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Postdiagnostic use of antihypertensive medications and survival in colorectal, lung, corpus uteri, melanoma and kidney cancer patients with hypertension

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Abstract

Background Arterial hypertension is one of the most frequent comorbidities in patients with cancer. Studies have indicated that drugs used to control hypertension may alter cancer patient survival; however, epidemiological findings for their impact on cancer survival remain inconsistent. The aim of this study was to examine the effect of the consumption of antihypertensive (AH) medication on the risk of death in cancer patients.

Methods The association between 1-year postdiagnostic AH medication intake and the risk of death was examined in a population-based cohort of cancer patients including colorectal ($N=1104$), lung ($N=344$), melanoma ($N=334$), corpus uteri ($N=832$) and kidney cancer ($N=714$), diagnosed between 2013 and 2015, and identified from the Lithuanian Cancer Registry. Multivariate Cox proportional hazards models were used to estimate hazard ratios (HRs), and corresponding 95% confidence intervals (95% CI) to assess associations between AH medications and cancer-specific and overall mortality.

Results We found a statistically significant decrease in mortality among colorectal cancer patients who were users of angiotensin receptor blockers (ARBs) (HR: 0.68, 95% CI: 0.47–0.98) or angiotensin converting enzyme inhibitors (ACEIs) (HR: 0.69, 95% CI: 0.52–0.91). A higher usage of ARBs and ACEIs was related to further improved colorectal cancer survival (HR 0.62, 95% CI: 0.39–1.00 and HR 0.60, 95% CI: 0.42–0.86, respectively). The subgroup analyses also demonstrated significantly better cancer specific survival in ARB users and ACEI users versus non-users in colorectal cancer patients with adenocarcinoma, surgery treatment, chemotherapy treatment and ARB or ACEI use before diagnosis. The results suggest a lower mortality among colorectal cancer patients with a higher usage of diuretics. Increased cancer-specific mortality was observed among corpus uteri cancer patients using ARBs and among melanoma patients using beta blockers (BBs); however, there was no evidence of consistent statistically significant associations in subgroup analyses.

Conclusion This study supports a link between ARB and ACEI use and increased survival among colorectal cancer patients. Further research is needed to provide a detailed evaluation of the effects of AH medications on cancer survival.

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Keywords Cancer survival, Antihypertensive drugs, Colorectal cancer, Lung cancer, Melanoma, Corpus uteri cancer, Kidney cancer

Introduction

Arterial hypertension is one of the most frequently reported comorbidities in patients with cancer. Cancer and hypertension have common risk factors, overlapping pathophysiological mechanisms; also, hypertension may be a risk factor for some cancer types [1, 2]. Both hypertension and cancer are more prevalent in the elderly population. Observational data suggest that the lifetime risk of developing hypertension is >90% for an individual aged 55 to 65 years [3]. In Lithuanian adults aged 65 and older, 70% of women and 56% of men have hypertension [4].

Treatment of hypertension in cancer patients is guided by guidelines for the general population [1, 5, 6]. In Lithuania, for anticancer therapy-induced cardiac damage treatment or for cardiac protection during anticancer therapies, the 2022 European Society of Cardiology Guidelines on cardio-oncology are used [6]. The Guidelines recommend angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) as first-line therapy to reduce the risk of cancer therapy-related cardiac dysfunction [6]. Furthermore, as recommended [6], the cancer survivors are treated according to the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension [5], using the first-line antihypertensive therapies, including renin-angiotensin system inhibitors (RASi), beta-adrenergic receptor antagonists (beta blockers, BBs), dihydropyridine calcium channel blockers (CCBs), and thiazide or thiazide-like diuretics.

Evidence indicates that drugs used for the control of hypertension may alter cancer patient survival. Several mechanisms of the relationship between AH medications and cancer have been proposed, although the findings are still inconsistent [7]. Studies have reported that antihypertensive (AH) medications can decrease the proliferation, angiogenesis, invasion and/or metastasis by inhibiting vascular endothelial growth factor (VEGF) expression, affecting the apoptotic activity of malignant cells or interfering with intracellular calcium levels/distribution [7–10]. Multiple studies have evaluated AH medications in association with cancer survival, but the results have been mixed [11–21]. Similarly, systematic reviews or meta-analyses of BBs, ACEIs, ARBs, CCBs, and/or diuretics found no association [14, 22], or improved or reduced cancer-specific survival [17, 23–26]. Notably, some of the individual studies were restricted to participants recruited from a single centre, or to patients who had early stage or metastatic cancer [11], or had undergone chemotherapy, immune checkpoint inhibitors (ICI) or surgery treatment [15, 18, 19]. Compared with national registry-based studies, cancer patients included in studies of monocentric hospital-acquired data may not be representative of the general cancer patient population. Furthermore, misclassification of drug exposure might have occurred when hospital medical records were used as an information source on drug intake. In addition, comorbidities and simultaneous use of several different drugs can also be a challenge for studies on AH medications. In the present study, in order to address the issues of generalizability, drug exposure misclassification and simultaneous use of several medications, we used a nationwide cohort of cancer patients and data from the National Health Insurance Fund (NHIF) on all purchases of physician-prescribed AH medications, antidiabetic medicines, statins and anticoagulants.

Colorectal, lung, corpus uteri, kidney cancer and melanoma are among the most common cancers in Europe and Lithuania [27]. The results of studies for the association between the use of AH agents and survival in patients with these cancers have been mixed and further studies for the replication of results in more diverse study populations, time intervals, etc. were recommended [7, 8, 11–23]. In order to better understand the clinical significance of AH medications use and whether there is a differential impact according to specific cancer sites or clinical factors, we evaluated the association between the use of antihypertensive drug classes and the cancer-specific and overall death risk.

Methods

Study subjects

This retrospective cohort study was performed using data from patients with cancer diagnosed between 2013 and 2015, and identified from the Lithuanian Cancer Registry (LCR). The LCR has population-based information available since 1978. It covers the entire population of the Republic of Lithuania (2.8 million at the 2021 census). The LCR contains demographic data as well as information on date and methods of diagnosis, tumour characteristics, date and cause of death. The main sources of the data are compulsory notifications from primary, secondary and tertiary health care institutions in Lithuania. All physicians, hospitals and diagnostic centres in

the country must send notification to the LCR of all cancer cases that come to their attention. This information is complemented by death certificates, and by notifications from the National Centre of Pathology. All cancer patients are followed up to their death. The LCR regularly performs data linkage with the Lithuanian Causes of Death Registry to obtain information on date and cause of death as well as other information from death certificates. Nearly 80% of cancer cases are microscopically verified, approximately 14% of cases are identified only through death certificates [28]. The usual delay is 5–6 years for data completeness and publication. The LCR data since 1988 have been included in 'Cancer Incidence in Five Continents' [28]. For the present study, cancer codes C18-C21, C34, C43, C54 and C64 for colorectal, lung, melanoma, corpus uteri and kidney cancer, respectively, were used according to the International Statistical Classification of Diseases,10th Revision, ICD-10. We excluded individuals with multiple cancers (except for non-melanoma skin cancer), with a diagnosis based on death certificate, age less than 25 years or more than 80 years. In all, 8,959 records were available for the analysis. To avoid immortal time bias [29], we applied a 1-year fixed baseline period during which exposure was defined and after which person-time and events were counted. Thus, follow-up time started one year after cancer diagnosis. Patients who died within the first year after diagnosis were excluded. Only cases with primary, histologically confirmed cancer of interest and hypertension within 1 year prior to diagnosis were included. The final number of participants included in the current analysis, was 3,328 [see Additional file 1].

Information on demographic factors (age at the time of diagnosis, sex, location of residence), as well as cancer-related factors (tumour type, histology, stage at diagnosis, prior cancers), date and cause of death, was available from the LCR. Information on receipt of cancer treatment (surgery, chemotherapy and radiotherapy), as well as on other health-related factors, was collected from the National Health Insurance Fund (NHIF) database. To estimate the Charlson Comorbidity Index (CCI), comorbidities were identified, including myocardial infarction, congestive heart disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatological disease, dementia, hemiplegia, diabetes, diabetes with complications, renal disease, mild liver disease, moderate or severe liver disease, peptic ulcer disease, and AIDS [30]. The CCI was calculated based on the information during the 1 year prior to diagnosis period. Information on potentially confounding statin, antidiabetic and antithrombotic medicines use (dates of prescription and purchase, dose, strength and amount of the drug) was also extracted from the NHIF database, because previous studies have suggested that these drugs could reduce mortality in patients with cancer [31–33].

Antihypertensive medication use

Data on patients' use of AH medications during 2012–2016 was obtained by linkage with the NHIF database. The NHIF's database contains information on all purchases in outpatient settings of physician-prescribed reimbursed medicines and covers up to 100% of the insured Lithuanian population (about 98% of the population is covered by health insurance) [34]. The following information about each purchase was obtained: the drug's Anatomical Therapeutic Chemical (ATC) classification system code, the brand name of the medicine, dates of prescription and purchase, and dose, strength and amount of the drug (pills, ampoules, inhalators, etc.). The daily defined doses (DDDs) in each prescription were calculated by multiplying the quantity by the strength (in mg) and dividing by the mg in a DDD from the World Health Organization [35]. In order to account for the dose, the total number of DDDs in each AH medication class for the first year after cancer diagnosis was calculated.

Statistical analyses

The primary exposure of interest was the use of AH medications, categorized into the following classes: (a) centrally and peripherally acting antiadrenergic agents (SNS-AH); (b) diuretics; (c) beta blockers (BBs); (d) calcium channel blockers (CCBs), and (d) agents acting on the renin-angiotensin system, i.e. angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). When fixed-dose combinations (several drugs in the same tablet) were used (e.g. BB and diuretics), each combined agent was included in the respective AH medication class. Participants were considered users of a given type of AH medication if they had a record of one or more purchases of a drug in that AH medication class during the first year following cancer diagnosis. Non-users of the AH drug class being investigated were classified as a reference group. Dose dependence was evaluated by stratifying users of each AH medication class into two groups (low and high usage), the cut-point used was the median DDD amount use during the first year after diagnosis.

The association between AH medication use within 1 year after diagnosis and the risk of cancer-specific and overall death was estimated using hazard ratios (HRs) and 95% confidence intervals (CIs). We used Cox proportional hazards models to estimate associations of cancer-specific and overall death risk with the use of AH medications of interest. The time scale was the time

beginning 1 year after cancer diagnosis. All patients were followed up until the date of death, or the end of follow-up December 31, 2020. | Deaths were identified from the LCR, but information on emigration was not available, so it is possible that mortality data for some emigrated study participants was not obtained. However, emigration is less common among patients with cancer than among the general population; also deaths of Lithuanian citizens that occur abroad are reported to Lithuanian institutions. In our previous study, among a cohort of patients with tuberculosis, 3.1% of the cohort had unknown vital status, and 0.8% had emigrated [36]. Similarly, in the present study, the percentage lost to follow-up is likely to be < 5%. There is no method to determine if the loss to follow-up was at random (there would be no important bias) or not at random [37]. Notably, it has been observed that not at random loss to follow-up < 5% does not substantially change risk estimates [37].

The analyses were performed using fully adjusted models including potential confounding as covariates: age at diagnosis (25–50, 51–55, 56–60, 61–65, 66–70, 71–75, 76–80 years), place of residence (urban, less urban, rural), CCI (0, 1, 2, 3+), stage at diagnosis (I, II, III, IV, unknown), histology, receipt of surgery or chemotherapy within a year after cancer diagnosis (yes/no), use of diabetes medication or statins or anticoagulants in the year prior to diagnosis (yes/no), use of AH medication in the year prior to diagnosis (yes/no) and mutual adjustment for SNS-AH, diuretics, BB, CCB, ARB and ACEI use in the year after diagnosis (yes/no). P-values for trend were calculated by adding the ordinal AH medication usage variable (low/high) as continuous into the regression analyses. We tested the proportional hazards assumption using the Schoenfeld test. The PH assumption was sufficiently met for all the variables.

In addition, stratified analyses were conducted among subgroups by age at diagnosis (51–65 years and > 65 years), stage at diagnosis (I–II and III–IV), histological type, cancer treatment (surgery, chemotherapy) and pre-diagnosis use of specific AH medication group.

To determine whether our results were robust, competing risks analysis was performed using the Fine-Gray hazard models for cancer-specific mortality, with deaths from non-cancer causes as the competing event, because antihypertensive medication users might have more comorbidity [38].

All analyses were performed using STATA/IC, 11.0 by STATA software (Stata Corporation, College Station, Texas, USA). All statistical tests were based on 2-sided probability, and, if less than 0.05, considered statistically significant.

Results

Characteristics of each of the cancer site cohorts - colorectal (N=1,104), lung (N=344), melanoma (N=334), corpus uteri (N=832) and kidney (N=714) cancer - are presented in Table 1. Overall, approximately half of cancer patients were 66–80 years old, 40% were 51–65 years old, and the remaining were 50 years old or younger. Compared to other cancer sites, colorectal cancer patients tended to be older (60% of subjects 66–80 years old). The distribution by sex was similar for colorectal and kidney cancer patients, whereas the majority of melanoma patients were women, and the majority of lung cancer patients were men. The 1 year post-diagnosis use of AH medications was very common in this study population of cancer patients with hypertension. It varied from 84% in colorectal cancer patients to 91% in melanoma patients. The AH medication classes used by most patients were ACEIs and BBs.

In total, 1056 subjects died during the follow-up, including 705 cancer-specific deaths (Table 1). The median follow-up time after diagnosis was 5.9 years, the maximum was 8.0 years.

Antihypertensive drug class' users versus non-users: overall analyses

The results of Cox regression analyses in users compared to non-users by cancer type and AH drug class are presented in Table 2.

After adjustment for relevant covariates in multivariable analyses, no associations were observed for post-diagnosis SNS-AH, diuretics and CCB use.

There was no evidence of an association of BB use compared to BB non-use for all cancers except an increase in the risk of cancer-specific death among melanoma patients, HR: 2.27, 95% CI: 1.00–5.15.

Post-diagnosis use of ARB or ACEI showed statistically significant associations with reduced risk of death for colorectal cancer (HR: 0.68, 95% CI: 0.47–0.98 and HR: 0.69, 95% CI: 0.52–0.91, respectively). ARB use was also associated with an increased risk of death for corpus uteri cancer (HR: 2.33, 95% CI: 1.21–4.51). Cancer-specific mortality for other cancer types was not related to ARB or ACEI use.

When we evaluated whether there is an association between AH medication use and overall mortality, we observed a significant inverse association with ARB and ACEI use in colorectal cancer patients and a positive association between diuretics use and risk of death in kidney cancer patients (Table 2).

Table 1 Participant characteristics by cancer site

	Colorectal (*N* = 1104)		Lung (*N* = 344)		Melanoma (*N* = 334)		Corpus uteri (*N* = 832)		Kidney (*N* = 714)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Age										
25–50	37	3.3	21	6.1	25	7.5	52	6.2	65	9.1
51–65	402	36.4	133	38.7	135	40.4	393	47.2	303	42.4
66–80	665	60.2	190	55.2	174	52.1	387	46.5	346	48.5
Sex										
Men	507	45.9	237	68.9	116	34.7	-	-	376	52.7
Women	597	54.1	107	31.1	218	65.2	832	100	338	47.3
Stage										
I	239	21.6	65	18.9	170	50.9	620	74.5	456	63.9
II	330	29.9	64	18.6	133	39.8	66	7.9	32	4.5
III	346	31.3	120	34.9	20	6.0	59	7.1	171	23.9
IV	103	9.3	64	18.6	3	0.9	21	2.5	49	6.9
Unknown	86	7.8	31	9.0	8	2.4	66	7.9	6	0.8
Surgery	995	90.1	185	53.8	286	85.6	775	93.1	653	91.5
Chemotherapy	462	41.8	225	65.4	32	9.6	70	8.4	31	4.3
Radiotherapy	141	12.8	123	35.8	1	0.3	299	35.9	6	0.8
CCI[a], n (%)										
0	585	53.0	141	41.0	190	56.9	429	51.6	318	44.5
1	123	11.1	80	23.3	20	6.0	93	11.2	102	14.3
2	277	25.1	76	22.1	95	28.4	208	25.0	199	27.9
3+	119	10.8	47	13.7	29	8.7	102	12.3	95	13.3
Diabetes	199	18.0	33	9.6	50	15.0	196	23.6	142	19.9
Use of AH medications[b]										
SNS-AH	223	20.0	70	20.3	73	21.9	206	24.8	211	29.5
Diuretics	452	40.9	135	39.2	153	45.8	428	51.4	339	47.5
BBs	569	51.5	172	50.0	179	53.6	480	57.7	424	59.4
CCBs	363	32.9	113	32.8	124	37.1	283	34.0	327	45.8
ARBs	242	21.9	66	19.2	79	23.6	243	29.2	207	29.0
ACE inhibitors	613	55.5	179	52.0	195	58.4	470	56.5	435	60.9
AH medications, any	932	84.4	292	84.9	303	90.7	753	90.5	646	90.5
Use of other medications[c]										
Statins	90	8.1	24	7.0	26	7.8	41	4.9	63	8.8
Metformin	145	13.1	26	7.6	37	11.1	144	17.3	107	15.0
Insulin	36	3.3	8	2.3	6	1.8	47	5.6	39	5.5
Anticoagulants	112	10.1	31	9.0	16	4.8	60	7.2	71	9.9
Deaths										
All	380	34.4	259	75.3	84	25.1	141	16.9	192	26.9
Cancer-specific (% of all)	271	71.3	234	90.3	43	51.2	62	44.0	95	49.5

[a] Charlson comorbidity index

[b] Post-diagnosis

[c] Prior to diagnosis

Antihypertensive drug class users versus non-users: stratified analyses by patients' characteristics

A subgroup analysis of post-diagnosis use of SNS-AH and CCBs by patients' demographic and clinical characteristics did not show consistent significant associations with the risk of cancer-specific death [see Additional file 2 and Additional file 3].

In the stratified analyses evaluating the association of diuretics use with cancer-specific survival, there was a reduced mortality for colorectal cancer patients in the

Table 2 Antihypertensive (AH) medications use and risk of cancer-specific and all-cause mortality

Cancer site	AH drug class	Cancer-specific mortality			Ovarian mortality		HR[a] (95% CI)
		Deaths/ Cases, n		HR[a] (95% CI)	Deaths/ Cases, n		
		Use	Non-use		Use	Non-use	
Colorectal	SNS-AH	59/223	212/881	1.16 (0.84; 1.60)	86/223	294/881	1.08 (0.82; 1.41)
	Diuretics	93/452	178/652	0.78 (0.58; 1.06)	156/452	224/652	1.05 (0.82; 1.33)
	BBs	137/569	134/535	1.06 (0.81; 1.38)	193/569	187/535	1.02 (0.81; 1.27)
	CCBs	89/363	182/741	1.07 (0.80; 1.43)	131/363	249/741	1.08 (0.85; 1.37)
	ARBs	49/242	222/862	**0.68 (0.47; 0.98)**	76/242	304/862	**0.67 (0.50; 0.91)**
	ACEIs	143/613	128/491	**0.69 (0.52; 0.91)**	208/613	172/491	**0.71 (0.56; 0.90)**
Lung	SNS-AH	48/70	186/274	1.08 (0.74; 1.59)	53/70	206/274	1.03 (0.72; 1.49)
	Diuretics	96/135	138/209	1.17 (0.83; 1.64)	108/135	151/209	1.17 (0.85; 1.61)
	BBs	117/172	117/172	1.09 (0.81; 1.47)	125/172	134/172	1.01 (0.77; 1.34)
	CCBs	77/113	157/231	1.18 (0.85; 1.63)	86/113	173/231	1.15 (0.84; 1.57)
	ARBs	45/66	189/278	1.01 (0.68; 1.50)	49/66	210/278	1.01 (0.69; 1.46)
	ACEIs	120/179	114/165	0.88 (0.64; 1.22)	137/179	122/165	0.98 (0.72; 1.33)
Melanoma	SNS-AH	7/73	36/261	0.52 (0.19; 1.39)	18/73	66/261	0.67 (0.36; 1.24)
	Diuretics	20/153	23/181	1.22 (0.51; 2.91)	37/153	47/181	0.66 (0.37; 1.15)
	BBs	30/179	13/155	**2.27 (1.00; 5.15)**	49/179	35/155	1.26 (0.76; 2.08)
	CCBs	15/124	28/210	1.32 (0.60; 2.90)	34/124	50/210	1.49 (0.88; 2.52)
	ARBs	10/79	33/255	0.64 (0.26; 1.61)	24/79	60/255	1.03 (0.58; 1.85)
	ACEIs	24/195	19/139	0.79 (0.35; 1.78)	48/195	36/139	1.03 (0.61; 1.75)
Corpus uteri	SNS-AH	16/206	46/626	1.13 (0.58; 2.17)	45/203	96/626	1.19 (0.80; 1.78)
	Diuretics	31/428	31/404	0.87 (0.47; 1.63)	78/428	63/404	1.18 (0.79; 1.76)
	BBs	35/480	27/352	0.90 (0.51; 1.59)	86/480	55/352	1.20 (0.82; 1.75)
	CCBs	17/283	45/549	0.69 (0.36; 1.30)	57/283	84/549	1.17 (0.80; 1.72)
	ARBs	23/243	39/589	**2.33 (1.21; 4.51)**	45/243	96/589	1.21 (0.77; 1.90)
	ACEIs	33/470	29/362	1.36 (0.72; 2.57)	78/470	63/362	1.03 (0.68; 1.55)
Kidney	SNS-AH	31/211	64/503	1.50 (0.93; 2.44)	68/211	124/503	1.35 (0.96; 1.88)
	Diuretics	52/339	43/375	1.06 (0.65; 1.73)	119/339	73/375	**1.48 (1.06; 2.07)**
	BBs	52/424	43/290	0.71 (0.44; 1.14)	116/424	76/290	0.86 (0.62; 1.18)
	CCBs	46/327	49/387	0.92 (0.58; 1.46)	96/327	96/387	0.97 (0.71; 1.32)
	ARBs	27/207	68/507	1.38 (0.77; 2.48)	56/207	136/507	1.09 (0.74; 1.61)
	ACEIs	65/435	30/279	1.74 (0.98; 3.07)	134/435	58/279	1.37 (0.94; 2.01)

[a] COX model, adjusted for: age at diagnosis, sex, place of residence, stage at diagnosis, histology, receipt of surgery, chemotherapy, radiotherapy, CCI, use of anticoagulants, statins, antidiabetics, use of AH medications prior to diagnosis, mutually adjusted for post-diagnostic use of SNS-AH, diuretics, BBs, CCBs, ARBs and ACEIs

high usage category (HR: 0.57; 95% CI: 0.39–0.83); age group 51–65 years (HR: 0.47; 95% CI: 0.26–0.84); chemotherapy treatment (HR: 0.62; 95% CI: 0.41–0.93) and pre-diagnosis diuretics users (HR: 0.62; 95% CI: 0.40–0.96). However, in other specific analyses (stage, surgery, histology, etc.) there was no significant association (Table 3).

In the stratified analyses for BBs, there was an increased risk in cancer-specific mortality for melanoma patients in almost all strata-specific analyses; however, the statistically significant estimates were observed only in a subgroup of lower BB usage (HR: 3.05, 95% CI: 1.09–8.58) and stage I-II (HR: 2.44, 95% CI: 0.96–6.21) (Table 4).

The stratified analyses for ARB use showed a statistically significantly decreased risk of cancer-specific mortality in colorectal cancer patients among subgroups of higher usage (HR: 0.62, 95% CI: 0.39–1.00), age 66–80 years (HR: 0.59, 95% CI: 0.38–0.93), stage III-IV (HR: 0.49, 95% CI: 0.30–0.80), surgery (HR: 0.66, 95% CI: 0.45–0.98) and pre-diagnosis ARB use (HR: 0.43, 95% CI: 0.24–0.79) (Table 5). In contrast, HRs were increased in cancer of corpus uteri patients for the low use category (HR: 2.68, 95% CI: 1.22–5.91), stage III-IV (HR: 9.79, 95% CI: 2.13–44.99), the age group 66–80 years (HR: 2.41, 95% CI: 1.06–5.47) and surgery or chemotherapy

Table 3 Hazard ratios (95% confidence intervals) for diuretics use associated with risk of cancer-specific mortality by cancer type in the Lithuanian cohort of cancer patients ($n = 3,328$)

	Colorectal ($N = 1104$)		Lung ($N = 344$)		Melanoma ($N = 334$)		Corpus uteri ($N = 832$)		Kidney ($N = 714$)	
	Deaths, *n* Use/Non-use	HR[a] (95% CI)	Deaths, *n* Use/Non-use	HR[a] (95% CI)	Deaths, *n* Use/Non-use	HR[a] (95% CI)	Deaths, *n* Use/Non-use	HR[a] (95% CI)	Deaths, *n* Use/Non-use	HR (95% CI)
All Diuretics users	93/178	0.78 (0.58; 1.06)	96/138	1.17 (0.83; 1.64)	20/23	1.22 (0.51; 2.91)	31/31	0.87 (0.47; 1.63)	52/43	1.06 (0.65; 1.73)
low[b]	53/178	1.06 (0.75; 1.50)	49/138	1.19 (0.79; 1.77)	4/23	0.38 (0.10; 1.48)	13/31	1.29 (0.60; 2.78)	19/43	1.45 (0.76; 2.79)
high	40/178	**0.57 (0.39; 0.83)***	47/138	1.15 (0.76; 1.73)	16/23	2.05 (0.81; 5.21)	18/31	0.71 (0.35; 1.42)	33/43	0.95 (0.56; 1.60)
Age										
51–65 years	24/63	**0.47 (0.26; 0.84)**	33/55	0.99 (0.51; 1.93)	7/3	n.e.	6/11	**0.10 (0.01; 0.72)**	19/19	1.04 (0.45; 2.40)
66–80 years	69/106	0.95 (0.67; 1.36)	58/74	1.35 (0.86; 2.12)	12/15	1.07 (0.32; 3.58)	25/19	1.13 (0.55; 2.36)	31/23	1.08 (0.56; 2.09)
Stage										
I-II	19/36	0.74 (0.40; 1.38)	27/32	1.34 (0.66; 2.72)	15/15	1.08 (0.42; 2.77)	15/16	0.83 (0.35; 1.96)	7/12	0.40 (0.12; 1.25)
III-IV	66/126	0.92 (0.64; 1.32)	59/93	1.28 (0.80; 2.06)	5/8	n.e.	16/12	2.21 (0.70; 7.02)	44/30	1.48 (0.81; 2.73)
Histology [c]	82/151	0.89 (0.65; 1.22)	36/50	**2.08 (1.10; 3.93)**	13/16	0.86 (0.26; 2.77)	20/24	0.65 (0.30; 1.40)	50/39	1.39 (0.83; 2.31)
Surgery	79/153	0.89 (0.65; 1.22)	47/57	**2.05 (1.18; 3.56)**	17/21	1.18 (0.47; 2.97)	30/28	0.92 (0.48; 1.75)	39/38	1.15 (0.66; 1.99)
Chemotherapy	50/113	**0.62 (0.41; 0.93)**	62/115	0.93 (0.62; 1.39)	8/5	n.e.	11/13	3,24 (0,52; 20,01)	7/14	n.e.
Prediagnosis Diuretics use	75/46	**0.62 (0.40; 0.96)**	75/27	1.07 (0.61; 1.86)	17/2	16.30 (0.56;472.55)	26/9	0.51 (0.18; 1.42)	42/7	1.55 (0.59; 4.12)

n.e. - HR could not be reliably estimated in multivariable analysis due to too few events

[a] adjusted for: age at diagnosis, sex, place of residence, stage at diagnosis, histology, receipt of surgery, chemotherapy, radiotherapy, CCI, use of anticoagulants, statins, antidiabetics, use of AH medications within 1 year prior to diagnosis and mutually adjusted for SNS-AH, diuretics, BBs, CCBs, ARBs, ACE inhibitors

[b] low usage: ≤median of DDD amount; high usage: > median of DDD amount

[c] restricted to: adenocarcinoma (colorectal, lung cancer); melanoma (Melanoma), endometrioid adenocarcinoma (corpus uteri), renal cell carcinoma (kidney cancer)

[*] p for trend = 0.009

Table 4 Hazard ratios (95% confidence intervals) for BBs use associated with risk of cancer-specific mortality by cancer type in the Lithuanian cohort of cancer patients ($n = 3,328$)

	Colorectal (*N*=1104)		Lung (*N*=344)		Melanoma (*N*=334)		Corpus uteri (*N*=832)		Kidney (*N*=714)	
	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR (95% CI)
All BB users	137/134	1.06 (0.81; 1.38)	117/117	1.09 (0.81; 1.47)	30/62	**2.27 (1.00; 5.15)**	35/27	0.90 (0.51; 1.59)	52/43	0.71 (0.44; 1.14)
low[b]	57/134	0.97 (0.70; 1.36)	61/117	1.10 (0.76; 1.58)	17/62	**3.05 (1.09; 8.58)**	20/27	1.10 (0.58; 2.10)	16/43	0.63 (0.33; 1.19)
high	80/134	1.13 (0.83; 1.53)	56/117	1.09 (0.77; 1.54)	19/62	1.92 (0.78; 4.74)	15/27	0.70 (0.34; 1.43)	36/43	0.76 (0.45; 1.27)
Age										
51-65 years	44/43	0.87 (0.53; 1.44)	48/740	0.85 (0.50; 1.43)	8/2	n.e.	6/11	**0.17 (0.04; 0.68)**	18/20	0.54 (0.24; 1.22)
66-80 years	92/83	1.15 (0.83; 1.59)	63/69	1.07 (0.71; 1.62)	18/9	2.88 (0.98; 8.51)	29/15	1.33 (0.64; 2.79)	32/22	0.95 (0.49; 1.84)
Stage										
I-II	33/22	1.54 (0.85; 2.77)	30/29	1.18 (0.64; 2.18)	23/7	2.44 (0.96; 6.21)	14/17	0.57 (0.25; 1.27)	11/8	0.74 (0.25; 2.13)
III-IV	93/99	1.01 (0.73; 1.39)	76/76	1.42 (0.96; 2.11)	7/6	n.e.	18/10	1.54 (0.52; 4.56)	41/33	0.64 (0.36; 1.13)
Histology[c]	122/111	1.07 (0.80; 1.42)	47/39	1.51 (0.83; 2.75)	18/11	2.26 (0.78; 6.56)	27/17	0.95 (0.48; 1.88)	51/38	0.86 (0.53; 1.40)
Surgery	118/114	1.03 (0.78; 1.38)	32/36	1.26 (0.78; 2.04)	26/12	1.76 (0.73; 4.24)	33/25	0.98 (0.54; 1.78)	44/33	0.78 (0.45; 1.33)
Chemotherapy	83/80	1.05 (0.74; 1.49)	61/43	1.10 (0.77; 1.57)	9/6	n.e.	11/13	0.32 (0.09; 1.14)	11/10	n.e.
Prediagnosis BB use	118/23	1.25 (0.76; 2.06)	90/87	0.80 (0.47; 1.35)	25/24	1.14 (0.20; 6.52)	29/4	1.14 (0.36; 3.65)	47/9	0.80 (0.35; 1.78)

n.e. - HR could not be reliably estimated in multivariable analysis due to too few events

[a] adjusted for: age at diagnosis, sex, place of residence, stage at diagnosis, histology, receipt of surgery, chemotherapy, radiotherapy, CCI, use of anticoagulants, statins, antidiabetics, use of AH medications within 1 year prior to diagnosis and mutually adjusted for SNS-AH, diuretics, BBs, CCBs, ARBs, ACE inhibitors

[b] low usage: ≤ median of DDD amount; high usage: >median of DDD amount

[c] restricted to: adenocarcinoma (colorectal, lung cancer); melanoma (Melanoma), endometrioid adenocarcinoma (corpus uteri), renal cell carcinoma (kidney cancer)

Table 5 Hazard ratios (95% confidence intervals) for ARBs use associated with risk of cancer-specific mortality by cancer type in the Lithuanian cohort of cancer patients ($n = 3,328$)

	Colorectal (N=1104)		Lung (*N*=344)		Melanoma (*N*=334)		Corpus uteri (*N*=832)		Kidney (*N*=714)	
	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR[a] (95% CI)	Deaths, n Use/Non-use	HR (95% CI)
All ARB users	49/222	**0.68 (0.47; 0.98)**	45/189	0.98 (0.64; 1.48)	10/33	0.64 (0.26; 1.61)	23/39	**2.33 (1.21; 4.51)**	27/68	1.38 (0.77; 2.48)
low[b]	25/222	0.74 (0.47; 1.17)	29/189	**1.61 (1.04; 2.51)**	4/33	1.01 (0.29; 3.50)	11/39	**2.68 (1.22; 5.91)**	15/68	1.70 (0.87; 3.33)
high	24/222	**0.62 (0.39; 1.00)***	16/189	**0.53 (0.29; 0.95)**	6/33	0.48 (0.15; 1.50)	12/39	2.01 (0.87; 4.60)	12/68	1.04 (0.47; 2.29)
Age										
51-65 years	15/72	1.17 (0.59; 2.31)	13/75	0.87 (0.39; 1.96)	2/8	n.e.	6/11	2.64 (0.61; 11.44)	10/28	1.02 (0.38; 2.76)
66-80 years	34/141	**0.59 (0.38; 0.93)**	31/101	1.22 (0.73; 2.03)	7/20	0.83 (0.22; 3.15)	17/27	**2.41 (1.06; 5.47)**	17/37	**2.26 (1.02; 4.98)**
Stage										
I-II	15/40	1.13 (0.54; 2.35)	14/45	0.72 (0.30; 1.70)	9/21	1.02 (0.39; 2.64)	11/20	1.08 (0.42; 2.80)	8/11	2.66 (0.77; 9.23)
III-IV	26/166	**0.49 (0.30; 0.80)**	27/125	1.25 (0.75; 2.08)	1/12	n.e.	11/17	**9.79 (2.13; 44.99)**	19/55	0.99 (0.48; 2.05)
Histology[c]	44/189	**0.68 (0.46; 1.00)**	17/69	0.62 (0.31; 1.26)	8/21	0.64 (0.19; 2.15)	14/30	1.89 (0.82; 4.35)	27/62	1.18 (0.64; 2.17)
Surgery	40/192	**0.66 (0.45; 0.98)**	14/54	0.91 (0.48; 1.70)	7/31	0.44 (0.15; 1.25)	22/36	**2.26 (1.16; 4.42)**	22/55	1.50 (0.80; 2.83)
Chemotherapy	32/131	0.87 (0.55; 1.38)	23/81	1.01 (0.60; 1.71)	4/9	n.e.	9/15	**10.09 (1.86; 54.62)**	6/15	n.e.
Prediagnosis ARB use	42/27	**0.43 (0.24; 0.79)**	32/145	1.62 (0.59; 4.51)	10/2	n.e.	17/6	1.34 (0.39; 4.61)	22/10	0.78 (0.25; 2.37)

n.e. - HR could not be reliably estimated in multivariable analysis due to too few events

[a] adjusted for: age at diagnosis, sex, place of residence, stage at diagnosis, histology, receipt of surgery, chemotherapy, radiotherapy, CCI, use of anticoagulants, statins, antidiabetics, use of AH medications within 1 year prior to diagnosis and mutually adjusted for SNS-AH, diuretics, BBs, CCBs, ARBs, ACE inhibitors

[b] low usage: ≤median of DDD amount; high usage: >median of DDD amount

[c] restricted to: adenocarcinoma (colorectal, lung cancer); melanoma (Melanoma), endometrioid adenocarcinoma (corpus uteri), renal cell carcinoma (kidney cancer)

* p for trend < 0.05

treatment (HR: 2.26, 95% CI: 1.16–4.42 and HR: 10.09, 95% CI: 1.86–54.62, respectively) (Table 5). ARB use compared to ARB non-use had no consistent statistically significant effect on survival for other cancer types.

Stratified analyses showed significant associations between the use of ACEI and reduced HRs in colorectal cancer patients in subgroups of high usage (HR: 0.60, 95% CI: 0.42–0.86), age 66–80 years (HR: 0.63, 95% CI: 0.44–0.89), stage III-IV (HR: 0.60, 95% CI: 0.43–0.85), surgery or chemotherapy treatment (HR: 0.67, 95% CI: 0.50–0.91 and HR: 0.63, 95% CI: 0.44–0.94, respectively) (Table 6).

In a sensitivity analysis a competing risk analysis using Fine-Gray hazard models was performed, and the results remained similar to those reported here.

Discussion

In this population-based cohort study of primary colorectal, lung, corpus uteri, kidney cancer and melanoma we found a statistically significant decrease in colorectal cancer mortality by 32% among ARB users and by 31% among ACEI users. There was evidence of dose-response association; and the effect persisted in stratified analyses. Our results are also suggestive of an elevated risk of death among corpus uteri cancer patients receiving ARBs, and increased survival among colorectal cancer patients using diuretics; furthermore, there were some inconsistent associations for BB use and melanoma survival when stratifying for age, dose and anticancer treatment.

In the present study, no apparent associations were found between SNS-AH use and the outcomes of any cancer under investigation. To our knowledge, the SNS-AH impact on cancer has not been previously studied in great detail, and this is the first cohort study analysing the relationship between SNS-AH use and mortality risk in cancer patients [39]. We were able to examine the association, because the use of SNS-AH in Lithuania is relatively high (31.5 DDD/TID in Lithuania versus 2.5 DDD/TID in Sweden and 4.1 DDD/TID in Norway in 2012) [40]. Previous research has indicated the induction of apoptosis and inhibition of the proliferation of human cancer cells by SNS-AH both in vitro and in vivo [41]. Alpha-blocker Doxazosin use was shown to both inhibit the growth of human colorectal cancer cell lines in culture and decrease tumour size and number in a colorectal cancer mouse model [39]. The protective effect of Doxazosin on colorectal cancer risk was also demonstrated among humans; however, it is possible that favourable results were obtained due to a lack of adjustment for important clinical variables (stage, anticancer treatment, etc.) and higher concentration of Doxazosin in the cell proliferation assay than in human plasma levels [39].

The relationship between diuretics use and the survival of cancer patients was previously investigated in a small number of studies, with inconsistent results and there is a lack of biological evidence linking diuretics to cancer prognosis [21]. There was no relationship between diuretics use and overall or disease-specific survival in patients with colorectal and lung cancers [21]. The use of thiazide diuretics for a minimum of 1 year post-diagnosis was associated with decreased survival in patients with colorectal and lung cancer [8, 23], but with better survival and better prognosis in patients with colorectal stage I–III cancer [11]. In line with this investigation, our findings provide suggestive evidence of increased colorectal cancer survival among diuretics users. However, we did not observe a significant effect on risk of death in lung, corpus uteri, kidney cancer or melanoma patients.

The prognostic value of CCBs for the survival of patients with cancer remains controversial [15]. Studies have demonstrated that CCBs may inhibit cancer cell proliferation, migration differentiation, and cell apoptosis [7]. There is evidence that the use of CCBs may be beneficial in endometrial cancer [42] and lung cancer [8, 20], although no effect on lung and colorectal cancer prognosis was observed in a meta-analysis [23], or among the Shanghai population [21]. In agreement with these results, CCB intake was not associated with a risk of death in patients with any type of cancer.

Previous research evidence suggests that BBs may have a protective effect against cancer progression. The β-adrenergic signaling pathway modulates multiple cellular processes, including those that counteract tumour growth and metastasis, e.g., modulation of angiogenesis, cell proliferation, and cell survival [43, 44]. The anti-tumour effect of nonselective BB propranolol was shown in the colon cancer model [44]. Some previous epidemiologic investigations on colorectal cancer outcomes demonstrated a positive effect of BB use [11, 19, 45]; however, a systematic review and meta-analysis results did not show increased overall survival in BB users compared to non-users [14]. The present study is in line with these results: BBs did not have a significant effect on colorectal cancer survival. Our findings for lung cancer and corpus uteri cancer patients are consistent with studies and meta-analysis where no beneficial role of BBs use was found [13, 14, 16, 29], but in contrast with pooled results of ten retrospective cohort studies showing an association between BB use and improved survival in patients with stage III lung cancer [22]. The non-selective BB (pan-BB) Propranolol has been associated with a decreased risk of melanoma progression and recurrence and improved outcomes in patients undergoing immunotherapy [46, 47]. However, a systematic review and meta-analysis of clinical studies found no evidence of an association between BB use and overall survival in patients with melanoma or other solid cancers [8,

Table 6 Hazard ratios (95% confidence intervals) for ACEIs use associated with risk of cancer-specific mortality by cancer type in the Lithuanian cohort of cancer patients ($n = 3,328$)

	Colorectal ($N = 1104$)		Lung ($N = 344$)		Melanoma ($N = 334$)		Corpus uteri ($N = 832$)		Kidney ($N = 714$)	
	Deaths, n Use/Non-use	HR [a] (95% CI)	Deaths, n Use/Non-use	HR [a] (95% CI)	Deaths, n Use/Non-use	HR [a] (95% CI)	Deaths, n Use/Non-use	HR [a] (95% CI)	Deaths, n Use/Non-use	HR (95% CI)
All ACEI users	143/128	**0.69 (0.52; 0.91)**	120/114	0.83 (0.61; 1.13)	24/19	0.79 (0.35; 1.78)	33/29	1.36 (0.72; 2.57)	65/30	1.74 (0.98; 3.07)
low[b]	87/128	0.75 (0.55; 1.02)	70/114	0.84 (0.59; 1.20)	12/19	0.51 (0.18; 1.49)	12/29	1.15 (0.53; 2.49)	36/30	**2.16 (1.22; 3.84)**
high	56/128	**0.60 (0.42; 0.86)***	50/114	0.97 (0.64; 1.46)	17/19	1.07 (0.43; 2.66)	21/29	1.57 (0.76; 3.24)	29/30	1.06 (0.53; 2.12)
Age										
51–65 years	44/43	1.13 (0.66; 1.96)	45/43	1.23 (0.66; 2.30)	5/5	n.e.	7/10	0.95 (0.18; 5.12)	26/12	1.91 (0.74; 4.91)
66–80 years	98/77	**0.63 (0.44; 0.89)**	68/64	0.80 (0.50; 1.27)	14/13	0.29 (0.08; 1.05)	25/19	1.52 (0.72; 3.23)	36/18	1.89 (0.85; 4.19)
Stage										
I-II	28/27	0.70 (0.37; 1.32)	28/31	0.67 (0.33; 1.35)	15/15	0.73 (0.30; 1.77)	15/16	0.89 (0.35; 2.24)	13/6	2.42 (0.69; 8.53)
III-IV	102/90	**0.60 (0.43; 0.85)**	77/75	0.79 (0.51; 1.22)	9/4	n.e.	16/12	3.58 (0.82; 15.56)	50/24	1.20 (0.60; 2.39)
Histology[c]	125/108	0.77 (0.56; 1.05)	45/41	0.67 (0.39; 1.15)	14/15	0.60 (0.19; 1.84)	24/20	1.47 (0.68; 3.21)	60/29	1.67 (0.93; 3.00)
Surgery	120/112	**0.67 (0.50; 0.91)**	30/38	0.67 (0.40; 1.13)	22/16	0.85 (0.36; 2.04)	30/28	1.22 (0.63; 2.35)	54/23	1.65 (0.89; 3.06)
Chemotherapy	81/82	**0.63 (0.44; 0.94)**	49/55	0.92 (0.61; 1.31)	7/6	n.e.	16/14	0.59 (0.12; 2.83)	14/7	n.e.
Prediagnosis ACEI use	121/38	0.77 (0.51; 1.16)	93/84	0.90 (0.55; 1.46)	26/4	0.19 (0.03; 1.05)	30/7	1.19 (0.45; 3.15)	50/9	**2.64 (1.02; 6.80)**

n.e. - HR could not be reliably estimated in multivariable analysis due to too few events

[a] adjusted for: age at diagnosis, sex, place of residence, stage at diagnosis, histology, receipt of surgery, chemotherapy, radiotherapy, CCI, use of anticoagulants, statins, antidiabetics, use of AH medications within 1 year prior to diagnosis and mutually adjusted for SNS-AH, diuretics, BBs, CCBs, ARBs, ACE inhibitors

[b] low usage: ≤median of DDD amount; high usage: > median of DDD amount

[c] restricted to: adenocarcinoma (colorectal, lung cancer); melanoma (Melanoma), endometrioid adenocarcinoma (corpus uteri), renal cell carcinoma (kidney cancer)

[*] p for trend = 0.005

48]. In contrast, we observed a negative impact among melanoma patient BB users compared to non-users. It is plausible that selective and nonselective BB have differential effects on cancer progression, with BBs blocking β2-adrenergic receptors likely being most effective [43]. In Lithuania, selective BB use is a standard practice for arterial hypertension treatment [30]; therefore, all BB users were β1 antagonist users in our study. This might explain the no protective effect of BBs in cancer patients, although our results should be interpreted with caution, given no dose-response association and the sparse numbers of melanoma deaths.

Previous reports have suggested that ACEIs and ARBs, may improve cancer prognosis by blocking the RAS signal pathway and inhibiting tumour angiogenesis, tumour cell proliferation and cancer progression, stimulating cell apoptosis and reducing metastasis; and that beneficial anticancer effects depend on the primary site of cancer [9, 49]. RASi use can also enhance the benefit of antiangiogenic agents, antiepidermal growth factor receptor inhibitors and chemotherapy, or prevent ICI-induced toxicity by suppressing chronic inflammation [15]. ARBs have been shown to slow proliferation, inhibit fibrosis, and prevent stress-induced injury in cancer cell line and animal model studies. Our results on the beneficial effect of using ACEI and ARB medications on colorectal cancer patient survival are consistent with the findings from a number of previous studies, including several meta-analyses and studies in the USA and Japan, showing that RASi could reduce tumour recurrence and improve survival in patients with colorectal cancer [11, 23, 25, 50]. Moreover, data from the study by Cui et al., 2019 showed better cancer-specific survival among colorectal cancer patients using ARBs, but no effect among ACEI users [21]. In contrast, a study from Canada suggests that ACEIs, ARBs and other antihypertensive drugs do not improve survival in patients with colorectal cancer [8]. However, prediagnostic use was evaluated in this study and although the regression models were adjusted for age, stage, gender, history of cancer, and area of residence, no adjustment for other potentially relevant confounders such as comorbidity, use of other drugs or anticancer treatment was performed.

As far as we are aware, no studies have been conducted to investigate whether the use of ARBs is associated with survival in corpus uteri cancer. Previous cell-based studies showed that angiotensin II influences endometrial cancer cells and is responsible for increased proliferation, reduction in apoptosis, increased mobility and modulation of adhesion potential [51, 52]. Our study showed significantly increased cancer-specific mortality among corpus uteri cancer patient ARB users, although there was no association with the dose. This result contrasts with previous investigation showing that losartan (angiotensin receptor 1 (AT1R) inhibitor) significantly reduces the proliferation of endometrial cancer cells [53]. Our result of increased risk and in particular in the low dose usage category, may be due to the previously observed complex effects of angiotensin II, highly associated with the differentiation status of cancer cells, the dose of angiotensin II or the ability of cancer cells to redirect the path of signal transduction to other receptors on the cell surface, and to increase the production of AT1R to overcome the silencing effect [52]. In addition, we cannot rule out the possibility of a chance finding in our study due to the relatively small number of deaths of corpus uteri cancer patients using ARBs.

The results on the effect of RASi use for other specific primary sites of cancer (lung, urothelial and renal cancers) remain contradictory, and range from a negative relationship [8], to indifferent results [15], to an improvement in overall or cancer-specific survival in lung cancer [54], melanoma [55] and renal cell carcinoma [12, 19] patients using either ARBs, ACEIs, or both. In the present study, the results suggest that the anticancer effects of ARB or ACEI use are not uniform across the sites of cancer. When we estimated the ARB or ACEI consumption effect in lung, kidney cancer and melanoma patients, we observed no significant association with cancer-specific or overall mortality.

The strength of our study is a nationwide population-based study cohort, covering all colorectal, lung, corpus uteri, kidney cancer and melanoma patients in Lithuania diagnosed during 2013–2015. We used NHIF data on the time and amount of medication purchased that was detailed and free of recall bias. This allowed us to analyse the use of AH drugs by drug class separately, taking into account patients' simultaneous use of multiple AH and other drugs. A 1 year post-diagnosis exposure assessment period was used prior to the start of the follow-up time to reduce the effect of immortal time bias. We attempted to control for possible bias due to competing risks by performing a competing risk analysis using Fine-Gray hazard models, and the results were similar to those reported here. The available information on clinical factors (cancer stage, histology, anticancer treatment, comorbidities and use of other medications that have been previously linked to cancer survival (statins, antidiabetics, etc.)), allowed subgroup analyses and control for a wide range of potential confounders.

On the other hand, the present study has limitations. First, the study had a relatively low number of cancer-specific deaths in this cohort, which limited the statistical power, particularly among patients with cancer of the corpus uteri, kidney or melanoma. Therefore, our results may be chance findings. The modest sample size

also limited a more detailed analysis of the data, e.g. by individual AH drugs. Second, our data on AH medication use was based on recorded medication purchases, and we had no information on whether the drugs were actually consumed. There is a potential for misclassification of exposure because some non-users might have been incorrectly classified as users. However, as the majority of our study population is middle aged or older (over 90% aged > 50 years) and consists of cancer patients, it is likely that non-adherence rates are lower compared to the general population. Also, information for drug exposure obtained from prescription/purchases is less likely to be affected by misclassification than from hospital records. Because of the study design (cohort study, data source – NHIF database), the misclassification of AH medication consumption would be non-differential, and would tend to attenuate the effect estimates towards null. In addition, the subgroup analysis among pre-diagnosis users of AH medications would have reduced this misclassification, as people generally do not refill prescriptions if they are not using the medication. Third, the use of data on AH medication intake at baseline (i.e. one year after diagnosis) was a weakness of the study, because during the follow-up, the medication use of study participants may have changed. Thus, there is a potential for exposure misclassification, which may have affected our risk estimates. If AH medication consumption increased with time, this could lead to an overestimation of the risk among low consumers. Fourth, patients receiving AH medication may have health conditions that may influence clinical outcomes and be confounding factors [42]. Although the study included subjects only with pre-diagnosis hypertension and multivariable models were adjusted for stage at diagnosis, CCI, use of statins, antidiabetics, etc., it is likely that there are more potential confounding clinical variables. Fifth, we had no information on lifestyle factors such as smoking, BMI, diet or physical activity. In particular, smoking is an important risk factor for lung cancer; furthermore, quitting smoking after cancer diagnosis has an impact on survival. We assume that the majority of lung cancer patients in our study were current or former smokers (> 90%, based on our previous study among lung cancer patients [56]), and most continued smoking after diagnosis, as tobacco cessation treatment for cancer patients in Lithuania is unavailable. We cannot rule out residual confounding by factors that we have not accounted for; however, our results are consistent with previously reported data, adjusted for potential confounders (BMI, smoking, alcohol consumption, etc.) [21, 57]. In addition, the possibility of residual confounding by smoking or other lifestyle variables was likely to be reduced by the inclusion of cancer patients with pre-diagnosis hypertension only.

Conclusion

This study provides epidemiological evidence of improved survival in colorectal cancer patients with hypertension using ACEIs or ARBs. ACEIs and ARBs could be considered as potential candidates for drug repurposing due to their low price and favourable safety profile; however, large prospective randomised trials are needed to validate our data.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13273-8.

Additional file 1: Supplementary Figure 1. Flow diagram of data management and selection of subjects for the study.

Additional file 2: Supplementary Table 1. Hazard ratios (95% confidence intervals) for SNS-AH use associated with risk of cancer-specific mortality by cancer type in the Lithuanian cohort of cancer patients ($n = 3,328$).

Additional file 3: Supplementary Table 2. Hazard ratios (95% confidence intervals) for CCB use associated with risk of cancer-specific mortality by cancer type in the Lithuanian cohort of cancer patients ($n = 3,328$).

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Authors' contributions

RE: conceptualization, methodology, investigation, software, validation, writing, supervision, project administration. IK: data curation, software, validation. BB: conceptualization, methodology, interpretation of the results. IV: resources, software, validation. BI: conceptualization, methodology, interpretation of the results. SC: methodology. IL: conceptualization, methodology, interpretation of the results. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request and with permission of Vilnius Regional Biomedical Research Ethics Committee.

Declarations

Ethics approval and consent to participate

Ethics approval for the study has been obtained from the Vilnius Regional Biomedical Research Ethics Committee, reference number: 2021/3-1322-798. A waiver of written informed consent was granted by the Vilnius Regional Biomedical Research Ethics Committee, based at the Medical Faculty of Vilnius University.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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