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Angiotensin receptor blockers associated with improved breast cancer survival- a nationwide cohort study from Finland

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ABSTRACT

Introduction: Breast cancer (BCa) has been associated with hypertension which might adversely affect disease prognosis. It is however unclear whether use of anti-HT drugs would improve BCa prognosis.

Materials and Methods: A cohort of 73,170 women diagnosed BCa during 1995-2013 identified from the Finnish Cancer Registry and information on anti-HT drug use based on national prescription database during the same time period was combined. Anti-HT drug use was analysed separately by drug use before and after BCa diagnosis. Analyses were performed using time-dependent variables for use of each six anti-HT drug group, statins, antidiabetic drugs and anticoagulative drugs to model for simultaneous use of multiple drugs. Association between cumulative dose, duration and intensity of anti-HT drug use and risk of BCa death was evaluated.

Results: In pre-diagnostic use only ATR-blockers associated with decreased risk of BCa death compared to non-users (HR: 0.76 95% CI: 0.69-0.82) and risk decreased in inverse association with cumulative dose and duration of use. Diuretics and furosemide associated with statistically significant increase in BCa death risk.

In post-diagnostic analyses ATR-blockers and also ACE-inhibitors, beta-blockers and calcium-channel blockers were associated with better BCa survival compared to non users. The results were dose-dependent in all mentioned drug groups. The risk decrease was however highest among users of ATR-blockers (HR: 0.69 95% CI: 0.63-0.75).

Conclusions: ATR-blockers were the only antihypertensive drug group associated with improved BCa survival in both pre- and post-diagnostic use. The association was dose-dependent and supported by biological rationale which suggests a direct, causal explanation. However, for post-diagnostic use similar lowering was found also for other anti-HT groups which also supports prognostic role of hypertension control. Risk estimates for post-diagnostic ATR-blocker use were however lower compared to others drug groups. Inhibiting angiotensin receptor could be a promising novel way to affect risk of breast cancer progression.

INTRODUCTION

Breast cancer (BCa) is the most common cancer among women worldwide and it causes huge losses in life-expectancy. BCa is mainly a women´s disease but few new cases are diagnosed also among men yearly(1).

Many modifiable risk factors for BCa diagnosis have been observed such as smoking and use of oral contraceptives (2) (3) (4) . Metabolic factors such as hypertension, high blood glucose and abdominal obesity are also linked with higher BCa risk and impaired prognosis (5) (6), whereas physical exercise may decrease risk of BCa death (7). Hypertension is very common among breast cancer patients (8). It is unclear whether use of antihypertensive (anti-HT) medication could decrease the risk of BCa diagnosis or improve disease prognosis. One study has reported higher BCa incidence among women using calcium-channel blockers (9) and another study for anti-HT drug use in general (10) . Many studies have found no association between anti-HT drugs use and BCa incidence (11) (12) (13) .

To our knowledge only few previous studies have explored anti-HT drug use as risk factor for BCa death. Beta-blocker use has been associated with better BCa survival compared to non-users (14) but not all studies agree (15). No clear association has been found with other anti-HT drugs and risk of BCa death (16) (17). A big challenge is to take into account simultaneous use of multiple drug groups and comorbidities as these are common in anti-HT drug users. It is also important to try to separate the direct influence of a drug from the indirect influence of underlying conditions such as obesity among hypertensive participants.

Here we analyse the association between anti-HT drug use and BCa death among Finnish women in a large nationwide cohort taking into account these challenges.

MATERIALS AND METHODS

Study cohort

The study cohort was obtained from Finnish Cancer Registry (FCR) which registers new cancer diagnoses in Finland by obligatory reports from all health care units (18).

A total of 73,170 new BCa cases among women were obtained from the database. Cases were diagnosed between 1995-2013. Data contained information on date and method of diagnosis, tumor extent at diagnosis (recorded in the registry as local, advanced into regional lymph nodes, advanced, no information), information on participation in national mammography screening program, histology of tumor (ductal, lobular,other, unknown), treatment methods. The data also included dates and causes of cancer death as well as all-cause deaths until the end of 2015. In Finnish national mammography screening program every 50-69 year old women is invited to free breast x-ray imaging study every second year to screen BCa.

Information on antihypertensive medication use

The cohort was linked to national prescription database maintained by the Finnish Social Insurance Institution (SII) for information on anti-HT drug use during 1995-2013. It provides reinbursements for every Finnish citizen on drugs in an outpatient setting. Drugs used in hospitals are not recorded. The information on each purchase includes the date, package size, number of packages and dose for each purchase.

Anti-HT drugs were identified using unique ATC-codes (Table S1). Anti-HT drugs were divided into six different groups based on the mechanism of action: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor (ATR) blockers, furosemide, other diuretics, beta-blockers and calcium channel blockers. The other diuretics group includes thiazides and potassium-sparing diuretics but not furosemide as it is mostly used for management of oedema rather than hypertension.

Information on co-morbidities

The cohort was linked to nationwide Care Registry (HILMO) which is maintained by the National Institute of Health and Welfare (THL) for information on diagnoses and procedures in the cohort population during 1995-2013. The Registry records all diagnoses and medical procedures from in- and outpatient hospital visits in Finland. Diagnoses recorded in HILMO were used to calculate

Charlson co-morbidity index for each participant (19). Conditions used in the index calculation are listed in Table S2.

Information on hormone receptor status

Information on tumor pathological characteristics was supplemented from archives of pathology departments of university hospitals in Tampere and Turku, two of the largest cities in Finland. Information on estrogen-receptor (ER), progesterone-receptor (PR) and human epidermal growth factor- receptor 2 (HER2) status was obtained from the databases. These were used in subgroup analyses to evaluate possible effect modification by hormone receptor status.

Statistical analyses

Analyses were run separately for drug use before and after BCa diagnosis. Risk of BCa death was compared between anti-HT drugs users and non-users for all six anti-HT drug groups in a model including all drug groups simultaneously.

The total yearly mg amount of each anti-HT drug was calculated for each participant based on the dosing, package size and number of packages from each purchase. Total purchased yearly mg amount was divided by the dose corresponding to the drug specific Defined Daily Dose (DDD) for total number of DDDs purchased per year (20). Each year with any recorded purchase was considered as year of usage regardless of the purchased amount.

Cumulative number of usage years and DDDs was calculated separately for each year before and after BCa diagnosis. Amount of use before the diagnosis was calculated by adding together all usage between 1995 and the year of BCa diagnosis. Intensity (DDDs/year of use) was evaluated by dividing cumulative amount of DDDs with cumulative number of usage years.

Post-diagnostic use was analysed as time-dependent variable to control for immortal time bias. Time-dependent variables were formed by updating medication user status as well as cumulative amount, duration and intensity of use separately for each follow-up year after BCa diagnosis according to recorded purchases. Dose-dependence was evaluated by categorizing medication users in three groups (tertiles) by DDD amount, duration and intensity of use based on the level reached on each follow-up year. After discontinuation of usage the participants remained in the user category to minimize error based on selective discontinuation of medication for example in advanced stage of BCa.

Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of BCa-specific death. Time metric was years since BCa diagnosis. Follow up continued until death, emigration or the closing date Dec 31st, 2015. Cox regression analyses were adjusted for age at diagnosis, tumor extent at diagnosis, treatment methods of BCa (surgery, other), obesity, CCI, participation in national BCa screening program and use of hormone-antagonist therapy after BCa diagnosis.

Simultaneous use of multiple anti-HT drug groups was modelled forming separate time-dependent variables for every six anti-HT drug group as also for statins, antidiabetics and anticoagulative drugs use in post-dg analyses. These variables were included in the Cox regression model together to model simultaneous usage.

Latency of the risk association between anti-HT drug use and BCa death was evaluated in lag time analyses where the exposure was lagged forward in the follow-up time analysing medication use that occurred one, three or five years earlier.

The data were analysed using the IBM SPSS statistics 25 program.

RESULTS

Population characteristics

Anti-HT drug use was very common in our breast cancer cohort as 36,427 (49.8%) women had used at least one groups of anti-HT medication during the follow up (Table 1). Only total of 11,258 (15.4%) BCa had been found in BCa screening program. Anti-HT drug users were older at diagnosis and also at time of BCa death and they also used more statins and antidiabetic drugs compared to non-users. A total of 10,900 women died of BCa during the follow-up of which 4542 (124/1000) among non-users and 6358 (175/1000) among anti-HT drug users.

Antihypertensive drug usage before BCa diagnosis

In pre-diagnostic age-adjusted analysis use of ACE-inhibitors, ATR-blockers and beta-blockers was associated with statistically significant reduction in BCa death risk (Table 2). However in multivariable adjusted analysis only use of ATR-blockers remained associated with reduced risk of BCa death (HR: 0.76 95% CI: 0.69-0.82). When analyzing the amount of use among ATR-blockers, risk of BCa death decreased in association with increasing amount of dose, duration and intensity of ATR-blocker use (Table 2). Similar results were not seen with other anti-HT drug groups. Only

low intensity of beta-blocker use associated with better BCa survival (HR: 0.86 95% CI: 0.79-0.93). Furosemide and other diuretics use associated with increased risk of BCa death in high intensity of use.

Antihypertensive drug use after the BCa diagnosis

Use of all anti-HT drugs except furosemide and other diuretics was associated with decreased risk of BCa death in age-adjusted analyses. Also in multivariable-adjusted analysis use of ATR-blockers, beta-blockers and calcium-channel blockers associated with better BCa survival compared to non-users (Table 3). The risk estimates were lowest among ATR-blocker users (HR: 0.77 95% CI: 0.71-0.84). Furosemide associated with statistically significant increase in BCa death risk. When analyzing cumulative dose and intensity of anti-HT drug use ACE-inhibitors, ATR-blockers, beta-blockers and calcium-channel blockers associated with statistically significant decrease in BCa death risk (Table 4). The risk decrease was dose-dependent among ACE-inhibitors, beta-and calcium-channel blockers and decreased in inverse association with increasing dose and intensity of use. Furosemide associated with increased risk of BCa death and the risk estimates were highest for lowest dose and intensity and shortest duration of use; risk decreased in association with dose, intensity and duration but stayed elevated in all groups (Table 4). The same direction results were observed also for other diuretics. When analyzing duration of anti-HT drug use the same direction results were seen in all anti-HT drug groups; the risk of BCa death was lowest with longest duration of use in all six drug groups.

In lag-time analyses a decreased risk of BCa death among ATR-blocker users persisted after time lag of one and three years but not longer (Table 3). Calcium-channel blockers associated with reduced BCa death risk after three and five years´ lag-time. Use of furosemide associated with increased BCa death risk in one years´ lag-time. Other anti-HT drugs did not have effect on BCa survival in lag-time analyses.

Subgroup analyses

We evaluated the association between post-diagnostic anti-HT drug use and risk of BCa death also stratified by hormone-receptor status. The groups and results are shown in Table 5. ACE-inhibitors and calcium-channel blockers were associated with decreased risk of BCa death among HER-negative women and ACE-inhibitors also among triple negative women. Other diuretics associated with reduced risk among HER-positive women.

DISCUSSION

ATR-blockers differ from other anti-HT drugs as they were associated with dose-dependent improvement in BCa survival both in pre-and post-diagnostic use compared to non-users. That could indicate a causal risk association, supporting prognostic role of angiotensin receptor inhibiton.

ACE-inhibitors and ATR-blockers both inhibit RAA-system. However ATR-blockers block selectively only AT_1-receptor and leave others (for example AT_2-receptors) free while ACE-inhibitors block the whole pathway by inhibiting formation of angiotensin. Mechanism of action in ATR-blockers thus leads to angiotensin activating only AT_2-receptors which in turn has been proved to induce apoptosis for example in heart endocardial endothelial cells (24).

In post-diagnostic analyses also beta-blockers and calcium-channel blockers were associated with better BCa survival compared to non users. The same direction results were seen also among ACE-inhibitors. The results among cumulative use, duration and intensity of use were dose-dependent and statistically significant in all anti-HT drug with different mechanisms of action. This may indicate that the underlying condition ie hypertension partly explains the results and better control of hypertension might improve BCa prognosis.

Use of furosemide and other diuretics associated with elevated risk of BCa death. The risk of BCa death decreased with increased intensity of furosemide and diuretics use. Furosemide is not primarily used to control hypertension but to treat oedema or heart failure for example. Conditions like oedema are seen also in terminal BCa which could partly explain the results. Other diuretics are also used to treat ie heart failure and are not recommended as first-line treatment for hypertension alone. The dose-dependence can be explained by lowering dose of furosemide in advanced stage of heart failure or cancer when any response for drug is not achieved. Time period of furosemide use is also short in advanced cancer compared to chronic heart failure for example which might explain better survival when duration of use increases.

There are only a few previous studies on the association between anti-HT drugs and risk of BCa death. Our results are partly same direction as beta-blockers associated with better BCa survival in this study as in previous studies also (14, 21, 22, 23). However we evaluated separately association in pre-and post-diagnostic use while previous studies have concentrated on anti-HT drug use general (use or not use) or only pre-diagnostic use during the follow-up. Previous studies have also

not reported better BCa survival among ATR-blockers or ACE-inhibitor users even when evaluated separately.

The strength of our study was our reliable registry-based data on drug use which was detailed and free of bias. We also had a long follow-up time and large national cohort consisting of all BCas diagnosed in Finland between 1995-2013. We were able to take into account simultaneous use of different anti-HT drugs, statins, anticoagulative drugs and antidiabetic drugs, thus controlling for possible confounding. We were also able to adjust the analysis for different treatments as anti-HT drug users likely had more comorbidities limiting possibilities for curative surgery. However we managed to evaluate comorbidities also with CCI.

We didn´t have information on blood pressure levels which may affect results if hypertension is a prognostic factor. However we take into account simultaneous use of different anti-HT drug groups so that role of hypertension should be seen in all groups. We did not have information if anti-HT drugs purchased were actually consumed. We didn´t have information on socioeconomical or lifestyle factors such as physical activity, smoking, BMI or nutrition which could have served as confounders depending on their association with BCa survival. Compared to other anti-HT drugs ATR-blockers are the newest drug group and use of ATR-blockers has come more general during the 90s in Finland. ATR-blockers have been more expensive at least in the 80s so that ie. socioechonomical and lifestyle factors behind could at least partly explain the differing results among ATR-blockers especially compared to ACE-inhibitors.

In conclusion pre-diagnostic use of ATR-blockers associated with better BCa survival compared to non-users. In post-diagnostic use ATR-blockers, beta-blockers and calcium-channel blockers associated with better BCa survival. The association found was highest among ATR-blockers which may indicate a molecular mechanism for example. However underlying better control of hypertension may partly explain the same direction results in many different drug groups and it may have prognostic role in BCa. More research particularly comparing ACE-inhibitors and ATR-blockers in for example mice studies or other way in tumour cells is recommended to compare possible differences in signal-pathways which could explain results in BCa survival.

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Table 1. Population characteristics.

	Non-users	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
n of women	36,743	20,742	16,552	33,611	20,367	18,347	33,753
BCa found in national screening program (%)	11,258 (30.6)	5180 (25.0)	4795 (29.0)	8162 (24.3)	4654 (22.9)	2799 (15.3)	7440 (22.0)
Median follow time years (IQR)	5.8 (0-20.01)	6.3 (0-21.01)	6.6 (0-19.85)	6.2 (0-21.01)	6.2 (0-21.01)	5.6 (0-19.93)	5.8 (0-19.53)
n of BCa deaths (% of users)	4542 (12.4)	2500 (12.1)	1314 (7.9)	4416 (13.1)	2474 (12.1)	4133 (22.5)	6077 (18.0)
n of all deaths (% of users)	7495 (20.4)	7080 (34.1)	3653 (22.1)	11,270 (33.5)	6997 (34.4)	10,288 (56.1)	14,269 (42.2)
Charlson comorbidity index points:							
0	28,594	14,220	11,587	23,600	14,146	11,582	23,332
1	1248	1511	1245	2145	1542	1348	2200
2 or over	6901	5011	3720	7866	4679	5417	8221
Age at diagnosis, median (IQR)	56(18-104)	67 (27-102)	64 (23-102)	66 (20-102)	68 (24-102)	71 (20-104)	67 (20-105)
Age at death (IQR)	65 (20-108)	76 (34-104)	73 (28-103)	74 (22-105)	77 (33-106)	79 (27-107)	76 (27-107)
Tumor extent at diagnosis, n(%)							
Localized	18,538 (50.5)	10,744 (51.8)	8825 (53.3)	17,227 (51.3)	10,589 (52.0)	8394 (45.8)	16,448 (48.7)
Locally advanced	12,441 (33.9)	6456 (31.1)	5227 (31.6)	10,681 (31.8)	6323 (31.0)	6081 (33.1)	10,988 (32.6)
Advanced	2877 (7.8)	1665 (8.0)	1080 (6.5)	2708 (8.1)	1572 (7.7)	1994 (10.9)	3127 (9.3)
Unknown	2877 (7.8)	1877 (9.0)	1420 (8.6)	2995 (8.9)	1903 (9.3)	1878 (10.2)	3190 (9.5)
Surgery a part of treatment, n	25,125	13,760	11,161	22,298	13,461	11,624	21,975
PostBCa hormone antagonist use, n	15,059	6745	5568	11,573	6603	6488	11,946
Statin use, n (%)	2809 (7.6)	6425 (31.0)	4990 (30.1)	9480 (28.2)	6549 (32.2)	4884 (26.6)	8904 (26.4)

Antidiabetic medication use; n (%)	2776 (7.6)	6260 (30.2)	4418 (26.7)	7766 (23.1)	5612 (27.6)	4976 (27.1)	8368 (24.8)

IQR= interquartile range, n= number, locally advanced: advanced only to regional lymphnodes, advanced: advanced widely than to regional lymphnodes. BCa=breast cancer

Table 2. Risk of breast cancer death by antihypertensive drug use before BCa diagnosis.

		Risk of BCa death	
Drug group	n of users/BCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multiavariable\ adjusted*}$
ACE inhibitors	11,216/1545	1.01 (0.95-1.07)	1.00 (0.94-1.06)
ATR-blockers	7411/684	0.77 (0.71-0.84)	0.76 (0.69-0.82)
Average yearly dose of ATR-blocker (DDDs/yr)			
0-252	2489/277	0.87 (0.77-0.98)	0.82 (0.73-0.93)
252-394	2453/225	0.72 (0.63-0.83)	0.72 (0.63-0.82)
394→	2469/182	0.70 (0.60-0.81)	0.71 (0.61-0.82)
Beta-blockers	20,312/2831	0.92 (0.87-0.96)	0.95 (0.91-1.00)
Calcium-channel blockers	11,657/1644	0.94 (0.88-0.99)	0.98 (0.93-1.04)
Furosemide	6609/1186	1.35 (1.25-1.45)	1.26 (1.17-1.35)
Other diuretics	19,179/2990	1.07 (1.00-1.13)	1.07 (1.01-1.14)

ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent, charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg

Table 3. Risk of BCa death by antihypertensive drug use after BCa diagnosis.

		Risk of BCa death		Lag-time		
Drug group	n of users/BCa deaths	HR (95% CI)$_{multiavariable\ adjusted*}$	HR (95% CI) age-adjusted	1 year	3 years	5 years
ACE inhibitors	7467/1116	0.94 (0.88-1.00)	0.92 (0.86-0.98)	0.96 (0.90-1.03)	0.97 (0.90-1.05)	1.02 (0.93-1.11)
ATR blockers	6669/591	0.77 (0.71-0.84)	0.69 (0.63-0.75)	0.79 (0.72-0.86)	0.84 (0.76-0.93)	0.90 (0.78-1.02)
Beta-blockers	15,330/2280	0.93 (0.88-0.98)	0.92 (0.88-0.97)	0.96 (0.91-1.01)	0.98 (0.93-1.04)	0.97 (0.91-1.03)
Calcium-channel blockers	8553/1281	0.93 (0.87-0.99)	0.93 (0.88-0.99)	0.96 (0.90-1.02)	0.92 (0.86-0.99)	0.91 (0.84-0.99)
Furosemide	5902/1269	1.22 (1.13-1.32)	1.63 (1.51-1.76)	1.14 (1.06-1.23)	1.00 (0.92-1.10)	1.01 (0.90-1.13)
Other diuretics	16,226/2785	1.02 (0.96-1.08)	1.05 (0.99-1.11)	1.05 (0.99-1.12)	1.05 (0.99-1.12)	1.00 (0.93-1.08)

ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent, statins, antidiabetic medication, antikoagulative drugs, charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg

Table 4. Risk of BCa death by antihypertensive drug use after BCa diagnosis. Risk esimates by cumulative dose, duration and intensity of anti-HT drug use.

	Antihypertensive drug groups, HR (95% CI)*					
Amount of use DDDs	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	1.03 (0.96-1.12)	0.79 (0.73-0.86)	1.16 (1.10-1.23)	1.07 (1.00-1.15)	4.02 (3.79-4.26)	1.71 (1.62-1.80)
2nd tertile	0.85 (0.78-0.91)	0.70 (0.63-0.79)	0.88 (0.82-0.94)	0.85 (0.78-0.92)	2.44 (2.27-2.61)	1.09 (1.02-1.17)
3rd tertile	0.80 (0.71-0.90)	0.82 (0.69-0.96)	0.87 (0.80-0.95)	0.68 (0.60-0.77)	1.52 (1.38-1.67)	0.99 (0.90-1.07)
Duration of use (years)	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	0.95 (0.89-1.02)	0.74 (0.68-0.80)	1.05 (1.00-1.11)	0.99 (0.93-1.06)	3.57 (3.38-3.78)	2.34 (2.22-2.45)
2nd tertile	0.86 (0.78-0.94)	0.82 (0.73-0.93)	0.92 (0.84-1.00)	0.85 (0.78-0.93)	2.38 (2.20-2.57)	1.46 (1.36-1.56)
3rd tertile	0.82 (0.72-0.93)	0.82 (0.69-0.98)	0.90 (0.81-1.00)	0.75 (0.65-0.87)	1.64 (1.48-1.82)	1.30 (1.17-1.45)
Intensity of use, (DDDs/year)	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	1.06 (0.98-1.16)	0.94 (0.86-1.03)	1.26 (1.18-1.34)	1.16 (1.08-1.25)	3.84 (3.62-4.07)	1.92 (1.81-2.04)
2nd tertile	0.96 (0.88-1.04)	0.69 (0.62-0.77)	0.99 (0.92-1.05)	0.94 (0.86-1.02)	2.63 (2.44-2.84)	1.14 (1.06-1.23)
3rd tertile	0.73 (0.66-0.80)	0.62 (0.55-0.71)	0.82 (0.77-0.88)	0.62 (0.56-0.69)	1.76 (1.62-1.91)	1.06 (0.99-1.13)

1st tertile= lowest dose/duration/ intensity of use, 2nd tertile= between lowest and highest dose/duration/intensity of use, 3rd tertile= highest dose/duration/intensity of use. ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent, charlson-

comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg.

Table 5. Risk of BCa death among different antihypertensive drug use based on hormone-receptors.

Antihypertensive drug group	Risk of BCa death by hormone-receptor status (HR, 95% CI)*							
	ER-	ER+	PR-	PR+	HER2-	HER2+	All neg	All pos
ACE-inhibitors	0.60 (0.32-1.02)	0.81 (0.62-1.07)	0.73 (0.49-1.09)	0.81 (0.58-1.12)	0.63 (0.49-0.82)	1.49 (0.89-2.49)	0.45 (0.21-0.97)	1.52 (0.56-4.14)
ATR-blockers	0.60 (0.35-1.00)	0.85 (0.61-1.18)	0.76 (0.51-1.15)	0.89 (0.61-1.31)	0.80 (0.61-1.05)	0.95 (0.48-1.89)	0.53 (0.29-1.00)	0.22 (0.03-1.88)
Beta-blockers	1.18 (0.83-1.68)	0.97 (0.79-1.20)	1.01 (0.78-1.31)	1.06 (0.83-1.35)	1.04 (0.87-1.23)	1.00 (0.66-1.52)	1.07 (0.69-1.67)	0.64 (0.27-1.56)
Calcium-channel blockers	0.97 (0.63-1.49)	0.81 (0.62-1.06)	0.76 (0.55-1.06)	0.85 (0.62-1.16)	0.76 (0.61-0.95)	0.93 (0.56-1.54)	1.13 (0.66-1.95)	1.53 (0.52-4.50)
Furosemide	1.53 (0.91-2.60)	1.48 (1.08-2.04)	1.25 (0.85-1.84)	1.61 (1.10-2.36)	1.49 (1.15-1.93)	2.32 (1.12-4.77)	1.09 (0.58-2.05)	3.26 (0.80-13.30)
Other diuretics	1.11 (0.71-1.73)	0.92 (0.71-1.18)	1.18 (0.86-1.63)	0.88 (0.65-1.20)	0.97 (0.78-1.20)	0.51 (0.28-0.93)	1.37 (0.83-2.28)	0.45 (0.16-1.28)

ER-=estrogen- receptor negative, ER+=estrogen- receptor positive, PR-=progesterone- receptor negative, PR+= progsterone -receptor positive, HER2-= HER2 -negative, HER2+= HER2 -positive, All neg= All three receptors (ER,PR, HER2) negative, All pos= All three receptors positive. ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg.

Table S1.

Drug	ATC-code
Enalapril	C09AA02 , C09BA02, C09BB02
Imidapril	C09AA16
Captopril	C09AA01, C09AB01
Cinapril	C09AA06, C09BA06
Lisinopril	C09AA03 ,C09BA03
Perindopril	C09AA04 , C09BA04 ,C09BB04
Ramipril	C09AA05 ,C09BA05 ,C09BB05
Trandolapril	C09AA10 ,C09BB10
Other ACE-inhibitors	C09AA08, C09BA08, C09AA07, C09BA07, C09AA09, C09BA09, C09AA11, C09AA12, C09BA12, C09BB12, C09AA13, C09BA13, C09AA14, C09AA15, C09BA15
Eprosartan	C09CA02, C09DA02
Candesartan	C09CA06, C09DA06
Losartan	C09CA01, C09DA01
Olmesartan	C09CA08, C09DA08, C09DB02
Telmisartan	C09CA07, C09DA07
Valsartan	C09CA03, C09DA03, C09DB01, C09DX01
Irbesartan	C09CA04, C09DA04
Other sartans	C09CA05
Clonidine	C02AC01, C02LC01, C02LC51
Moxonidine	C02AC05, C02LC05
Rauwolfia-alkaloids	C02AA01, C02AA02, C02AA03, C02AA04, C02AA05, C02AA06, C02AA07, C02AA52, C02AA53, C02AA57
Other antagonist of imidatsoline receptor	C02AC02, C02AC04, C02AC06
Antiadrenergics	C02BA01, C02BB01
Prazosine	C02CA01, C02LE01
Other alfa-blocking antihypertensives	C02CA02, C02CA03, C02CA04, C02CA06

Guanidiines	C02CC01, C02CC02, C02CC03, C02CC04, C02CC05, C02CC06, C02CC07, C02LF01
Smooth muscle relaxants	C02DA01, C02DB01, C02DB02, C02DB03, C02DB04, C02DD01, C02DG01
Other antihypertensives	C02KA01, C02KB01, C02KC01, C02KD01
Acebutolol	C07AB04, C07BB04
Atenolol	C07AB03, C07BB03, C07CB03, C07CB53, C07DB01, C07FB03
Betaksolol	C07AB05
Bisoprolol	C07AB07, C07BB07
Carvedilol	C07AG02
Labetalol	C07AG01, C07BG01, C07CG01
Metoprolol	C07AB02, C07AB52, C07BB02, C07BB52, C07CB02, C07FB02
Pindolol	C07AA03, C07CA03
Propranolol	C07AA05, C07BA05, C07FA05
Seliprolol	C07AB08
Timolol	C07AA06, C07BA06, C07DA06
Nebivolol	C07AB12
Other beta-blockers	C07AA01, C07AA12, C07AA14, C07AA15, C07AA16, C07AA17, C07AA19, C07AA23, C07AA27, C07AB01, C07AB06, C07AB09, C07AB10. C07AB11, C07AB13, C07BA12, C07BA68, C07BB06, C07CA17 ,C07CA23
Amiloride	C03DB01, C03EA01
Furosemide	C03CA01, C03CB01, C03EB01
Hydrochlorothiazide	C03AA03, C03AB03, C03AX01, C02LB01 ,C02LC01, C02LC05, C02LC51 ,C02LE01, C07BA02, C07BA05, C07BA06 ,C07BA07, C07BA12, C07BA68 ,C07BB02

	C07BB03, C07BB04, C07BB06, C07BB07, C07BB52, C07BG01, C07DA06, C07DB01 C08GA01, C09BA01, C09BA02, C09BA03 ,C09BA05, C09BA06, C09BA07,C09BA08, C09BA09, C09BA12, C09BA13, C09BA15, C09DA01, C09DA02, C09DA03 C09DA04, C09DA06, C09DA07 C09DA08, C03EA01
Indapamide	C03BA11, C09BA04
Spironolaktone	C03DA01
Triamteren	C03DB02, C03EA02, C03EA03, C03EA04, C03EA05, C03EA06, C03EA07, C03EA12, C03EA13 ,C03EA14, C03EB01, C03EB02
Trichloromethiazide	C03AA06, C03AB06, C03EA02
Other diuretics	C03AA01, C03AA02, C03AA04, C03AA05, C03AA07, C03AA08, C03AA09,C03AA13, C03AB01, C03AB02, C03AB04,C03AB05, C03AB07, C03AB08, C03AH01, C03AH02, C03BA02, C03BA03, C03BA04, C03BA07, C03BA09, C03BA10, C03BA12,C03BA13, C03BA82, C03BB02, C03BB03, C03BB04, C03BB07, C03BC01, C03BD01, C03BX03, C03CA03, C03CA04, C03CC01,C03CC02, C03CD01, C03CX01, C03DA02, C03DA03, C03DA04, C03EA03, C03EA04, C03EA05, C03EA06, C03EA07, C03EA13, C03EA14, C03XA01, C03XA02
Amlodipine	C08CA01, C09DB01, C09DB02, C09DX01, C09BB04
Diltiazem	C08DB01
Felodipine	C08CA02, C09BB05, C07FB02

Isradipine	C08CA03
Lerkanidipine	C08CA13, C09BB02
Nifedipine	C08CA05, C08CA55, C08GA01, C07FB03
Nilvadipine	C08CA10
Nimodipine	C08CA06
Nisoldipine	C08CA07
Verapamil	C08DA01, C08DA51, C09BB10
Other calcium-channel blockers	C08CA04, C08CA08, C08CA09, C08CA11, C08CA12, C08CA14, C08CA15, C08CX01, C08DA02, C08EA01, C08EA02, C08EX01, C08EX02, C09BB12
Aliskiren	C09XA02

Table S2.

Charlson co-morbidity index scoring system[1]

Score	Condition
1	Myocardial infarction
	Congestive heart failure
	peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease
	Diabetes without end organ-damage
2	Hemiplegia
	Moderate or severe liver disease
	Diabetes with end-organ damage
	Tumor without metastases
	Leukemia acute or chronic
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic tumour
	AIDS (not just HIV positive)

1 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.