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EPIDEMIOLOGY

Adjuvant aromatase inhibitor therapy and early markers for cardiovascular disease in breast cancer survivors

Annemiek van Ommen-Nijhof[1] · Judy N. Jacobse[2] · Lars C. Steggink[3] · Joop D. Lefrandt[4] · Jourik A. Gietema[5] · Flora E. van Leeuwen[6] · Michael Schaapveld[6] · Gabe S. Sonke[7,8]

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Abstract

Purpose Aromatase inhibitors (AIs) are an important component of the adjuvant treatment of hormone receptor positive breast cancer (BC) but concerns regarding their cardiovascular safety remain. In this cross-sectional study nested in a breast cancer cohort, we investigated the association between AI exposure and early markers for cardiovascular disease in BC survivors.

Methods The study population consisted of 569 women, who were 5–7 years ($n=277$) or 10–12 years ($n=292$) after BC diagnosis. All participants underwent carotid ultrasound, skin autofluorescence measurement and laboratory evaluation. To quantify AI exposure, we obtained the AI ratio by dividing the duration of AI use by the total duration of endocrine therapy (ET). Patients were classified according to their AI ratio into low (no ET or AI ratio <0.40), intermediate ($0.40 \leq$ AI ratio ≤ 0.60) or high AI exposure (AI ratio >0.60). The association between AI ratio and carotid intima media thickness (cIMT), advanced glycation end products (AGEs) and the presence of dyslipidemia was assessed using linear and logistic regression.

Results Median age at study visit was 55.5 years (range 45.2–63.8). Forty percent ($n=231$) of the study population had used AIs, of whom the majority sequentially with tamoxifen; median duration of AI use was 3.0 years. Mean cIMT and mean AGEs did not differ across AI exposure groups in univariable and multivariable analysis. The occurrence of dyslipidemia did not vary across AI exposure groups. Intermediate AI exposure was associated with more frequent occurrence of the combined endpoint (elevated cIMT, elevated AGEs and/or dyslipidemia). This association, however, was not present in the group with highest AI exposure.

Conclusion AI exposure was not associated with cIMT, AGEs or the presence of dyslipidemia. These results do not prompt a change in current clinical practice, although further research is warranted to validate our findings over time and in different BC populations.

Trial registration number (clinicaltrials.gov): NCT02485626, June 30, 2015.

Keywords Breast cancer · Endocrine therapy · Aromatase inhibitor · Cardiovascular disease

Judy N. Jacobse, Lars C. Steggink, Michael Schaapveld and Gabe S. Sonke contributed equally to this work.

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Abbreviations

AGEs	Advanced glycation end products
AI(s)	Aromatase inhibitor(s)
AU	Arbitrary units
BC	Breast cancer
BMI	Body mass index
CI	Confidence interval
cIMT	Carotid intima media thickness
CVD	Cardiovascular disease
DCIS	Ductal carcinoma in situ
ET	Endocrine therapy
HDL	High-density lipoprotein
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
ICD10	International classification of diseases, 10th edition
IQR	Interquartile range
LDL	Low-density lipoprotein
NKI–AVL	Netherlands Cancer Institute–Antoni van Leeuwenhoek
OR	Odds ratio

Introduction

Endocrine therapy (ET) is a key component in the adjuvant treatment of hormone receptor positive early breast cancer (BC). Tamoxifen was one of the first endocrine agents that became available, followed by aromatase inhibitors (AIs) [1]. Both tamoxifen and AIs negate the proliferative effects of estrogen on breast cancer cells, but their working mechanism differs [2]. Tamoxifen competitively antagonizes estrogen at its receptor site, but also has partial estrogen-agonist effects. AIs inhibit the enzyme aromatase, thereby inhibiting estrogen synthesis in peripheral tissue. Oncologic outcomes in early BC improved substantially as a result of the addition of AIs to the ET armamentarium [3]. Furthermore, AIs are not associated with an increased risk of thromboembolic events or endometrial cancer, whereas tamoxifen is [4, 5].

An important unresolved issue, however, is the cardiovascular safety of AIs. Several clinical trials raised concern about higher rates of cardiovascular events in patients treated with AIs compared to tamoxifen [6, 7]. Whether or not this reflects a true detrimental effect of AIs on cardiovascular disease (CVD) risk or a cardioprotective effect of tamoxifen (mainly attributed to the favorable effect on lipid profile [8]) is a matter of controversy. Several systematic reviews and meta-analyses have addressed the issue, with varying outcomes [9–16]. Given the oncological relevance of AIs, it is important to gain more insight into the cardiovascular safety of AIs and identify potential mechanisms for AI-induced CVD.

Previous studies on AI-induced CVD have mainly focused on clinically apparent CVD. Whilst clinical CVD is the most important outcome from a patient's perspective, these studies often require long follow-up and large patient numbers. In our study, we focus on subclinical measures for CVD, which are more readily available. Subclinical measures can increase knowledge on the underlying biology of the potential relation between endocrine therapy and CVD, and provide early clues for increased CVD risk, thereby enabling early interventions.

Intima media thickness (IMT) functions as a surrogate measure for atherosclerosis, and carotid-wall IMT (cIMT) predicts CVD and CVD mortality [17]. Advanced glycation end products (AGEs) are metabolic or oxidative stress-derived end products of sugars, usually protein-bound. The presence of AGEs in the skin is independently associated with adverse cardiovascular events [18]. Cholesterol is a widely acknowledged independent risk factor for CVD, and is often mentioned as an important intermediate factor in the relation between AI use and CVD [19].

In this cross-sectional study nested in an established BC cohort, we aimed to investigate the association between AI use and subclinical measures for CVD (cIMT, AGEs and cholesterol) in BC survivors.

Methods

Study design

We performed a cross-sectional study in an established cohort of women treated for invasive BC or ductal carcinoma in situ (DCIS) [20, 21]. Eligible patients had received treatment for invasive BC (TNM stage I-III) or DCIS at age 40–50 years in the Netherlands Cancer Institute–Antoni van Leeuwenhoek (NKI-AVL) or University Medical Center Groningen (UMCG) between 2002 and 2012. They were either 5–7 or 10–12 years after initial treatment. Patients could not participate if they had previously received radiotherapy or chemotherapy unrelated to BC/DCIS. Patients with a locoregional BC/DCIS recurrence or second BC/DCIS after initial diagnosis could participate if there was no ongoing therapy for recurrent or second disease. Patients with a history of overt CVD (defined as heart failure, acute coronary syndrome, coronary revascularization intervention, symptomatic valvular dysfunction or cardiomyopathy) before BC/DCIS diagnosis were excluded; patients who developed overt CVD after BC/DCIS diagnosis were included. The institutional review board of the NKI-AVL approved the study and it is registered with ClinicalTrials.gov, identifier NCT02485626.

Procedures

A written invitation describing the study objectives and procedures was sent to all eligible women. Non-responders received up to two reminders. Of 911 invited women, 569 provided informed consent and completed the study visit. Participants filled out a baseline questionnaire, including items on current and past lifestyle factors, the presence of cardiovascular risk factors, family history of CVD, and the use of and compliance with ET. Detailed data on tumor and treatment characteristics, including the use and duration of ET, medical history, cardiovascular risk factors and medication use were abstracted from medical records or obtained from hospital registries and the participants' general practitioner. At study visit, sociodemographic variables, recent medical history and current medication use were recorded. Participants underwent standardized physical examination, blood sampling, electrocardiography, ultrasound of the common carotid and femoral arteries for IMT measurement, and skin autofluorescence to measure AGEs.

Measurements

Mean cIMT was measured in millimeters (mm) at the far wall of the left and right common carotid arteries using the Logiq E9 (GE Healthcare) ultrasound system at the NKI-AVL and the MyLab One (Esaote) ultrasound system at the UMCG. For our analysis, we used the average of the three left-sided and three right-sided mean cIMT measurements.

Skin autofluorescence was measured at the volar side of the lower arm left and right, three times at each side using the AGE reader mu (Diagnoptics). AGEs are expressed in arbitrary units (AU), with higher values indicating higher CVD risk. The mean value of all six measurements (three left, three right) was used in the analysis.

We used fasting serum blood samples to determine a complete cholesterol profile, including high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol and triglycerides.

Statistical analysis

Baseline characteristics were compared between patients who received no ET, tamoxifen only, AI only or both tamoxifen and AI using Kruskal–Wallis tests for continuous variables and chi squared tests for categorical variables. To quantify AI exposure, we calculated the AI ratio by dividing the duration of AI use by the total duration of ET: the higher the ratio, the longer the (relative) AI exposure [22]. For patients who did not receive any ET, the AI ratio was set to zero. The use of the AI ratio enabled us to account for accessory tamoxifen use and to (at least partially) overcome the effect of missing data: even if absolute ET duration was missing, the AI ratio could be determined for patients who used tamoxifen or AI only (0 and 1, respectively). We categorized patients into three groups according to their AI ratio. The first group (low AI exposure) consisted of patients who had used no ET or only/predominantly tamoxifen (AI ratio < 0.40). The second group (intermediate AI exposure) consisted of patients who had used both tamoxifen and AI for approximately equal durations ($0.40 \leq$ AI ratio ≤ 0.60), and the third group (high AI exposure) consisted of patients who had used only/predominantly AI (AI ratio > 0.60). To assess the robustness of the chosen categories, we performed sensitivity analyses with different AI ratio categorizations, absolute AI duration and long versus short AI use (AI use ≥ 5 years versus < 5 years) as independent variables.

We examined the association between AI ratio and cIMT and AGEs as continuous variables in linear regression models. We also assessed association with high cIMT and high AGEs in logistic regression models. High cIMT was defined as a cIMT value above the 90th percentile threshold per institute. High AGEs were defined as an AGE value above 1 standard deviation of the age-adjusted mean reference value [23]. For cholesterol, we tested the association between AI ratio and the presence of dyslipidemia at study visit, defined as fasting LDL cholesterol > 4.0 mmol/L, HDL cholesterol < 1.2 mmol/L, triglycerides > 4.0 mmol/L, or current lipid lowering treatment [23]. In search of any signal for association, we also assessed associations of the AI ratio with a combined endpoint, which consisted of either high cIMT, high AGEs or dyslipidemia, or a combination of these. Participants with dyslipidemia at time of breast cancer diagnosis were excluded from all analyses that included dyslipidemia as endpoint.

Potential patient-related confounders included age at study visit, body mass index (BMI) at study visit, diagnosis of hypertension at BC diagnosis (defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive drugs or as specified in the medical record), the presence of other circulatory disease at BC diagnosis (defined as any diagnosis from category I00-I99, except I10-I15, according to the International Classification of Diseases, 10th revision (ICD10)) or endocrine disease at BC diagnosis (defined as any diagnosis from category E00-E90 according to ICD10), smoking habits and menopausal status at study visit (based on medical records and patient questionnaires at BC diagnosis, and estradiol and FSH levels at study visit). Because oophorectomy status and luteinizing hormone releasing-hormone (LHRH) therapy were both strongly correlated with menopausal status, we excluded these parameters. Treatment-related confounders included the use of chemotherapy, trastuzumab and radiotherapy. Each potential independent predictor was tested in a univariable analysis first and included in multivariable analysis if the p-value

in univariable analysis was ≤ 0.1. If relevant, we tested for interaction between variables.

Significance tests were two-sided, and a p value of < 0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics 27.

Results

Study population

The total study population consisted of 569 patients. Median age at BC diagnosis differed significantly between patients who did not receive ET (46.7, interquartile range (IQR) 43.7–49.4), tamoxifen only (45.9, IQR: 43.0–48.4), AI only (46.2, IQR: 43.2–49.0) or both tamoxifen and AI (47.4, IQR:

Table 1 Baseline characteristics (at breast cancer diagnosis)

	No ET	%	Tam only	%	AI only	%	Tam and AI	%	p value[a]
	N		*N*		*N*		*N*		
Total	250		88		47		184		
Age in years, median (IQR)	46.7 (43.7–49.4)	NA	45.8 (42.9–48.4)	NA	46.2 (43.2–49.0)	NA	47.5 (44.5–49.5)	NA	**0.020**
Follow-up group									
5–7 years	99	39.6	60	68.2	22	46.81	96	52.2	
10–12 years	151	60.4	28	31.8	25	53.2	88	47.8	**< 0.001**
Menopausal status[b]									
Pre-/perimenopausal	192	76.8	77	87.5	34	72.3	142	77.2	
Postmenopausal	55	22.0	11	12.5	13	27.7	41	22.3	
Unknown	3	1.2	0	0.0	0	0.0	1	0.5	0.128
Hypertension[c]	49	19.6	25	28.4	11	23.4	43	23.4	0.403
Comorbidity									
Circulatory disease (other than hypertension)[d]	16	6.4	5	5.7	3	6.4	4	2.2	0.216
Pulmonary disease[e]	18	7.2	8	9.1	5	10.6	11	6.0	0.649
Endocrine disease[f]	21	8.4	3	3.4	3	6.4	12	6.5	0.454
Body mass index (BMI)									
< 25 kg/m^2	164	65.6	66	75.0	28	59.6	111	60.3	
25–30 kg/m^2	65	26.0	16	18.2	13	27.7	46	25.0	
≥ 30 kg/m^2	17	6.8	6	6.8	5	10.6	25	13.6	
Unknown		0.0	0	0.0	1	2.1	2	1.1	0.125
Smoking									
Never smoked	86	34.4	36	40.9	19	40.4	85	46.2	
Former smoker	94	37.6	27	30.7	12	25.5	47	25.5	
Current smoker	65	26.0	24	27.3	14	29.8	48	26.1	
Unknown	5	2.0	1	1.1	2	4.3	4	2.2	0.145
Known BRCA germline mutation									
Yes	13	5.2	2	2.3	1	2.1	7	3.8	
No	237	94.8	86	97.7	46	97.9	177	96.2	0.563

ET endocrine therapy, *tam* tamoxifen, *AI* aromatase inhibitor, *IQR* interquartile range, *BC* breast cancer, *BRCA* breast cancer gene

[a]p value for between-group differences, calculated with Kruskal–Wallis test or chi squared tests (excluding the unknown category)

[b]Based on medical file and patient questionnaires

[c]Defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive drugs or the medical record

[d]Defined as any diagnosis from category I00-I99, except I10-I15, according to the Internatinal Classification of Diseases, 10th revision (ICD10)

[e]Defined as any diagnosis from category J00-J99 according to the ICD10

[f]Defined as any diagnosis from category E00-E90 according to the ICD10; includes 14 patients with hypercholesterolemia and 5 patients with diabetes mellitus

Table 2 Breast cancer and treatment characteristics

	No ET	%	Tam only	%	AI only	%	Tam and AI	%	*p* value[a]
	N		*N*		*N*		*N*		
Total	250		88		47		184		
Breast cancer subtype									
ER and/or PR-positive	154	61.6	88	100.0	47	100.0	181	98.4	
ER and PR negative	77	30.8	0	0.0	0	0.0	2	1.1	
Unknown	19	7.6	0	0.0	0	0.0	1	0.5	**< 0.001**
HER2-negative	159	63.6	75	85.2	24	51.1	142	77.2	
HER2-positive	26	10.4	8	9.1	19	40.4	16	8.7	
Unknown[b]	65	26.0	5	5.7	4	8.5	26	14.1	**< 0.001**
TNM-stage[c]									
I	189	75.6	42	47.7	23	48.9	50	27.2	
II	43	17.2	38	43.2	16	34.0	88	47.8	
III	6	2.4	7	8.0	7	14.9	41	22.3	
Unknown	2	0.8	1	1.1	1	2.1	5	2.7	
DCIS	10	4.0	0	0.0	0	0.0	0	0.0	**< 0.001**
Grade									
I	81	32.4	12	13.6	5	10.6	29	15.8	
II	101	40.4	54	61.4	21	44.7	92	50.0	
III	57	22.8	18	20.5	18	38.3	51	27.7	
Unknown	11	4.4	4	4.5	3	6.4	12	6.5	**< 0.001**
Patients with known duration of endocrine therapy[d]	NA		68	77.3	38	80.9	157	85.3	
Median duration endocrine therapy in years (IQR)	NA		5.00 (4.80–5.00)		5.00 (5.00–6.78)		5.20 (5.00–7.20)		**< 0.001**
Surgery									
Lumpectomy	233	93.2	62	70.5	32	68.1	128	69.6	
Mastectomy	16	6.4	26	29.5	14	29.8	56	30.4	
Unknown	1	0.4	0	0.0	1	2.1	0	0.0	**< 0.001**
Radiotherapy									
No radiotherapy	8	3.2	8	9.1	6	12.8	7	3.8	
Right-sided	124	49.6	42	47.7	31	66.0	81	44.0	
Left-sided	118	47.2	38	43.2	10	21.3	96	52.2	**0.001**
Chemotherapy									
Yes	70	28.0	53	60.2	34	72.3	153	83.2	
No	180	72.0	35	39.8	13	27.7	31	16.8	**< 0.001**
Trastuzumab									
Yes	15	6.0	7	8.0	13	27.7	15	8.2	
No	235	94.0	81	92.0	34	72.3	169	91.8	**< 0.001**
Use of LHRH-analogue									
Yes	1	0.4	25	28.4	18	38.3	36	19.6	
No	249	99.6	57	64.8	27	57.4	145	78.8	
Unknown	0	0.0	6	6.8	2	4.3	3	1.6	**< 0.001**
Oophorectomy									
Yes	19	7.6	10	11.4	17	36.2	46	25.0	
No	231	92.4	78	88.6	30	63.8	138	75.0	**< 0.001**

ET endocrine therapy, *tam* tamoxifen, *AI* aromatase inhibitor, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factorreceptor 2, *TNM* TNM classification of malignant tumors, *DCIS* ductal carcinoma in situ, *NA* not applicable, *IQR* interquartile range, *LHRH* luteinizing hormone releasing-hormone

[a]*p* value for between-group differences, calculated with Kruskal–Wallis test or chi squared tests (excluding the unknown category)

[b]Year of diagnosis was later than 2005 (the year the Netherlands implemented HER2-testing nationwide) in 75/100 missing cases

[c]Based on clinical staging in case of neoadjuvant therapy, otherwise pathological staging

[d]Patients that had used tam&ai were classified valid if both durations were known

44.5–49.5). Menopausal status at BC diagnosis did not differ between these groups. Patients with a more recent diagnosis more often received tamoxifen only, compared to patients diagnosed in earlier years. Cardiovascular risk factors at BC diagnosis were equally distributed among groups (Table 1).

Almost all patients who had received ET had estrogen receptor positive and/or progesterone receptor positive BC (99.1%). The prevalence of human epidermal growth factor receptor 2 (HER2)-positive disease was unknown in 17.5% of patients, and was relatively high (40.4%) among patients who had received treatment with an AI only. Patients who had received ET in general had higher risk disease (higher TNM-stage, higher tumor grade) compared to those not treated with ET. Patients who had received ET more often underwent mastectomy (versus lumpectomy) than patients who had not received ET. Approximately 75% of patients treated with ET had also received chemotherapy, whereas only 28% of the no ET-group had received chemotherapy. The vast majority of chemotherapy regimens contained anthracyclines. Table 2 summarizes breast cancer and treatment characteristics.

Endocrine therapy exposure

Forty percent of patients had used an AI, either alone ($n = 47$, 8.2%) or sequentially with tamoxifen ($n = 184$, 32.3%), and median duration of AI use was 3.0 years (IQR 2.0–5.0). Forty-seven percent of patients ($n = 272$) had received tamoxifen with a median duration of use of 3.0 years (IQR 2.3–5.0). In the group of patients with low AI exposure (no ET or AI ratio < 0.40), 250 patients had used no ET and 132 had only/predominantly used tamoxifen. The median duration of AI use in this group was 0.0 years (IQR 0.0–0.0 years). Sixty-nine patients had received an AI and tamoxifen in approximately equal duration (intermediate AI exposure: $0.40 \leq$ AI ratio ≤ 0.60); median absolute AI duration in this group was 2.6 years (IQR 2.0–3.1 years). The third group (high AI exposure: AI ratio > 0.60) consisted of 90 patients and median absolute duration of AI use in this group was 5.0 years (IQR 4.8–6.9 years) (Fig. 1).

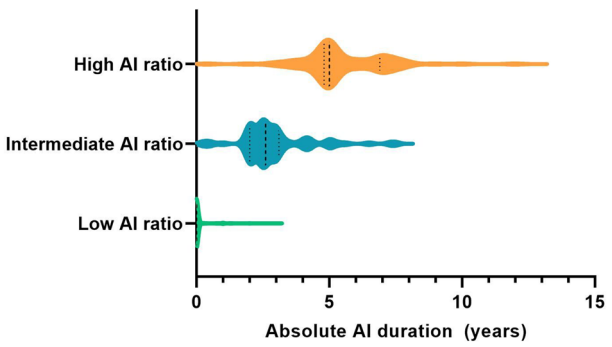

Fig. 1 Absolute AI duration by AI ratio group. AI aromatase inhibitor. The black interrupted lines represent the median, the black dotted lines represent the 25th en 75th percentile boundaries

cIMT

cIMT did not differ between AI ratio groups; median cIMT was 0.63 mm (IQR 0.56–0.71 mm) among patients with low AI exposure, 0.66 mm (IQR 0.59–0.75 mm) among patients with intermediate AI exposure and 0.64 mm (IQR 0.59–0.73 mm) among patients with high AI exposure (Table 3 and Fig. 2a). Each year increase in age at study visit was associated with an increase in cIMT of 0.01 mm (95% confidence interval (CI) 0.01 − 0.01). Overweight and obese patients had higher cIMT (0.02 mm (95% CI 0.00–0.04) and 0.04 mm (95% CI 0.02–0.06) respectively) than patients with a BMI < 25 kg/m^2. In UMCG-patients, cIMT was 0.12 mm (95% CI 0.10–0.14) higher than in NKI-AVL-patients. Although AI ratio in itself was not significantly associated with cIMT, we did observe a significant interaction between institute and AI ratio. UMCG-patients with intermediate AI exposure had a 0.02 mm (95% CI − 0.07 − 0.03) lower cIMT than NKI-AVL-patients, and UMCG-patients with high AI exposure had a 0.05 mm (95% CI − 0.10 − 0.01) lower cIMT than NKI-AVL-patients.

Fifty patients had a cIMT above their institute specific 90th percentile cut-off. Only age at study visit (odds ratio (OR) 1.2, 95% CI 1.12–1.34) was associated with a cIMT value above the institute specific cut-off (Table 4).

AGEs

AI ratio was associated with AGEs on a continuous scale neither in univariable analysis nor after adjusting for potential confounders in multivariable analysis (Table 3). Median AGEs was 2.13 AU (IQR: 1.90–2.40 AU) among patients with low AI exposure, 2.20 AU (IQR: 1.90–2.51 AU) among patients with intermediate AI exposure and 2.11 AU (IQR: 1.90–2.43 AU) among patients with high AI exposure (Fig. 2b). AGEs increased by 0.01 AU (95% CI 0.01–0.02) per year increase in age at study visit, and patients with a history of endocrine disease (compared to those without endocrine disease history) and current smokers (compared to never smokers) had higher AGEs (0.15 AU (95% CI 0.01–0.30) and 0.37 AU (95% CI 0.28–0.46), respectively). In UMCG-patients, AGEs were 0.11 AU (95% CI 0.04–0.18) higher than in NKI-AVL patients. Overweight patients had lower AGEs (− 0.08 AU, 95% CI − 0.16 − 0.00) than those with a BMI < 25 kg/m^2.

In all, 91 patients had elevated AGEs based on age-specific reference values. Patients with a history of endocrine disease (OR 2.35, 95% CI 1.10–5.03) and those who

Table 3 Association between AI ratio and cIMT &AGEs in multivariable analyses

	Mean cIMT[a]				Mean AGEs			
	β	95% CI		*p* value	*β*	95% CI		*p* value
AI ratio								
Low AI exposure: no ET or AI ratio < 0.40	ref				ref			
Intermediate AI exposure: AI ratio ≥ 0.40 and ≤ 0.60	0.01	− 0.03	0.04	0.792	0.01	− 0.10	0.12	0.803
High AI exposure: AI ratio > 0.60	0.03	0.00	0.06	0.066	− 0.01	− 0.10	0.09	0.978
Institute								
NKI–AVL, Amsterdam	ref				ref			
UMCG, Groningen	0.12	0.10	0.14	**< 0.001**	0.11	0.04	0.18	**0.003**
Age at study visit	0.01	0.01	0.01	**< 0.001**	0.01	0.01	0.02	**0.004**
BMI at study visit								
BMI < 25 kg/m^2	ref				ref			
BMI ≥ 25 and < 30 kg/m^2	0.02	0.00	0.04	**0.026**	− 0.08	− 0.16	0.00	**0.039**
BMI ≥ 30 kg/m^2	0.04	0.02	0.06	**< 0.001**	− 0.03	− 0.13	0.07	0.510
History of hypertension (ref: no)[b]	NA				NA			
History of other circulatory disease (ref: no)[c]	NA				NA			
History of endocrine disease (ref: no)[d]	NA				0.15	0.01	0.30	**0.040**
Smoking status								
Never smoked	ref				ref			–
Former smoker	NA				0.03	− 0.06	0.11	0.551
Current smoker	NA				0.37	0.28	0.46	**< 0.001**
Radiotherapy								
None	ref				ref			
Left-sided	NA				NA			
Right-sided	NA				NA			
Trastuzumab (ref: no)	− 0.02	− 0.07	0.03	0.376	− 0.06	− 0.18	0.07	0.376
Chemotherapy (ref: no)	NA				NA			
Menopausal status at BC diagnosis and study visit[e]								
Pre-/premenopausal	ref				ref			–
Pre-/postmenopausal	NA				− 0.02	− 0.12	0.07	0.633
Post-/postmenopausal	NA				0.04	− 0.08	0.17	0.480
Interaction terms								
Institute (UMCG) x intermediate AI ratio	− 0.02	− 0.07	0.03	0.376	NA			
Institute (UMCG) x high AI ratio	− 0.05	− 0.10	− 0.01	**0.019**	NA			

cIMT carotis intima media thickness, *AGEs* advanced glycation end products, *CI* confidence interval, *AI* aromatase inhibitor, *ET* endocrine therapy, *ref* reference category, *NKI–AVL* Netherlands Cancer Institute–Antoni van Leeuwenhoek, *UMCG* University Medical Center Groningen, *BMI* body mass index, *NA* not applicable (only variables with *p* value ≤ 0.1 in univariable analysis were entered in multivariable model), *BC* breast cancer

[a]The *β*- and *p* values for cIMT are derived from the model that included the interaction term for AI ratio and insitute

[b]Defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive drugs or the medical record

[c]Defined as any diagnosis from category I00-I99, except I10-I15, according to the Internatinal Classification of Diseases, 10th revision (ICD10)

[d]Defined as any diagnosis from category E00-E90 according to the ICD10

[e]Menopausal status was classified according to medical records and patient questionnaires at BC diagnosis and according to laboratory values at study visit

currently smoked (OR 3.75, 95% CI 2.17–6.47) had elevated AGEs in this analysis (Table 4).

Dyslipidemia

At study visit, 195 (34.2%) patients had dyslipidemia. In univariable logistic regression analysis, women with intermediate AI exposure had higher odds of dyslipidemia at study

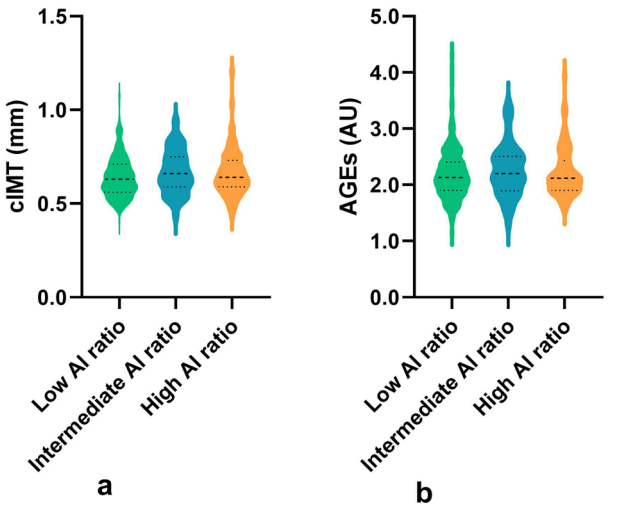

Fig. 2 cIMT (**a**) and AGEs (**b**) by AI ratio group. cIMT carotis intima media thickness, AGEs advanced glycation end products, AI aromatase inhibitor, mm, millimeters, AU arbitrary units. The black interrupted lines represent the median, the grey dotted lines represent the 25th en 75th percentile boundaries

visit than women with low AI exposure. This association was not present in the group with high AI exposure. After adjusting for confounders in multivariable analysis, the association between intermediate AI exposure and dyslipidemia disappeared (Table 4). Older age at study visit (OR 1.08, 95% CI 1.03–1.13) and higher BMI (compared to BMI < 25; OR 1.50, 95% CI 0.99–2.27 for BMI ≥ 25 and < 30 kg/m^2, OR 1.86, 95% CI 1.12–3.09 for BMI ≥ 30 kg/m^2) were associated with higher odds of dyslipidemia.

Combined endpoint: cIMT, AGEs and/or dyslipidemia

Of the 569 study participants, 260 (45.7%) had elevated cIMT, elevated AGEs and/or dyslipidemia at study visit. In a multivariable logistic regression model, intermediate AI exposure was associated with higher odds of the combined endpoint (OR 2.06, 95% CI 1.17–3.62) than low AI exposure. High AI exposure, however, was not associated with higher odds of the combined endpoint than low AI exposure (OR 1.32, 95% CI 0.80–2.16). Factors that were significantly associated with higher odds for the combined endpoint in the multivariable model were older age at study visit (OR 1.07, 95% CI 1.02–1.13), a higher BMI (OR 1.53, 95% CI 1.02–2.30 for BMI ≥ 25 and < 30 kg/m^2; OR 1.55, 95% CI 0.92–2.60 for BMI ≥ 30 kg/m^2), and current smoking (compared to never smokers; OR 2.43, 95% CI 1.54–3.84) (Table 4).

For all outcomes, sensitivity analyses with absolute AI duration, a different AI ratio categorization or long AI use (≥ 5 years versus < 5 years) provided similar results (Supplementary Data).

Discussion

In this study, we investigated the association between exposure to AIs and early markers for CVD. We observed no statistically significant association between AI exposure and cIMT, AGEs or the presence of dyslipidemia; results were robust across several sensitivity analyses. Current treatment guidelines do not provide specific recommendations on AI use and CVD risk; our results do not call for a change in these guidelines [24].

Three previous studies showed cIMT results similar to those in our study. Blondeaux et al. found no significant difference in cIMT between AI users (median duration of use 53 months) and healthy controls [25]. Gallicchio et al. investigated several vascular parameters including cIMT in a small group ($n = 112$) of breast cancer patients and found no significant changes after 1 year of AI use [26]. An even smaller study ($n = 85$) also found no difference in median cIMT when comparing BC patients treated with AI (mean duration of use 34 months) to those not receiving endocrine treatment [27]. Carotid plaques, however, were seen more frequently among AI users in this study. Two other small studies suggested a detrimental effect of AI-use on endothelial function, although these effects were most pronounced in patients with additional CVD risk factors [28, 29].

Several randomized controlled trials measured lipid spectrum in a subset of their trial participants. The ATENA study randomized patients to receive either 5 years of exemestane or no treatment after 5–7 years of tamoxifen and found no detrimental effect on lipid profile after two years follow-up [30]. In a Japanese substudy of the TEAM study, in which patients received exemestane, anastrozole or tamoxifen as adjuvant therapy, the lipid profile of tamoxifen users changed favorably, but in AI users, no significant effect on lipids was seen at 3 months and 1 year on treatment [31]. Atalay et al. found no detrimental effects of exemestane on cholesterol levels at 8, 24 and 48 weeks of treatment in patients with metastatic breast cancer who received either exemestane or tamoxifen as first-line therapy in a substudy of the EORTC trial 10951 [32]. To our knowledge, no other studies have evaluated the association between the use of AIs and AGEs in the skin.

Our results do not explain why several large cohort studies suggest an association between the use of AIs and a higher risk of overt CVD, such as myocardial infarction (MI) and heart failure (HF). Abdel-Qadir et al. observed a higher risk of hospitalization for MI in AI users compared to tamoxifen users in a cohort of 9350 BC patients after a mean follow-up of 3.2 years [33]. The cohort study by Khosrow-Kavar et al. included 23,525 patients and had similar results with a higher risk of HF and cardiovascular mortality in AI users (median follow-up 1.4 years) compared to

Table 4 Association between AI ratio and cIMT, AGEs & dyslipidemia (separately and combined) in multivariable analysis

	cIMT > 90th percentile[a]				AGEs > mean + 1SD				Dyslipidemia				Combined endpoint			
	OR	95% CI		*p* value	OR	95% CI		*p* value	OR	95% CI		*p* value	OR	95% CI		*p* value
AI-ratio																
Low AI exposure: no ET or AI ratio < 0.40	ref				ref				ref				ref			
Intermediate AI exposure: AI ratio ≥ 0.40 and ≤ 0.60	0.89	0.37	2.13	0.788	1.30	0.68	2.49	0.425	1.51	0.88	2.59	0.139	2.06	1.17	3.62	**0.012**
High AI exposure: AI ratio > 0.60	0.88	0.38	2.00	0.753	0.93	0.50	1.73	0.809	1.18	0.72	1.96	0.511	1.32	0.80	2.16	0.278
Institute																
NKI–AVL, Amsterdam	ref				ref				ref				ref			
UMCG, Groningen	NA				0.70	0.44	1.10	0.123	NA				NA			
Age at study visit	1.23	1.12	1.34	**< 0.001**	NA[b]	NA	NA	NA	1.08	1.03	1.13	**0.003**	1.07	1.02	1.13	**0.006**
BMI at study visit																
BMI < 25 kg/m^2	ref				ref				ref				ref			
BMI ≥ 25 and < 30 kg/m^2	NA				NA				1.50	0.99	2.27	0.059	1.53	1.02	2.30	**0.040**
BMI ≥ 30 kg/m^2	NA				NA				1.86	1.12	3.09	**0.016**	1.55	0.92	2.60	0.101
History of hypertension (ref: no)[c]	NA				NA				NA				NA			
History of other circulatory disease (ref: no)[d]	NA				NA				NA				2.32	0.94	5.73	0.069
History of endocrine disease (ref: no)[e]	NA				2.35	1.10	5.03	**0.028**	NA				NA			
Smoking status																
Never smoked	ref				ref				ref				ref			
Former smoker	NA				1.30	0.72	2.35	0.392	0.76	0.49	1.19	0.230	0.89	0.59	1.36	0.598
Current smoker	NA				3.75	2.17	6.47	**< 0.001**	1.55	0.99	2.43	0.057	2.43	1.54	3.84	**< 0.001**
Radiotherapy																
None	ref				ref				ref				ref			
Left-sided	NA				NA				NA				NA			
Right-sided	NA				NA				NA				NA			
Trastuzumab (ref: no)	NA				NA				NA				NA			
Chemotherapie (ref: no)	NA				NA				NA				NA			
Menopausal status at BC diagnosis and study visit[f]																
Pre-/premenopausal	NA				NA				NA				ref			
Pre-/postmenopausal	NA				NA				NA				1.15	0.72	1.84	0.565
Post-/postmenopausal	NA				NA				NA				1.29	0.69	2.41	0.429

cIMT carotis intima media thickness, *AGEs* advanced glycation end products, *SD* standard deviation, *OR* odds ratio, *CI* confidence interval, *AI* aromatase inhibitor, *ET* endocrine therapy, ref reference category, *NKI–AVL* Netherlands Cancer Institute–Antoni van Leeuwenhoek, *UMCG* University Medical Center Groningen, *NA* not applicable (only variables with *p* value ≤ 0.1 in univariable analysis were entered in multivariable model), *BMI* body mass index, *B*C breast cancer

[a]Institute-specific 90th percentile

[b]Because the cut-off was age-adjusted, we removed age as a variable in this analysis

[c]Defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive drugs or the medical record

[d]Defined as any diagnosis from category I00-I99, except I10-I15, according to the Internatinal Classification of Diseases, 10th revision (ICD10)

[e]Defined as any diagnosis from category E00-E90 according to the ICD10

[f]Menopausal status was classified according to medical records and patient questionnaires at BC diagnosis and according to laboratory values at study visit

tamoxifen users (median follow-up 1.3 years) [34]. Because the comparison group consisted of tamoxifen users in both studies, it remains elusive if these results reflect a cardioprotective effect of tamoxifen or a detrimental effect of AIs. The cohort study by Ligibel et al. ($n = 44{,}463$) suggests the former: when BC patients using AI were compared with BC patients not receiving ET, there was no association between AI use and risk of MI or stroke with a median follow-up of 2.5 years [35]. Sund et al. also observed no association of AI use and MI or HF when compared to non-users in their cohort study including 15,815 women with a median follow-up of 3.9 years [36].

When comparing our study with the abovementioned cohorts, it should first be noted that the majority of AI users in our study had used AI as well as tamoxifen whereas AI users in the cohort studies typically had used AI only. It is possible that favorable effects of tamoxifen counterbalanced potential negative effects of AIs in our study. The fact that sensitivity analysis with absolute AI duration provided the same results, however, is reassuring. Secondly, our study mainly included pre-/perimenopausal women, in contrast to the abovementioned cohort studies which consisted of postmenopausal women only. We cannot rule out that the effect of AIs on cardiovascular risk differs across age groups or menopausal status.

Our study has several strengths compared to previous studies. First, we not only examined AI exposure as a dichotomous variable, but also quantified AI exposure by using the AI ratio. Second, we had detailed information on important potential confounders (comorbidity, smoking habits and body composition for example). Third, follow-up in our study (5–12 years) was notably longer than in previous studies. Fourth, we systematically collected valid subclinical CVD measures and were thus able to reliably capture early signs of cardiotoxicity.

Some limitations of our study require consideration. A first limitation is that the exact ET duration was unknown in 18% of the study population. We tried to overcome this problem by using the AI ratio. A second potential drawback of our study is the risk of survival bias. It is possible that patients who developed (severe) CVD after BC diagnosis had already died at the time of study start and were therefore underrepresented in the study population. However, prevalence of symptomatic CVD in this young cohort was low [20, 21]. Although our study had longer follow-up than previous studies, 5–12 years might still be too short to develop vascular or metabolic abnormalities, in particular in a relatively young and healthy population such as ours. We are therefore planning a repeat study visit for all participants after an additional 5–8 years of follow-up. A last issue to consider is the fact that we recruited and assessed study participants in two different institutes, and that we observed significant effect modification of institute on the association between AI exposure and cIMT. Perhaps this interaction can be explained by differences in cardiovascular health between institutes (although baseline cardiovascular parameters did not significantly differ), but we cannot rule out that interinstitute variability in outcome measurements played a role as well.

In conclusion, our study did not show a clear association between exposure to AIs and early signs of cardiovascular damage in breast cancer survivors. Our results do not prompt a change in current clinical practice. Future studies should validate our findings over time (additional follow-up of this cohort is planned) and in different BC populations.

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Author contributions All authors contributed to the study conception and design. JJ and LS collected the data. AvO-N and MS prepared the data and performed the analyses. AvO-N wrote the first draft of the manuscript. All authors reviewed and revised the manuscript; all authors read and approved the final version of the manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Jourik Gietema reports institutional research support from Roche, Abbvie and Siemens. Gabe Sonke reports institutional research support from Agendia, AstraZeneca, Merck, Novartis, Roche and Seagen and consultancy fees paid to the institution from Biovica and Seagen. Annemiek van Ommen-Nijhof, Lars Steggink, Judy Jacobse, Joop Lefrandt, Flora van Leeuwen and Michael Schaapveld report no competing interests.

Ethical approval The institutional review board of the NKI-AVL approved the study and it is registered with ClinicalTrials.gov, identifier NCT02485626. The study was carried out according to the principles of the Declaration of Helsinki.

Consent to participate All participants provided written informed consent prior to enrolment in the study.

References

1. Dellapasqua S, Castiglione-Gertsch M (2005) The choice of systemic adjuvant therapy in receptor-positive early breast cancer. Eur J Cancer 41(3):357–364. https://doi.org/10.1016/j.ejca.2004.11.017

2. Smith IE, Dowsett M (2003) Aromatase inhibitors in breast cancer. N Engl J Med 348(24):2431–2442. https://doi.org/10.1056/NEJMra023246
3. Early Breast Cancer Trialists Collaborative G (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365(9472):1687–717. https://doi.org/10.1016/s0140-6736(05)66544-0
4. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, Thürlimann B, Paridaens R, Smith I et al (2009) Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 361(8):766–776. https://doi.org/10.1056/NEJMoa0810818
5. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M (2008) Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 9(1):45–53. https://doi.org/10.1016/s1470-2045(07)70385-6
6. van de Velde CJ, Rea D, Seynaeve C, Putter H, Hasenburg A, Vannetzel JM et al (2011) Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 377(9762):321–331. https://doi.org/10.1016/s0140-6736(10)62312-4
7. Buzdar A, Howell A, Cuzick J, Wale C, Distler W, Hoctin-Boes G et al (2006) Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol 7(8):633–643. https://doi.org/10.1016/s1470-2045(06)70767-7
8. Grey AB, Stapleton JP, Evans MC, Reid IR (1995) The effect of the anti-estrogen tamoxifen on cardiovascular risk factors in normal postmenopausal women. J Clin Endocrinol Metab 80(11):3191–3195. https://doi.org/10.1210/jcem.80.11.7593425
9. Cuppone F, Bria E, Verma S, Pritchard KI, Gandhi S, Carlini P et al (2008) Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. Cancer 112(2):260–267. https://doi.org/10.1002/cncr.23171
10. Goldvaser H, Barnes TA, Šeruga B, Cescon DW, Ocaña A, Ribnikar D et al (2017) Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. JNCI: J National Cancer Inst 110(1):31–9. https://doi.org/10.1093/jnci/djx141
11. Amir E, Seruga B, Carlsson L, Niraula S, Ocaña A (2011) Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. JNCI: J National Cancer Inst 103(17):1299–309. https://doi.org/10.1093/jnci/djr242
12. Aydiner A (2013) Meta-analysis of breast cancer outcome and toxicity in adjuvant trials of aromatase inhibitors in postmenopausal women. Breast 22(2):121–129. https://doi.org/10.1016/j.breast.2013.01.014
13. Younus M, Kissner M, Reich L, Wallis N (2011) Putting the cardiovascular safety of aromatase inhibitors in patients with early breast cancer into perspective: a systematic review of the literature. Drug Saf 34(12):1125–1149. https://doi.org/10.2165/11594170-000000000-00000
14. Zhao X, Liu L, Li K, Li W, Zhao L, Zou H (2015) Comparative study on individual aromatase inhibitors on cardiovascular safety profile: a network meta-analysis. Onco Targets Ther 8:2721–2730. https://doi.org/10.2147/ott.S88179
15. Matthews A, Stanway S, Farmer RE, Strongman H, Thomas S, Lyon AR et al (2018) Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: systematic review. BMJ 363:k3845. https://doi.org/10.1136/bmj.k3845
16. Khosrow-Khavar F, Filion KB, Al-Qurashi S, Torabi N, Bouganim N, Suissa S et al (2017) Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol 28(3):487–496. https://doi.org/10.1093/annonc/mdw673
17. Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE et al (2013) The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. J Am Heart Assoc 2(2):e000087. https://doi.org/10.1161/jaha.113.000087
18. de Vos LC, Mulder DJ, Smit AJ, Dullaart RP, Kleefstra N, Lijfering WM et al (2014) Skin autofluorescence is associated with 5-year mortality and cardiovascular events in patients with peripheral artery disease. Arterioscler Thromb Vasc Biol 34(4):933–938. https://doi.org/10.1161/atvbaha.113.302731
19. Mendelsohn ME, Karas RH (1999) The protective effects of estrogen on the cardiovascular system. N Engl J Med 340(23):1801–1811. https://doi.org/10.1056/nejm199906103402306
20. Boekel NB, Jacobse JN, Schaapveld M, Hooning MJ, Gietema JA, Duane FK et al (2018) Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer. Br J Cancer 119(4):408–418. https://doi.org/10.1038/s41416-018-0159-x
21. Jacobse JN, Steggink LC, Sonke GS, Schaapveld M, Hummel YM, Steenbruggen TG et al (2020) Myocardial dysfunction in long-term breast cancer survivors treated at ages 40–50 years. Eur J Heart Fail 22(2):338–346. https://doi.org/10.1002/ejhf.1610
22. Dackus G, Jóźwiak K, Sonke GS, van der Wall E, van Diest PJ, Hauptmann M et al (2018) Optimal adjuvant endocrine treatment of ER+/HER2+ breast cancer patients by age at diagnosis: a population-based cohort study. Eur J Cancer 90:92–101. https://doi.org/10.1016/j.ejca.2017.11.010
23. den Dekker MA, Zwiers M, van den Heuvel ER, de Vos LC, Smit AJ, Zeebregts CJ et al (2013) Skin autofluorescence, a non-invasive marker for AGE accumulation, is associated with the degree of atherosclerosis. PLoS One 8(12):e83084. https://doi.org/10.1371/journal.pone.0083084
24. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT et al (2019) Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. Ann Oncol 30(8):1194–220. https://doi.org/10.1093/annonc/mdz173
25. Blondeaux E, Musio D, Bruzzi P, Lambertini M, Gazzola V, Poggio F et al (2016) Treatment with aromatase inhibitors and markers of cardiovascular disease. Breast Cancer Res Treat 160(2):261–267. https://doi.org/10.1007/s10549-016-3985-7
26. Gallicchio L, Calhoun C, Helzlsouer K (2016) Effect of aromatase inhibitor therapy on the cardiovascular health of black and white breast cancer patients. Clin Breast Cancer 16(3):e23-31. https://doi.org/10.1016/j.clbc.2016.02.011
27. Seo DH, Cho Y, Lee S, Park S, Kim SI, Park BW et al (2019) Aromatase inhibitor use is a risk factor of carotid plaque presence in endocrine-responsive breast cancer patients. Korean J Intern Med 34(3):579–587. https://doi.org/10.3904/kjim.2016.205
28. Blaes A, Beckwith H, Florea N, Hebbel R, Solovey A, Potter D et al (2017) Vascular function in breast cancer survivors on aromatase inhibitors: a pilot study. Breast Cancer Res Treat 166(2):541–547. https://doi.org/10.1007/s10549-017-4447-6
29. Maor R, Sara JDS, Wanous AA, Maor E, Pruthi S, Lerman A et al (2018) Attenuated peripheral endothelial function among women treated with aromatase inhibitors for breast cancer. Coron Artery Dis 29(8):687–693. https://doi.org/10.1097/mca.0000000000000666
30. Markopoulos C, Dafni U, Misitzis J, Zobolas V, Tzoracoleftherakis E, Koukouras D et al (2009) Extended adjuvant hormonal therapy with exemestane has no detrimental effect on the lipid profile of postmenopausal breast cancer patients: final results of

the ATENA lipid substudy. Breast Cancer Res 11(3):R35. https://doi.org/10.1186/bcr2320
31. Hozumi Y, Suemasu K, Takei H, Aihara T, Takehara M, Saito T et al (2011) The effect of exemestane, anastrozole, and tamoxifen on lipid profiles in Japanese postmenopausal early breast cancer patients: final results of national surgical adjuvant study BC 04, the TEAM Japan sub-study. Ann Oncol 22(8):1777–1782. https://doi.org/10.1093/annonc/mdq707
32. Atalay G, Dirix L, Biganzoli L, Beex L, Nooij M, Cameron D et al (2004) The effect of exemestane on serum lipid profile in postmenopausal women with metastatic breast cancer: a companion study to EORTC Trial 10951, 'randomized phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients.' Ann Oncol 15(2):211–217. https://doi.org/10.1093/annonc/mdh064
33. Abdel-Qadir H, Amir E, Fischer HD, Fu L, Austin PC, Harvey PJ et al (2016) The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer. Eur J Cancer 68:11–21. https://doi.org/10.1016/j.ejca.2016.08.022
34. Khosrow-Khavar F, Filion KB, Bouganim N, Suissa S, Azoulay L (2020) Aromatase inhibitors and the risk of cardiovascular outcomes in women with breast cancer: a population-based cohort study. Circulation 141(7):549–559. https://doi.org/10.1161/circulationaha.119.044750
35. Ligibel JA, James O'Malley A, Fisher M, Daniel GW, Winer EP, Keating NL (2012) Risk of myocardial infarction, stroke, and fracture in a cohort of community-based breast cancer patients. Breast Cancer Res Treat 131(2):589–597. https://doi.org/10.1007/s10549-011-1754-1
36. Sund M, Garcia-Argibay M, Garmo H, Ahlgren J, Wennstig AK, Fredriksson I et al (2021) Aromatase inhibitors use and risk for cardiovascular disease in breast cancer patients: a population-based cohort study. Breast 59:157–164. https://doi.org/10.1016/j.breast.2021.07.004

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