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Examining the Influence of Beta Blockers and ACE Inhibitors on the Risk for Breast Cancer Recurrence: Results from the LACE Cohort

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Abstract

There is increasing interest in the relationship between host lifestyle factors and the outcomes of cancer treatment. Behavioral factors, comorbid conditions, and non-cancer related pharmaceutical exposures may affect breast cancer (BC) outcomes. We used observational data from the LACE Study cohort (women with early stage BC from the Kaiser Permanente Northern California Cancer Registry) to examine the association between beta-blockers (BB) and/or angiotensin converting enzyme inhibitors (ACEi) and BC recurrence, BC-specific mortality, and overall mortality. Among 1,779 women, there were 292 BC recurrences, 174 BC deaths, and 323 total deaths. 23% were exposed to either a BB and/or an ACEi. These drugs were associated with older age, postmenopausal status, tamoxifen therapy, greater pre-diagnosis BMI, hypertension, and diabetes. In Cox proportional hazards models, ACEi exposure was associated with BC recurrence (HR 1.56, 95% CI 1.02, 2.39, p=0.04), but not cause-specific mortality or overall mortality. Combined ACEi and BB was associated with overall mortality (HR 1.94, 95% CI 1.22, 3.10, p=0.01). BB exposure was associated with lower hazard of recurrence and cause-specific mortality. However, there was no evidence of a dose response with either medication. For recurrence and cause-specific mortality, BB combined with ACEi was associated with a lower HR for the outcome than when ACEi alone was used. These hypothesis generating findings suggest that BC recurrence and

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survival were associated with exposure to two commonly used classes of anti-hypertensive medications. These observations need to be confirmed and suggest that greater attention should focus on the potential role of these commonly used medications in BC outcomes.

Introduction

During the past decade there has been increasing scientific interest in understanding the complex relationship between epithelial cancers and their microenvironment. [1–4] This is particularly relevant in breast and prostate cancers where non-invasive or low grade cancers may remain dormant for many years, failing to invade and metastasize.[5–7] Historically, cancer research has focused on the cancer cell and not the microenvironment in which it arises, proliferates and then invades.

A wide range of host lifestyle factors may influence the biological aggressiveness of cancers, as well as the likelihood of their metastasis.[8] Relevant factors considered in this context include obesity, diabetes, hypertension,[9–16] as well as regular physical activity and alcohol consumption.[17–20] There is increasing interest in chronically used medications that may influence the risk for, as well as progression of cancer, e.g. aspirin, non-steroidal anti-inflammatory medications, statins, and metformin.[21–26] Chronic inflammation in the tissue microenvironment has been proposed as a potential unifying mechanism for many of these host factors affecting the progression or inhibition of cancer. [27] Further, preclinical models in ovarian and breast cancer suggest a possible role for stress as a factor influencing inflammatory processes in the tumor microenvironment that may lead to earlier dissemination of tumors, working through the complex signaling between adrenergic receptors in the tumor and macrophages that are recruited in response. [28–32] This process can be successfully blocked through administration of a commonly used non-selective beta 2 adrenergic antagonist, propanolol, suggesting a potential pharmacological strategy for prevention of cancer metastases.[30]

Two recent reports in women with breast cancer (BC) suggest that receipt of beta blockers (BB) reduces the risk for BC recurrence and improves survival.[33,34] Preclinical studies suggest a favorable biological role of angiotensin converting enzyme inhibitors (ACEi) in the development and progression of cancer,[35,36] although clinical data have been mixed [37–39] The Life After Cancer Epidemiology (LACE) Study [40] includes a well-described cohort of BC patients in whom detailed pharmacy records were available from the year prior to and after the diagnosis of BC. We used this cohort to examine risks for BC recurrence, cause-specific mortality, and overall mortality in relation to BB and ACEi exposure, controlling for relevant medical, demographic and comorbid prognostic factors.

Patients and Methods

Study Population

The LACE Study cohort contained 2,269 women with early stage invasive BC diagnosed between 1997 and 2000 and recruited primarily from the Kaiser Permanente Northern California (KPNC) Cancer Registry (83%) and the Utah Cancer Registry (12%) from 2000 to 2002. Further details are provided elsewhere. [40] For this evaluation, only patients enrolled from KPNC and in whom pharmacy records were available were included. We also required complete data on tumor characteristics, cancer treatment, pre-diagnosis body mass index (BMI), comorbidities, cancer recurrence and pharmacy medication records, which yielded 1,779 in the final analysis cohort. Mean follow-up time for this sample was 8.2 years. Participants provided informed consent for the study, which was reviewed by the institutional review board of the Kaiser Permanente Division of Research.

Clinical and Pharmacy Data Base Information

Clinical information was obtained through electronic data sources available from KPNC and confirmed by medical record review. Data included tumor size, number of positive lymph nodes, hormone receptor status, and treatment (i.e. surgery, chemotherapy, radiation therapy, and hormone therapy). Tumor stage was calculated according to criteria of the American Joint Committee on Cancer (third edition). Data on race, menopausal status, hypertension, diabetes, menopausal status, and pre-diagnosis BMI were obtained from the mailed baseline questionnaire. Information on medications was obtained from the KPNC electronic pharmacy database, which records each dispensed outpatient prescription and includes information on the date a prescription was dispensed and the drug name, dose, quantity and days supplied.

Outcome Ascertainment

Health outcomes in the LACE cohort were monitored through semi-annual questionnaires through the first five years of follow-up and then annually thereafter. These questionnaires asked about any events that might have occurred in the preceding time interval, including recurrences or new primary BC, other cancers, and hospitalizations. Those reporting an event were contacted by telephone for an interview to provide more details and medical records were reviewed to verify reported outcomes. All reported deaths from any cause, including date, were confirmed by death certificate as well as KPNC electronic data sources.

Three outcomes were considered. Breast cancer recurrence includes a loco-regional cancer recurrence, distant recurrence or metastasis, and the development of a contralateral breast cancer. Cause-specific mortality includes death attributable to BC as a primary or underlying cause on the death certificate. Overall death includes death from any cause including BC. These outcomes were last updated November 10, 2010.

Statistical Analysis

Comparisons of baseline cohort characteristics by ACEi and BB use were conducted using Pearson chi-square and Kruskal-Wallis (K-W) tests. Follow-up began at date of study entry and ended at date of first confirmed BC recurrence or date of death, depending on the specific analysis. Individuals who did not have an event were censored at date of last contact. Hazard ratios (HR) and 95% confidence intervals (CI) representing the association between a defined event and medication use were computed adjusting for covariates using the delayed-entry Cox proportional hazards model. Covariates included in the main models were: age at diagnosis, race, stage of disease, pre-diagnosis BMI, adjuvant treatment, hormone receptor status, tamoxifen use, and self-reported hypertension and diabetes, as specified in Table 1.

Sensitivity analyses were conducted to examine whether observed associations with BC recurrence, BC-specific mortality and all-cause mortality were strengthened with increasing duration of use of BB and ACEi. Although power was limited by small numbers, such a pattern would be supportive of a causal association. In these exploratory analyses, duration of BB alone and use of ACEi alone were categorized as none, ≤ 300, 301– 700, and > 700 days of supply in the year prior to or after BC diagnosis. We included the same covariates as those in the main models. Given patients who used ACEi more frequently had 4+ lymph nodes, we also examined potential confounding by number of positive lymph nodes.

Results

Characteristics of Study Sample

Table 1 shows the characteristics of the LACE study sample according to exposure to ACEi, BB, or the combination of ACEi and BB. Sixty-one percent of the sample were age 55 or older at cohort entry, and those using the drugs of interest were significantly older ($p<0.0001$). However, there were no significant differences in stage or race by drug exposure. Not surprisingly, use of ACEi and BB medications were more frequent among those with hypertension and diabetes. Postmenopausal women were more likely to be exposed to these drugs ($p<0.0001$), reflecting the older age of those taking these drugs, and chemotherapy was less frequently used in those exposed to either ACEi or BB ($p=0.001$).

Completeness of pharmacy data and types of medication

There were 1,372 patients who did not have a prescription filled for either a BB or and ACEi in the year prior to or year after BC diagnosis. Of the 407 patients who filled one or more prescriptions for a BB or ACEi during this period, 66 patients filled a prescription for both, 137 filled a prescription for ACEi only and 204 filled a prescription for BB only. The majority of BB prescriptions were for beta-1-selective antagonists, with approximately 74% of fills for atenolol and 8% for metoprolol. Propanolol was the only non-selective beta blocker used with any frequency (14% of all BB prescriptions). The majority of ACEi prescription fills were for the first generation medications: 85% for lisinopril, 10% for prinivil, and the remaining 5% for other ACEi. Among those using ACEi, 72% used both before and after their BC diagnosis; among the users of BB, before and after use occurred in approximately 70%.

Breast Cancer Recurrence

There were 292 BC recurrences among 1,779 in the LACE cohort at this analysis. In the model examining BC recurrence, controlling for important covariates, ACEi was significantly associated with a greater hazard of recurrence (HR = 1.56, 95% CI 1.02, 2.39; $p=.04$) (see Table 2). BB exposure was not statistically significantly associated with recurrence, although the HR was 0.86 and the combination of ACEi and BB exposure had an intermediate HR of 1.14. When this same analysis was restricted to patients with a diagnosis of hypertension (sample size 569 with 107 events), ACEi use was still associated with an increased HR of 1.77 (95% CI 1.10, 2.85) with $p=0.02$ (data not shown). The pattern for BB exposure was similar to the full model, and was not statistically significantly associated with the HR.

Other covariates that were significantly associated with greater hazard of BC recurrence in this model (Table 2) included older age and higher stage, while Hispanic race was associated with significantly lower hazard of recurrence. In the analysis restricted to patients with a diagnosis of hypertension, age was no longer significant in the model while stage and Hispanic race remained significant (data not shown).

Cause specific mortality

There were 174 BC deaths among 1,779 women. Neither exposure to ACEi or BB was associated with hazard of BC deaths in this sample, although the event rate was low (see Table 3). As in the previous model for recurrence, older age was associated with a greater hazard of death, as was more advanced stage, and combined use of chemotherapy and radiation as initial therapy. Hispanic race women had a lower hazard of BC specific death.

All cause mortality and sensitivity analyses

There were 323 deaths among 1,779 women. For this model, the combined use of ACEi and BB were associated with significantly greater hazard of death (HR 1.94, 95% CI 1.22, 3.10; p=0.01), while individually, neither ACEi nor BB therapy affected this outcome (see Table 4). Hispanic race women continued to show a significantly lower hazard of death, along with those who received chemotherapy, while advanced stage and older age were associated with a greater hazard of death (see Table 4). When the model was restricted to only those with a hypertension diagnosis (event rate 136 among 569 women), only stage II cancer, diabetes, and treatment with combined ACEi and BB were associated with an increased hazard of death, with parameter estimates and p-values similar in magnitude to the full model (data not shown). When the model was restricted to those with hypertension who were less than 70 years (65 events among 384 women), the risk associated with combined ACEi and BB was no longer statistically significant (data not shown).

In sensitivity analyses, there was no pattern of increasing risk of recurrence, BC-specific mortality or overall mortality with increasing days of supply of ACEi medication in the year prior to or after BC diagnosis (data not shown). In contrast, there was a pattern of decreasing risk of each of these endpoints with decreasing days supply of BB (data not shown). Adding number of positive lymph nodes to our models only modestly attenuated our HR estimates. For example, the HR for BC recurrence associated with ACEi went from 1.56 (95% CI 1.02, 2.39) to 1.43 (95% CI 0.93, 2.19).

Discussion

There will be a dramatic increase in the number of BC cases based on the aging of the population of US women. Standard risk factors for recurrence and prognosis focus on the tumor stage and the biological characteristics of the tumor, [41,42] as well as the receipt of appropriate adjuvant therapies. The extent to which other comorbid conditions and their associated medications influence BC recurrence and mortality is an area of recent interest. [13,14,26,43–45] Factoring these exposures into BC recurrence prediction may be important and potentially affect follow-up care. In addition, medications that are implicated in the prevention of recurrence may become candidates for use in primary prevention and adjuvant therapy settings. [26,44,46]

The findings from the LACE cohort provide a window on the biology of BC recurrence in a diverse population of women who are insured and have access to care in a group model health maintenance organization, with access to both specialist and generalist care. In this setting, there is no evidence of racial disparity in BC outcomes for Black women controlling for cancer specific variables (stage, treatment), demographic and chronic disease variables (age, obesity, diabetes, hypertension), as well as the medications studied. Consistent with an expanding literature on host lifestyle factors, diabetes was significantly associated with greater hazard for overall mortality, as in the general population of women. However, in this patient sample there was no association of diabetes with BC recurrence or cause-specific mortality. Among other findings, being overweight or obese was not statistically significantly associated with recurrence, cause-specific mortality or mortality, which likely relates to the access to care in this setting as well as the control for other chronic disease variables that may be in the causal pathway.

What about the relationship between the pharmacological agents studied and the risk for BC recurrence? We did not find a statistically significant relationship between use of BB and any of the BC outcomes. This evaluation is hampered by the small number of women who took a non-selective BB, i.e. propanolol (14% of BB sample), which would be the best therapeutic agent to affect the beta-2-adrenergic receptor implicated as a therapeutic target

in BC metastasis preclinical models.[30] While one recent study has suggested clinical benefit from both selective beta 1 adrenergic antagonists as well as non-selective BB therapy,[33] another study of a large BC sample only found benefit in women receiving a non-selective BB.[34] In our analyses, it is noteworthy that women receiving BB therapy had lower HR for recurrence and cause- specific mortality, although these findings were not statistically significant given the low event rate in the LACE cohort. In contrast, we found that use of ACEi therapy was associated with an increased hazard of recurrence (HR 1.56, 95% CI 1.02, 2.39, p=0.04), but not for cause-specific mortality or overall mortality. Interestingly, patients on both a BB and an ACEi did not have an increased hazard of recurrence (HR 1.14, 95% CI 0.61, 2.14, p=0.69), suggesting that the addition of the BB to ACEi therapy may have a beneficial effect on recurrence.

The present data indicate divergent effects of two commonly prescribed anti-hypertensive medication classes (BB and ACEi) on the risk of BC recurrence. Such results and those from previous BB studies [33,34] suggest that the observed alterations in recurrence risk are unlikely to stem from reductions in hypertension per se, and instead likely reflect differences in the biological pathways through which those agents act. Preclinical studies suggest that BBs can influence the progression of solid epithelial tumors (including experimental BC) by inhibiting macrophage recruitment and neovascularization within the primary tumor. [29,30] Those effects are mediated predominately by inhibition of beta-2 adrenergic receptor signaling in tumor cells, vascular endothelial cells, and monocyte/macrophages, resulting in reduced signal transduction to support the expression of pro-metastatic and pro-angiogenic genes. [29,30] Beta adrenergic signaling may also support the survival of disseminated carcinoma cells (anoikis). [47] The reduced BC recurrence observed here in BB-treated patients, although not reaching statistical significance in this cohort, is thus consistent with BB biological processes observed in preclinical experimental data and other BB epidemiological studies in BC. [33,34]

In contrast, the mechanisms by which ACEi might increase BC recurrence are more obscure. Such effects are unlikely to stem from antihypertensive effects per se, and more likely to involve the specific biology of angiotensin and its receptor system. Angiotensin is therapeutically manipulated chiefly to modulate vasoconstriction, but this oligopeptide has a diverse array of other physiologic effects on other aspects cardiovascular function, neural function (including brain regulation of thirst and salt balance, and peripheral sympathetic norepinephrine outflow), and aldosterone production by the adrenal cortex. The increased hazard of BC recurrence observed here in ACEi-treated patients is consistent with previous reports linking these drugs to inflammation;[48,49] however, most studies of ACEi, as well as a recent study of angiotensin receptor blocker (ARB) exposure have focused on cancer incidence rather than progression or metastases.[50–52] Given that ACEi and ARB medications target different specific molecules but are associated with similar effects on cancer risk, there could be a specific protective effect of angiotensin signaling on BC-related biology. Identifying the biological mechanisms by which BC biology is regulated by angiotensin signaling and its pharmacologic modulation by ACEi medications represents an important area for further preclinical research.

Strengths of this study include careful case ascertainment and follow-up for disease recurrence and mortality in the LACE cohort, an ethnically diverse patient sample, and access to a pharmacy database capturing medication use before and after BC diagnosis. Without the latter, questions related to potential benefits or harms of BB and ACEi therapy could not have been examined. However, caution should be used in interpreting the drug exposure findings, as we cannot exclude confounding of medication use with indication (e.g., heart disease and ACEi) or other types of bias in this observational study setting. In addition, there are other limitations that relate specifically to the cohort, including access to

treatment for many chronic conditions that might favorably influence survival and BC specific outcomes. These access factors may have influenced the lack of survival disparities for Black women, although we may have reduced potential for observing disparities by controlling for diabetes and hypertension which are more prevalent in Black women.

Nevertheless, the findings from this study are provocative, and raise concerns about the potential harm of commonly prescribed ACEi therapy. Although the low event rates and small number of patients on BB limited our power to detect the potential benefits of individual BB medications, the main findings for BB are consistent with the hypothesis that this class of drugs may be risk reducing. However, our sensitivity analysis findings of decreasing risk with decreasing days of supply of medication, while only exploratory due to sample size, would argue against a causal association. Finally, the findings of an association of ACEi exposure with poor outcomes are hypothesis generating only, as they were not specified a priori, and were in fact counter to suggestions in the literature. Thus, they need further corroboration in other clinical databases and, if confirmed, their potential mechanism for adverse outcomes needs more detailed examination in the laboratory.

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Table 1

Demographic and Tumor Characteristics by Angiotensin Converting Enzyme Inhibitor (ACEi) and Beta Blocker (BB) Use

	Overall n=1,779		None n=1372		ACEi only n=137		BB only n=204		Both n=66		
	n	%	n	%	n	%	n	%	n	%	p-value
Age at diagnosis											
<45	189	10.6	179	13.0	2	1.5	8	3.9	0	0.0	**<0.0001**
45–54	511	28.7	433	31.6	27	19.7	37	18.1	14	21.2	
55+	1079	60.7	760	55.4	108	78.8	159	77.9	52	78.8	
Menopausal status											
Pre	391	22.0	349	25.4	14	10.2	23	11.3	5	7.6	**<0.0001**
Post	1153	64.8	827	60.3	111	81.0	158	77.5	57	86.4	
Unknown	235	13.2	196	14.3	12	8.8	23	11.3	4	6.1	
Race											
White	1381	77.6	1067	77.8	104	75.9	158	77.5	52	78.8	0.29
Black	101	5.7	71	5.2	15	10.9	12	5.9	3	4.5	
Hispanic	117	6.6	93	6.8	10	7.3	9	4.4	5	7.6	
Asian	121	6.8	92	6.7	6	4.4	18	8.8	5	7.6	
Other	59	3.3	49	3.6	2	1.5	7	3.4	1	1.5	
Stage											
I	822	46.2	625	45.6	67	48.9	100	49.0	30	45.5	0.93
II	902	50.7	702	51.2	67	48.9	99	48.5	34	51.5	
IIIA	55	3.1	45	3.3	3	2.2	5	2.5	2	3.0	
Number Positive Nodes											
none	1120	63.0	869	63.3	88	64.2	122	59.8	41	62.1	0.30
1–3	477	26.8	372	27.1	28	20.4	59	28.9	18	27.3	
4+	182	10.2	131	9.5	21	15.3	23	11.3	7	10.6	
ER Status/Tamoxifen Use											
ER −	307	17.3	248	18.1	24	17.5	19	9.3	16	24.2	0.02
ER+, no tamox	138	7.8	98	7.1	11	8.0	22	10.8	7	10.6	
ER+, tamox	1334	75.0	1026	74.8	102	74.5	163	79.9	43	65.2	

	Overall n=1,779		None n=1372		ACEi only n=137		BB only n=204		Both n=66		
	n	%	n	%	n	%	n	%	n	%	p-value
Treatment											
None	314	17.7	218	15.9	33	24.1	45	22.1	18	27.3	**0.004**
Chemo only	335	18.8	273	19.9	19	13.9	30	14.7	13	19.7	
Rad only	465	26.1	345	25.1	43	31.4	59	28.9	18	27.3	
Both	665	37.4	536	39.1	42	30.7	70	34.3	17	25.8	
Pre-dx BMI											
<25	804	45.2	672	49.0	39	28.5	77	37.7	16	24.2	**<0.0001**
25–29	539	30.3	407	29.7	42	30.7	70	34.3	20	30.3	
30+	436	24.5	293	21.4	56	40.9	57	27.9	30	45.5	
Hypertension											
No	1210	68.0	1136	82.8	18	13.1	50	24.5	6	9.1	**<0.0001**
Yes	569	32.0	236	17.2	119	86.9	154	75.5	60	90.9	
Diabetes											
No	1637	92.0	1312	95.6	97	70.8	185	90.7	43	65.2	**<0.0001**
Yes	142	8.0	60	4.4	40	29.2	19	9.3	23	34.8	
Recurrence											
No	1487	83.6	1156	84.3	103	75.2	174	85.3	54	81.8	**0.04**
Yes	292	16.4	216	15.7	34	24.8	30	14.7	12	18.2	
Death from Breast Cancer											
No	1605	90.2	1242	90.5	117	85.4	187	91.7	59	89.4	0.23
Yes	174	9.8	130	9.5	20	14.6	17	8.3	7	10.6	
Overall Death											
No	1456	81.8	1151	83.9	100	73.0	164	80.4	41	62.1	**<0.0001**
Yes	323	18.2	221	16.1	37	27.0	40	19.6	25	37.9	

Table 2

Breast Cancer Recurrence (n=292 events)

		HR	LL	UL	p-value
Medication Usage					
	ACEi only	**1.56**	**1.02**	**2.39**	**0.04**
	BB only	0.86	0.57	1.32	0.49
	Both ACEi and BB	1.14	0.61	2.14	0.69
Covariates					
	Age: 45–54	1.25	0.78	1.98	0.36
	Age: 55+	**1.58**	**1.00**	**2.50**	**0.05**
	Race: Hispanic	**0.44**	**0.22**	**0.86**	**0.02**
	Race: Black	1.20	0.77	1.88	0.42
	Race: other	0.94	0.62	1.43	0.77
	Stage II	**1.69**	**1.27**	**2.24**	**0.0003**
	Stage III	**5.05**	**3.15**	**8.08**	**<.0001**
	BMI: overweight	0.96	0.72	1.27	0.76
	BMI: obese	0.94	0.69	1.28	0.70
	Treatment: chemo only	1.20	0.79	1.83	0.40
	Treatment: radiation only	1.11	0.75	1.65	0.61
	Treatment: both	1.35	0.91	2.00	0.13
	ER+, no tamox	1.28	0.78	2.12	0.33
	ER+, tamox	0.99	0.72	1.37	0.96
	Diabetes	1.04	0.67	1.61	0.85
	Hypertension	1.14	0.84	1.56	0.40

Note: HR=hazard rate; LL=lower limit of confidence interval; UL=upper limit of confidence interval

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Table 3

Breast Cancer Cause-Specific Mortality (n=174 events)

	Variable	HR	LL	UL	p
Medication Usage					
	ACEi only	1.27	0.74	2.19	0.39
	BB only	0.76	0.44	1.33	0.34
	Both ACEi and BB	1.04	0.46	2.38	0.92
Covariates					
	Age: 45–54	1.14	0.59	2.20	0.70
	Age: 55+	**2.34**	**1.25**	**4.38**	**0.01**
	Race: Hispanic	**0.25**	**0.08**	**0.78**	**0.02**
	Race: Black	1.45	0.86	2.43	0.17
	Race: other	0.63	0.33	1.22	0.17
	Stage II	**2.19**	**1.48**	**3.25**	**<.0001**
	Stage III	**7.01**	**3.91**	**12.58**	**<.0001**
	BMI: overweight	0.92	0.63	1.33	0.64
	BMI: obese	0.94	0.64	1.40	0.77
	Treatment: chemo only	1.39	0.79	2.47	0.26
	Treatment: radiation only	1.14	0.66	1.99	0.64
	Treatment: both	**1.85**	**1.10**	**3.11**	**0.02**
	ER+, no tamox	1.01	0.49	2.10	0.98
	ER+, tamox	1.02	0.68	1.52	0.93
	Diabetes	1.21	0.71	2.06	0.49
	Hypertension	1.18	0.80	1.74	0.41

Note: HR=hazard rate; LL=lower limit of confidence interval; UL=upper limit of confidence interval

Table 4

All cause mortality (n=323 events)

	Variable	HR	LL	UL	p
Medication Usage					
	ACEi only	1.23	0.82	1.83	0.31
	BB only	1.04	0.72	1.51	0.83
	Both ACEi and BB	**1.94**	**1.22**	**3.10**	**0.01**
Covariates					
	Age: 45–54	1.29	0.71	2.35	0.41
	Age: 55+	**3.21**	**1.82**	**5.64**	**<.0001**
	Race: Hispanic	**0.46**	**0.25**	**0.84**	**0.01**
	Race: Black	0.89	0.56	1.42	0.63
	Race: other	0.68	0.43	1.08	0.10
	Stage II	**1.98**	**1.52**	**2.57**	**<.0001**
	Stage III	**5.68**	**3.49**	**9.24**	**<.0001**
	BMI: overweight	0.84	0.64	1.09	0.19
	BMI: obese	0.82	0.61	1.09	0.17
	Treatment: chemo only	**0.67**	**0.46**	**0.98**	**0.04**
	Treatment: radiation only	0.86	0.63	1.19	0.37
	Treatment: both	0.84	0.61	1.17	0.31
	ER+, no tamox	0.99	0.59	1.67	0.98
	ER+, tamox	0.95	0.69	1.30	0.75
	Diabetes	**1.67**	**1.18**	**2.36**	**0.004**
	Hypertension	1.14	0.86	1.51	0.36

Note: HR=hazard rate; LL=lower limit of confidence interval; UL=upper limit of confidence interval

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