Endocrine therapy use and cardiovascular risk in postmenopausal breast cancer survivors

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ABSTRACT

Objective Examine the effect of tamoxifen and aromatase inhibitors (AIs) on the risk of 12 clinically relevant cardiovascular outcomes in postmenopausal female breast cancer survivors.

Methods We carried out two prospective cohort studies among postmenopausal women with breast cancer in UK primary care and hospital data (2002–2016) and US Surveillance, Epidemiology and End Results-Medicare data (2008–2013). Using Cox adjusted proportional hazards models, we compared cardiovascular risks between AI and tamoxifen users; and in the USA, between users of both drug classes and women receiving no endocrine therapy.

Results 10 005 (UK) and 22 027 (USA) women with postmenopausal breast cancer were included. In both countries, there were higher coronary artery disease risks in AI compared with tamoxifen users (UK age-standardised incidence rate: 10.17 vs 7.51 per 1000 person-years, HR: 1.29, 95% CI 1.04 to 1.76; US age-standardised incidence rate: 36.82 vs 26.02 per 1000 person-years, HR: 1.29, 95% CI 1.06 to 1.55). However, comparisons with those receiving no endocrine therapy (US data) showed no higher risk for either drug class and a lower risk in tamoxifen users (age-standardised incidence rate tamoxifen vs unexposed: 26.02 vs 35.19 per 1000 person-years, HR: 0.74, 95% 0.60 to 0.92; age-standardised incidence rate AI vs unexposed: 36.82 vs 35.19, HR: 0.96, 95% CI 0.83 to 1.10). Similar patterns were seen for other cardiovascular outcomes (arrhythmia, heart failure and valvular heart disease). As expected, there was more venous thromboembolism in tamoxifen compared with both AI users and those unexposed.

Conclusions Higher risks of several cardiovascular outcomes among AI compared with tamoxifen users appeared to be driven by protective effects of tamoxifen, rather than cardiotoxic effects of AIs.

BACKGROUND

Oestrogen or progesterone receptor positive breast cancer (ER/PR+) accounts for 83% of all breast cancer, and endocrine therapies are recommended to minimise risk of recurrence.1 2 Since 2006, aromatase inhibitors (AIs) have been recommended over tamoxifen for postmenopausal women due to greater efficacy.3 However, it has recently been suggested that AI users have a higher risk of subsequent cardiovascular disease (CVD) compared with tamoxifen users.4 It is unclear whether this reflects cardiotoxicities of AIs or a protective effect of tamoxifen.

METHODS

Study design and data sources

We assembled two prospective cohorts of women with incident postmenopausal breast cancer using prospectively collected data from the UK and USA. In the UK, we used Clinical Practice Research Datalink primary care data (CPRD) and linked Hospital Episode Statistics (HES).11 In the USA, we used the Surveillance, Epidemiology, and End Results program (SEER) and Medicare linked database.12 Full data source details are in online supplemental appendix 1.
Study populations
Differences in available data within the two cohorts are explained in online supplemental appendix 2.

UK cohort
We identified women with CPRD and HES data over 54 years (median age of the menopause in Europe13), with any incident breast cancer in CPRD (after at least 1 year of CPRD follow-up), who initiated AIs or tamoxifen in primary care after their diagnosis, from 1 January 2008 (date from which preliminary analysis showed that third-generation AIs came into widespread use) to 31 March 2016 (latest CPRD and HES linkage). Follow-up began at the latest of 1 year after breast cancer diagnosis or first AI or tamoxifen prescription (hereafter index date). Women were excluded if prior to their index date they: died, transferred out of CPRD, had any other cancer diagnosis or were diagnosed with the CVD event of interest (at any point prior to index date).

US cohort
We identified women over 65 years with incident ER/PR+ and stage 1–3 breast cancer and continuous Medicare Parts A, B and D enrolment (and no managed care coverage) for 12 months prior to the month of cancer diagnosis from 1 January 2008 (Medicare Part D data are available from 2007) and 31 December 2013 (last capture of cancer cases in SEER). Women with an endocrine therapy prescription prior to their breast cancer diagnosis were excluded. Follow-up began 1 year after the date of breast cancer (hereafter index date). Women were excluded if prior to their index date they: died, discontinued from Medicare Parts A, B or D, had any other cancer diagnosis or were diagnosed with the CVD event of interest (within a 3-year look back period to ensure likelihood of capturing a prior event was not dependent on age as Medicare follow-up starts at 65 years).

Exposure, outcomes and covariates
Tamoxifen and AI exposures were identified using prescription codes in the UK (available at https://doi.org/10.17037/DATA.177), and National Drug Codes and Healthcare Common Procedural Coding System (HCPCS) procedure codes in the USA (online supplemental appendix 3). Primary exposure was ever use of tamoxifen, ever use of AI or ever use of both drugs, with ever use defined as at least one prescription (UK) or fill (USA) of the endocrine therapy medication; the US study additionally included no exposure to any endocrine therapy (which did not exist in the UK study, because receipt of endocrine therapy was an inclusion criterion). Exposure was time-updated to indicate a woman had been exposed to both drugs if they switched endocrine therapies during follow-up. The baseline exposure group was classified as ever exposure to tamoxifen for the ever AI versus tamoxifen analyses in both the UK and USA. The baseline exposure group was also changed to no exposure to any endocrine therapy for the ever AI/tamoxifen versus unexposed analyses that was only possible in the USA. Visualisations of exposure categorisations are shown in online supplemental appendix 4. The main CVD outcomes were: coronary artery disease (angina, MI, revascularisation procedures and sudden cardiac arrest); peripheral vascular disease; stroke; arrhythmia; HF (including cardiomyopathy); pericarditis; valvular heart disease (VHD); and venous thromboembolism (VTE) (deep vein thrombosis (DVT) and pulmonary embolism). Composite CVD outcomes and individual components of the composite outcomes were analysed separately. Events were identified through clinical diagnoses using NHS Read codes in the CPRD and International Classification of Disease (ICD), 10th edition codes in HES in the UK (available at https://doi.org/10.17037/DATA.177) and ICD-9 and HCPCS codes in the US study (online supplemental appendix 5).

In both studies, we adjusted for age, cardiovascular history and risk factors, use of cardioprotective medications, other comorbidities, time since index date and calendar year. In the UK, we were additionally able to adjust for smoking, alcohol, body mass index and index of multiple deprivation (ie, socio-economic status); in the US study, we were additionally able to adjust for race, region and use of anticancer therapies (anthracyclines, taxanes, trastuzumab and other systemic treatments). A full comparison of the covariates considered in the UK and USA is in online supplemental appendix 6. Algorithms to define confounders in the UK are in online supplemental appendix 7, and code lists used for variable definitions are at https://doi.org/10.17037/DATA.177. Codes used to identify prescriptions in the US are in online supplemental appendix 8.

Statistical analysis
Observation began at index date and ended at the earliest of: a CVD event of interest; diagnosis of another (non-breast) cancer; death; and transfer out of CPRD/end of Medicare Parts A, B or D enrolment. Observation could also end at the end of the study period, which was 31 March 2016 in UK and 31 December 2014 in USA.

Separate analyses were conducted in UK and USA and for each CVD outcome. Distributions of characteristics at index date were described. Number of events and crude incident rates of each outcome of interest by exposure were calculated. Cox proportional hazards models with an age timescale were fitted for each outcome of interest to obtain unadjusted HRs and 95% CIs for the association between endocrine therapy use and outcome; those with a diagnosis of the specific outcome of interest before the index date were excluded from the analysis for that outcome. All covariates were then added to obtain fully adjusted HRs. We then fitted interactions, with pre specified variables considered clinically important to investigate effect modification by current age (54–69 and 70+ years in the UK; 66–84 and 85+ years in the USA); time since index date (0–1 years, 1–3 years and 3+ years); and history of any CVD prior to index date (other than the CVD outcome of interest) for the coronary artery disease (composite), arrhythmia, stroke, pericarditis (USA only), HF, VHD and VTE (composite) outcomes (interactions were not investigated for other outcomes due to limited power). We statistically tested for interactions using likelihood ratio tests. Women with missing data (8.7% in the UK, and 5.1% in the USA) were excluded from all analyses (complete case analysis), which is valid in a regression context if missingness is conditionally independent of the outcome.14 Unfortunately, this is an untestable assumption (as it includes conditioning on the missing values themselves), but this assumption is more plausible than the missing at random assumption required for multiple imputation in the UK data; in the US data, it is possible that missingness was either at random and conditionally independent of the outcome, but we used a complete case analysis in order to have a consistent approach across the UK and US studies. We also calculated age-standardised incidence rates for each outcome by fitting a Poisson regression model with exposure and age, setting all individuals to each level of exposure separately and predicting the number of events, then dividing by the total person-years.

Sensitivity analyses
The main analyses were repeated with the UK and US study populations and covariates modified to be as similar as possible (details in online supplemental appendix 9). A post hoc quantitative bias
analysis explored potential unmeasured confounding in the large estimated protective effect of tamoxifen use on the risk of MI (online supplemental appendix 10). Finally, the primary analysis in the US data was additionally adjusted adjuvant radiotherapy to assess any additional confounding of the effect of endocrine therapy on the risk of CVD.

RESULTS
The UK study included 10005 women, with 4716 (47%) initially prescribed tamoxifen and 5289 (53%) initially prescribed an AI (table 1, flow diagram in figure 1); the median person-years of follow-up in each exposure group was: ever tamoxifen: 2.3 years (IQR: 1.2–5.4 years), ever AI: 2.2 years (IQR: 0.9–4.3 years) and both: 3.5 years (IQR: 1.5–6.3 years). The US study included 22027 women, with 4667 (22%) and 2286 (10%) and 15074 (68%) initially filling no endocrine therapy, tamoxifen and an AI, respectively (table 2, flow diagram in figure 1); the median person-years of follow-up in each exposure group were as follows: unexposed: 1.6 years (IQR: 0.6–3.3 years), tamoxifen 2.2 years (IQR: 1.0–3.8 years), AI: 2.0 years (IQR: 0.9–3.6 years) and both: 1.9 years (IQR: 0.8–3.5 years).

Ever AI versus tamoxifen use
In both the UK and USA, there was a higher observed rate of most CVDs, excluding VTE outcomes, among those ever exposed to an AI compared with tamoxifen (online supplemental appendices 11 and 12). In adjusted analyses, there was evidence of a higher risk of HF in AI compared with tamoxifen users in the UK (HR: 1.68, 95% CI 1.24 to 2.26; figure 2), which was not replicated in the USA (HR: 0.96, 95% CI 0.83 to 1.12). Other adjusted HRs were consistent between the two settings; there was evidence in one or both settings that AI users compared with tamoxifen users had higher risk of coronary artery disease, MI, arrhythmia, pericarditis and VHD (HRs ranged from 1.29 to 3.25 in the UK, and 1.21 to 1.81 in the USA; figure 2) and lower risk of DVT (UK HR: 0.63, 95% 0.43 to 0.93; US HR: 0.81, 95% CI 0.50 to 1.09).

Table 1 Characteristics of study population based on their initial exposure in the UK

|              | Tamoxifen | AI | Total |
|--------------|-----------|----|-------|
| N            | 4716 (100)| 5289 (100)| 10005 (100) |
| Age (years)  |           |     |       |
| 54–59        | 911 (19.3)| 716 (13.5)| 1627 (16.3) |
| 60–69        | 1850 (39.2)| 1972 (37.3)| 3822 (38.2) |
| Median (IQR) | 1955 (41.3)| 2601 (49.2)| 4556 (45.5) |
| Year of breast cancer |          |     |       |
| 2002–2005     | 2267 (48.1)| 670 (12.7)| 2937 (29.4) |
| 2006–2009     | 1523 (32.3)| 1846 (34.9)| 3369 (33.7) |
| 2010–2013     | 823 (17.5)| 2248 (42.5)| 3071 (30.7) |
| 2014–2015     | 103 (2.2) | 525 (9.9) | 628 (6.3) |
| BMI (kg/m²)   |           |     |       |
| <18          | 59 (1.3) | 63 (1.2) | 122 (1.2) |
| 18–24        | 1693 (35.9)| 1619 (30.6)| 3312 (33.1) |
| 25–29        | 1549 (32.8)| 1801 (34.1)| 3350 (33.5) |
| 30–34        | 800 (17)  | 979 (18.5)| 1779 (17.8) |
| ≥35          | 345 (7.3) | 548 (10.4)| 893 (8.9) |
| Missing      | 270 (5.7) | 279 (5.3) | 549 (5.5) |
| Smoking status |         |     |       |
| None         | 2423 (51.4)| 2517 (47.6)| 4940 (49.4) |
| Current      | 503 (10.7) | 482 (9.1) | 985 (9.8) |
| Missing      | 1761 (37.3)| 2268 (42.9)| 4029 (40.3) |
| Alcohol use  |           |     |       |
| Non-drinker  | 618 (13.1) | 613 (11.6)| 1231 (12.3) |
| Current      | 3320 (70.4)| 3628 (68.6)| 6948 (69.4) |
| Missing      | 178 (3.8)  | 251 (4.8) | 429 (4.3) |
| Systolic BP  |           |     |       |
| Low/ideal    | 530 (11.2) | 599 (11.3)| 1129 (11.3) |
| Pre/ideal    | 1862 (39.3) | 2327 (44)| 4189 (41.9) |
| High         | 2314 (49.1)| 2355 (44.5)| 4669 (46.7) |
| Missing      | 10 (0.2)   | 8 (0.2)   | 18 (2.2) |
| Diastolic BP |           |     |       |
| Low/ideal    | 2130 (45.2)| 2650 (50.1)| 4780 (47.8) |
| Pre/ideal    | 1988 (42.2)| 2568 (38.9)| 4546 (40.4) |
| High         | 588 (12.5) | 573 (10.8)| 1161 (11.6) |
| Missing      | 10 (0.2)   | 8 (0.2)   | 18 (2.2) |
| Index of Multiple deprivation category |          |     |       |
| 1            | 870 (1.8)  | 962 (1.8) | 1832 (1.8) |
| 2            | 943 (20)   | 1214 (23) | 2157 (21.6) |
| 3            | 935 (19.8) | 1054 (19.9)| 1979 (19.8) |
| 4            | 1052 (22.3)| 936 (17.7)| 1988 (19.9) |
| 5            | 926 (19.6) | 1122 (21.2)| 2048 (20.5) |
| Missing      | 0 (0)      | 1 (0)    | 1 (0)    |
| CVD-related treatment before index |          |     |       |
| Statins      | 1100 (23.3)| 1903 (36)| 3003 (30) |
| ACEi         | 1195 (25.3)| 1823 (34.5)| 3018 (30.2) |
| CCB          | 1195 (25.3)| 1764 (33.4)| 2959 (29.6) |
| ARB          | 493 (10.5) | 795 (15)| 1288 (12.9) |
| Antiplatelets| 1132 (24)  | 1639 (31)| 2771 (27.7) |
| Comorbidities before index |          |     |       |
| RA           | 138 (2.9)  | 137 (2.6) | 275 (2.7) |
| Diabetes     | 462 (9.8)  | 728 (13.8)| 1190 (11.9) |
| CKD          | 867 (18.4) | 1090 (20.6)| 1957 (19.6) |

Continued
Cardiac risk factors and prevention

Table 1  Continued

| CVD before index | Tamoxifen | AI | Total |
|-----------------|-----------|----|-------|
| Non-venous CVD   | 1031 (21.9) | 1636 (30.9) | 2667 (26.7) |
| VTE before index | 144 (3.1) | 324 (6.1) | 468 (4.7) |

ACEI, Angiotensin-converting-enzyme inhibitors; AI, aromatase inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, Chronic kidney disease; CVD, cardiovascular disease; RA, Rheumatoid arthritis; VTE, venous thromboembolism.

Sensitivity analyses

Following modification of study populations, methodology and covariates in the UK and USA to make them as similar as possible, the risk of all CVDs associated with ever AI compared with tamoxifen use were generally in the same direction (online supplemental appendix 15). However, the discrepant results for HF between the two cohorts persisted. Quantitative bias analyses suggest that unmeasured confounding was unlikely to fully explain the large HR for the effect of ever tamoxifen use on MI risk (online supplemental appendix 16). Effect estimates in US data after additional adjustment for adjuvant radiotherapy were similar to primary results (online supplemental appendix 17).

DISCUSSION

Our results suggest that higher observed risks of cardiovascular outcomes including coronary artery disease, MI, arrhythmia, HF, pericarditis and VHD in AI users compared with tamoxifen users are driven by protective associations of tamoxifen with CVD outcomes, rather than any cardiotoxic effects of AIs. These two population-based cohort studies using UK and US data are the first to apply similar methodology to two large populations to assess the effects of endocrine therapies on a range of CVD outcomes in postmenopausal women with breast cancer. Both countries’ results suggested a higher risk of several CVD outcomes in AI compared with tamoxifen users. However, when compared with patients receiving no endocrine therapy, there was no raised risk of any CVD outcome in users of either drug class, other than VTE in tamoxifen users. Furthermore, tamoxifen users had lower risks of coronary artery disease, MI, stroke, arrhythmia, pericarditis and VHD than unexposed women. This protective effect of tamoxifen might be explained by the drug’s effect on lipid levels; previous studies have found tamoxifen to reduce cholesterol.5 16

Comparison with other studies

A recent meta-analysis of trials reported an increased risk of CVD, excluding VTE, in tamoxifen compared with AI users (RR: 1.18, 95% CI 1.05 to 1.33),10 with results suggestive of a cardioprotective effect of tamoxifen, consistent with the results of this study.10

Most (5/6) previous studies directly comparing the risk of MI in AI and tamoxifen users have reported a higher risk in AI users, similar to our results (RRs ranged from 0.99 to 2.02).10 18–22 Two previous trials and five observational studies have compared MI risk in tamoxifen users with non-use/placebo, with 4/7 studies finding a reduced risk in tamoxifen users (RRs ranged from 0.20 to 0.83)23–29, two analogous studies of AI use versus placebo or non-use found no association.28 30 Seven studies (five trials and two observational) directly compared the risk of stroke in AI and tamoxifen users, but effects in both directions have been reported.20 22 31–34 Three out of five studies (one trial and four observational) comparing tamoxifen use with non-use/placebo found a protective association with stroke, as in our study (RRs ranged from 0.52 to 0.81).23 26–28 33 In the present analysis, we found AI users to be at lower risk of stroke compared with unexposed women; one previous study found a similar association but a second reported the opposite.28 30 Three previous studies (one trial and two observational) have reported results for the comparison between AI and tamoxifen use on the risk of HF,10 31 34 for which we reported discrepant results between the UK and USA. Two reported a higher risk in AI users and the other reported no association. The discrepant results in our study could be due to residual confounding by variables not available in both datasets (cancer therapies in the UK and lifestyle factors in the USA), or the nature of the data sources (routinely collected records in the UK and claims in the USA).

Six previous trials compared the risk of VTE in AI and tamoxifen users, with five reporting a lower risk in AI compared with tamoxifen users (RR ranged from 1.25 to 0.61), as reported in both UK and US data in this study.18 20 22 31 36–37 Six out of eight studies (five trials and three observational) also suggested a higher risk in tamoxifen users (RRs ranged from 1.64 to 7.10), which is in the same direction, but larger than the effect in US data here.

**Figure 1** Flow diagrams of study populations in the UK and USA. CPRD, Clinical Practice Research Datalink; GP, general practitioner; HES, Hospital Episode Statistics; ER, oestrogen; PR, progesterone.
Table 2  Characteristics of study population based on their initial exposure in the USA

|                | Unexposed | Tamoxifen | AI    | Total |
|----------------|-----------|-----------|-------|-------|
| N              | 4667 (100)| 2286 (100)| 15 074 (100) | 22027 (100) |
| Age at index date (years) |          |           |       |       |
| 66–74          | 1538 (31) | 897 (39.2)| 7505 (49.8) | 9940 (45.1) |
| 75–84          | 1937 (41.5)| 994 (43.5)| 5894 (39.1) | 8825 (40.1) |
| 85+            | 1192 (25.5)| 395 (17.3)| 1675 (11.1) | 3262 (14.8) |
| Median (IQR)   | 79 (73–85)| 77 (72–83)| 75 (71–81) | 76 (71–82) |
| Ethnicity*     |           |           |       |       |
| White          | 4002 (85.6)| 2028 (88.7)| 12 782 (84.8) | 18 912 (85.4) |
| Black          | 360 (7.7) | 102 (4.5) | 1099 (7.3) | 1561 (7.1) |
| Other          | 93 (2)   | 47 (2.1)  | 335 (2.2)  | 475 (2.2)  |
| Asian          | 123 (2.6)| 68 (3)    | 498 (3.3)  | 689 (3.1)  |
| Hispanic       | –        | –         | 85 (0.6)   | 128 (0.6)  |
| Native American| –        | –         | 52 (2)     | 52 (2)     |
| Missing        | –        | –         | 41 (2)     | 41 (2)     |
| SEER region    |           |           |       |       |
| North East     | 760 (16.3)| 283 (12.4)| 3320 (22)  | 4363 (19.8) |
| South          | 1023 (21.9)| 605 (26.5)| 3778 (25.1) | 5406 (24.5) |
| North Central  | 695 (14.9)| 448 (19.6)| 1763 (11.7)| 2904 (13.2) |
| West           | 2157 (46.2)| 939 (41.1)| 6130 (40.7)| 9226 (41.9) |
| Year of breast cancer |       |           |       |       |
| 2008–2009      | 1678 (36) | 1231 (53.8)| 6609 (43.8) | 10247 (46.5) |
| 2010–2011      | 1473 (31.6)| 701 (30.7)| 5019 (33.3) | 7193 (32.7) |
| 2012–2013      | 1516 (32.5)| 722 (31.6)| 5840 (38.7) | 8078 (36.7) |
| Stage of breast cancer |     |           |       |       |
| Stage I        | 3034 (65)| 1486 (65)| 8379 (55.6)| 12 899 (58.6) |
| Stage II       | 1275 (27.3)| 660 (28.9)| 5267 (34.9)| 7202 (32.7) |
| Stage III      | 358 (7.7)| 140 (6.1)| 1428 (9.5)| 1926 (8.7)  |
| Grade of breast cancer |     |           |       |       |
| 1              | 1522 (32.6)| 765 (33.5)| 4273 (28.3)| 6560 (29.8) |
| 2              | 2071 (44.4)| 1109 (48.5)| 7350 (48.8) | 10530 (47.8) |
| 3              | 853 (18.3)| 324 (14.2)| 2810 (18.6)| 3987 (18.1) |
| Missing        | 221 (4.7)| 88 (3.8)| 641 (4.3)| 950 (4.3)   |
| Cancer treatments |        |           |       |       |
| Taxane         | 570 (12.2)| 162 (7.1)| 2415 (16)  | 3147 (14.3) |
| Anthracyclines  | 259 (5.5)| 68 (3)    | 820 (5.4)  | 1147 (5.2) |
| Trastuzumab     | 226 (4.8)| 39 (1.7)| 687 (4.6)| 952 (4.3)  |
| Other treatment | 753 (16.1)| 244 (10.7)| 2992 (19.8) | 3989 (18.1) |
| Comorbidities   |           |           |       |       |
| RA             | 185 (4)  | 103 (4.5)| 547 (3.6)| 835 (3.8) |
| CKD            | 383 (8.2)| 155 (6.8)| 1113 (7.4)| 1651 (7.5) |
| Hypertension    | 3426 (73.4)| 1612 (70.5)| 11 113 (73.7)| 16 151 (73.3) |
| Diabetes       | 1313 (28.1)| 598 (26.2)| 4545 (30.2)| 6456 (29.3) |
| CVD-related treatment before index |       |           |       |       |
| Statins        | 1778 (38.1)| 948 (41.5)| 6986 (44.8)| 9714 (44.1) |
| Hypertensives   | 169 (3.6)| 83 (3.6)| 577 (3.8)| 829 (3.8) |
| ACEi           | 962 (20.6)| 477 (20.9)| 3251 (21.6)| 4690 (21.3) |
| CCB            | 850 (18.2)| 364 (15.9)| 2696 (17.9)| 3910 (17.8) |
| ARB            | 593 (12.7)| 255 (11.2)| 2063 (13.7)| 2911 (13.2) |
| Past CVD       |NON-VERUS CVD | 2989 (64)| 1281 (56)| 8896 (59)| 13 166 (59.8) |
| VTE            | 162 (3.5)| 31 (1.4)| 385 (2.6)| 578 (2.6) |

*Cell numbers within ethnicity suppressed due to some cells containing numbers <1.1.

Cardiac risk factors and prevention

17 CONCLUSION

Among postmenopausal women diagnosed with ER/PR+ breast cancer, we found convincing evidence of a higher risk of several CVDs in AI compared with tamoxifen users. However, our results indicated no excess cardiotoxicities of either drug class, other than the known raised risk of VTE.

Matthews AA, et al. Heart 2021;107:1327–1335. doi:10.1136/heartjnl-2020-317510
Cardiac risk factors and prevention

Figure 2  Adjusted HRs for the association between ever AI use compared with ever tamoxifen use and the risk of a range of clinical CVD outcomes in the UK and USA. *UK results adjusted for the following covariates at baseline: for age (54–59, 60–69 and 70+ years); smoking status (non-smoker, current smoker and ex-smoker); BMI (underweight/healthy weight, overweight and obese); alcohol status (non-drinker, current drinker and ex-drinker); IMD score (levels 1–5 based on GP level IMD data); use of statins; use of ACE inhibitors; use of calcium channel blockers; use of angiotensin II receptor blockers; diabetes; chronic kidney disease; rheumatoid arthritis; systolic blood pressure (low/normal, prehigh and high); diastolic blood pressure (low/normal, prehigh and high); history of non-venous CVD year of breast cancer diagnosis; time since index (0–1 years, 1–3 years, 3–5 years and 5+ years); and current year. US results adjusted for year of breast cancer diagnosis (2007–2013); age at index date (66–74, 75–84 and 85+ years); race (white, black Asian, Hispanic, Native American and other); SEER region (North East, South, North Central and West); breast cancer stage (1–3); breast cancer grade (1–3); time since index date (0–1 years, 1–3 years, 3–5 years and 5+ years); current calendar year; use of taxanes, anthracycline, trastuzumab, other systemic cancer treatments, statins, antihypertensive drugs, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers; diagnosis of rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, VTE and non-venous CVD. **Numbers of events for each outcome in the AI and tamoxifen groups are shown in online supplemental appendices 11 and 12. AI, aromatase inhibitor; BMI, body mass index; CVD, cardiovascular disease; DVT, deep vein thrombosis; HF, heart failure; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; SEER, Surveillance, Epidemiology, and End Results; VHD, valvular heart disease; VTE, venous thromboembolism.
**Figure 3** Adjusted HRs, events and crude rate per 1000 person-years for the association between ever exposure to endocrine therapy and a range of clinical CVD outcomes in the USA. *Adjusted for year of breast cancer diagnosis (2007–2013); age at index date (66–74, 75–84 and 85+ years); race (white, black, Asian, Hispanic, Native American and other); SEER region (North East, South, North Central and West); breast cancer stage (1–3); breast cancer grade (1–3); time since index date (0–1 year, 1–3 years, 3–5 years and 5+ years); current calendar year; use of taxanes, anthracyclines, trastuzumab, other systemic cancer treatments, statins, antihypertensive drugs, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers; and diagnosis of rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, VTE and non-venous CVD. **Events and follow-up suppressed if number of events ≤11. CVD, cardiovascular disease; DVT, deep vein thrombosis; HF, heart failure; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; SEER, Surveillance, Epidemiology, and End Results; VHD, valvular heart disease; VTE, venous thromboembolism.
Cardiac risk factors and prevention

with tamoxifen use. There was no evidence of raised risk of any specific CVD with AI use, including in stratified results restricted to those with other prior CVDs, suggesting that a history of CVD is unlikely to be an important contraindication for prescription of an AI. Our results contribute to the evidence base regarding the risk–benefit balance of endocrine therapies with respect to cancer survival and cardiovascular outcomes and ultimately can help identify subgroups of postmenopausal women who are likely to benefit from tamoxifen over AIs.

Key messages

What is already known on this subject?

► Women with oestrogen or progesterone receptor positive breast cancer typically receive endocrine therapies, either tamoxifen or aromatase inhibitors (AIs), to reduce cancer recurrence risk. Recent studies have suggested raised cardiovascular risks in AI compared with tamoxifen users, but it is unclear whether this reflects cardiotoxicities of AIs or a protective effect of tamoxifen.

What might this study add?

► Among postmenopausal women with breast cancer, we found a higher risk of several cardiovascular diseases in AI compared with tamoxifen users across two countries, which appeared to be driven by protective effects of tamoxifen, rather than toxic effects of AIs. We also found the known higher venous thromboembolism risk in tamoxifen users.

How might this impact on clinical practice?

► Previous evidence could lead to reduced uptake of AIs among those at a high risk of cardiovascular disease. However, there is no current evidence to suggest that the cardiovascular benefits of tamoxifen outweigh the far superior effect that AIs have on breast cancer recurrence in this population, and there is no higher cardiovascular risk when prescribing AIs to these patients. These results should allay any concerns about postulated cardiototoxicities of AIs, and modifications to clinical practice could reduce the risk of patients being prescribed inappropriate endocrine therapies.

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