studies suggested that postmenopausal women who received hormone replacement therapy (estrogen either with or without progestogen [progestin]) had fewer CV events than those who did not receive treatment.[12,21] This led to the encouraging premise that there was a role for estrogen replacement therapy for the prevention of CV disease; however, recent randomised clinical trials have disagreed with these initial reports.[22-26]

The HERS (Heart and Estrogen/progestin Replacement Study) and ERA (Estrogen Replacement Atherosclerosis) studies concluded that among postmenopausal women with established coronary disease, neither estrogen nor estrogen in combination with progestogen reduced the risk of CV disease.[22-25] Consistent with these reports, the Women's Health Initiative concluded that among healthy postmenopausal women, the combined use of estrogen and progestogen resulted in increased rates of coronary heart disease, cerebrovascular and thromboembolic events. This led to the recommendation that this treatment should not be initiated or continued for the primary prevention of coronary heart disease.[26] Therefore, these studies suggest that the addition of estrogen does not have any cardioprotective effects in postmenopausal women.

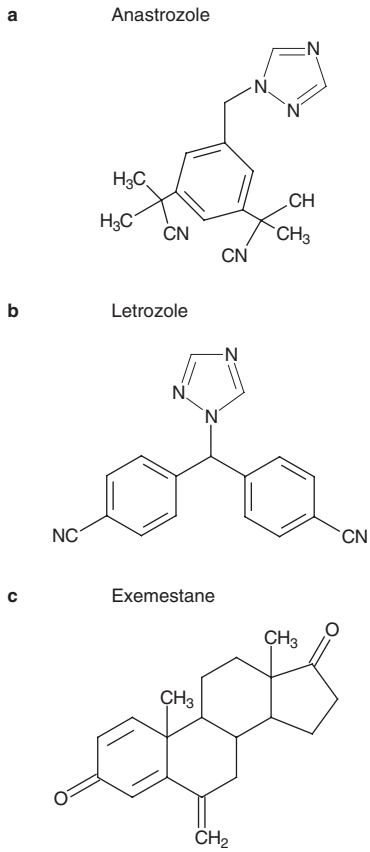

Fig. 1. Structural differences between the aromatase inhibitors: (**a**) anastrozole, (**b**) letrozole and (**c**) exemestane.[28]

4. Pharmacology of Aromatase Inhibitors

Third-generation AIs are potent inhibitors of the aromatase enzyme, which catalyses the last step in estrogen biosynthesis: the conversion of androgen to estrogen.[27] Third-generation AIs are categorised into two types, nonsteroidal and steroidal, and differ in their modes of interaction with the aromatase-enzymatic complex and its inactivation. The nonsteroidal AIs, anastrozole and letrozole, are imidazole-based (figures 1a and 1b, respectively) and compete with endogenous substrates for access to the cytochrome P450 moiety of aromatase where they form a reversible co-ordinate bond with the haem iron atom. The steroidal AI exemestane is an analogue of androgen (figure 1c) that competes with the endogenous substrates androstenedione and testosterone for access to the cytochrome P450 moiety of aromatase. On interaction with aromatase, exemestane is processed to intermediates that cause irreversible enzyme inhibition.[28]

4.1 Selectivity for Aromatase

The molecular differences between anastrozole, letrozole and exemestane (figure 1) appear to affect their selectivity for the aromatase enzyme and thus their capability to interfere in other metabolic pathways, such as adrenal steroidogenesis, in a way that has the potential to further impact on the CV system. Changes in aldosterone or cortisol levels can affect blood pressure and electrolyte balance; in addition, changes in cortisol level can also affect stress adaptation and the immune system.[29]

CV disease is characterised by an inflammatory component at some stage in its pathology,[30] and it has been suggested that an inadequate morning increase in cortisol production may cause failure to prevent the inflammatory effect of interleukin-6 on the vascular tree. In patients with coronary heart disease, it was observed that 75% of patients with unstable angina and 50% of patients with stable angina had inadequate morning cortisol levels.[29] Hence, if long-term use of an AI results in impaired cortisol synthesis, it may lead to a reduced ability of the hypothalamic-pituitary-adrenal axis to exert a proper anti-inflammatory effect on the vascular system, resulting in an unmasking of the inflammatory aspects of arterial disease and promoting CV events.

Anastrozole appears to be a highly selective inhibitor for aromatase, with no discernible effect on adrenocorticoid hormone synthesis in preclinical studies.[31] In an open-label, multicentre trial in 19 postmenopausal women with advanced breast cancer, anastrozole, administered at doses both 5- and 10-fold greater than the recommended clinical dose, demonstrated no significant changes in basal or corticotropin (ACTH)-stimulated cortisol and aldosterone levels, at baseline or after 115 days of treatment.[32]

A study of letrozole, in 46 postmenopausal women with advanced breast cancer, showed no significant effects on basal cortisol or aldosterone levels.[33] However, a significant impact on ACTH-stimulated cortisol and aldosterone levels at the standard clinical dose was reported in this trial. After 3 months of treatment, letrozole 2.5mg administered orally (PO) demonstrated a significant decrease in peak cortisol ($p = 0.015$) and aldosterone ($p = 0.04$) levels after stimulation with ACTH.[33] These alterations in aldosterone and cortisol levels suggest that letrozole appears to be less selective for the aromatase enzyme than anastrozole; however as no studies have directly compared the two drugs, the observed difference may be due to differences in study design or patient population.

Exemestane (at doses up to 200mg daily) has shown no significant effects on basal cortisol or aldosterone levels in a small study involving 13 postmenopausal women with advanced breast cancer.[34] However, the impact of exemestane on ACTH-stimulated cortisol and aldosterone has yet to be established.

4.2 Aromatase Inhibition and Estrogen Suppression

The molecular differences between anastrozole, letrozole and exemestane may also be responsible for small differences in inhibition of total-body aromatisation and, as a result, plasma estrogen suppression.[35,36] It is clear that a reduction in endogenous estrogen is associated with an increased risk of CV disease.[12]

The effectiveness of the nonsteroidal AIs anastrozole and letrozole in suppressing total-body aromatisation and plasma estrogen levels have been compared in a randomised, cross-over study.[35] Twelve postmenopausal women with estrogen receptor-positive metastatic breast cancer were randomised to anastrozole 1mg PO or letrozole 2.5mg PO for 6 weeks. Treatment with anastrozole inhibited total-body aromatisation by a mean of 97.3%, which coincided with ≥81% suppression of plasma estrone, estradiol and estrone-sulfate levels (table I). In comparison, treatment with letrozole inhibited total-body aromatisation by a mean of >99.1%, which coincided with >84% suppression of plasma estrone, estradiol and estrone-sulfate levels ($p = 0.0022$ for anastrozole vs letrozole). Many of the estradiol and estrone-sulfate values were undetectable during treatment with anastrozole and letrozole; therefore, these percentages represent underestimates of the extent of suppression (table I).[35]

The effectiveness of exemestane in suppressing total-body aromatisation and, thus, plasma estrogen levels, has been evaluated by the same group in an earlier study.[36] Of the ten postmenopausal women with advanced breast cancer treated with exemestane 25mg PO for 6–8 weeks, total-body aromatisation was inhibited by a mean of 97.9%, which coincided with >92% suppression of plasma estrone, estradiol and estrone-sulfate levels (table I).[36]

It has been suggested that the third-generation AIs are able to achieve a threshold of estrogen

Table I. Percentage of mean suppression of plasma estrone, estradiol and estrone-sulfate levels in patients treated with anastrozole, letrozole or exemestane[35,36]

Aromatase inhibitor	Estrone	Estradiol	Estrone-sulfate
Anastrozole	81.0	84.9[a]	93.5
Letrozole	84.3[b]	87.8[c]	98.0
Exemestane	94.5	92.2	93.2

a Nine patients had their plasma levels of estradiol suppressed below the sensitivity limit of the assay during anastrozole treatment.

b Three patients had their plasma levels of estrone suppressed below the sensitivity limit of the assay during treatment.

c Twelve patients had their plasma levels of estradiol suppressed below the sensitivity limit of the assay during letrozole treatment.

suppression that is adequate for good clinical efficacy, and that further reductions may not significantly influence the overall response.[28] This was substantiated by an open-label, randomised trial that found no differences in overall efficacy between anastrozole and letrozole as second-line treatment for postmenopausal women with advanced breast cancer.[37] In addition, a trial comparing two doses of letrozole in postmenopausal women concluded there was no correlation between estrogen suppression and anti-tumour response.[33] Therefore, there is no evidence to suggest that the small differences in estrogen suppression between the AIs will affect clinical efficacy.

4.3 Lipid Composition

Postmenopausal women have increased levels of low-density lipoprotein-cholesterol (LDL-C) and decreased levels of high-density lipoprotein-cholesterol (HDL-C) compared with premenopausal women of the same age, and these unfavourable changes are considered to be a risk factor for the development of coronary heart disease.[21] It is, therefore, important to ascertain whether treatment with anastrozole, letrozole or exemestane impacts on lipid composition.

4.3.1 Anastrozole

In a combined analysis of the North American and TARGET (Tamoxifen or Arimidex Randomised Group Efficacy and Tolerability) trials, the effects of anastrozole on serum lipid levels in >600 postmenopausal women with advanced breast cancer were evaluated.[38] Non-fasting blood samples for lipid assessment were taken at baseline, 84 weeks and 108 weeks. The study concluded that neither anastrozole nor tamoxifen had a clinically significant impact on total cholesterol level.[38]

In another study, consistent with this analysis, fasting samples from postmenopausal women with breast cancer who switched from tamoxifen to anastrozole treatment (n = 51), were analysed at baseline and at three subsequent time points: at minimum 24 (median: 26, range: 24–33 weeks); 60 (median: 63, range: 60–70 weeks); and 130 (median: 134, range: 130–147 weeks) weeks of anastrozole administration.[39] Results showed no significant change in total cholesterol ($p = 0.51$), LDL-C ($p = 0.61$), HDL-C ($p = 0.43$) or triglyceride ($p = 0.78$) levels. Furthermore, there was no change in the atherogenic risk ratios of total cholesterol **:** HDL-C ($p = 0.56$), LDL-C **:** HDL-C ($p = 0.33$) as well as the mean body mass index values ($p = 0.93$).

Another recent study evaluated the effects of anastrozole on lipid profiles in postmenopausal women with early breast cancer (n = 54).[40] Anastrozole induced no significant effect on serum levels of apolipoprotein A1, apolipoprotein B, triglycerides, total cholesterol, HDL-C and LDL-C nor in the atherogenic risk ratios of total cholesterol **:** HDL-C, LDL-C **:** HDL-C and apolipoprotein A1 **:** apolipoprotein B, when measured at baseline and 1, 3, 6 and 12 months.

Furthermore, a substudy of a prospective, randomised, multicentre trial in postmenopausal patients with breast cancer (n = 176) investigated the effects of neoadjuvant therapy with anastrozole or tamoxifen alone or in combination on serum lipid profiles.[41] Non-fasting blood samples were taken at baseline, 2 and 12 weeks. Treatment with either tamoxifen or anastrozole for 12 weeks was associated with a significant increase in HDL-C levels in both groups, whereas total cholesterol levels decreased in the tamoxifen group and increased in the anastrozole group, although not significantly. Treatment with anastrozole and tamoxifen in combina-

tion was associated with a significant increase in HDL-C levels and a decrease in total cholesterol levels.

Additional data for anastrozole in the first-line adjuvant setting in 27 postmenopausal women demonstrated no significant change in the mean values of apolipoprotein A1 ($p = 0.73$), apolipoprotein B ($p = 0.66$) and the atherogenic risk ratio of apolipoprotein A1 **:** apolipoprotein B ($p = 0.78$) after 6 months of treatment.[42]

4.3.2 Letrozole

The impact of letrozole on lipid composition was measured in a study of 20 postmenopausal women with advanced breast cancer previously treated with tamoxifen.[43] Following the analysis of fasting samples before treatment and at 8 and 16 weeks, results showed a significant increase in total cholesterol ($p = 0.05$), LDL-C ($p < 0.01$) and apolipoprotein B ($p = 0.05$) levels after 16 weeks. In addition, there was evidence of unfavourable changes in the atherogenic risk ratios of total cholesterol **:** HDL-C ($p < 0.005$), LDL-C **:** HDL-C ($p < 0.005$) and apolipoprotein A1 **:** apolipoprotein B ($p = 0.005$).

In the BIG (Breast Investigation Group) 1–98 trial, hypercholesterolaemia was significantly more prevalent in patients treated with letrozole compared with patients receiving tamoxifen (43.5% vs 19.1%, respectively).[5]

However, recent results from the National Cancer Institute of Canada MA-17 trial lipid substudy showed no significant impact of letrozole on cholesterol (including LDL or HDL fractions), triglyceride or lipoprotein levels over a treatment period of 3 years following 5 years of tamoxifen therapy.[44]

4.3.3 Exemestane

Exemestane was first evaluated in a 9-week study, in which plasma changes in fasting samples from patients with breast cancer demonstrated a significant decrease in total cholesterol ($p < 0.01$), triglyceride ($p = 0.023$) and apolipoprotein A1 ($p < 0.01$) levels.[45] Additionally, there was also a significant decrease in HDL-C ($p < 0.01$) levels and the apolipoprotein A1 **:** apolipoprotein B atherogenic risk ratio ($p < 0.01$).

In contrast, a substudy of a phase II randomised trial did not find that treatment with either exemestane or tamoxifen had a significant effect on total cholesterol, HDL-C, apolipoprotein A1 or apolipoprotein B levels in postmenopausal women with metastatic breast cancer (samples measured at 8, 24 and 48 weeks).[46] At week 24, treatment with exemestane was associated with a significant decrease in triglyceride levels from baseline ($p = 0.002$), whilst tamoxifen was associated with a non-significant increase in triglyceride levels over time ($p = 0.08$). The apolipoprotein A1 **:** apolipoprotein B and total cholesterol **:** HDL-C atherogenic risk ratios remained unchanged throughout the treatment period in both groups.

4.3.4 Comparative Studies

An additional study has compared the effects of adjuvant exemestane and anastrozole on serum lipids in 180 postmenopausal women with operable breast cancer.[47] After 12 weeks of treatment, exemestane and anastrozole had no clinically significant impact on total cholesterol, HDL-C, LDL-C or triglyceride levels compared with baseline. However, anastrozole did show a numerical increase in HDL-C levels whereas exemestane showed a decrease in HDL-C levels.

Finally, a recent randomised study, the LEAP (Letrozole, Exemestane, and Anastrozole Pharmacodynamics) trial, compared the lipid profiles of 90 evaluable healthy volunteers, receiving either anastrozole 1mg, letrozole 2.5mg or exemestane 25mg once daily for 24 weeks.[48] Fasting serum samples were taken at baseline and after 2, 12, 24 and 36 weeks (12 weeks post-treatment). Results showed no significant changes of lipid parameters for women exposed to anastrozole, whereas letrozole induced a significant increase of triglyceride levels without effect on the atherogenic ratios. Exposure to exemestane resulted in a significant increase of the atherogenic ratios LDL-C **:** HDL-C and apolipoprotein B **:** apolipoprotein A1 compared with anastrozole and letrozole (table II).

Therefore, the molecular differences between anastrozole, letrozole and exemestane could play a role in the small variations seen in the lipid altera-

Table II. Percentage change from baseline in lipid parameters in the LEAP (Letrozole, Exemestane, and Anastrozole Pharmacodynamics) study[48]

Aromatase inhibitor	Sample date (weeks after baseline)	TC	TG	LDL-C : HDL-C	Non-HDL-C	APO-B : APO-A1
Anastrozole	12	−2.34	−2.93	−0.01	−2.74	−1.03
	24	+0.37	+0.28	+4.58	+1.35	−0.02
Letrozole	12	−3.77	+9.58[a]	−3.09	−4.16	−3.26
	24	−0.01	+5.40	+3.39	+1.22	−0.77
Exemestane	12	−5.58	+7.75	+8.81[b]	−3.49	+4.36[b]
	24	−3.94	+2.15	+16.97[b]	−0.57	+8.98[b]

a Significantly different from anastrozole.

b Significantly different from anastrozole and letrozole.

APO-A1 = Apolipoprotein A1; **APO-B** = Apolipoprotein B; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **TC** = total cholesterol; **TG** = triglycerides.

tions induced by the third generation AIs. Although these differences between the AIs may not significantly influence clinical efficacy,[37] it is not known whether these modified lipid profiles may translate into a long-term increased risk of CV disease.

5. CV Risk and Aromatase Inhibitors

5.1 Aromatase Inhibitors in Advanced Breast Cancer

The randomised, double-blind, multicentre, North American study of 353 patients has evaluated the effects of anastrozole (n = 171) and tamoxifen (n = 182) as first-line treatment for advanced breast cancer. At a median follow-up of 17.7 months, thromboembolic events were reported in fewer patients who received anastrozole than in those who received tamoxifen (4.1% vs 8.2%, respectively).[2] Other CV events were not predefined and were, therefore, not reported.

There are no data on predefined CV adverse events for letrozole or exemestane in the first-line advanced breast cancer setting; however, in a large randomised trial of 907 patients comparing letrozole (n = 453) with tamoxifen (n = 454), thromboembolic events were less frequent with letrozole (<1% vs 2%).[3]

In the second-line setting, an open-label, randomised trial has compared anastrozole (n = 357) with letrozole (n = 356) in patients progressing on tamoxifen (median duration of treatment 5.6 vs 5.9 months, respectively).[37] Beyond showing no differences in overall efficacy between the two AIs, this study unveiled only some slight numerical differences in the incidence of CV events: one case of myocardial infarction (MI) was reported in the group of patients receiving anastrozole compared with three cases with letrozole; one cerebrovascular accident was observed in patients receiving anastrozole compared with two with letrozole; and venous thromboembolism was seen in one patient re-

Table III. Number (percentage) of patients with prespecified cardiovascular (CV) events in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial at 33 and 68 months' median follow-up[7,49]

CV events	Median follow-up 33 months[49]			Median follow-up 68 months[7]		
	anastrozole (n = 3092)	tamoxifen (n = 3094)	p-value	anastrozole (n = 3092)	tamoxifen (n = 3094)	p-value
Ischaemic CV disease[a]	76 (2.5)	59 (1.9)	0.14	127 (4.1)	104 (3.4)	0.1
Ischaemic cerebrovascular	31 (1.0)	65 (2.1)	0.0006	62 (2.0)	88 (2.8)	0.03
Venous thromboembolic	64 (2.1)	109 (3.5)	0.0006	87 (2.8)	140 (4.5)	0.0004
Deep venous thromboembolic	32 (1.0)	54 (1.7)	0.02	48 (1.6)	74 (2.4)	0.02

a The events included in this category were angina pectoris, coronary artery disorder, myocardial ischaemia and myocardial infarction.

Table IV. Number of total deaths and cardiovascular deaths in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial at 68 months' median follow-up[7]

Deaths	Anastrozole (n = 3125)	Tamoxifen (n = 3116)	p-Value
Total	411	420	NR
breast cancer	235	265	0.2
non-breast cancer	176	155	NR
Cerebrovascular	14	21	NR
Cardiac	49	46	NR

NR = not reported.

ceiving anastrozole compared with two patients receiving letrozole.[37] The CV adverse events for exemestane in this setting were not predefined and therefore not reported.[50]

In summary, no CV-safety issues were identified for any of the AIs in the advanced breast cancer setting. However, there was only a relatively short drug exposure and CV events were not a focus of the safety analyses in these trials performed in patients with advanced disease.

5.2 Aromatase Inhibitors in Early Breast Cancer

5.2.1 Anastrozole

The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial is a large, randomised, double-blind trial comparing upfront anastrozole alone or in combination with tamoxifen in postmenopausal women in the primary adjuvant setting (figure 2a).[49] Of the 9366 women enrolled in the ATAC trial, 84% were HR-positive and 34% were node-positive. Initial analyses were conducted at 33[49] and 47[51] months' median follow-up, whereas recent data from 68 months' median follow-up extend beyond the scheduled 5-year treatment period, with only 8% of patients remaining on trial treatment.[7,52]

Consistent with the initial analyses of the ATAC trial data, the incidence of ischaemic cerebrovascular and thromboembolic events at 68 months was significantly reduced in patients treated with anastrozole compared with those treated with tamoxifen (table III).[7,49,52] There was a slight numerical increase, although not statistically significant, in ischaemic CV events with anastrozole compared with tamoxifen (127 [4.1%] vs 104 [3.4%], p = 0.1). The most common event was angina (71 vs 51, p = 0.07) in majority mild to moderate in severity. The incidence of other ischaemic CV events did not significantly differ between anastrozole and tamoxifen (73 vs 66, p = 0.5), whereas the frequency of MIs was comparable between the two treatment groups (37 vs 34, p = 0.7). The numbers of CV deaths remained low and similar for the two groups (49 vs 46, respectively) [table IV], with the majority of such deaths occurring only after treatment completion or discontinuation.[49,52]

ABCSG trial 8/ARNO 95 (Austrian Breast and Colorectal Cancer Study Group trial 8/Arimidex-Nolvadex 95) is a prospectively planned, event-driven combined analysis of two trials, both of which were randomised, open-label, multicentre studies with nearly identical inclusion criteria.[53] This analysis is assessing the efficacy of switching to anastrozole compared with continued tamoxifen treatment in 3224 postmenopausal women who have completed 2 years' adjuvant tamoxifen and who remain recurrence-free (figure 2b). Almost all patients (98%) enrolled were HR-positive and 26% were node-positive. Recent analyses of this trial were conducted at 28 months' median follow-up and at the time of disclosure of trial data, 55% of patients had completed 5 years of treatment.

According to data from the ABCSG trial 8/ARNO 95 combined analysis, the incidence of thromboses at 28 months' median follow-up was significantly reduced in patients who switched to anastrozole treatment compared with continued tamoxifen treatment (table V).[53] Patients who switched to anastrozole treatment also showed a trend towards fewer emboli. Consistent with the ATAC anastrozole data in the primary adjuvant

Table V. Number (percentage) of patients reporting cardiovascular (CV) events in the ABCSG trial 8/ARNO 95 (Austrian Breast and Colorectal Cancer Study Group trial 8/Arimidex-Nolvadex 95) combined analyses at 28 months' median follow-up[53]

CV events	Anastrozole (n = 1602)	Tamoxifen (n = 1597)	p-Value
Thromboses	3 (<1)	12 (<1)	0.034
Embolism	2 (<1)	9 (<1)	0.064
Myocardial infarction	3 (<1)	2 (<1)	1.0

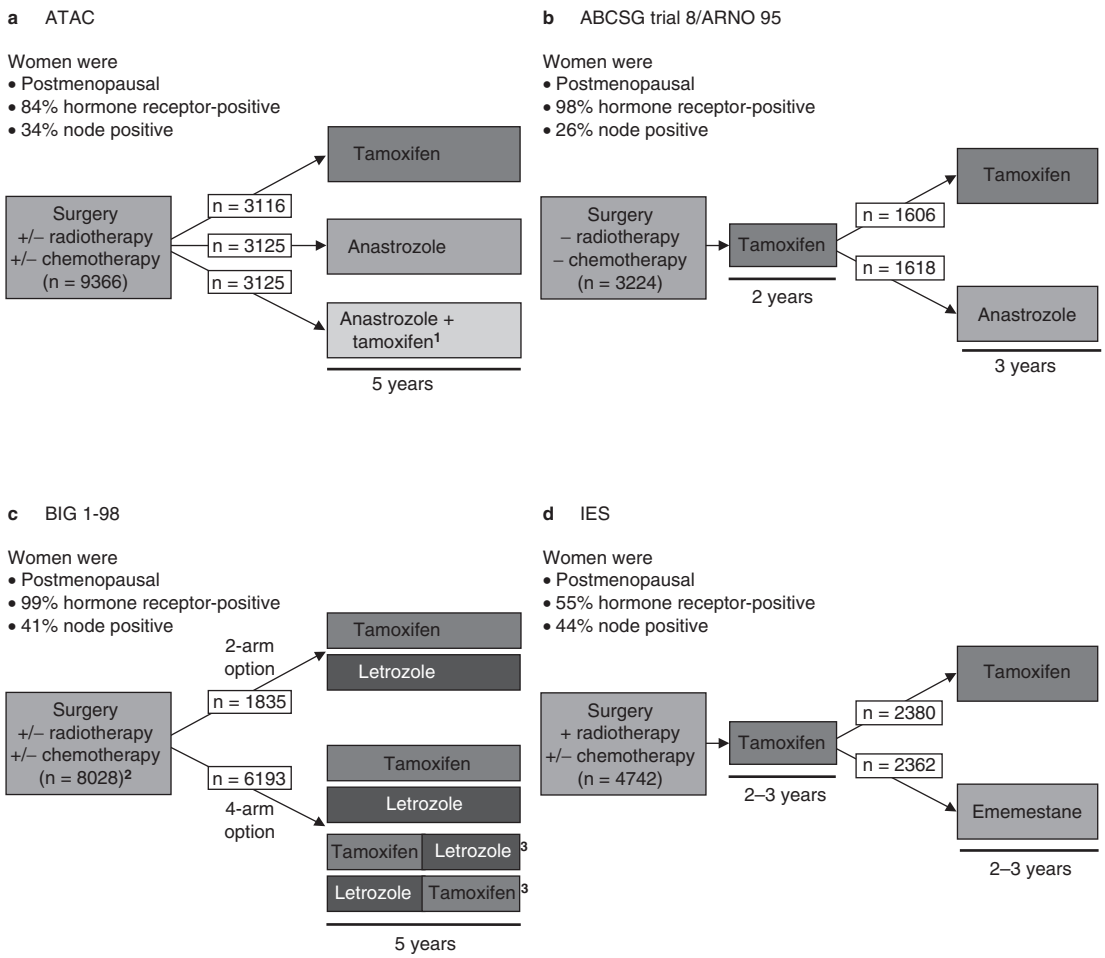

Fig. 2. Trial design for: (**a**) the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial;[49] (**b**) the ABCSG trial 8/ARNO 95 (Austrian Breast and Colorectal Cancer Study Group trial 8/Arimidex-Nolvadex 95) combined analysis;[53] (**c**) the BIG (Breast International Group) 1–98 trial;[5] and (**d**) the IES (Intergroup Exemestane Study).[6] **1** = Based on the findings of the first analysis at 33 months' median follow-up, the combination arm was discontinued because it demonstrated no efficacy or tolerability benefit compared with tamoxifen monotherapy. **2** = 4007 patients randomised to receive tamoxifen and 4003 patients randomised to receive letrozole as their initial adjuvant treatment were included in the primary core analysis (18 withdrew consent and received no study treatment). **3** = Sequential data not available until 2008.

setting,[7,49,52] there was no difference in MI in patients switching to anastrozole compared with those who continued tamoxifen treatment (table V).[53] CV deaths in this trial were not predefined and therefore not reported.

A similar, though smaller trial, the ITA (Italian Tamoxifen Anastrozole) trial, is a randomised, multicentre trial of continued tamoxifen versus switching to anastrozole in 448 postmenopausal women, of whom 89% were HR-positive, who had already received 2–3 years of tamoxifen. Data from the ITA trial are available at a follow-up of 36 months.[54]

CV data from the ITA trial are limited to the incidence of CV disease, which showed no significant difference between the tamoxifen group and the anastrozole group (9.3% and 7.9%, respectively; p = 0.4); CV deaths have not been reported.[54]

Table VI. Percentage of patients reporting grade 3–5 cardiovascular (CV) events in the BIG (Breast International Group) 1-98 trial at 26 months' median follow-up[5]

CV events	Letrozole (n = 3975)	Tamoxifen (n = 3988)	p-Value
All cardiac	2.1	1.1	0.0003
Ischaemic heart disease	1.1	0.6	0.013
Cardiac failure	0.5	0.1	0.006
CVA/TIA	1.0	1.0	1.0
Thromboembolic	0.8	2.1	<0.0001

CVA/TIA = cerebrovascular adverse events/transient ischaemic attack.

5.2.2 Letrozole

The BIG 1–98 trial is a prospective, randomised, double-blind, four-arm trial comparing upfront letrozole to either upfront tamoxifen, a sequence of tamoxifen followed by letrozole or a sequence of letrozole followed by tamoxifen in 8028 postmenopausal women in the primary adjuvant setting (figure 2c).[5] Almost all patients (99%) enrolled into the trial were HR-positive and 41% had node-positive disease (figure 2c). Only a limited number of patients (15%) have so far been followed up for 5 years. Preliminary data from the primary core analysis comparing letrozole with tamoxifen have been released with a 26 months' median follow-up and the majority of patients still on study treatment.

In keeping with previous observations in advanced disease,[3] the number of thromboembolic events in the BIG 1-98 trial was significantly reduced with letrozole compared with tamoxifen ($p < 0.0001$) [table VI].[5] There was no difference in the incidence of cerebrovascular adverse events/transient ischaemic attack with letrozole versus tamoxifen. However, patients treated with letrozole experienced a significantly greater incidence of grade 3–5 cardiac events than patients treated with tamoxifen (2.1% vs 1.1%, respectively; $p = 0.0003$). These events consisted mostly of ischaemic heart disease and cardiac failures. A total of seven cerebrovascular deaths were reported with letrozole therapy compared with one with tamoxifen. A doubled number of cardiac deaths was also reported with letrozole compared with tamoxifen (13 vs 6, respectively) [table VII]. However, the number of thromboembolic deaths was the same for both letrozole and tamoxifen. The majority of CV deaths with letrozole occurred whilst on study treatment. However, these CV deaths should be put in the context of the total deaths without recurrence (letrozole 55 vs tamoxifen 38) and the total number of deaths in the trial (letrozole 166 vs tamoxifen 192; p = not significant [ns]).

The MA-17 trial differs significantly from the other adjuvant AIs trials from the fact that the AI (letrozole) is being compared with placebo after 5 years of adjuvant therapy with tamoxifen in patients with receptor-positive breast cancer.[30] A total of 5187 patients (letrozole 2593 patients and placebo 2594 patients) were randomised in this double-blind, placebo-controlled trial and results are available with 30 months' median follow-up.

CV data from the MA-17 trial showed no overall significant difference between letrozole and placebo (5.8% and 5.6%, respectively; $p = 0.76$) [table VIII]. This reported in terms of ischaemic heart disease, stroke/transient ischaemic attacks as well as for thromboembolic events (0.4% vs 0.2%).[30]

5.2.3 Exemestane

The IES (Intergroup Exemestane Study) is assessing the efficacy of switching to exemestane compared with continued tamoxifen treatment in postmenopausal women (figure 2d).[6,50] The IES differs from the ATAC and BIG 1–98 studies in that it does not compare an AI with tamoxifen in the primary adjuvant setting, but is similar to ABCSG trial 8/ARNO 95 as this trial compares switching to

Table VII. Number (percentage) of total deaths and cardiovascular deaths in the BIG (Breast International Group) 1-98 trial at 26 months' median follow-up[5]

Deaths	Letrozole (n = 4003)	Tamoxifen (n = 4007)	p-Values
Total	166 (4.1)	192 (4.8)	0.155
Deaths without recurrence	55 (1.4)	38 (0.9)	0.077
Cardiac	13 (0.3)	6 (0.1)	NR
Cerebrovascular	7 (0.2)	1 (<0.1)	NR
Venous thromboembolic	2 (<0.1)	2 (<0.1)	NR
Sudden/other	10/23	10/19	NR

NR = not reported.

Table VIII. Number (percentage) of patients reporting cardiovascular (CV) events in the MA-17 trial at 30 months' median follow-up[30]

CV events	Letrozole (n = 2572)	Placebo (n = 2577)	p-Value
Total CV events	149 (5.8)	144 (5.6)	0.76
Myocardial infarctions	9 (0.3)	11 (0.4)	NR
new or worsening angina	31 (1.2)	23 (0.9)	NR
angina with intervention[a]	8 (0.3)	19 (0.8)	NR
CVA/TIA	17 (0.7)	15 (0.6)	NR
Thromboembolic disease	11 (0.4)	6 (0.2)	NR

a Percutaneous transluminal coronary angioplasty or coronary artery bypass graft.

CVA/TIA = cerebrovascular adverse events/transient ischaemic attack; **NR** = not reported.

an AI after 2–3 years of tamoxifen with continued tamoxifen treatment for a total of 5 years of adjuvant treatment. IES has a large patient population (4742 patients) with a higher percentage of patients with node-positive disease (44%), but a lower percentage of patients with HR-positive disease (55%) than the ABCSG trial 8/ARNO 95 trials. Two interim analyses of the IES were conducted at 30.6 and 37.4 months.[6,50] A recent update at 55 months' median follow-up was presented at the 2006 ASCO meeting.[56]

In the early analysis at 37.4 months' median follow-up, there was no significant difference in the overall incidence of CV events between the two treatment arms in the IES (exemestane: 42.6% vs tamoxifen: 39.2%; p = 0.11).[6] Thromboembolic disease was significantly less frequent with exemestane compared with tamoxifen (1.0% vs 1.9%, respectively, p = 0.003). There were significantly more MIs in the exemestane arm compared with tamoxifen (20 vs 8, respectively; p = 0.02) [table IX].[55] However, 14 MIs occurred when patients were on exemestane versus seven on tamoxifen (p = ns).

In the recent updated analysis at 55 months' follow-up, the overall incidence of CV events was similar between exemestane and tamoxifen (22.1% vs 20.9%, respectively, p = 0.34), with confirmation of less thromboembolic events with exemestane (1.9% vs 3.1%, respectively, p = 0.01) [table X]. The incidence of ischaemic cardiac events was not significantly different between exemestane and tamoxifen (9.9% vs 8.6%, respectively; p = 0.12) as was the frequency of MIs (1.3% vs 0.8%, respectively, p = 0.08) and angina (7.1% vs 6.5%, respectively, p = 0.44). There was no difference in terms of cardiac failure (1.8% vs 1.8%, respectively, p = 0.94) and peripheral vascular disease (1.0% vs 0.8%, respectively, p = 0.51) between the two treatment groups. Additionally, the number of cardiac deaths was similar in both arms (table XI).

The TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial is currently underway to compare upfront exemestane with tamoxifen, but the first analysis is not yet available.

6. Potential Clinical Issues Arising from Aromatase Inhibitor Use

Except for a beneficial effect on thromboembolic events compared with tamoxifen or megestrol, the use of AIs in advanced breast cancer did not identify any CV issues when evaluated in large randomised trials.[1-3,28] The duration of exposure to AIs in these metastatic breast cancer studies was usually limited and therefore may have underestimated the toxicity profile related to the long-term use of these compounds. In this regard, large-scale adjuvant trials are fundamental for endocrine therapy in defining the long-term therapeutic index and establishing a mature drug safety profile. Since, no particular CV

Table IX. Number of patients reporting cardiovascular (CV) events in the IES (Intergroup Exemestane Study) at 37.4 months' median follow-up[55]

CV events	Exemestane[a]	Tamoxifen[a]	p-Value
CV disease other than MI	984 (42.6)	913 (39.2)	0.11
All MIs	20 (0.9)	8 (0.4)	0.02
MIs on treatment	14 (0.7)	7 (0.3)	ns
Thromboembolic disease	24 (1.0)	45 (1.9)	0.003
Serious adverse events	30 (1.3)	55 (2.4)	0.007

a Data on CV disease were available for 2309 patients in the exemestane group and 2322 patients in the tamoxifen group. Data for thromboembolic disease was available for 2305 patients in the exemestane group and for 2329 patients in the tamoxifen group.

MI = myocardial infarction; **ns** = not significant.

concerns were raised in the metastatic trials with AIs, the majority of adjuvant studies evaluating anastrozole, letrozole and exemestane did not predefine CV parameters (except usually for thromboembolic events) in their trial design and statistical plans.

The only available mature data are coming from the ATAC trial, in which the long-term adjuvant treatment with anastrozole (5 years) showed similar incidences of MI and CV death compared with adjuvant treatment with tamoxifen.[7] Additionally, anastrozole significantly reduced the relative incidence of cerebrovascular and thromboembolic events. This CV-safety profile of anastrozole was further confirmed by the ABCSG 8/ARNO 95 trials, in which no significant difference in MIs compared with continued tamoxifen treatment was found.[53,57]

Data on letrozole from the BIG 1–98 trial showed a significant increase of grade 3–5 cardiac events with letrozole compared with tamoxifen ($p = 0.0003$) with an increased rate of cardiac failure ($p = 0.006$) and a doubling incidence of ischaemic heart disease ($p = 0.013$) and cardiac deaths.[5] In contrast, the MA-17 trial did not identify any significant difference in terms of CV events between the two patient groups.[30] These results are important because so far they are the only documented CV-safety data comparing letrozole with placebo. All the other trials are actually evaluating the differential CV impact between AIs and tamoxifen, which is known to have a significant CV impact consisting of more thromboembolic events and slightly less CV adverse effects.[16,17] Interestingly, there were more thromboembolic events in MA-17 in the letrozole group (11 events, 0.4%) compared with placebo (6 events, 0.2%). However, the number of thromboembolic events was significantly reduced with letrozole compared with tamoxifen ($p < 0.0001$) in the BIG 1-98 trial.[5]

The available data with exemestane (55 months' median follow-up) showed that switching to exemestane after 2–3 years' tamoxifen treatment was not associated with an increased risk of overall cardiac events nor a significant increase of MI ($p = 0.08$) compared with tamoxifen treatment.[6,55]

These increases in CV events and potentially CV deaths with letrozole in the BIG 1-98 should be interpreted with caution. These CV events were observed only in a trial comparing this endocrine agent with tamoxifen, whereas no difference in CV toxicity was reported in the MA-17 trial comparing letrozole and placebo. Moreover, the durations of exposure to AIs in these studies are 2–3 years, and, thus, longer follow-up is needed to evaluate more thoroughly the real CV impact of letrozole and exemestane. Unfortunately, these data will not come from the switching or extended therapy trials in which the exposure to AIs is limited to 2–3 years. Thus, we will have to wait for mature data from the BIG 1–98 and the TEAM trials.

Are there reasons which could account for differences of incidence of CV disease between the three AIs? Beyond the evident structural and molecaular differences between the AIs, a potential explanation for the differences in CV safety could be the differences between the three compounds in terms of selectivity for the aromatase enzyme. Anastrozole appears to be highly selective for the aromatase enzyme and, therefore, does not have any clinically relevant effect on adrenal function,[32,33] whereas letrozole may be slightly less selective for the aromatase enzymatic complex with a significant impact on ACTH-stimulated cortisol and aldosterone.[34] Although exemestane has no significant effect on

Table X. Percentage of patients with cardiovascular (CV) events in the IES (Intergroup Exemestane Study) at 55 months' median follow-up[56]

CV events	Exemestane[a]	Tamoxifen[a]	p-Value
All CV disease	22.1	20.9	0.34
Iscaemic cardiac	9.9	8.6	0.12
MIs	1.3	0.8	0.08
angina	7.1	6.5	0.44
Other cardiac events	11.3	11.2	0.96
heart failure	1.8	1.8	0.94
Thromboembolic disease	1.9	3.1	0.01
Cerebrovascular events	2.5	2.4	0.89

a Data available for 2320 patients in the exemestane group and 2338 patients in the tamoxifen group.

MI = myocardial infarction.

Table XI. Number of cardiovascular (CV) deaths in the IES (Intergroup Exemestane Study) at 55 months' median follow-up

CV events	Exemestane	Tamoxifen	p-Value
Total	222	261	0.08
Vascular	17	11	ns
Cardiac	14	13	ns

ns = not significant.

basal cortisol and aldosterone levels, the effect of exemestane on ACTH-stimulated cortisol and aldosterone levels is unknown.[35] It has also frequently been questioned whether the small differences in plasma estrogen suppression induced by the third-generation AIs could be of biological importance. It is clear that a reduction in endogeneous estrogen is associated with an increased risk of CV disease;[18] therefore, the slightly increased inhibition of aromatase by letrozole and exemestane compared with anastrozole could, although not impacting on clinical efficacy, have the potential to increase the risk of CV disease when used long-term.

The effects of AIs on lipid profiles may also be a contributing factor to the increased risk of CV disease, although it is not known if small alterations of the lipid profile may translate into different risks of CV events in adjuvant setting.

The differences between anastrozole, letrozole and exemestane, in their molecular structure, their selectivity for the aromatase enzyme, their ability to reduce plasma estrogen levels and their impact on lipid composition, may play a role in explaining the potential differences in CV safety profiles. Whilst these differences may not influence the clinical efficacy, the overall risk-benefit profile, including the potential for increased risk of CV disease, must be considered when choosing an AI for the treatment of postmenopausal women with HR-positive breast cancer.

7. Conclusions

The reduction in endogenous estrogen induced by menopause appears to reduce any cardioprotective effects, accelerating the incidence of CV disease. There is also an increased risk of venous thromboembolism in oncology patients, which is further increased in postmenopausal women receiving chemotherapy and/or certain endocrine therapies, such as tamoxifen.[16,17,19] However, third-generation AIs, anastrozole, letrozole and exemestane, have been shown to reduce the risk of thromboembolic events compared with tamoxifen in postmenopausal women with HR-positive breast cancer,[5,7,55] but until recently there has been insufficient evidence to determine the effects of these AIs on CV disease.

AIs are molecularly distinct, which is reflected in their differential abilities to inhibit aromatisation, reduce plasma estrogen levels and impact on lipid composition. Although there appear to be no significant differences in clinical efficacy, data from the use of AIs in the adjuvant setting suggest that some differences between the AIs may result in different CV safety profiles. Anastrozole has the only set of mature data with 5 years exposure compared with tamoxifen in primary adjuvant therapy.[7,52] No CV-safety concerns have arisen from these results showing a similar number of CV events and deaths in both treatment arms. Moreover, there was a significant reduction in cerebrovascular and thromboembolic events with anastrozole compared with tamoxifen. Additionally, the ABCSG trial 8/ARNO 95 trials confirmed no significant difference in MIs in patients switching to 2–3 years of anastrozole compared with those continuing the tamoxifen treatment. Analysis of the BIG 1–98 trial showed a significantly higher number of grade 3–5 cardiac events with upfront adjuvant letrozole compared with tamoxifen, contributing to a higher number of cerebrovascular and cardiac deaths. However, these findings were not observed in the MA-17 trial. In the switch IES, there was no overall increase in the incidence of CV events, whereas the MIs were numerically increased (without reaching the statistical significance [p = 0.08]) for patients switching to exemestane compared with those who continued

tamoxifen treatment. Additionally, there was no difference in cardiac deaths between the two treatments.

Clearly, more data are needed to fully evaluate the CV effects of letrozole and exemestane. Mature results from upfront trials evaluating 5 years exposure to letrozole (BIG 1–98) or to exemestane (TEAM) versus tamoxifen will define the real CV-safety profiles and therapeutic index of these two AIs.

The differences between anastrozole, letrozole and exemestane, in their molecular structure, their selectivity for the aromatase enzyme, their ability to reduce plasma estrogen levels and their impact on lipid composition, may play a role in explaining the potential differences in CV safety profiles. Whilst these differences may not influence the clinical efficacy, the overall benefit-risk profile, including the potential for increased risk of CV disease, must be considered when choosing an AI for the treatment of postmenopausal women with HR-positive breast cancer.

Acknowledgements

The authors would like to thank Dr Sarah Goodger from CMC, who provided partial medical writing and editing support. Dr Goodger's services were covered by a grant from AstraZeneca. No other funding was received for the preparation of this paper. Professor Nabholtz is a member of the AstraZeneca Speakers Bureau. Dr Gligorov has no conflicts of interest relevant to the contents of this review.

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