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ORIGINAL REPORT

Use of β-Blockers, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Risk of Breast Cancer Recurrence: A Danish Nationwide Prospective Cohort Study

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ABSTRACT

Purpose
To estimate associations between use of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) and breast cancer recurrence in a large Danish cohort.

Patients and Methods
We enrolled 18,733 women diagnosed with nonmetastatic breast cancer between 1996 and 2003. Patient, treatment, and 10-year recurrence data were ascertained from the Danish Breast Cancer Cooperative Group registry. Prescription and medical histories were ascertained by linkage to the National Prescription Registry and Registry of Patients, respectively. β-Blocker exposure was defined in aggregate and according to solubility, receptor selectivity, and individual drugs. ACE inhibitor and ARB exposures were defined in aggregate. Recurrence associations were estimated with multivariable Cox regression models in which time-varying drug exposures were lagged by 1 year.

Results
Compared with never users, users of any β-blocker had a lower recurrence hazard in unadjusted models (unadjusted hazard ratio [HR] = 0.91; 95% CI, 0.81 to 1.0) and a slightly higher recurrence hazard in adjusted models (adjusted HR = 1.3; 95% CI, 1.1 to 1.5). Associations were similar for exposures defined by receptor selectivity and solubility. Although most individual β-blockers showed no association with recurrence, metoprolol and sotalol were associated with increased recurrence rates (adjusted metoprolol HR = 1.5, 95% CI, 1.2 to 1.8; adjusted sotalol HR = 2.0, 95% CI, 0.99 to 4.0). ACE inhibitors were associated with a slightly increased recurrence hazard, whereas ARBs were not associated with recurrence (adjusted ACE inhibitor HR = 1.2, 95% CI, 0.97 to 1.4; adjusted ARBs HR = 1.1, 95% CI, 0.85 to 1.3).

Conclusion
Our data do not support the hypothesis that β-blockers attenuate breast cancer recurrence risk.

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INTRODUCTION

β-Blockers competitively inhibit the binding of norepinephrine and epinephrine to β-adrenergic receptors, interrupting downstream signaling.[1] The stress hormone norepinephrine may affect the progression of various cancers, and laboratory models show that the β-blocker propranolol inhibits norepinephrine-induced breast cancer migration to metastatic sites.[2-6] Recent epidemiologic studies suggest that β-blockers prevent breast cancer progression.[7-12] Some studies have associated β-blockers with reduced recurrence risk or improved survival in patients with breast cancer, and this association may depend on the receptor selectivity of the drug.[7-10] Another study showed no association between β-blockers and breast cancer survival.[13]

Several studies suggest that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) also have anticancer properties,[14] whereas others report increased cancer risk[15] or no association.[16-19] Two studies have specifically addressed breast cancer outcomes among users of ACEi and ARBs. One showed a decreased recurrence risk in users of ARBs or ACEi.[20] The other showed no association for patients taking both ACEi and β-blockers, but an increased recurrence risk in exclusive ACEi users.[10]

To address conflicting evidence from earlier studies, we estimated associations between use of β-blockers, ACEi, and ARBs and the breast cancer recurrence rate in a large cohort of Danish breast cancer survivors.

PATIENTS AND METHODS

Source Population and Data Collection

We conducted a nationwide cohort study using the population-based medical and prescription registries of Denmark, which cover all of the country's ~5.6 million inhabitants. A unique civil personal registration number is assigned to all Danish residents, allowing individual-level linkage of registries.[21]

The Danish Breast Cancer Cooperative Group (DBCG) registry has prospectively enrolled nearly all Danish patients with breast cancer since 1977.[22,23] DBCG enrollees undergo follow-up examinations every 3 to 6 months for the first 5 years after diagnosis and then annually for years 6 to 10.[23] Recurrences diagnosed between examinations are also reported to the registry. From this registry we identified all women diagnosed with an incident invasive breast cancer (Union for International Cancer Control stage I to III) between 1996 and 2003 who were placed on a standard DBCG treatment protocol. We ascertained age and menopausal status at diagnosis, type of primary therapy, Union for International Cancer Control stage, histologic grade, tumor estrogen receptor (ER) status, receipt of adjuvant chemotherapy, radiotherapy, and endocrine therapy (ET), date and anatomic site of recurrence, and date of death or emigration.

The Danish National Prescription Registry has automatically recorded all prescriptions dispensed at Danish pharmacies since 1995. For each prescription the database records the date, patient's civil personal registration number, drug prescribed (using the Anatomic Therapeutic Chemical classification system), and fill quantity.[24] We linked the breast cancer cohort to this registry to ascertain exposure to β-blockers, ACEi, and ARBs (Appendix Table A1, online only). We also characterized exposure to potentially confounding comedications previously associated with breast cancer outcomes (ie, simvastatin,[25] aspirin,[26] and prediagnosis combination hormone replacement therapy[27]) and to other drugs (Appendix Table A2, online only).

We used the Danish National Registry of Patients to summarize each patient's medical history from 1977 until her breast cancer diagnosis.[28] We searched the registry for diagnoses that comprise the Charlson comorbidity index,[29] excluding breast cancer (Appendix Table A3, online only). We also ascertained history of diagnosed obesity, arrhythmia, angina pectoris, esophageal varices, tremor, thyrotoxicosis, migraine, chronic obstructive pulmonary disease, and asthma (Appendix Table A4, online only).

Definitions of Analytic Variables

Age at diagnosis was categorized by decade in stratified analyses, but modeled continuously in multivariate models. Person-time at risk for recurrence was defined as the number of days elapsed between the date of primary surgery and the first of breast cancer recurrence, death, emigration, or December 31, 2010. Breast cancer recurrence is defined by DBCG protocol as any local, regional, or distant recurrence or cancer of the contralateral breast.[23] We estimated site-specific recurrence associations for the following anatomic sites: bone, lymph nodes, ipsilateral breast, contralateral breast, lung, liver, or CNS. We also defined a distant recurrence outcome in which women with ipsilateral recurrence or contralateral recurrence were censored on their event dates. Histologic grade was classified as low, moderate, or high. Receipt of adjuvant chemotherapy and radiotherapy were defined dichotomously. ER status and receipt of ET were summarized into a joint variable (ER+/ET+, ER–/ET–, ER+/ET–). Patients with ER-negative tumors who received ET contrary to indication (ER–/ET+, n = 36) were excluded from the cohort. Because this group accounted for a miniscule proportion of patients, we deemed exclusion to be the most appropriate technique by which to account for their anomalous treatment profile. Results from analyses including this subgroup did not differ from the analyses reported herein.

Time-dependent drug exposures were updated yearly over follow-up. Positive exposure in each year was defined as having at least one prescription during that year for the drug class of interest. Exposures to β-blockers, ACEi, and ARBs were defined in several ways. In the simplest case, we defined ever/never exposure to each drug class. These drugs are available as combination tablets containing either calcium channel blockers or diuretics, so we also defined pure exposure to each class (ie, noncombination tablets only). β-Blockers with α-adrenergic effects were excluded from the pure β-blocker group. β-Blocker exposures were also defined by receptor selectivity (nonselective or β1-selective) and by lipid solubility (highly, moderately, or weakly lipophilic). β-Blocker and ARB exposures were also defined by specific drugs. We made our exposure definitions exclusive to avoid misclassification from class switching. For example, nonselective β-blocker exposure was positive if 100% of a woman's β-blocker prescriptions were for nonselective drugs. We calculated duration of exposure as the cumulative number of years exposed since 1995. Duration was categorized as 0 (no exposure history), 1 to 5, 6 to 10, and more than 10 cumulative years of exposure.

To evaluate the effect of prediagnosis exposure, we conducted a subanalysis in the subset of women with ≥ 3 years of prescription data before their breast cancer diagnosis (n = 14,424). We defined prediagnostic exposure in categories of total tablets prescribed in the 3 years preceding breast cancer diagnosis (1 to 100, 101 to 1,000 and ≥ 1,001 tablets). We accounted for drug discontinuation by modeling the gap (in days) between completing the last prescription and the diagnosis date. Duration of the last prescription was estimated as the product of the fill quantity and the tablet strength, divided by the defined daily dose associated with the Anatomic Therapeutic Chemical code.[30]

Statistical Analysis

We tabulated the frequency and proportion of ever-users and never-users of β-blockers, ACEi, and ARBs within categories of covariates (Table 1).

We estimated 10-year recurrence associations using Cox regression models. Time-varying drug exposures were lagged by 1 year to allow a reasonable induction period for an effect on recurrence and to guard against the possibility that subclinical recurrences affected prescribing or adherence. Drug exposure durations were modeled as time-varying covariates in separate analyses. Multivariate models featured mutual adjustment for β-blockers, ACEi, and ARBs as well as for prognostic factors, Charlson comorbidity index,[29] and potentially confounding coprescriptions. Proportionality of hazard functions was checked by evaluating Wald tests of cross-product terms between main exposures and the logarithm of person-time.[31]

To evaluate potential residual confounding by a secondary list of comorbidities and comedications while managing model dimensionality, we calculated a recurrence risk score from the logistic regression of recurrence on dichotomously defined prediagnosis exposure to the medications listed in Appendix Table A2 and prediagnosis history of the conditions listed in Appendix Table A4. Coefficients from this model were adjusted for use of β-blockers, ACEi, and ARBs and were used to calculate each patient's probability of recurrence as a function of their observed exposure to the additional drugs and diagnoses. The continuous probability was categorized into deciles and modeled with design variables in multivariate proportional hazards models as described previously. Hazard ratios for main exposures were compared between multivariate models with and without the risk score to judge whether the risk score encoded substantial confounding.

We evaluated effect measure modification by ER status, histologic grade, and menopausal status in stratified multivariate models. Heterogeneity of associations by recurrence site was explored using competing risks proportional hazards models.[31]

In the subcohort of women with at least 3 years of prediagnosis prescription data, we simultaneously modeled categories of the number of tablets prescribed in the 3-year period before diagnosis, longitudinal postdiagnosis exposures (as previously), and the gap between last prediagnosis exposure and diagnosis (continuous).

All analyses were performed with SAS v.9.2 (SAS Institute, Cary, NC). The study was approved by the DBCG and the Danish Data Protection Agency (record no. 2010-41-4979).

Table 1. Baseline Characteristics of Patients With Breast Cancer Diagnosed in Denmark 1996 to 2003 (N = 18,733)

	Any β-Blocker				Any ACE Inhibitor				Any ARB			
	Ever Use (n = 3,660)		Never Use (n = 15,073)		Ever Use (n = 3,075)		Never Use (n = 15,658)		Ever Use (n = 1,989)		Never Use (n = 16,744)	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at diagnosis, years												
≤ 29	2	0.1	68	0.5	0	0	70	0.5	0	0	70	0.4
30-39	63	1.7	856	5.7	21	0.7	898	5.7	12	0.6	907	5.4
40-49	390	11	3,121	21	252	8.2	3,259	21	158	7.9	3,353	20
50-59	1,091	30	5,138	34	899	29	5,330	34	596	30	5,633	34
60-69	1,358	37	4,214	28	1,247	41	4,325	28	803	40	4,769	28
70-79	727	20	1,581	10	629	20	1,679	11	403	20	1,905	11
≥ 80	29	0.8	95	0.6	27	0.9	97	0.6	17	0.9	107	0.6
Menopausal status at diagnosis												
Premenopausal	620	17	4,968	33	410	13	5,178	33	257	13	5,331	32
Postmenopausal	3,040	83	10,102	67	2,665	87	10,477	67	1,732	87	11,410	68
Missing	0		3		0		3		0		3	
Medical history at diagnosis*												
Myocardial infarction	136	3.7	85	0.6	101	3.3	120	0.8	41	2.1	180	1.1
Congestive heart failure	83	2.3	87	0.6	90	2.9	80	0.5	35	1.8	135	0.8
Cerebrovascular disease	148	4.0	316	2.1	146	4.8	318	2.0	68	3.4	396	2.4
Peripheral vascular disease	96	2.6	172	1.1	76	2.5	192	1.2	36	1.8	232	1.4
Renal disease	37	1.0	55	0.4	30	1.0	62	0.4	17	0.9	75	0.5
Liver disease	8	0.2	16	0.1	0	0	24	0.2	1	0.05	23	0.1
Obesity	93	2.5	172	1.1	105	3.4	160	1.2	69	3.5	196	1.2
Medical history at diagnosis†												
Thyrotoxicosis	146	4.0	300	2.0	77	2.5	369	2.4	54	2.7	392	2.3
Arrhythmia	251	6.8	237	1.6	145	4.7	343	2.2	77	3.9	411	2.5
Angina pectoris	456	12	444	2.9	302	9.8	598	3.8	164	8.3	736	4.4
Migraine	383	10	1,111	7.4	245	8.0	1,249	8.0	202	10	1,292	7.7
Diabetes	139	3.8	272	1.8	216	7.0	195	1.3	97	4.9	314	1.9
COPD or asthma	996	27	3,191	21	905	29	3,282	21	618	31	3,569	21
UICC stage												
I	1,423	39	5,757	38	1,172	38	6,008	39	759	38	6,421	38
II	1,667	46	6,458	43	1,424	46	6,701	43	941	47	7,184	43
III	568	16	2,853	19	478	16	2,943	19	288	14	3,133	19
Missing	2		5		1		6		1		6	
Histologic grade												
Low	1,016	35	4,068	33	880	35	4,204	33	568	35	4,516	33
Moderate	1,282	44	5,316	43	1,098	44	5,500	43	723	44	5,875	43
High	615	21	2,994	24	507	20	3,102	24	347	21	3,262	24
Missing	747		2,695		590		2,852		351		3,091	

(continued on following page)

Table 1. Baseline Characteristics of Patients With Breast Cancer Diagnosed in Denmark 1996 to 2003 (N = 18,733) (continued)

	Any β-Blocker				Any ACE Inhibitor				Any ARB			
	Ever Use (n = 3,660)		Never Use (n = 15,073)		Ever Use (n = 3,075)		Never Use (n = 15,658)		Ever Use (n = 1,989)		Never Use (n = 16,744)	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ER/adjuvant ET status												
ER–/ET–	616	18	3,179	22	486	16	3,309	22	326	17	3,469	22
ER+/ET–	1,168	33	4,729	33	912	30	4,985	33	557	29	5,340	33
ER+/ET+	1,726	49	6,577	45	1,563	52	6,740	45	1,041	54	7,262	45
Missing	150		588		114		624		65		673	
Type of primary therapy												
Mastectomy	2,504	68	10,053	67	2,094	68	10,463	67	1,337	67	11,220	67
BCS + RT	1,155	32	5,020	33	981	32	5,194	33	651	33	5,524	33
Missing	1		0		0		1		1		0	
Adjuvant chemotherapy received												
Yes	683	19	4,757	32	530	17	4,910	31	356	18	5,084	31
No	2,977	81	10,316	68	2,545	83	10,748	69	1,633	82	11,660	70
Prediagnosis exposure to												
Postmenopausal HRT (E + P)	983	27	3,223	21	737	24	3,469	22	528	27	3,678	22
Postmenopausal HRT (E)	1,020	28	3,173	21	841	27	3,352	21	588	30	3,605	22
Drug exposures during study period												
Any β-blocker	3,660	100	0	0	1,320	43	2,340	15	937	47	2,723	16
Any ACE inhibitor	1,320	36	1,755	12	3,075	100	0	0	959	48	2,116	13
Any ARB	937	26	1,052	7.0	959	31	1,030	6.6	1,989	100	0	0
Calcium channel blocker	1,428	39	1,635	10	1,425	46	1,638	10	1,001	50	2,062	12
Diuretics	2,461	67	4,794	32	2,329	76	4,926	31	1,487	75	5,768	34
α-Receptor blockers	130	3.6	118	0.8	119	3.9	129	0.8	104	5.2	144	0.9
Aspirin (high and low doses)	1,585	43	1,990	13	1,277	42	2,298	15	826	42	2,749	16
NSAIDs	2,677	73	9,495	63	2,254	73	9,918	63	1,480	74	10,692	64
Anticoagulants	431	12	387	2.6	279	9.1	539	3.4	151	7.6	667	4.0
Valproic acids	43	1.2	108	0.7	33	1.1	118	0.8	26	1.3	125	0.8
Glucocorticoids (systemic)	1,040	28	3,205	21	853	28	3,392	22	608	31	3,637	22
Simvastatin	1,185	32	1,790	12	1,168	38	1,807	12	776	39	2,199	13
Digoxin	363	9.9	229	1.5	254	8.3	338	2.2	119	6.0	473	2.8

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BCS, breast-conserving surgery; COPD, chronic obstructive pulmonary disease; E, estrogen; ER, estrogen receptor; ET, adjuvant endocrine therapy; ICD, International Classification of Diseases; HRT, hormone replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; P, progesterone; RT, radiotherapy; UICC, Union for International Cancer Control.

*The conditions were defined as in the Carlson Comorbidity index (see Appendix Table A3, online only, for ICD codes).

†The conditions were defined by combining ICD codes for the diseases (see Appendix Table A4, online only) and the history of any redeemed prescription for the condition (defined by Anatomical Therapeutic Chemical codes listed in Appendix Table A2, online only). Hypertension was not included as a variable because most people in Denmark are treated for hypertension by their primary care provider so the number of patients with a hospital admission code for hypertension would underestimate the true prevalence. For the same reason we also did not include hospital admission codes for stress/anxiety or depression, because most people in Denmark with these conditions will be treated by their primary care provider or at outpatient clinics at psychiatric hospitals.

RESULTS

We enrolled 18,733 women diagnosed with invasive breast cancer between 1996 and 2003 (Table 1). There were 3,414 recurrences over 113,799 person-years of follow-up (median = 6.8 years). There were 3,660 users of β-blockers, 3,075 users of ACEi, and 1,989 users of ARBs. The median total number of tablets prescribed to patients with one to five, six to 10, and more than 10 years of cumulative exposure were 400, 2,541, and 3,770, respectively, for any β-blocker; 330, 2,530, and 3,730, respectively, for any ACEi; and 588, 2,282, and 3,717, respectively, for any ARB. Median cumulative duration of exposure under our various definitions is reported in Table 2.

Table 1 shows the distribution of prognostic factors, comorbidities, and comedications among never and ever users of β-blockers, ACEi, and ARBs. Users of these drugs were older (median age, 62 to 63 years for users *v* 56 to 57 for nonusers), more likely to be postmenopausal at diagnosis (83% to 87% of users *v* 67% to 68% of nonusers), and less likely to receive adjuvant chemotherapy (17% to 19% of users *v* 30% to 32% of nonusers). Users generally had more coprescriptions and comorbidities than nonusers.

Results from multivariate models were similar with and without adjustment for the recurrence risk score, and conclusions did not differ between models using cumulative exposure duration and those using lagged exposure status. We therefore present associations estimated with lagged exposure models that were not adjusted for the risk score.

β-Blockers and Breast Cancer Recurrence

Most β-blocker prescriptions were for β1-selective drugs (71%). Only 3.4% of prescriptions were for combination tablets. Twenty-two percent of β-blocker prescriptions were for highly lipophilic drugs, 56% were for moderately lipophilic drugs, and 22% were for weakly lipophilic drugs. The most prevalent individual drugs were metoprolol (49% of all β-blocker prescriptions), atenolol (17%), and propranolol (16%) (Appendix Table A1).

During a maximum of 10 years of follow-up, there were 466 recurrences among β-blocker users (Table 2). Compared with never users, users of any β-blocker had a slightly lower recurrence hazard in unadjusted models (unadjusted hazard ratio [HR] = 0.91; 95% CI, 0.81 to 1.0) and a slightly higher recurrence hazard in adjusted models (adjusted HR = 1.3; 95% CI, 1.1 to 1.5). Exposure definitions were specified a priori to isolate exposure by purity (noncombination tablets), receptor selectivity, and lipid solubility. Crude and adjusted models under these definitions showed either null-centered or slightly

Table 2. Crude and Multivariable-Adjusted Associations Between Use of Antihypertensive Drugs and 10-Year Breast Cancer Recurrence in Patients With Stage I, II, or III Breast Cancer Diagnosed in Denmark in 1996 to 2003 (n = 18,733)

Exposure Definition*	No.	%	Minimum No. of Years Exposed			No. of Recurrences	Total Person-Years at Risk	Unadjusted HR	95% CI	Adjusted HR†	95% CI
			Median	q1	q3						
β-Blockers											
Never use	15,073	80	NA			2,948	91,394	1	Ref	1	Ref
Any use	3,660	20	4	2	8	466	19,616	0.91	0.81 to 1.0	1.3	1.1 to 1.5
Noncombination tablets	3,463	18	4	2	8	425	17,414	0.94	0.83 to 1.1	1.4	1.2 to 1.6
β1 receptor selective	2,812	15	4	2	8	296	12,723	0.92	0.81 to 1.1	1.3	1.1 to 1.6
Nonselective	1,183	6.3	4	1	8	120	4,485	0.99	0.79 to 1.2	1.2	0.92 to 1.6
Highly lipophilic	980	5.2	3	1	7	95	3,875	0.89	0.68 to 1.2	1.1	0.79 to 1.5
Moderately lipophilic	2,327	12	4	2	8	227	9,699	0.93	0.80 to 1.1	1.4	1.2 to 1.7
Weakly lipophilic	789	4.2	6	2	10	80	3,006	1.0	0.81 to 1.3	1.2	0.85 to 1.6
Metoprolol	2,077	11	3	2	7	190	8,105	0.96	0.81 to 1.1	1.5	1.2 to 1.8
Propranolol	756	4.0	3	2	7	85	3,195	0.98	0.73 to 1.3	1.3	0.92 to 1.9
Atenolol	596	3.2	5	2	9	60	2,325	0.89	0.68 to 1.2	1.1	0.76 to 1.6
Carvedilol	224	1.2	4	2	8	9	567	0.74	0.47 to 1.2	0.49	0.18 to 1.3
Sotalol	149	0.8	7	2	10	15	302	1.0	0.65 to 1.6	2.0	0.99 to 4.0
Bisoprolol	199	1.1	4	2	8	13	699	0.66	0.41 to 1.1	0.90	0.43 to 1.9
ACE inhibitors											
Never use	15,658	84	NA			3,085	94,840	1	Ref	1	Ref
Any use	3,075	16	2	1	5	329	14,482	0.92	0.80 to 1.0	1.2	0.97 to 1.4
Noncombination tablets	2,843	15	3	1	7	276	11,383	0.98	0.84 to 1.1	1.2	1.0 to 1.5
ARBs											
Never use	16,744	89	NA			3,196	101,801	1	Ref	1	Ref
Any use	1,989	10	2	1	5	218	10,209	0.90	0.77 to 1.0	1.1	0.85 to 1.3
Noncombination tablets	1,635	8.7	3	1	7	121	5,316	1.0	0.84 to 1.3	1.3	0.95 to 1.7

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker, UICC, Union for International Cancer Control; ER, estrogen receptor; HRT, hormone replacement therapy; NA, not applicable; q, quartile; Ref, reference.

*All prescription exposure characterizations were updated yearly over follow-up and coded as time-varying variables. All prescription exposures were lagged by 1 year. Subexposures were made exclusive (eg, for noncombination β-blockers, exposure was considered positive only if 100% of a woman's β-blocker prescriptions were for noncombination drugs).

†Adjusted for age at diagnosis (continuous), menopausal status at diagnosis, UICC stage (design variables), histologic grade (design variables), ER status and receipt of adjuvant endocrine therapy (conjugated, design variables), receipt of adjuvant chemotherapy, type of primary surgery received, Charlson comorbidity index (design variables), prediagnosis combination HRT, and coprescriptions (time-varying, updated yearly, and lagged by 1 year) of any β-blockers, ACE inhibitors, ARBs, aspirin, and simvastatin.

positive associations (Table 2). The pattern of associations across solubility categories suggested a dominant association for one of the component drugs in the moderately lipophilic category, which motivated estimation of associations for individual drugs. Exclusive use of metoprolol and sotalol were positively associated with recurrence, whereas the remaining drugs seemed to have null associations (metoprolol: adjusted HR = 1.5, 95% CI, 1.2 to 1.8; sotalol: adjusted HR = 2.0, 95% CI, 0.99 to 4.0).

Single addition of covariates showed that three variables had the largest impact on the progression from somewhat protective unadjusted associations to somewhat positive adjusted associations between β-blockers and recurrence. These were use of simvastatin (15.6% increase in the estimate), use of ARBs (10.8% increase in the estimate), and histologic grade (9.9% increase in the estimate).

ACEi, ARBs, and Breast Cancer Recurrence

Enalapril (47%) and ramipril (17%) accounted for most of the ACEi prescriptions, and 12% of prescriptions were for combination tablets. The most prevalent ARBs were losartan (50%), candesartan (22%), and valsartan (11%). Approximately one third of all ARB prescriptions were for combination tablets (Appendix Table A1).

There were 329 and 218 breast cancer recurrences among users of ACEi and ARBs, respectively, over a maximum of 10 years of follow-up. We observed near-null associations between use of any ACEi or any ARB and breast cancer recurrence, compared with never users (ACEi: adjusted HR = 1.2, 95% CI, 0.97 to 1.4; ARBs: adjusted HR = 1.1, 95% CI, 0.85 to 1.3). The null associations persisted for exposure to noncombination ACEi and ARB tablets (Table 2) and for individual ARB tablets (data not shown).[19]

Table 3 reports associations stratified by ER status, histologic grade, and menopausal status. We did not observe modification by these variables of the HRs for overall exposure to β-blockers, ACEi, and ARBs. We found that exclusive use of metoprolol was associated with an increased recurrence risk only in ER-positive patients (for ER-positive: adjusted HR = 1.5, 95% CI, 1.2 to 1.9; for ER-negative: adjusted HR = 1.0, 95% CI, 0.61 to 1.8). The metoprolol association was also stronger in the premenopausal stratum than in the postmenopausal stratum (premenopausal HR = 2.6, 95% CI, 1.6 to 4.4; postmenopausal HR = 1.3, 95% CI, 1.0 to 1.6).

For all exposures, associations with specific sites of recurrence and with distant recurrence did not differ substantially from the broader outcome of any recurrence (data not shown). We also conducted our analyses in the subset of the cohort without another malignancy diagnosed before breast cancer (n = 18,213), with essentially identical results (data not shown).

In the restricted cohort (n = 14,424) evaluating intensity and timing of drug exposures in the 3 years preceding breast cancer diagnosis, we found no pattern of association. Recurrence associations for lagged postdiagnosis drug exposures moved nearer to the null when modeled simultaneously with prediagnosis exposure (Appendix Table A5, online only).

DISCUSSION

In this large, prospective cohort study, we found no evidence for a protective effect of β-blockers, ACEi, or ARBs on breast cancer recurrence. Null associations were apparent under most drug exposure definitions, including those isolating tablet purity, selectivity and solubility of β-blockers, and individual β-blocker and ARB drugs. Some definitions of β-blocker exposure were associated with an increased recurrence rate, and these seem to have been driven by positive associations with metoprolol and sotalol. These may reflect chance findings arising from small subgroups. Exploration of pre- and postdiagnostic exposure timing and intensity continued to show null associations.

The main strengths of our study are its large size and use of high-quality, prospectively collected exposure and outcome data from independent registries. The population-based design within the setting of a tax-supported universal health care system greatly reduces the threat of selection bias. The DBCG registry provides detailed information on prognostic factors, and each patient is followed closely for recurrence after breast cancer diagnosis, yielding data quality and completeness of follow-up similar to that of most clinical trials.[32]

In our main analysis, the associations between β-blocker use and recurrence shifted from protective-to-null in unadjusted models to null-to-positive in multivariate models. Three covariates—use of simvastatin, use of ARBs, and histologic grade—accounted for the majority of that shift.

Several limitations qualify the interpretation of our findings. Body mass index (BMI) data were not available and could potentially confound our results. However, a previous study that overlapped with our source population showed BMI to be positively associated only with distant recurrences.[33] The null-centered recurrence associations we observed across specific anatomic sites argue against the attenuation of truly protective associations by positive confounding from BMI. We used prescriptions logged in a registry to stand proxy for actual use of the drugs we studied, potentially leading to misclassification of exposures. However, only filled prescriptions are logged in the registry, and because patients had to pay a portion of the drug cost, it is likely that dispensed medications were received by patients who complied with the prescription. In support of this expectation, a validation study of hormone replacement therapy use among Danish nurses showed strong agreement between self-reported use and use ascertained from the registry.[34] It is also important to note that prediagnosis drug exposure data were left truncated because the prescription registry start date. Cumulative exposure duration was thus misclassified, and our categories define only the lower limits of true duration. Prediagnosis exposure intensity was defined as the cumulative number of tablets prescribed; intensity may therefore be underestimated for women taking extended-release drug formulations.

In contrast with our null-centered results, some earlier studies suggested a protective effect of β-blockers on breast cancer recurrence or mortality, but each had important limitations. Powe et al[7] were first to suggest a protective role of β-blockers on survival and recurrence in patients with breast cancer. Their study included 43 β-blocker–exposed breast cancer survivors, most of whom (74%) were treated with β1-selective drugs. The Barron study compared women taking propranolol or atenolol during the year before breast cancer diagnosis with matched nonusers; cancer-specific mortality was lower among users of the nonselective agent propranolol (n = 70; HR = 0.19; 95% CI, 0.06 to 0.60), whereas there was no association among users of the β1-selective agent atenolol (n = 525; HR = 1.08; 95% CI, 0.84 to 1.61).[9] The Melhem-Bertrandt study found that 102 patients taking β-blockers (of whom 89% were prescribed a β1-selective agent) during neoadjuvant chemotherapy had longer relapse-free survival

Table 3. Associations Between Use of β-Blockers, ACE Inhibitors, and ARBs and 10-Year Breast Cancer Recurrence Stratified by ER Status, Histologic Grade, and Menopausal Status at Diagnosis

	ER Status				Histologic Grade						Menopausal Status at Diagnosis			
	Negative (n† = 875, 27%)		Positive (n† = 2,372, 73%)		Low (n† = 631, 22%)		Moderate (n† = 1,274, 45%)		High (n† = 940, 33%)		Premenopausal (n† = 1,052, 31%)		Postmenopausal (n† = 2,361, 69%)	
Exposure Drug*	HR‡	95% CI	HR‡	95% CI	HR‡	95% CI	HR‡	95% CI	HR‡	95% CI	HR‡	95% CI	HR‡	95% CI
β-Blockers														
Never use	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
Any use	1.4	1.1 to 1.9	1.3	1.1 to 1.5	1.4	1.0 to 1.9	1.2	0.99 to 1.5	1.3	1.0 to 1.7	1.5	1.0 to 2.1	1.3	1.1 to 1.5
Propranolol	2.1	1.1 to 3.8	1.1	0.71 to 1.7	0.65	0.24 to 1.7	1.5	0.91 to 2.4	1.4	0.76 to 2.7	1.1	0.47 to 2.4	1.4	0.92 to 2.0
Sotalol	1.9	0.61 to 6.1	1.9	0.79 to 4.7	3.6	0.90 to 15	1.4	0.51 to 3.9	1.7	0.42 to 6.9	NA		2.1	1.1 to 4.3
Metoprolol	1.0	0.61 to 1.8	1.5	1.2 to 1.9	1.8	1.2 to 2.8	1.5	1.1 to 2.0	1.2	0.84 to 1.8	2.6	1.6 to 4.4	1.3	1.0 to 1.6
Atenolol	2.1	1.1 to 3.8	0.86	0.53 to 1.4	1.0	0.46 to 2.4	1.2	0.75 to 2.0	0.95	0.35 to 2.6	1.1	0.43 to 2.6	1.1	0.75 to 1.8
Bisoprolol	0.85	0.21 to 3.5	0.96	0.40 to 2.3	0.41	0.06 to 3.0	1.1	0.35 to 3.5	1.0	0.32 to 3.2	1.3	0.18 to 9.3	0.85	0.38 to 1.9
Carvedilol	0.49	0.07 to 3.5	0.54	0.17 to 1.7	1.8	0.44 to 7.3	0.17	0.02 to 1.2	0.86	0.12 to 6.2	NA		0.50	0.19 to 1.4
ACE inhibitors														
Never use	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
Any use	1.3	0.86 to 1.9	1.1	0.92 to 1.4	1.0	0.72 to 1.5	1.1	0.87 to 1.5	1.4	0.99 to 1.9	1.3	0.83 to 2.2	1.1	0.94 to 1.4
ARBs														
Never use	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
Any use	1.1	0.67 to 1.8	1.0	0.79 to 1.3	1.2	0.80 to 1.9	1.0	0.73 to 1.5	0.90	0.58 to 1.4	1.2	0.67 to 2.3	1.0	0.80 to 1.3

NOTE. HRs adjusted for prognostic and major risk factors are shown.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ER, estrogen receptor; HRT, hormone replacement therapy; NA, not applicable; Ref, reference; UICC, Union for International Cancer Control.

*All prescription exposure characterizations were updated yearly over follow-up and coded as time-varying variables. All prescription exposures were lagged by 1 year. Only exclusive users of the individual β-blockers were included.

†Number of recurrences.

‡Comparing users with patients never prescribed the same drug class. Adjusted for age at diagnosis (continuous), menopausal status at diagnosis, UICC stage (design variables), histologic grade (design variables), ER status and receipt of adjuvant endocrine therapy (conjugated, design variables), receipt of adjuvant chemotherapy, type of primary surgery received, Charlson comorbidity index (design variables), prediagnosis combination HRT, and coprescriptions (time-varying, updated yearly, and lagged by 1 year) of any β-blockers, ACE inhibitors, ARBs, aspirin, and simvastatin. Stratification variables were removed from models when appropriate.

compared with nonusers (HR = 0.52; 95% CI, 0.31 to 0.88), conflicting with the results of the Barron study.[8] In the Ganz study, 204 patients taking β-blockers (the majority of whom were prescribed a β1-selective agent) during the year before or after breast cancer diagnosis had a slightly lower risk of recurrence and breast cancer–specific mortality (HR = 0.86, 95% CI, 0.57 to 1.32; and HR = 0.76, 95% CI, 0.44 to 1.33, respectively).[10] Our results agree with another recent study, which showed no association between β-blocker use and survival in 984 patients with breast cancer.[13]

Only two previous population-based studies have been published on the associations between ACEi and ARBs and breast cancer outcomes, and their results are discordant. One study reported an increased risk of recurrence in patients taking ACEi during the year before or after breast cancer diagnosis (n = 137; HR = 1.56; 95% CI, 1.02 to 2.39).[10] Another study reported a decreased risk in patients treated with ACEi or ARBs, either contemporaneously with or after a breast cancer diagnosis (n = 168; HR = 0.60; 95% CI, 0.37 to 0.96).[20]

In summary, we saw no evidence of a protective effect of β-blockers, ACEi, or ARBs on breast cancer recurrence in a nationwide prospective cohort of Danish breast cancer survivors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Main Exposure Variables and Associated ATC Codes

Drug Name	ATC Code	Lipophilicity
β-Blockers		
Nonselective		
Pure		
Alprenolol	C07AA01	High
Oxprenolol	C07AA02	Moderate
Pindolol	C07AA03	Moderate
Propranolol	C07AA05	High
Timolol	C07AA06	Weak
Sotalol	C07AA07	Weak
α-Adrenergic blocker effect		
Labetalol	C07AG01	Moderate
Carvedilol	C07AG02	High
Combination tablets		
Timolol + thiazide	C07BA06	Weak
Pindolol + other diuretics	C07CA03	Moderate
β1-Selective		
Pure		
Metoprolol	C07AB02	Moderate
Atenolol	C07AB03	Weak
Acebutolol	C07AB04	Moderate
Betaxolol	C07AB05	High
Bisoprolol	C07AB07	Moderate
Nebivolol	C07AB12	High
Combination tablets		
Metoprolol + thiazides	C07BB02	Moderate
Atenolol + chlorthalidone	C07CB03	Weak
Metoprolol + felodipine	C07FB02	Moderate
ACE inhibitors		
Pure		
Captopril	C09AA01	
Enalapril	C09AA02	
Lisinopril	C09AA03	
Perindopril	C09AA04	
Ramipril	C09AA05	
Quinapril	C09AA06	
Benazepril	C09AA07	
Fosinopril	C09AA09	
Trandolapril	C09AA10	
Moexipril	C09AA13	
Combination tablets		
Captopril + diuretic	C09BA01	
Enalapril + diuretic	C09BA02	
Lisinopril + diuretic	C09BA03	
Perindopril + diuretic	C09BA04	
Ramipril + diuretic	C09BA05	
Benazepril + diuretic	C09BA07	
Angiotensin II receptor blockers		
Pure		
Losartan	C09CA01	
Eprosartan	C09CA02	
Valsartan	C09CA03	
Irbesartan	C09CA04	
Candesartan	C09CA06	
Telmisartan	C09CA07	
Olmesartan medoxomil	C09CA08	

(continued on following page)

Table A1. Main Exposure Variables and Associated ATC Codes (continued)

Drug Name	ATC Code	Lipophilicity
Combination tablets		
Losartan + diuretic	C09DA01	
Eprosartan + diuretic	C09DA02	
Valsartan + diuretic	C09DA03	
Irbesartan + diuretic	C09DA04	
Candesartan + diuretic	C09DA06	
Telmisartan + diuretic	C09DA07	
Olmesartan medoxomil + diuretic	C09DA08	
Valsartan + amlodipine	C09DB01	

Abbreviations: ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical.

Table A2. Potential Confounding Drugs and Drug Groups With Associated ATC Codes

Individual drugs
Calcium channel blockers (C08C, C08D)
Diuretics (C03)
α-Receptor blockers (C02A, C02C)
Aspirin, high and low dose (B01AC06, N02BA01, N02BA51)
NSAIDs (M01A)
Anticoagulants (B01A)
Valproic acid (N03AG01)
Glucocorticoids (systemic) (H02AB)
Simvastatin (C10AA01)
Digoxin (C01AA05)
Postmenopausal HRT (E + P) (G03F)
Postmenopausal HRT (E alone) (G03C)
Drug groups
Thyrotoxicosis drugs*
Antithyroid drugs (H03B), Iodine-therapy (H03C)
Antiarrhythmic drugs†
Adenosine (C01EB10), amiodarone (C01BD01), digoxin (C01AA05), dronedarone (C01BD07), flecainide (C01BC04), lidocaine (C01BB01 and N01BB02), propafenone (C01BC03), vernakalant (C01BG11)
Angina pectoris drugs†
Nitrates (C01DA), nicorandil (C01DX16)
Antimigraine drugs*
Selective serotonin receptor agonists (N02CC), nonselective serotonin receptor agonists (N02CA), pizotifen (N02CX01), clonidine (N02CX02), flunarizine (N07CA03), topiramate (N03AX11)
Antidiabetics
Oral antidiabetics and insulin (A10A, A10B)
COPD and asthma drugs (respiratory drugs) (R03)

Abbreviations: ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; E, estrogen; HRT, hormone replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; P, progesterone.
*Other than β-blockers.
†Other than β-blockers and calcium cannel blockers.

Table A3. Charlson Comorbidity Index and Comorbidity Groups

Charlson Comorbidity Category	ICD-8	ICD-10	Charlson Score	Comorbidity groups
Myocardial infarction	410	I21;I22;I23	1	Myocardial infarction
Congestive heart failure	427.09;427.10; 427.11;427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1	Congestive heart failure
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1	Peripheral vascular disease
Cerebrovascular disease	430-438	I60-I69; G45; G46	1	Cerebrovascular disease
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1	—
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1	Chronic pulmonary disease
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1	—
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1	Peptic ulcer disease
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1	Liver disease
Diabetes type 1	249.00;249.06; 249.07; 249.09	E10.0, E10.1; E10.9	1	Diabetes
Diabetes type 2	250.00;250.06; 250.07; 250.09	E11.0; E11.1; E11.9		
Hemiplegia	344	G81; G82	2	—
Moderate to severe renal disease	403; 404; 580-583;584;590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2	Renal disease
Diabetes with end organ damage type 1, type 2	249.01-249.05; 249.08 250.01-250.05; 250.08	E10.2-E10.8 E11.2-E11.8	2	Diabetes
Any tumor	140-194	C00-C75	2	Cancer
Leukemia	204-207	C91-C95	2	Cancer
Lymphoma	200-203;275.59	C81-C85; C88; C90; C96	2	Cancer
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3	Liver disease
Metastatic solid tumor	195-198; 199	C76-C80	6	Cancer
AIDS	079.83	B21-B24	6	—

Abbreviation: ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Table A4. ICD Codes for Potentially Confounding Comorbidities

Obesity (ICD-8: 277.99, ICD-10: E66)
Thyrotoxicosis (ICD-8: 242.00, 242.01, 242.08, 242.09, ICD-10: E05, E06.2)
Arrhythmia (ICD-8: 427.90-427.97, ICD-10: I47–I49)
Angina pectoris (ICD-8: 413, ICD-10: I20)
Esophageal varices (ICD-8: 456.00-456.09, ICD-10: I85)
Tremor (ICD-8: 780.32, ICD-10: G25.0, G25.2, R25.1)
Migraine (ICD-8: 346, ICD-10: G43)
Diabetes (ICD-8: 249-250, ICD-10: E10-E11)
COPD (ICD-8: 490-492, ICD-10: J40-J44, J47)
Asthma (ICD-8: 493, ICD-10: DJ45-DJ46)

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Table A5. Associations Between Pre- and Postdiagnosis Use of Antihypertensive Drugs and 10-Year Breast Cancer Recurrence, Restricted to Cohort Members With ≥ 3 Years of Prescription Data Preceding Breast Cancer Diagnosis (n = 14,424)

		Prediagnosis Exposure (total number of tablets prescribed during the 3 years before diagnosis)									Postdiagnosis Exposure§	
		1-100 Tablets			101-1,000 Tablets			≥1,001 Tablets				
Exposure Definition*	Unexposed	No. of Exposed Recurrences	HR†‡	95% CI	No. of Exposed Recurrences	HR†‡	95% CI	No. of Exposed Recurrences	HR†‡	95% CI	HR	95% CI
Adjusted												
β-Blockers	1 (ref)											
Any use	(never used a β-blocker)	47	0.92	0.59 to 1.4	115	1.1	0.80 to 1.4	90	1.2	0.90 to 1.6	1.1	0.90 to 1.4
Noncombination		51	0.99	0.63 to 1.6	101	1.0	0.75 to 1.4	89	1.2	0.88 to 1.6	1.2	0.94 to 1.5
β1 Selective		22	0.91	0.50 to 1.6	78	1.2	0.82 to 1.6	56	1.2	0.88 to 1.8	1.1	0.85 to 1.4
Nonselective		25	0.89	0.44 to 1.8	26	0.83	0.46 to 1.5	29	1.3	0.81 to 2.1	1.1	0.69 to 1.7
Highly lipophilic		29	0.76	0.35 to 1.7	17	0.55	0.27 to 1.1	18	1.1	0.61 to 2.0	1.1	0.67 to 1.8
Moderately lipophilic		17	1.0	0.53 to 2.0	60	1.2	0.81 to 1.7	38	1.3	0.86 to 1.9	1.2	0.88 to 1.5
Slightly lipophilic		7	0.82	0.28 to 2.4	23	1.2	0.63 to 2.1	29	1.4	0.82 to 2.3	0.94	0.58 to 1.5
Metoprolol		15	0.96	0.47 to 2.0	46	1.1	0.69 to 1.6	27	1.3	0.83 to 2.1	1.2	0.92 to 1.7
Propranolol		22	0.82	0.36 to 1.9	14	0.53	0.23 to 1.2	17	1.0	0.54 to 1.9	1.4	0.80 to 2.4
Atenolol		6	0.89	0.26 to 3.0	12	0.91	0.43 to 1.9	21	1.3	0.72 to 2.5	0.92	0.53 to 1.6
Carvedilol		1	0.21	0.01 to 5.0	2	0.77	0.14 to 4.1	1	0.92	0.11 to 7.6	0.61	0.20 to 1.9
Sotalol		1	1.2	0.09 to 17	6	2.5	0.73 to 8.6	4	1.3	0.35 to 5.1	1.2	0.30 to 4.9
Bisoprolol		1	0.59	0.05 to 7.0	6	1.2	0.33 to 4.4	1	0.31	0.04 to 2.5	0.89	0.29 to 2.8
ACE inhibitors	1 (ref)											
Any use	(never used an ACE inhibitor)	21	1.0	0.59 to 1.7	73	1.2	0.89 to 1.7	51	0.91	0.62 to 1.4	1.0	0.80 to 1.3
Noncombination		21	1.1	0.64 to 1.9	63	1.2	0.88 to 1.7	46	0.87	0.58 to 1.3	1.1	0.87 to 1.4
ARBs	1 (ref)											
Any use	(never used an ARB)	10	0.63	0.27 to 1.5	52	0.93	0.62 to 1.4	32	1.1	0.70 to 1.8	0.94	0.72 to 1.2
Noncombination		8	0.45	0.17 to 1.2	41	0.85	0.55 to 1.3	22	0.99	0.58 to 1.7	1.1	0.82 to 1.5
Crude												
β-Blockers	1 (ref)											
Any use	(never used a β-blocker)	47	0.85	0.58 to 1.2	115	0.96	0.75 to 1.2	90	1.0	0.77 to 1.3	1.1	0.91 to 1.3
Noncombination		51	0.87	0.59 to 1.3	101	0.93	0.72 to 1.2	89	1.0	0.78 to 1.3	1.1	0.92 to 1.3
β1 Selective		22	0.75	0.45 to 1.2	78	1.1	0.80 to 1.4	56	1.1	0.78 to 1.5	1.1	0.88 to 1.3
Nonselective		25	0.92	0.50 to 1.7	26	0.66	0.41 to 1.1	29	0.95	0.61 to 1.5	1.1	0.79 to 1.7
Highly lipophilic		29	0.85	0.44 to 1.7	17	0.50	0.28 to 0.88	18	0.81	0.47 to 1.4	1.2	0.79 to 1.8
Moderately lipophilic		17	0.79	0.45 to 1.4	60	1.1	0.79 to 1.5	38	1.1	0.77 to 1.6	1.1	0.85 to 1.4
Slightly lipophilic		7	0.75	0.29 to 1.9	23	1.1	0.67 to 1.9	29	1.1	0.71 to 1.8	1.1	0.70 to 1.6
Metoprolol		15	0.74	0.41 to 1.4	46	0.96	0.67 to 1.4	27	1.1	0.73 to 1.7	1.1	0.89 to 1.5
Propranolol		22	0.91	0.45 to 1.8	14	0.50	0.27 to 0.94	17	0.81	0.45 to 1.5	1.3	0.84 to 2.1
Atenolol		6	0.73	0.24 to 2.2	12	0.85	0.44 to 1.7	21	1.2	0.74 to 2.0	1.0	0.70 to 1.5
Carvedilol		1	0.35	0.03 to 4.2	2	0.30	0.06 to 1.6	1	0.48	0.07 to 3.5	1.1	0.66 to 2.0
Sotalol		1	0.70	0.07 to 7.0	6	1.6	0.62 to 4.3	4	0.85	0.31 to 2.4	1.2	0.66 to 2.1
Bisoprolol		1	0.30	0.02 to 3.8	6	0.85	0.28 to 2.6	1	0.28	0.04 to 2.0	1.0	0.58 to 1.8

(continued on following page)

Table A5. Associations Between Pre- and Postdiagnosis Use of Antihypertensive Drugs and 10-Year Breast Cancer Recurrence, Restricted to Cohort Members With ≥ 3 Years of Prescription Data Preceding Breast Cancer Diagnosis (n = 14,424) (continued)

		Prediagnosis Exposure (total number of tablets prescribed during the 3 years before diagnosis)									Postdiagnosis Exposure§	
		1-100 Tablets			101-1,000 Tablets			≥1,001 Tablets				
Exposure Definition*	Unexposed	No. of Exposed Recurrences	HR†‡	95% CI	No. of Exposed Recurrences	HR†‡	95% CI	No. of Exposed Recurrences	HR†‡	95% CI	HR	95% CI
ACE inhibitors	1 (ref)											
Any use	(never used an ACE inhibitor)	21	1.1	0.68 to 1.7	73	1.1	0.82 to 1.4	51	1.0	0.73 to 1.4	1.0	0.83 to 1.2
Noncombination		21	1.2	0.72 to 1.8	63	0.99	0.75 to 1.3	46	0.99	0.71 to 1.4	1.1	0.89 to 1.4
ARBs	1 (ref)											
Any use	(never used an ARB)	10	0.52	0.25 to 1.1	52	0.88	0.62 to 1.2	32	1.1	0.72 to 1.6	1.0	0.81 to 1.3
Noncombination		8	0.46	0.21 to 1.0	41	0.94	0.65 to 1.3	22	1.1	0.69 to 1.7	1.1	0.81 to 1.4

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ER, estrogen receptor; HR, hazard ratio; HRT, hormone replacement therapy; Ref, reference; UICC, Union for International Cancer Control.

*Subexposures were made exclusive (eg, for noncombination β-blockers, exposure was considered positive only if 100% of a woman's β-blocker prescriptions were for noncombination drugs).

†Adjusted for age at diagnosis (continuous), menopausal status at diagnosis, UICC stage (design variables), histologic grade (design variables), ER status and receipt of adjuvant endocrine therapy (conjugated, design variables), receipt of adjuvant chemotherapy, type of primary surgery received, Charlson comorbidity index (design variables), prediagnosis combination HRT, and postdiagnosis coprescriptions (time-varying, updated yearly, and lagged by 1 year) of any β-blockers, ACE inhibitors, ARBs, aspirin, and simvastatin.

‡Adjusted for discontinuation of prediagnosis exposures (ie, estimated gap between completion of last prescription and time of diagnosis).

§Coded as time-varying ever/never exposure in each year after diagnosis and lagged by 1 year (see text for details). Adjusted for categories of the number of tablets prescribed in the 3-year period before diagnosis.