

# The effects of aromatase inhibitors on lipids and thrombosis

NJ Bundred\*,<sup>1</sup>

<sup>1</sup>South Manchester University Hospital, Academic Surgery, Education and Research Centre, Southmoor Road, Manchester M23 9LT, UK

Oestrogen is known to influence blood lipid levels and though its cardioprotective effects are less clear than once thought, there remains concern that reduction of oestrogen levels during hormonal treatment for breast cancer may have an adverse effect on cardiovascular risk. While tamoxifen has been shown to improve lipid profiles, the aromatase inhibitors have a very different mode of action and do not possess the oestrogen-agonistic effects of tamoxifen. At present, there are few data on the effects of these agents on lipid profiles. Available data are mixed, but suggest that the different aromatase inhibitors have different effects on lipid profiles. Some studies show anastrozole as generally having little effect on lipids, while others have indicated adverse effects on lipid profiles/increased hypercholesterolaemia. Letrozole has been associated with adverse effects on lipid profiles in some studies, including BIG 1-98, but short-term data from randomised trials do not show increased cardiovascular morbidity. By contrast, exemestane, which has been studied in slightly more detail, may either have little effect or may be associated with slightly improved lipid profiles. In general, the changes have been small and are likely to be of little relevance in women with advanced breast cancer, but if these agents come to be used in early breast cancer, their impact on lipid profiles may become more important. Many studies are currently underway with the aromatase inhibitors, with safety assessments including monitoring lipid levels. The results of these studies are keenly awaited. *British Journal of Cancer* (2005) **93**(Suppl 1), S23–S27. doi:10.1038/sj.bjc.6602692 www.bjcancer.com  
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Clinical evidence points to low-density lipoprotein (LDL) cholesterol as the key factor in the pathogenesis of atherosclerosis and coronary heart disease (CHD), while high-density lipoprotein (HDL) cholesterol appears to have a protective effect. Increases in LDL cholesterol are associated with increased risk for CHD, even when total cholesterol concentration is within the normal range. Women generally appear to have higher levels of HDL cholesterol than men. Furthermore, some studies have suggested that low levels of HDL cholesterol, particularly high total/HDL ratio or low HDL<sub>2</sub> subfraction, could be a more significant risk factor for women than men, with total cholesterol being less important for women (Kannel, 1987; Miller-Bass *et al*, 1993). The role of triglycerides is controversial, but elevated triglycerides have been suggested to be a stronger predictor of cardiovascular diseases in women than in men (Korhonen *et al*, 1996; La Rosa, 1997). Finally, high lipoprotein (a) (Lp(a)) levels have been associated with an increased risk both in women and men (Danesh *et al*, 2000).

Oestrogen is known to affect blood lipids, with levels of HDL cholesterol increasing and LDL cholesterol decreasing with rising levels of oestrogen. Reduced oestrogen levels, such as occurs at menopause, has been found to cause atherogenic alterations in lipid and lipoprotein profiles in epidemiological studies comparing premenopausal women with menopausal and postmenopausal women (Schaefer *et al*, 1994; de Aloysio *et al*, 1999; Tremollieres *et al*, 1999), and also in longitudinal trials (Do *et al*, 2000). Increases in both total and LDL cholesterol concentrations are seen during menopause. Additionally, a shift to smaller, denser and potentially more atherogenic LDL particle sizes has been noted (Campos *et al*, 1988). Data on HDL cholesterol have been

inconsistent, as HDL cholesterol has been reported to remain unaffected in some studies (Kannel, 1987), while others have noted a decline of HDL cholesterol, particularly HDL<sub>2</sub> subfraction, with a rise of HDL<sub>3</sub> cholesterol, which may result in an unfavourable net effect (Matthews *et al*, 1994). Increases in plasma triglycerides and Lp(a) concentrations have also been reported after menopause (Stevenson *et al*, 1993).

However, there has been controversy about the importance of endogenous oestrogens to cardiovascular risk, because age and menopause are closely related and lipid profiles change with age. In fact, the influence of menopause on lipoprotein changes varies between different studies (Stevenson *et al*, 1993), and its influence has been suggested to be lower when age and other confounding factors are taken into account (Matthews *et al*, 1994; de Aloysio *et al*, 1999).

For many years it was accepted that hormone replacement therapy with oestrogen could partly reverse the increase in cardiovascular risk occurring at menopause. However, the cardioprotective effects of exogenous oestrogen have now been called into question (Hulley *et al*, 1998; Women's Health Initiative Steering Committee, 2004). Despite doubts surrounding the effects of oestrogen on cardiovascular risk, there remains concern that lowering oestrogen levels during adjuvant therapy for breast cancer might have detrimental effects on lipid levels and might also increase cardiovascular risk. This is particularly relevant given that the greatest cause of death in women with early stage breast cancer is heart disease (Levi *et al*, 2002). Although tamoxifen has not been shown to increase the risk of cardiovascular disease, it has a very different mode of action from the aromatase inhibitors, which are increasingly being used in the adjuvant setting. This has triggered considerable interest in the lipid effects of these agents.

\*Correspondence: Professor NJ Bundred;  
E-mail: Nigel.J.Bundred@manchester.ac.uk

## EFFECTS OF ANTI-OESTROGEN TREATMENT ON LIPID PROFILES

### Tamoxifen

Tamoxifen has oestrogenic agonist effects on blood lipids, with several studies describing small changes in plasma lipoprotein concentrations, most of the changes potentially reducing the risk of cardiovascular disease (Dziewulska-Bokiniec *et al*, 1994; Thangaraju *et al*, 1994; Love *et al*, 1994; Grey *et al*, 1995; Decensi *et al*, 1998; Vrbanec *et al*, 1998; Cushman *et al*, 2001). Total and LDL cholesterol levels are decreased (Grey *et al*, 1995) and there is a tendency for HDL cholesterol levels to be increased, although this is often marginal (Thangaraju *et al*, 1994; Love *et al*, 1994; Decensi *et al*, 1998; Vrbanec *et al*, 1998). Tamoxifen has also been shown to lower Lp(a) levels (Decensi *et al*, 1998). Triglyceride levels appear to increase (Dziewulska-Bokiniec *et al*, 1994; Grey *et al*, 1995). Levels of apolipoprotein B-100 and apolipoprotein A-I are also reduced with tamoxifen (Elisaf *et al*, 1996). These effects are thought to be caused by the ability of tamoxifen to act as a partial agonist in some tissues. By contrast, the aromatase inhibitors do not have oestrogenic effects, which has led to concern about possible detrimental effects to lipid profiles.

### Aromatase inhibitors

To date, few studies have been conducted that include an assessment of lipid effects, and conflicting results have been obtained from those that have. The different aromatase inhibitors appear to have different effects on lipid profiles (Table 1). This may be a result of their different modes of action. Anastrozole and letrozole are nonsteroidal aromatase inhibitors, while exemestane is a steroidal aromatase inhibitor. The steroidal inhibitors are analogues of androstenedione and bind to the same site on the aromatase molecule, but unlike androstenedione they bind irreversibly, because of their conversion to reactive intermediates by aromatase. The nonsteroidal agents, by contrast, bind reversibly to the heme group of the enzyme.

**Anastrozole** In several small studies, anastrozole showed no marked effects on lipid profile (Dewar *et al*, 2000; Kataja *et al*, 2002; Sawada and Sato, 2003; Wojtacki *et al*, 2004). Kataja *et al*, (2002) showed LDL levels fell with both exemestane and anastrozole and triglycerides fell with exemestane, but remained stable with anastrozole. However, anastrozole was associated with a higher incidence of hypercholesterolaemia than tamoxifen in the ATAC study (ATAC Trialists Group, 2002). In the Italian Tamoxifen Arimidex (ITA) trial, patients switching to anastrozole after 2 or more years of tamoxifen were also found to have higher levels of hypercholesterolaemia than those continuing on tamoxifen, 8.1 and 2.7%, respectively (Boccardo *et al*, 2003). In addition, a recent study of the effect of anastrozole on serum lipid profiles in 38 postmenopausal patients with breast cancer found significant increases in total cholesterol, LDL and HDL cholesterol, apolipoprotein A1, B and Lp(a) (Hozumi *et al*, 2004). Anastrozole was

associated with a slightly higher incidence of ischaemic cardiovascular disease than tamoxifen in the ATAC study, but this was not significant (ATAC Trialists Group, 2002).

**Letrozole** Increases in total serum cholesterol, LDL cholesterol, apo B and serum-lipid risk ratios for cardiovascular disease were found in some studies (Nicolaidis *et al*, 2000; Elisaf *et al*, 2001), while others have found no changes in lipid profile (Harper-Wynne *et al*, 2001). In the first interim analysis of a 5-year study of letrozole therapy after the completion of 5 years' tamoxifen treatment, Goss *et al* (2003) found no significant differences in the rates of cardiovascular events between the letrozole group (4.1%) and the placebo group (3.6%), and there were no reports of drug-related hypercholesterolaemia. By contrast, the first results of the BIG 1-98 trial comparing letrozole with tamoxifen have shown that 43.6% of letrozole-treated patients developed mild to moderate hypercholesterolaemia vs 18.2% of tamoxifen-treated patients (Thurlimann, 2005). While more tamoxifen-treated patients suffered thromboembolic events than letrozole patients (grades 3-5, 2 vs 0.8%), a higher incidence of cardiovascular events was seen with letrozole-treated patients than tamoxifen patients (grades 3-5, 3.6 vs 2.5%), although this was not significant. Longer-term follow-up will be required to establish the significance of hypercholesterolaemia seen in the BIG 1-98 trial (Thurlimann, 2005).

**Exemestane** The lipid effects of exemestane have, perhaps, been more closely studied than those of the other aromatase inhibitors. In animal studies, exemestane reversed the increase in LDL cholesterol and total cholesterol seen in ovariectomized cycling Sprague-Dawley rats (Goss *et al*, 2001).

In a 3-month study compared with anastrozole and tamoxifen in postmenopausal women with breast cancer ( $n = 30$ ), exemestane produced a small decrease in serum cholesterol and LDL cholesterol, decreases in triglycerides and HDL cholesterol (Kataja *et al*, 2002). In the same study, anastrozole showed similar results except for a small increase in HDL cholesterol (Kataja *et al*, 2002). The EORTC trial 10951 randomized 382 postmenopausal breast cancer patients to exemestane or tamoxifen once daily as first-line treatment in the metastatic setting (Atalay *et al*, 2004; Paridaens *et al*, 2004). A companion substudy to this trial analysing effects on lipid profiles revealed no adverse effects on total cholesterol, HDL cholesterol, apolipoprotein A1 and B or Lp(a) levels at 8, 24 and 48 weeks of treatment with either exemestane or tamoxifen (72 patients included in the statistical analysis) (Atalay *et al*, 2004). By contrast, exemestane decreased but tamoxifen increased triglyceride levels. In the Greek substudy of the TEAM trial, which is comparing tamoxifen with exemestane as initial therapy, baseline lipid levels have been compared with levels at 3 and 6 months of treatment in 37 patients. At 6 months, exemestane appeared to stabilize total cholesterol and HDL cholesterol levels as did tamoxifen (Markopoulos *et al*, 2003). Exemestane had a non-significant trend to increase LDL cholesterol levels at 3 and 6 months, but reduced triglyceride levels at both time points and

**Table 1** Effects of anti-oestrogen therapy on plasma lipid levels (Dewar *et al*, 2000; Nicolaidis *et al*, 2000; Elisaf *et al*, 2001; Goss *et al*, 2001, 2003; Harper-Wynne *et al*, 2001; ATAC, 2002; Kataja *et al*, 2002; Boccardo *et al*, 2003; Markopoulos *et al*, 2003; Sawada and Sato, 2003; Atalay *et al*, 2004; Coombes *et al*, 2004; Hozumi *et al*, 2004; Paridaens *et al*, 2004; Wojtacki *et al*, 2004)

	LDL cholesterol	HDL cholesterol	Total cholesterol	Triglycerides	Total:HDL cholesterol	Lp(a)	Apo B
Tamoxifen	↓	—	↓	?	?	↓	↓
Anastrozole	↑/—	↑/—	↑/—	—	—	↑/—	↑/—
Letrozole	↑/—	—	↑/—	—	↑/—	?	↑/—
Exemestane	↓/—	↓/—	↓/—	↓	?	—	—

Key: ↑ = increased; ↓ = decreased; — = no change; ? = unknown.

**Table 2** Incidence of thromboembolic events with aromatase inhibitors and comparators

Reference	Thromboembolic events (% of patients)		P-value
	Aromatase inhibitor	Comparator	
ATAC (2002)	Anastrozole 64 (2.1%)	Tamoxifen 109 (3.5%)	= 0.0006
Coombes <i>et al</i> (2004) (IES Trial)	Exemestane 30 (1.3%)	Tamoxifen 55 (2.4%)	= 0.007
Dombornowsky <i>et al</i> (1998)	Letrozole (2.5 mg) 1 (0%)	Megestrol acetate 15 (7.9%)	Unknown
Goss <i>et al</i> (2003) (MA-17 trial) (cardiovascular events)	Letrozole (0.5 mg) 2 (1%) Letrozole (2.5 mg) 88 (4.1%)	Placebo 77 (3.6%)	= 0.4

by about 10% at 6 months (Markopoulos *et al*, 2003). Finally, although cholesterol levels were not systematically measured in the recent IES study comparing exemestane with tamoxifen in 4742 women, it was noted that there was no significant difference in the incidence of myocardial infarction between the two groups (Coombes *et al*, 2004).

With regard to postmenopausal patients with early breast cancer, results were reported at the 2004 ASCO meeting of the effects of exemestane, 25 mg day<sup>-1</sup>, vs placebo on lipid and coagulation profiles (Krag *et al*, 2004). After 2 years, lipid profiles were similar for exemestane and placebo with decreased levels of cholesterol, LDL cholesterol, triglycerides, apolipoprotein A1 and B and Lp(a) seen in both groups. The only difference was a small decrease in HDL cholesterol seen with exemestane only (Krag *et al*, 2004).

### CLINICAL SIGNIFICANCE OF LIPID EFFECTS

The significance of changes in lipid profiles seen with different aromatase inhibitors is impossible to assess from the limited data available. The changes seen are generally small. For example, in the study by Elisaf *et al*, (2001), mean LDL cholesterol levels increased from 148 ± 50 to 170 ± 53 mg dl<sup>-1</sup> after 16 weeks with letrozole, while the total cholesterol to HDL cholesterol ratio increased from 3.94 ± 1.46 to 4.48 ± 1.40 after 16 weeks. Such a change might be sufficient to alter a patient's risk category from low to moderate depending on other risk factors, therefore triggering the need for lipid-lowering treatment.

The benefits of receiving an aromatase inhibitor are likely to outweigh the disadvantages of any changes to lipid profiles, particularly for patients with advanced disease. However, when aromatase inhibitors are used in early disease or in the prevention setting, an increase of 10–15% in circulating cholesterol and triglycerides may have a significant impact on the risk of cardiovascular disease, and monitoring of blood lipid levels and instigation of lipid lowering treatment if required should be undertaken. In such instances, the choice of agent may be particularly important in the adjuvant and prevention settings, and agents that have minimal effects on lipids will be preferred, especially if evidence of reduced cardiovascular morbidity can be demonstrated in clinical trials.

### EFFECTS OF ANTI-OESTROGEN TREATMENT ON STROKE AND THROMBOEMBOLISM

Tamoxifen increases the risk of venous thromboembolism, but it has been unclear as to the implications of this for risk of stroke. However, a recently published meta-analysis of tamoxifen breast cancer trials revealed an increased risk of stroke with tamoxifen compared with placebo/control (Bushnell and Goldstein, 2004). Results of the meta-analysis showed tamoxifen-treated patients had an 82% and a 29% increased risk of ischaemic stroke and

any stroke, respectively, although the authors noted that the absolute risk was small (Bushnell and Goldstein, 2004). The notable increased risk in ischaemic stroke was suggested to be a consequence of the tamoxifen-associated increase in thrombosis. Further studies with tamoxifen to include measurements of prespecified cerebrovascular outcomes will help to clarify the stroke risk with tamoxifen; meanwhile, tamoxifen may be best avoided for women with a history of stroke or thrombosis.

The risk of cerebrovascular and thromboembolic events has been seen to be significantly higher with tamoxifen than the aromatase inhibitors; for example, anastrozole was associated with significantly fewer ischaemic cerebrovascular events ( $P=0.0006$ ) and thromboembolic events ( $P=0.0006$ ) than tamoxifen in the ATAC trial (ATAC Trialists Group, 2002). Results of the IES study also showed thromboembolic events as more frequent with tamoxifen than exemestane ( $P=0.007$ ) (Coombes *et al*, 2004). In addition, no thromboembolic events were observed with letrozole at a dose of 2.5 mg in a study compared with megestrol acetate for advanced breast cancer (Table 2) (Dombornowsky *et al*, 1998). Since the aromatase inhibitors are not usually associated with thrombosis, women with a previous history of thrombosis or stroke should receive an aromatase inhibitor in preference to tamoxifen.

### ONGOING AND PLANNED CLINICAL TRIALS

Clearly, more data are needed before the relevance of the changes in lipid levels with aromatase inhibitors on cardiovascular morbidity can be determined. Indeed, most of the ongoing clinical trials are including analysis of lipid effects as part of their protocol. However, care needs to be taken when evaluating lipid effects in studies comparing aromatase inhibitors with tamoxifen, because tamoxifen itself influences lipid values.

Among the ongoing trials that will report on lipid changes are:

- MA17L: is a substudy of the MA17 study involving 300 patients randomised to letrozole or placebo after completing 5 years with tamoxifen.
- BIG FEMTA(1-98): is comparing 5 years of tamoxifen, 5 years of letrozole or sequenced therapy of 2–3 years each starting with either tamoxifen or letrozole.
- NSABP B33: is a randomised, placebo-controlled, double-blind trial evaluating the effect of exemestane in 3000 clinical stage T1-3 N0-1 M0 postmenopausal breast cancer patients completing at least 5 years of tamoxifen therapy.
- TEAM: preliminary lipid results have already been reported from this phase III randomised study of adjuvant exemestane vs adjuvant tamoxifen in 4400 postmenopausal women with early breast cancer (Markopoulos *et al*, 2003). Final results are awaited.
- ARNO: in this study, women receive 2 years of tamoxifen followed by randomisation to 3 years of either anastrozole or tamoxifen.

- ICCG: in this study, women receive 3 years of tamoxifen followed by 2 years of either tamoxifen or exemestane.
- IMPACT: compares anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of oestrogen receptor positive operable breast cancer in postmenopausal women.
- NCIC CTG MAP2: is a randomised study of the effect of exemestane vs placebo on breast density in postmenopausal women at increased risk for development of breast cancer.

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## CONCLUSIONS

Concern about lipid changes associated with aromatase inhibitors leading to increased cardiovascular deaths has not so far been borne out in the limited data from adjuvant trials. Of the available data on effects of aromatase inhibitors on serum lipids from short-term studies, exemestane has little or possibly a slight beneficial effect on serum lipids, and anastrozole appears to have little effect or possibly an adverse effect, while letrozole may have a detrimental effect.

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