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Effect of angiotensin receptor blockers on the development of cancer: A nationwide cohort study in korea

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Abstract

The potential cancer risk associated with long-term exposure to angiotensin receptor blockers (ARBs) is still unclear. We assessed the risk of incident cancer among hypertensive patients who were treated with ARBs compared with patients exposed to

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angiotensin-converting enzyme inhibitors (ACEIs), which are known to have a neutral effect on cancer development. Using the Korean National Health Insurance Service database, we analyzed the data of patients diagnosed with essential hypertension from January 2005 to December 2012 who were aged ≥40 years, initially free of cancer, and were prescribed either ACEI or ARB (n = 293,962). Cox proportional hazard model adjusted for covariates was used to evaluate the risk of incident cancer. During a mean follow-up of 10 years, 24,610 incident cancers were observed. ARB use was associated with a decreased risk of overall cancer compared with ACEI use (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.72-0.80). Similar results were obtained for lung (HR 0.73, 95% CI 0.64-0.82), hepatic (HR 0.56, 95% CI 0.48-0.65), and gastric cancers (HR 0.74, 95% CI 0.66-0.83). Regardless of the subgroup, greater reduction of cancer risk was seen among patients treated with ARB than that among patients treated with ACEIs. Particularly, the decreased risk of cancer among ARB users was more prominent among males and heavy drinkers (interaction $P < .005$). Dose-response analyses demonstrated a gradual decrease in risk with prolonged ARB therapy than that with ACEI use. In conclusion, ARB use was associated with a decreased risk of overall cancer and several site-specific cancers.

1 | INTRODUCTION

Angiotensin receptor blockers (ARBs) are widely used in patients with hypertension, heart failure, and diabetic nephropathy due to their proven cardiovascular protective effect and excellent tolerability profile.[1-3] Currently, ARBs are used by approximately more than 200 million patients worldwide[4] and their use is expected to increase consistently, given the recent trends associated with single-pill combination therapy. Particularly, ARBs are more frequently prescribed than angiotensin-converting enzyme inhibitors (ACEIs) among Asian populations.[5]

However, it is associated with unresolved long-term safety concerns, including cancer development.[4,6-11] The potential for cancer risk among ARB users was first raised in the candesartan trial.[6] Since then, multiple studies have been performed with conflicting results.[7-11] In a meta-analysis, ARBs were associated with an increased risk of cancer development.[7] Conversely, two other subsequent meta-analyses indicated the lack of excess cancer risk among ARB users compared with the control.[8,9] However, these meta-analyses were based on randomized controlled trials. Therefore, their main outcomes were not designed to identify cancer risk. The study populations had relatively brief exposure and follow-up. Furthermore, other cohort studies were also limited by relatively short-term exposure (<3 years)[10] and follow-up (<5 years) to clarify the potential cancer risk.[11]

It is thus necessary to elucidate the long-term risk of cancer development among ARBs users in real-world practice. Using the Korea National Health Insurance Service (NHIS) data, we assessed the risk of cancer development among ARB users compared with patients who were treated with ACEIs. We set the control group as ACEI users because ACEIs are used under similar clinical conditions and do not seem to elevate the cancer risk.[8,12,13]

2 | METHODS

National Health Insurance Service is a single insurance provider in Korea and covers 97% of the Korean population. The NHIS claim database includes data regarding demographic characteristics, diagnoses, prescriptions, death, and health screening examination data (eg, health questionnaires and laboratory tests). The database is detailed elsewhere.[14,15] The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2019-01-018). The anonymized dataset was provided to the researchers from the NHIS, and informed consent was waived.

2.1 | Study population

We included patients who were diagnosed with essential hypertension (ICD codes I10-I13, Table S1 in the online-only Data Supplement) during the index period (from January 2005 to December 2012). To verify the new development of cancer, we excluded patients with known cancer diagnoses prior to the first prescription of ACEI or ARB. For this, we first excluded patients whose cancer diagnoses preceded hypertension within the index period. Then, we utilized the 2002-2004 cohort data to filter out patients diagnosed with cancer prior to 2005. Furthermore, we excluded patients with missing health screening examination data. Of the remaining patients, we excluded those who were never prescribed ACEI or ARB, those who

were switched from ARB to ACEI, and those with concurrent use of ACEI and ARB. Patients exposed to ACEI or ARB for less than 1 year were also excluded as short-term exposures are considered insufficient to cause cancer. Finally, 293,962 patients comprised the entire cohort, entered into the main analyses, and classified into the following groups: ACEI user (n = 12,784) and ARB user (n = 281,178). To further eliminate the bias from a prevalent user effect,[16] we performed the same analyses separately with a new-user cohort (n = 191,114; 5,915 for ACEI, 185,199 for ARB).

2.2 | Drug exposure

We extracted the prescription data on ACEIs and ARBs to ascertain their active ingredients, prescription dose, and duration. Available drugs during the index period were as follows: (1) ACEIs: benazepril, captopril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, temocapril, and zofenopril and (2) ARBs: candesartan, eprosartan, fimasartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. We considered an "exposure" if the active ingredient was included in the drug, as either a single or a combination drug (combined with a calcium channel blocker or diuretics) form.

2.3 | Outcomes (overall and site-specific cancer) and follow-up

Using the ICD-10 codes, we identified the overall cancer (ICD code, C00-C96) and the following site-specific cancers: lung, colorectal, breast, prostate, bladder, pancreatic, kidney, uterine, hepatic, and gastric cancers. We defined the development of cancer as hospitalization with a primary diagnosis corresponding to ICD code (C00-C96). We did not include any in situ neoplasms (ICD codes, D00-D09). The detailed definitions of the various diseases are provided in online-only Table S1. The patients were followed up until the first development of cancer, death, or the end of the study (December 2017), whichever occurred first.

2.4 | Statistical analyses

The baseline characteristics of the groups were compared using an independent t test for continuous variables, and *chi-square* test for categorical variables. The incidence rates were estimated using the total number of outcomes during the follow-up divided by 100,000 person-years. Using a Cox proportional hazards regression model, the risk of ARBs causing cancer occurrence was evaluated and compared with that of ACEIs (reference) with an adjustment for the following covariates: age (continuous variable), sex, systolic blood pressure (continuous variable), body mass index (continuous variable), smoking status (current-, ex-, never-smoker, and missing information), alcohol consumption frequency (none, 1-2/week, 3-4/week, ≥5/week, and missing information), income status (lower 30%, middle 40%, and upper 30%), and comorbidities (diabetes, heart failure, and chronic obstructive pulmonary disease). The monthly insurance contributions were used as a proxy for the income, and each comorbidity was defined by a medical claim for a hospitalization or outpatient visit for the corresponding ICD-10 codes (online-only Table S1). Given that death and cancer occurrence are competing risks, we used Fine and Gray competing risk regression hazards model.[17] Subgroup analyses were performed to identify any interaction with age (≥60 years or younger), sex, obesity (body mass index ≥25 kg/m^2 or lesser), alcohol consumption, smoking status, and income level. Sensitivity analyses were performed after excluding those switching from ACEI to ARB, using a lag period (1-3 years) after the exposure to drugs. All of these analyses were repeatedly performed in the new-user cohort. To reduce the potential confounding effects, we further performed propensity matching as a sensitivity analysis. The greedy, nearest-neighbor method with a caliper of 0.01 of the propensity scores was used for matching. In the 1:1 matched sample, the standardized mean difference of all baseline covariates between the groups was <0.1. Finally, we explored the dose-response relationship in the new-user cohort. Toward this end, the duration of the ARB prescription was classified into 3 periods (<5 years, 5-9 years, and ≥10 years) and the risk was compared with that of the reference group, which comprised the ACEI users. Statistical analyses were performed using SAS Statistical Software (version 9.4, SAS Institute, Cary, North Carolina, USA) and R Statistical Software (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria). All statistical analyses were two-sided, and $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

From January 2005 to December 2012, a total of 293,962 patients who were prescribed either ARBs (n = 281,178) or ACEIs (n = 12,784) were included in this study with a mean follow-up of 9.7 years. Among them, 55.3% were male, with a mean age of 57.0 years, and 35.0% were prevalent users. The drug prescription duration was 6.0 ± 3.1 years. In general, the ARB users were younger and mostly female. The other baseline characteristics of the entire cohort (prevalent user plus new-user) and the new-user cohort are summarized in Table 1. The detailed prevalence of each ARB and ACEI use is indicated in online-only Table S2. Overall, cancer occurred in 24,610 patients in the entire cohort.

3.2 | Effect of ARBs on the development of cancer

Overall, ARBs were associated with a significantly lower risk of cancer development than ACEIs (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.72-0.80, $P < .001$) after adjustment

TABLE 1 Study population characteristics

	Entire cohort (prevalent and new-user)				New-user cohort			
	Total	ACEI	ARB	*P* value	Total	ACEI	ARB	*P* value
Total, n	293,962	12,784	281,178	-	191,114	5,915	185,199	-
Prevalent user, n (%)	102,848 (35.0)	6,869 (53.7)	95,979 (34.1)	<0.001	-	-	-	-
Drug exposure duration, year	6.0 ± 3.1	6.0 ± 3.8	6.0 ± 3.0	<0.001	5.5 ± 2.7	5.2 ± 3.3	5.5 ± 2.7	<0.001
Male sex, n (%)	162,693 (55.3)	8,257 (64.6)	154,436 (54.9)	<0.001	106,153 (55.5)	3,849 (65.1)	102,304 (55.2)	<0.001
Age, years	57.0 ± 9.5	60.3 ± 9.7	56.8 ± 9.5	<0.001	56.5 ± 9.5	59.9 ± 9.8	56.4 ± 9.4	<0.001
Age categories, years				<0.001				<0.001
40-49, n (%)	72,571 (24.7)	1,997 (15.6)	70,574 (25.1)		50,278 (26.3)	1,007 (17.0)	49,271 (26.6)	
50-59, n (%)	103,879 (35.3)	3,845 (30.1)	100,034 (35.6)		68,431 (35.8)	1,786 (30.2)	66,645 (36.0)	
60-69, n (%)	80,837 (27.5)	4,165 (32.6)	76,672 (27.3)		50,263 (26.3)	1,870 (31.6)	48,393 (26.1)	
70-79, n (%)	36,675 (12.5)	2,777 (21.7)	33,898 (12.1)		22,142 (11.6)	1,252 (21.2)	20,890 (11.3)	
SBP, mmHg	138.5 ± 18.3	133.9 ± 18.7	138.7 ± 18.3	<0.001	139.4 ± 18.2	135.7 ± 19.0	139.6 ± 18.1	<0.001
BMI, kg/m^2	25.1 ± 3.1	24.4 ± 3.0	25.1 ± 3.1	0.061	25.0 ± 3.1	24.4 ± 3.1	25.1 ± 3.1	0.4305
BMI categories, kg/m^2				<0.001				<0.001
<18.5, n (%)	2,850 (1.0)	256 (2.0)	2,594 (0.9)		1,899 (1.0)	116 (2.0)	1,783 (1.0)	
18.5-24.9, n (%)	145,521 (49.5)	7,263 (56.8)	138,258 (49.2)		95,693 (50.1)	3,360 (56.8)	92,333 (49.9)	
≥ 25, n (%)	145,591 (49.5)	5,265 (41.2)	140,326 (49.9)		93,522 (48.9)	2,439 (41.2)	91,083 (49.2)	
Smoking status, n (%)				0.018				<0.001
Current smoker	58,403 (19.9)	2,656 (20.8)	55,747 (19.8)		39,836 (20.8)	1,344 (22.7)	38,492 (20.8)	
Ex-smoker	41,026 (14.0)	1,804 (14.1)	39,222 (13.9)		27,171 (14.2)	869 (14.7)	26,302 (14.2)	
Never smoker	194,533 (66.2)	8,324 (65.1)	186,209 (66.2)		124,107 (64.9)	3,702 (62.6)	120,405 (65.0)	
Alcohol frequency, n (%)				<0.001				<0.001
Never	166,881 (56.8)	7,754 (60.7)	159,127 (56.6)		106,013 (55.5)	3,495 (59.1)	102,518 (55.4)	
1-2/week	83,966 (28.6)	3,399 (26.6)	80,567 (28.7)		55,269 (28.9)	1,587 (26.8)	53,682 (29.0)	
3-4/week	27,333 (9.3)	946 (7.4)	26,387 (9.4)		18,902 (9.9)	499 (8.4)	18,403 (9.9)	
≥5/week	15,782 (5.4)	685 (5.4)	15,097 (5.4)		10,930 (5.7)	334 (5.6)	10,596 (5.7)	
Income status, n (%)				0.043				0.043
Lower 30%	73,261 (24.9)	3,122 (24.4)	70,139 (24.9)		47,901 (25.1)	1,440 (24.3)	46,461 (25.1)	
Middle 40%	101,748 (34.6)	4,353 (34.1)	97,395 (34.6)		66,408 (34.7)	2,005 (33.9)	64,403 (34.8)	
Upper 30%	118,953 (40.5)	5,309 (41.5)	113,644 (40.4)		76,805 (40.2)	2,470 (41.8)	74,335 (40.1)	
Comorbidities, n (%)								
Diabetes	74,017 (25.2)	4,292 (33.6)	69,725 (24.8)	<0.001	39,639 (20.7)	1,585 (26.8)	38,054 (20.5)	<0.001
Heart failure	2,587 (0.9)	282 (2.2)	2,305 (0.8)	<0.001	958 (0.5)	59 (1.0)	899 (0.5)	<0.001
COPD	8,707 (3.0)	590 (4.0)	8,198 (2.9)	<0.001	5,182 (2.7)	228 (3.9)	4,954 (2.7)	<0.001

Note: Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure.

for baseline covariates in the entire cohort (Table 2). Similarly, a decreased overall cancer risk in ARBs was also detected in the new-user cohort (aHR 0.71, 95% CI 0.66-0.77, *P* < .001). Compared with ACEIs, treatment with ARBs lowered the risk of developing lung cancer (aHR 0.73, 95% CI 0.64-0.82, *P* < .001), hepatic cancer (aHR 0.56, 95% CI 0.48-0.65, *P* < .001), and gastric cancer (aHR 0.74, 95%

CI 0.66-0.83, $P < .001$) in the entire cohort. In the case of the other representative cancers, such as colorectal, pancreatic, and kidney cancers, compared with ACEIs, treatment with ARBs showed a nonsignificant risk reduction (online-only Table S3). Compared with ACEIs, ARBs were associated with a nonsignificant risk elevation for breast, uterine, and prostate cancers (entire cohort; aHR 1.30, 95% CI 0.92-1.83, $P = .131$ for breast cancer; aHR 1.04, 95% CI 0.52-2.11, $P = .905$ for uterine cancer; aHR 1.14, 95% CI 0.95-1.38, $P = .168$ for prostate cancer).

3.3 | Subgroup and sensitivity analyses

Figure 1 presents subgroup analyses according to age, sex, body mass index, smoking status, alcohol consumption, and income status. Regardless of age, obesity, smoking status, alcohol consumption frequency, and income status, treatment with ARBs resulted in a greater reduction of cancer risk than in patients exposed to ACEIs. The decreased risk of cancer among ARB users was more prominent in males (interaction $P < .005$). Particularly, a decreased risk of cancer was more evident among heavy drinkers (alcohol consumption frequency of 5 or greater per week). Detailed information is provided in Tables S4 and Table S5 in the online-only Data Supplement. The sensitivity analyses after excluding those switching from ACEI to ARB and further excluding cancer developing within a maximum of 3 years did not alter the results substantially (online-only Figure S1 and Table S6). Furthermore, propensity matching analysis also yielded similar results (online-only Table S7 and Table S8 for the baseline characteristics after matching, Tables S9 and Table S10 for risk of overall and site-specific cancer development in the propensity score matching cohort). The use of ARBs was associated with a 22%-24% decrease in overall cancer (HR 0.78, 95% CI 0.72-0.83, $P < .001$ in the entire cohort; HR 0.76, 95% CI 0.68-0.85, $P = .002$ in the new-user cohort) compared to that with the use of ACEIs.

3.4 | Dose-response relationship

Patients showed gradually decreased risk of overall cancer with prolonged therapy with ARB than that in patients administered with ACEI (HR 0.82, 95% CI 0.76-0.89 for ARB use for <5 years; HR 0.63, 95% CI 0.58-0.68 for ARB use for 5-9 years; and HR 0.58, 95% CI 0.52-0.64 for ARB use ≥10 years). This was similarly applied to other representative site-specific cancers (Table 3).

4 | DISCUSSION

In this contemporary cohort involving a population of nearly 0.3 million Koreans, the use of ARBs was associated with a significant decrease in the risk of overall cancer compared with the use of ACEIs during a mean follow-up of 9.7 years (maximum, 15 years). This finding remained robust after adjustment for various demographic and socioeconomic factors and was generally similar across various subgroups. Furthermore, a dose-response relationship also supports the current findings. The decreased risks were evident for major site-specific cancers, including lung, liver, and gastric cancers. Our finding refutes findings of a previous meta-analysis, which suggested that ARBs may elevate the cancer risk.[7]

The present nationwide cohort study showed that ARBs did not elevate the overall cancer risk. Instead, they were associated with a decreased risk of cancer compared with ACEIs, which are known to be protective against or at least neutral toward cancer.[12,13] Similar to our findings, recent cohort studies demonstrated a significantly lower risk of lung cancer among ARB users than among ACEI users.[11,18] Another cohort study demonstrated a decreased risk of overall cancer and several site-specific cancers in ARB users compared with non-ARB users.[19] However, contrary to their findings,[19] the current study showed a marginal increase in the risk of breast and prostate cancers. Indeed, diverse outcomes regarding breast and prostate cancers have been reported.[6-11,18,19] A previous UK cohort study revealed a significantly increased risk of breast and prostate cancers,[11] although the dose-response relationship did not support a clear causal relationship, and the follow-up duration was relatively short (median of 4.6 years). Given the longer duration of exposure and follow-up, our results provide evidence suggesting that at least ARBs did not elevate the risk of cancer and even had a protective role in terms of hepatic and gastric cancers, particularly.

The underlying mechanism for a decreased cancer risk with ARBs is unclear. Accumulating evidence supports that the renin-angiotensin system plays a role in cancer development and metastasis.[4,20-25] Angiotensin II exerts its effect on cancer progression largely via the angiotensin type 1 (AT1) receptor by facilitating cell proliferation and neovascularization.[20-22] ARBs selectively inhibit the action of the AT1 receptor, whereas ACEIs block the conversion to angiotensin II, thereby broadly affecting all downstream pathways of both AT1 and AT2 receptors. Thus, theoretically, ARBs are expected to yield more favorable results compared with ACEIs via selective inhibition of unfavorable effects of AT1 receptor signaling, and by maintaining the protective function of AT2 receptor signaling. Indeed, several animal and human studies have demonstrated the safety of ARBs over ACEIs in terms of cancer development, progression, and survival.[23-25] Currently, however, the role of the AT2 receptor in cancer occurrence and progression is unclear.[20,26] Furthermore, additional cancers, particularly lung cancer, may be detected among ACEI users because of the frequent visit to the clinic owing to dry cough, which is the main side effect of ACEI use.

With regard to varying risk profiles (the direction and strength of association) of each site-specific cancer, the local expression of AT1 receptors might affect tumor microenvironment differentially via local growth factors and cytokines.[21] In the current study, the risk reduction was significant, particularly for hepatic and gastric cancers associated with viral infection (hepatitis virus, *Helicobacter* virus) and the resulting chronic inflammation/fibrosis. Moreover, the risk reduction was clearly evident in heavy drinkers (alcohol

TABLE 2 Risk of overall and site-specific carcinogenesis: ARB compared with ACEI

	Entire cohort (prevalent and new-user) (n = 293,962)					New-user cohort (n = 191,114)				
	Follow-up, person-year	Incident cancer, n	Incidence rate[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)	Follow-up, person-year	Incident cancer, n	Incidence rate[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Overall cancer										
ACEI	123,854	1,715	1384.7	1 (reference)	1 (reference)	56,249	777	1381.4	1 (reference)	1 (reference)
ARB	2,724,909	22,895	840.2	0.645 (0.614-0.678)	0.758 (0.721-0.797)	1,755,095	13,939	794.2	0.602 (0.560-0.647)	0.711 (0.661-0.765)
Lung cancer										
ACEI	129,424	281	217.1	1 (reference)	1 (reference)	58,922	118	200.3	1 (reference)	1 (reference)
ARB	2,813,697	2,825	100.4	0.508 (0.449-0.575)	0.727 (0.641-0.824)	1,809,255	1,700	94.0	0.508 (0.421-0.612)	0.745 (0.616-0.901)
Colorectal cancer										
ACEI	128,990	236	183.0	1 (reference)	1 (reference)	58,617	111	189.4	1 (reference)	1 (reference)
ARB	2,804,424	3,457	123.3	0.728 (0.638-0.830)	0.891 (0.779-1.018)	1,803,429	2,155	119.5	0.672 (0.555-0.813)	0.831 (0.685-1.008)
Hepatic cancer										
ACEI	129,474	218	168.4	1 (reference)	1 (reference)	58,947	93	157.8	1 (reference)	1 (reference)
ARB	2,815,455	1,885	67.0	0.434 (0.377-0.500)	0.559 (0.483-0.646)	1,810,434	1,054	58.2	0.396 (0.320-0.490)	0.508 (0.409-0.631)
Gastric cancer										
ACEI	128,583	335	260.5	1 (reference)	1 (reference)	58,394	171	292.8	1 (reference)	1 (reference)
ARB	2,802,894	3,916	139.7	0.578 (0.517-0.647)	0.743 (0.663-0.832)	1,802,893	2,364	131.1	0.475 (0.406-0.555)	0.628 (0.537-0.735)

Note: Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio.

[a]Incidence rate was presented as n/100,000 person-year.

[b]Adjusted for age, sex, systolic blood pressure, body mass index, smoking status, alcohol consumption frequency, income status, and comorbidities.

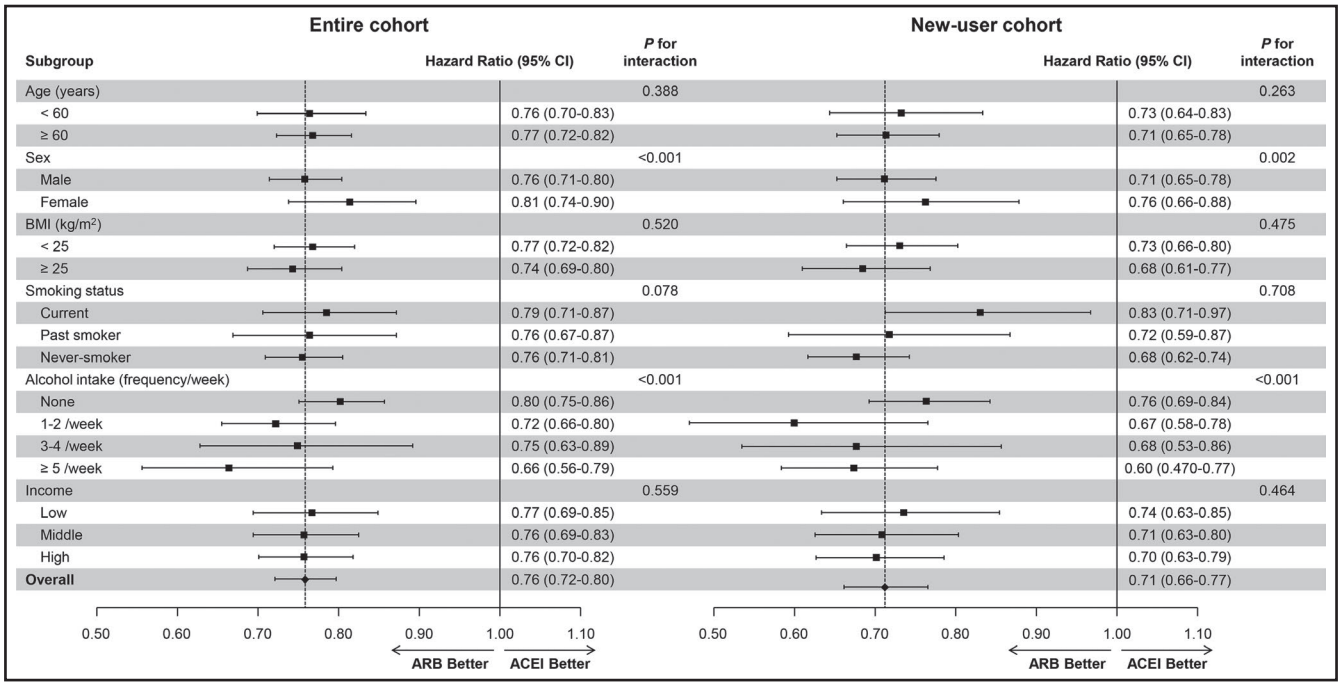

FIGURE 1 Forest plot of overall cancer risk according to subgroups. Subgroup analyses were performed based on sex, age, body mass index, alcohol consumption frequency, smoking habit, and income level. The dashed vertical line represents the hazard ratio for the overall study population of entire cohort and new-user cohort

consumption frequency of 5 or greater). Repeated alcohol exposure activates the renin-angiotensin system, leading to organ fibrosis and damage, mediated via generation of reactive oxygen species.[27,28] ARBs might play a beneficial role in reducing cancer incidence via regression of fibrosis, caused by viral infection or alcohol consumption.[27,29] Conversely, with regard to breast and prostate cancers, the tissue-specific renin-angiotensin pathway may exert its effect in conjunction with endocrine pathways, thereby weakening the action of ARBs on tumor development. However, this explanation is speculative at this time. Additional in vivo studies and prospective randomized studies are needed to elucidate the effect of renin-angiotensin pathways on cancer development.

Other characteristics of the study cohort need to be discussed. The number allocated in ARB users was disproportionately higher than that among ACEI users. However, since 2005, the ARB prescription rate is known to be higher than that of ACEI, and the difference is rapidly increasing in Korea (ARB is used approximately 23 times more than ACEI as a single drug, based on the 2016 NHIS database).[5] Unlike Europe and the USA,[30,31] the preference for ARB over ACEI is observed in other Asian countries, such as Japan and China.[32-34] A previous meta-analysis showed that ACEI-related dry cough was 2.7 times higher among the East Asian population than that among the Caucasian population,[35] which might be the reason ARB is preferred over ACEI.

This study has several strengths. From a clinical perspective, the current study provides appropriate long-term safety data, given that more patients were exposed to and maintained on ARBs. To our knowledge, this cohort study has the longest follow-up for various cancer subtypes and overall cancer incidence. Furthermore, it was an unselected real-world cohort representing the whole Korean population. From a research perspective, our study provided further evidence supporting an association between the renin-angiotensin system and cancer.

Several limitations of the current study should be discussed. First, the retrospective study design limited the investigation of a causal relationship. Second, a residual confounding factor-related bias may have persisted, although we rigorously controlled for various confounders including smoking, alcohol consumption, income status, and comorbidities. Third, the patients in the ARB group were approximately 3-4 years younger than those in the ACEI group, which might have affected the results. However, the results remained robust after controlling for various confounders, including age and comorbidities. Furthermore, the propensity matching analysis also demonstrated a consistent decreased risk of cancer among ARB users. Finally, our study findings may not be generalizable to other ethnicities. Given these limitations, our conclusions should be regarded only as possible hypotheses based on the data collected herein. We believe additional longitudinal and/or interventional studies of appropriately designed, randomized controlled trials with pre-specified cancer occurrence as the primary endpoint with a longer follow-up are warranted.

4.1 | Conclusions

ARB use was not associated with an elevated risk for cancer development among the Korean hypertensive patients who were

TABLE 3 Dose-response relationship between drug exposure and carcinogenesis in the new-user cohort (n = 191,114)

	Crude		Multivariate adjusted[a]	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Overall cancer				
ACEI	1 (reference)		1 (reference)	
ARB < 5 years	0.718	0.667-0.774	0.821	0.762-0.885
5 ≤ ARB <10 years	0.526	0.488-0.567	0.627	0.581-0.676
ARB ≥ 10 years	0.479	0.435-0.529	0.578	0.523-0.637
Lung cancer				
ACEI	1 (reference)		1 (reference)	
ARB < 5 years	0.726	0.600-0.880	0.958	0.790-1.161
5 ≤ ARB <10 years	0.376	0.309-0.458	0.572	0.468-0.699
ARB ≥ 10 years	0.222	0.163-0.303	0.364	0.266-0.498
Colorectal cancer				
ACEI	1 (reference)		1 (reference)	
ARB < 5 years	0.783	0.643-0.952	0.930	0.764-1.132
5 ≤ ARB <10 years	0.597	0.491-0.727	0.752	0.616-0.917
ARB ≥ 10 years	0.553	0.430-0.712	0.710	0.550-0.916
Hepatic cancer				
ACEI	1 (reference)		1 (reference)	
ARB < 5 years	0.546	0.439-0.679	0.678	0.544-0.846
5 ≤ ARB <10 years	0.301	0.240-0.378	0.384	0.305-0.484
ARB ≥ 10 years	0.219	0.153-0.312	0.279	0.195-0.399
Gastric cancer				
ACEI	1 (reference)		1 (reference)	
ARB < 5 years	0.579	0.493-0.680	0.728	0.619-0.855
5 ≤ ARB <10 years	0.409	0.348-0.481	0.551	0.468-0.650
ARB ≥ 10 years	0.341	0.271-0.429	0.470	0.373-0.592

Note: Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval.

[a]Adjusted for age, sex, systolic blood pressure, body mass index, smoking status, alcohol consumption frequency, income status, and comorbidities.

followed up for over an average duration of 10 years. Instead, it was shown to decrease the risk of cancer compared with ACEI use. This finding may be applicable to major site-specific cancers, including lung, gastric, and hepatic cancers. Furthermore, these findings were consistent across various subgroups. Although a prudent approach is needed when interpreting the results, our results represent evidence to reassure the physician and patients of the safety of long-term ARB use. Further preclinical and interventional studies are needed to corroborate these findings.

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CONFLICT OF INTEREST

The authors have declared no competing interest exists.

AUTHOR CONTRIBUTIONS

MHJ, JHL, MCC, and KCS designed this study. JH, SR, and CK performed statistical analysis. MHJ, JHL, CJL, JHS, SHK, CHK, DHK, WK HLK, HMK, IJC, IC, HYL, WJC, SHI, KIK, EJC, ISS, SP, JS, SKR, MYR, SMK, WBP, MCC, and KCS interpreted the data. MHJ and JHL wrote the first draft. CJL, JHS, SHK, CHK, DHK, WK HLK, HMK, IJC, IC, JH, SR, CK, HYL, WJC, SHI, KIK, EJC, ISS, SP, JS, SKR, MYR, SMK, WBP, MCC, and KCS revised the manuscript. All authors have reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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