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Original Article

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers might be associated with lung adenocarcinoma risk: a nationwide population-based nested case-control study

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Abstract: Objectives: To analyze the association of the use of different doses of angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) independently with lung cancer risk and to evaluate the lung cancer type that may be related to ARB or ACEI use. Patients and methods: A nationwide population-based nested case-control study was conducted using Taiwan National Health Insurance Research Database linked to the Taiwan Cancer Registry database between January 1, 2000, and December 31, 2016. The cumulative defined daily dose (DDD) was estimated. We divided all users of ACEI or ARB into three categories based on the DDD of ACEI or ARB: low dose, middle dose, and high dose. Results: We identified 16,091 patients with newly diagnosed lung cancer, and 80,455 controls with hypertension were selected. Univariate and multivariate conditional logistic regressions showed that the independent risk factor for lung cancer was high-dose (≥ 1095 DDD) ARB use (adjusted odds ratio [OR]: 1.069, 95% confidence interval [CI]: 1.02-1.12, $P = 0.003$). An increase in lung adenocarcinoma (ADC) risk was associated with middle-dose (adjusted OR: 1.073, 95% CI: 1.01-1.14, $P = 0.025$) to high-dose (adjusted OR: 1.106, 95% CI: 1.05-1.17, $P < 0.001$) ARB use and high-dose ACEI use (adjusted OR: 1.095, 95% CI: 1.01-1.19, $P = 0.033$). No association was observed between different ARB or ACEI dose levels and the risk of lung squamous cell carcinoma and small-cell lung carcinoma. Conclusions: Our results suggest that the use of both ACEI and ARB at a high cumulative dose is associated with the risk of lung ADC.

Keywords: ACEI, ARB, lung cancer risk, lung adenocarcinoma, dose levels

Introduction

Concerns regarding the long-term use of angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) have been increasing in the near years [1, 2]. The major risk of long-term ACEI or ARB use has been cancer and myocardial infarction (MI) [1, 2]. A meta-analysis of five trials suggested that patients treated with ARB had a significantly increased cancer risk compared with controls [1]. However, two subsequent meta-analyses have failed to confirm this finding of increasing cancer risk [3, 4]. Cancer incidence was similar in ARB- and ACEI-treatment and control groups. Another report suggested an increased MI risk among ARB users [2]. However, a meta-analysis of 37 randomized controlled trials (RCTs) showed no increase in MI risk with ARB and ACEI use [5]. The adverse effects of ARB or ACEI long-term use are still controversial.

In addition, a meta-analysis involving antihypertensive drugs showed that ARB and ACEI combi-

nation therapy was associated with a significant increase in cancer incidence compared with ACEI treatment alone [3]. By contrast, another meta-analysis found no cancer risk in patients treated with combination therapy compared with ACEI treatment alone [4]. However, significant heterogeneity was detected among the trials in the two meta-analysis studies [3, 4]. Cancer risk tended to be higher with combination therapy than with individual therapy in three trials with longer follow-up time (at a mean follow-up of 48 months) and somewhat lower with combination therapy than with individual therapy in the other four trials with shorter follow-up time (at a mean follow-up of 32 months) within the two meta-analysis studies [3, 4]. According to the aforementioned studies, the follow-up time of 3-4 years might be necessary for evaluating the cancer risk of ACEI or ARB use.

In 2018, a large population-based cohort study with a mean follow-up time of 6.4 years showed that ACEI use is associated with an increased lung cancer risk compared with ARB use [6]. Hicks and colleagues compared ACEI with ARB, as both act on the renin-angiotensin-aldosterone system and are used at the same disease stage. However, ARB may also affect lung cancer risk [1]. Hicks and colleagues indicated the relative risk of ACEI and ARB, but information on dose levels was lacking in their study. Furthermore, the association of ARB or ACEI use with lung cancer type is unclear. In our study, we investigated the association of the use of different doses of ACEI or ARB with lung cancer risk. Moreover, we evaluated the lung cancer type potentially associated with ARB or ACEI use.

Patients and methods

Data source

We conducted a nationwide population-based nested case-control study using Taiwan National Health Insurance Research Database (NHIRD) linked to the Taiwan Cancer Registry (TCR) database. The TCR was established in 1979 and contains data of 97% of the cancer cases in Taiwan [7]. The NHIRD includes all medical claims data on disease diagnoses, procedures, drug prescriptions, and demographics as well as enrollment profiles of all beneficiaries [8, 9]. The NHIRD and TCR are linked with encrypted patient identifiers. Our study protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB 201702019).

Study population

Our cohort consisted of patients with hypertension who visited the hospital at least twice within 1 year, with outpatient records of hypertension diagnosis between January 1, 2000, and December 31, 2016, in the NHIRD. The cumulative defined daily dose (DDD) was analyzed based on the method in our previous study [9]. The date of completion of 90 days of DDD of ARB or ACEI use was assigned as the index date for all identified patients. Patients with a primary diagnosis of lung cancer before the entry date were excluded. We only included patients who received 90 days of DDD before the entry date. In the hypertension cohort, we identified patients with a pathologic diagnosis of lung cancer. Only the first cancer diagnosis of lung cancer was included in our study. All potential patients were validated using the Catastrophic Illness Database (which includes patients with cancer and chronic renal failure) and TCR database. Moreover, this approach has been adopted in several cancer studies using data from the combination of the NHIRD and TCR database [10-18]. We defined the entry date as the date of the first pathologic diagnosis of lung cancer. The DDD of ACEI or ARB was calculated from 1 to 9 years before the entry date. For each patient, five matched controls were randomly selected from the same hypertension cohort. Controls were matched with the patients for age, sex, income, diabetes, chronic obstructive pulmonary disease (COPD), and entry date (± 90 days). Each control was assigned the entry date of the corresponding patient. Furthermore, we excluded patients with the entry date of lung cancer diagnosis within 3 years after the index date to decrease the nonassociation of drugs-related lung cancer risk. Moreover, we excluded patients with crossover use of ARB and ACEI but included those with crossover use of other antihypertensive medications such as thiazide diuretics, calcium channel blockers, and beta blockers.

Definition of exposure

To investigate the association of ACEI or ARB use with lung cancer risk, all prescriptions of

ACEI or ARB before the entry date were identified from the NHIRD. For each ACEI or ARB prescribed, the prescription records of the NHIRD including information on the starting date (prescription dispensing date), dosages, quantities, and prescription duration were collected. We categorized patients with ACEI or ARB use based on the timing and duration of use. The study individuals were defined as low-dose users, middle-dose users, or high-dose users if their prescribed DDDs were for < 365, 365-1094, and ≥ 1095 days, respectively, before the entry date. Exposure to ACEI or ARB was recorded separately to examine their individual effects on the risk of lung cancer and various other lung cancer types, including adenocarcinoma (ADC), squamous cell carcinoma (SQC), or small-cell lung carcinoma (SCLC). To decrease the effect of cigarette smoking as a major confounding factor, we investigated the association of ARB or ACEI use with lung cancer risk and different lung cancer types separately in the female group. This is because the prevalence of cigarette smoking in Taiwanese woman is only 3% and is decreasing persistently [19, 20].

Statistical analysis

Univariate and multivariate conditional logistic regressions were used to investigate the associations of ACEI or ARB use with lung cancer risk. Moreover, we examined the association between the dose levels of ACEI or ARB used and lung cancer risk. The associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Two-sided *P* values < 0.05 were considered statistically significant.

All models were adjusted for comorbidities and concomitant medications.

Comorbidities included pulmonary fibrosis, acquired immunodeficiency syndrome (AIDS), and coronary artery disease (CAD) and were evaluated using Charlson comorbidity index (CCI). SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA), was used for analyses.

Results

We identified 16,091 patients with newly diagnosed lung cancer and selected 80,455 controls from among patients with hypertension. Age, sex, COPD, income, and diabetes distribution in the case and control groups were well matched. No statistically significant difference was observed in ACEI and ARB doses used up to the entry date between the case and control groups. Furthermore, other comorbidities such as pulmonary fibrosis, AIDS, CAD, or CCI scores were balanced between the case and control groups (**Table 1**). Univariate and multivariate conditional logistic regressions showed that the independent risk factor for lung cancer was high-dose ARB use (adjusted OR: 1.069, 95% CI: 1.02-1.12, *P* = 0.003; **Table 2**). No association was observed between middle- or high-dose ACEI use and lung cancer risk. Moreover, no association was noted between comorbidities and lung cancer risk. All variables in the female case and control groups were identical as **Table 1**. ARB use at middle to high dose levels in female patients with hypertension (adjusted OR: 1.117, 95% CI: 1.03-1.22, *P* = 0.011 and adjusted OR: 1.101, 95% CI: 1.02-1.19, *P* = 0.011, respectively) was associated with lung cancer risk (Table S2).

Table 3 shows the baseline characteristics of lung ADC patients and risk set matching controls, and all variables were balanced between the case and control groups. Lung ADC risk was associated with middle- to high-dose ARB use (adjusted OR: 1.073, 95% CI: 1.01-1.14, *P* = 0.025 and adjusted OR: 1.106, 95% CI: 1.05-1.17, *P* < 0.001, respectively) and high-dose ACEI use (adjusted OR: 1.095, 95% CI: 1.01-1.19, *P* = 0.033) (**Table 4**). Even in female patients (where 97% did not smoke cigarettes), middle- to high-dose ARB use and high-dose ACEI use are associated with lung ADC risk (Table S2).

For other lung cancer types, including SQC or SCLC, we investigated an association of ARB and ACEI use with the risk of lung SQC or SCLC. Table S1 show no association between ARB or ACEI use at any dose and risks of lung SQC and SCLC. In the female group (nonsmoking group; Table S2), no association was observed between the different doses of ARB or ACEI and risks of lung SQC and SCLC irrespective of their cigarette smoking habit.

Discussion

The side effects of ACEI use are related to either reduced angiotensin II formation or increased kinins [21]. Those related to reduced

Table 1. Baseline characteristics of lung cancer patients and risk-matched controls

	Control cohort		Case group		*P* value
	N	(%)	N	(%)	
Total cumulative doses of ARB					0.388
Dose < 365 DDD	40,238	(50.01)	7963	(49.49)	
365 DDD ≤ Dose < 1095 DDD	16,091	(20.00)	3283	(20.40)	
Dose ≥ 1095 DDD	24,126	(29.99)	4845	(30.11)	
Total cumulative doses of ACEI					0.398
Dose < 365 DDD	63,879	(79.40)	12,850	(79.86)	
365 DDD ≤ Dose < 1095 DDD	9418	(11.71)	1832	(11.39)	
Dose ≥ 1095 DDD	7158	(8.90)	1409	(8.76)	
Sex					1
Female	31,920	(39.67)	6384	(39.67)	
Male	48,535	(60.33)	9707	(60.33)	
Age					1
Age < 40 years	545	(0.68)	109	(0.68)	
40 years ≤ Age < 50 years	4920	(6.12)	984	(6.12)	
50 years ≤ Age < 60 years	15,710	(19.53)	3142	(19.53)	
60 years ≤ Age < 70 years	28,355	(35.24)	5671	(35.24)	
Age ≥ 70 years	30,925	(38.44)	6185	(38.44)	
Low income					1
No	79,195	(98.43)	15,839	(98.43)	
Yes	1260	(1.57)	252	(1.57)	
Diabetes					1
Not	52,115	(64.78)	10,423	(64.78)	
Yes	28,340	(35.22)	5668	(35.22)	
Pulmonary fibrosis					0.652
No	79,044	(98.25)	15,817	(98.30)	
Yes	1411	(1.75)	274	(1.70)	
COPD					1
No	62,990	(78.29)	12,598	(78.29)	
Yes	17,465	(21.71)	3493	(21.71)	
CAD					0.854
No	38,201	(47.48)	7653	(47.56)	
Yes	42,254	(52.52)	8438	(52.44)	
AIDS					0.577
No	80,141	(99.61)	16,033	(99.64)	
Yes	314	(0.39)	58	(0.36)	
CCI (mean ± SD)	(3.21 ± 1.15)		(3.20 ± 1.14)		0.293

ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; CCI, Charlson comorbidity index; AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

angiotensin II formation include hypotension, acute renal failure, hyperkalemia, and problems during pregnancy [21]. Side effects considered related, at least in part, to increased kinins include cough, angioedema, and anaphylactoid reactions [21]. The side effect profile of ARB is generally similar to that of ACEI, including increased incidence of hyperkalemia and acute renal failure in renovascular hypertension or states of effective volume depletion [22-25]. The rate of certain side effects (e.g., renal dysfunction and syncope) appears to be similar for these two classes of drugs; however, ARB has lower rates of cough and angioedema

Table 2. Univariate and multivariate ORs for lung cancer patients according to the doses of ACEI or ARB used

	Crude OR (CI)		*P* value	Adjusted OR (CI)		*P* value
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.032	(0.99, 1.08)	0.161	1.045	(0.99, 1.1)	0.085
Dose ≥ 1095 DDD	1.066	(1.02, 1.11)	0.002	1.069	(1.02, 1.12)	0.003
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.973	(0.92, 1.03)	0.319	0.991	(0.93, 1.06)	0.791
Dose ≥ 1095 DDD	1.037	(0.98, 1.10)	0.242	1.066	(0.99, 1.14)	0.079
Pulmonary fibrosis (ref: No)						
Yes	0.953	(0.84, 1.09)	0.470	0.932	(0.82, 1.07)	0.306
CAD (ref: No)						
Yes	0.995	(0.96, 1.03)	0.773	0.994	(0.96, 1.03)	0.741
AIDS (ref: No)						
Yes	0.959	(0.73, 1.26)	0.765	0.965	(0.71, 1.31)	0.816
CCI score (ref: 0)						
CCI score ≥ 1	0.937	(0.90, 1.08)	0.721	0.939	(0.9, 1.07)	0.702

All the aforementioned variables were used in the multivariate analysis. ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; CCI, Charlson comorbidity index; AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

Table 3. Baseline characteristics of lung adenocarcinoma patients and risk-matched controls

	Control group		Case group		*P* value
	N	(%)	N	(%)	
Total cumulative doses of ARB					0.138
Dose < 365 DDD	26,984	(49.82)	5251	(48.48)	
365 DDD ≤ Dose < 1095 DDD	10,796	(19.93)	2221	(20.50)	
Dose ≥ 1095 DDD	16,380	(30.24)	3360	(31.02)	
Total cumulative doses of ACEI					0.392
Dose < 365 DDD	42,042	(77.63)	8454	(78.05)	
365 DDD ≤ Dose < 1095 DDD	6620	(12.22)	1273	(11.75)	
Dose ≥ 1095 DDD	5498	(10.15)	1105	(10.20)	
Sex					1
Female	28,495	(52.61)	5699	(52.61)	
Male	25,665	(47.39)	5133	(47.39)	
Age					1
Age < 40 years	450	(0.83)	90	(0.83)	
40years ≤ Age < 50 years	3720	(6.87)	744	(6.87)	
50 years ≤ Age < 60 years	11,040	(20.38)	2208	(20.38)	
60 years ≤ Age < 70 years	18,965	(35.02)	3793	(35.02)	
Age ≥ 70 years	19,985	(36.90)	3997	(36.90)	
Low income					1
No	53,440	(98.67)	10,688	(98.67)	
Yes	720	(1.33)	144	(1.33)	
Diabetes					1
No	35,580	(65.69)	7116	(65.69)	
Yes	18,580	(34.31)	3716	(34.31)	
Pulmonary fibrosis					0.925
No	53,230	(98.28)	10,648	(98.30)	

Yes	930	(1.72)	184	(1.70)	
COPD					1
No	45,050	(83.18)	9010	(83.18)	
Yes	9110	(16.82)	1822	(16.82)	
CAD					0.712
No	26,098	(48.19)	5198	(47.99)	
Yes	28,062	(51.81)	5634	(52.01)	
AIDS					0.480
No	53,910	(99.54)	10,788	(99.59)	
Yes	250	(0.46)	44	(0.41)	
CCI (mean ± SD)	(3.15 ± 1.16)		(3.14 ± 1.15)		0.4010

ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; CCI, Charlson comorbidity index; AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 4. Univariate and multivariate ORs for lung adenocarcinoma patients according to the doses of ACEI or ARB used

	Crude OR		*P* value	Adjusted OR		*P* value
	OR	(CI)		OR	(CI)	
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.104	(1.02, 1.19)	0.010	1.073	(1.01, 1.14)	0.025
Dose ≥ 1095 DDD	1.086	(1.02, 1.16)	0.016	1.106	(1.05, 1.17)	2.74E-04
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.965	(0.89, 1.05)	0.414	0.989	(0.91, 1.07)	0.795
Dose ≥ 1095 DDD	1.023	(0.94, 1.11)	0.577	1.095	(1.01, 1.19)	0.033
Pulmonary fibrosis (ref: No)						
Yes	0.992	(0.93, 1.10)	0.651	0.969	(0.82, 1.14)	0.703
CAD (ref: No)						
Yes	0.992	(0.94, 1.05)	0.790	1.006	(0.96, 1.05)	0.774
AIDS (ref: No)						
Yes	0.894	(0.63, 1.28)	0.539	0.868	(0.61, 1.23)	0.423
CCI score (ref: 0)						
CCI score ≥ 1	1.091	(0.84, 1.17)	0.907	1.035	(0.89, 1.19)	0.712

All the aforementioned variables were used in the multivariate analysis. ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; CCI, Charlson comorbidity index; AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

and perhaps a higher rate of hypotensive symptoms than ACEI [22]. ACEI decreases angiotensin II production, whereas ARB selectively blocks its binding to angiotensin receptors [26]. These drugs target the renin-angiotensin-aldosterone system and may cause cancer [27, 28].

Hicks and colleagues could not identify the role of individual drugs in lung cancer because they compared ACEI with ARB [6]. In our study, we examined the lung cancer risk of ARB and AECI at different doses individually. Moreover, we attempted to identify the lung cancer types potentially caused by ARB or ACEI. Hicks and colleagues' study was prone to residual confounding. Furthermore, information on socioeconomic status was lacking, which may differ in users of ACEI or ARB. ACEI became generically available in 1995 [29], whereas the first generic ARB was marketed in 2010. Accordingly, socioeconomic differences might influence prescribing patterns and lung cancer risk over a long-term period, even in the UK national healthcare setting [6]. Therefore, we matched low-income patients identified based on data from the Social Affairs Bureau of Taiwan

Government to prevent the bias of socioeconomic status (**Table 1**). In addition, ACEI use is associated with persistent cough, which may have prompted thorax imaging more frequently in ACEI users than in ARB users, but data on Hicks's scans were unavailable in the current analysis [6]. In our study, we compared middle- to high-dose ACEI use with low-dose ACEI use or middle- to high-dose ARB use with low-dose ARB use. Thus, the bias of more frequent thorax imaging in ACEI users than in ARB users could be avoided in our current study. Furthermore, as ACEI and ARB have varying pharmacological properties and pleotropic effects, the different lung cancer types induced by ACEI and ARB are unclear. Although the pathologies of all types of lung cancer were significantly associated with cigarette smoking, the association was stronger for SQC and SCLC than for ADC [30]. Therefore, the association of ACEI or ARB use with various lung cancer types might vary.

As shown in **Table 1**, sex, age, low income, diabetes, and COPD were well-matched between the case and control groups, and no statistically significant differences were noted in their lung cancer risk-related covariates. As shown in **Table 2**, high- and low-dose ARB users were associated with lung cancer risk. However, no association was noted between ACEI use and lung cancer risk. Table S2 present the female group, which was used to determine whether cigarette smoking is a risk factor for lung cancer risk because more than 97% of the Taiwanese female population does not smoke cigarettes [19, 20]. In the female group, middle-dose ARB users were associated with lung cancer risk. This might be because cigarette smoking as a competing risk factor for lung cancer was eliminated; thus, ARB use as a lung cancer risk factor was evident [31, 32]. In our female group (no-cigarette-smoking group), different doses of ARB or ACEI as a lung cancer risk factor could be investigated clearly.

To understand the association of ARB or ACEI use with different lung cancer types, we investigated the association of lung ADC risk with different doses of ARB and ACEI (**Tables 3** and **4**). Clarifying which lung cancer type is induced by ACEI and ARB is important because different lung cancer types have different survival prognosis and treatment approaches [33-35]. In the future, we will further check whether driver gene mutation is absent or present in ARB or ACEI use-related lung cancer. Furthermore, **Table 3** shows that covariates were all balanced between the case and control groups. In multivariate analysis, the independent risk factors for lung ADC were middle- and high-dose ARB use and high-dose ACEI use (**Table 4**). In the female group (Table S2), the trends were similar to that in **Table 4**. The adjusted ORs (95% CIs) of middle-dose ARB use in Table S2 (female group) and **Table 4** are 1.153 (95% CI: 1.05-1.26, $P = 0.002$) and 1.073 (95% CI: 1.01-1.14, $P = 0.0025$), respectively. The augmentation of adjusted OR of lung ADC risk and middle-dose ARB use in the female group was compatible with the finding of a previous study [31, 32] because of the removal of the cigarette smoking confounding factor. Our findings indicate lung cancer risk in nonsmokers and propose a new hypothesis of ACEI or ARB causing lung cancer, especially lung ADC, among nonsmokers. Although the etiology of lung cancer among nonsmokers is unclear, ADC is the most common pathology among nonsmokers and is more common among nonsmokers than among smokers [36, 37]. According to our results, both ARB and ACEI use might play a role in the etiology of lung ADC among nonsmokers.

Additionally, we investigated the association of ACEI or ARB use with the risk of lung SQC or SCLC (Tables S1 and S2). In our study, no association was noted between ARB or ACEI use and the risk of lung SQC or SCLC in the female group (nonsmoking group) and the overall case group (Tables S1 and S2). Our findings showed that both ARB and ACEI use independently resulted in lung cancer risk, especially lung ADC. Nevertheless, no association was noted between ACEI or ARB use and lung SQC and SCLC risks. This is the first study to demonstrate the association of ACEI and ARB use independently with lung ADC risk, and the association of ACEI and ARB use with lung ADC varies according to the dose. Not only ACEI use but also ARB use was linked with a high risk of lung ADC.

Until now, no clinical or epidemiological study has demonstrated the association between ACEI or ARB use and lung ADC risk. Moreover, the mechanism of ACEI or ARB use in lung ADC risk is scarcely known. The most frequently

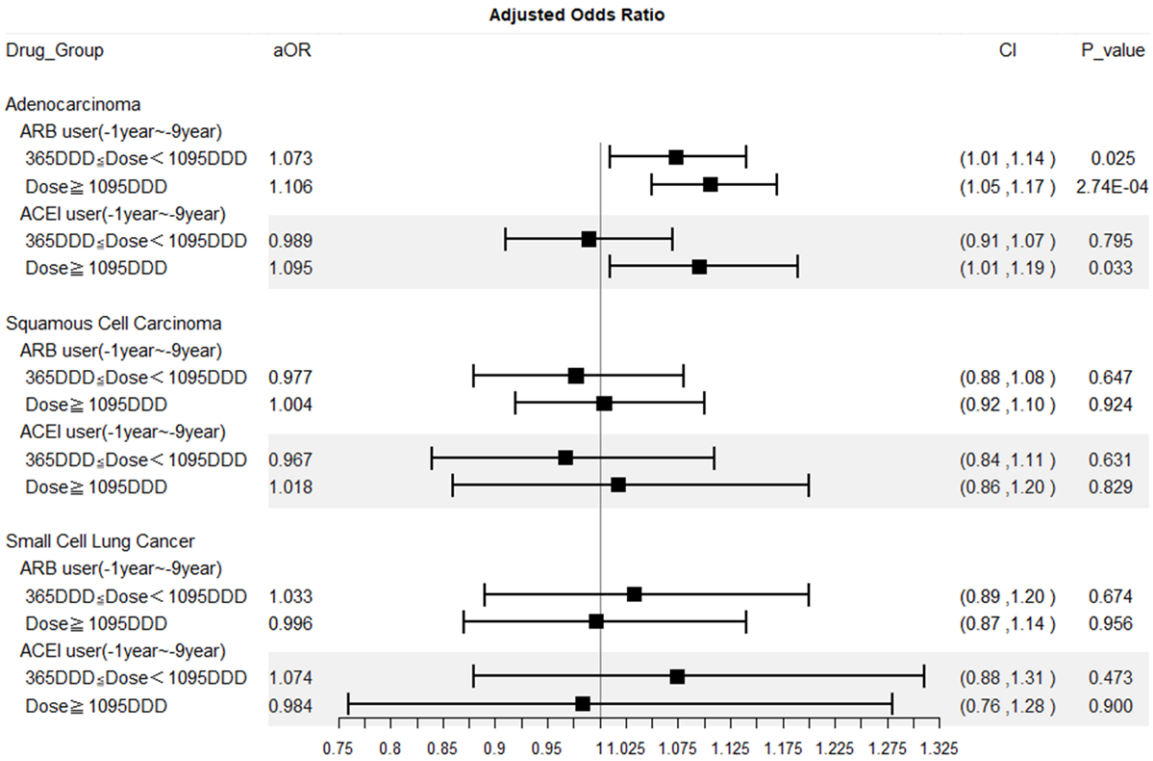

Figure 1. Forest plot of different lung cancer risk based on the doses of ACEI or ARB. All the variables mentioned in **Table 2** were used in multivariate analysis. ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; OR, odds ratio; CI, confidence interval.

reported possible mechanism is that angiotensin II exerts its actions through angiotensin II type-1 and type-2 receptors (AT1R and AT2R, respectively) [38, 39]. ARB drugs are antagonists of AT1R [38, 39]. Experimental studies using cancer cell lines and mouse models have implicated the role of the renin-angiotensin-aldosterone system in the regulation of cell proliferation, tumor growth, angiogenesis, and metastasis [38, 39]. Evidence shows that both AT1R blockade with an ARB (which is associated with unopposed AT2R stimulation) and direct stimulation of AT2R can promote tumor angiogenesis in vivo [40]. Moreover, in vitro or in vivo studies have indicated that blocking angiotensin-(1-7) with ACEI or ARB drugs might mediate the migration and invasion of A549 human lung ADC cells through the activation of phosphatidylinositol-3-kinase/Akt and mitogen-activated protein kinase signaling pathways [41-43]. The aforementioned experimental studies might explain the mechanism of ACEI or ARB use in lung ADC risk [41-43]. This is the first clinical and epidemiological study to demonstrate that both ARB and ACEI use might be associated with lung ADC risk.

This study has several strengths. First, to the best of our knowledge, this is the longest nested case-control cohort study examining the association between ACEI or ARB use and the risk of different lung cancer types. Second, we excluded patients with crossover ACEI and ARB use, thus minimizing biases related to the crossover use of ACEI and ARB in lung ADC risk. Third, we used a case-control cohort that eliminated immortal time bias, accounted for cancer latency, and avoided a competing risk bias of death. Fourth, this is the first study to show the association of different doses of ACEI or ARB with lung ADC risk (**Figure 1**). Fifth, this is the first study to demonstrate that no association exists between ACEI or ARB use and risks of lung SQC and SCLC (**Figure 1**). Sixth, all covariates were matched and balanced between the case and control groups. In clinical practice, we suggest that users with long-term or high cumulative doses of ACEI or ARB have a high risk of lung ADC and should receive regular lung cancer examination, including low-dose computed tomography [44]. Other antihypertensive drugs could be an alternative for these hypertension populations without other

metabolomics diseases, chronic kidney disease, and heart failure [21, 45]. In future, more randomized controlled trials are required to validate the findings, and our results may be a good reference for future trials involving ACEI or ARB users.

This study has some limitations. First, medication adherence was not examined in this study. However, the higher the compliance of ACEI or ARB use, the higher the lung ADC risk in the current condition. The conclusion of the association of both ACEI and ARB use independently with lung ADC risk could be impossible to be overturned. Second, we compared middle- to high-dose ACEI or ARB use with their low-dose use. The threshold of ACEI or ARB dose related with lung ADC risk could not be detected. Third, we adjusted for several essential confounders, but this study lacked information on other potential confounders such as diet, exposure to radon or asbestos, and a family history of lung cancer. However, an analysis of nonsmokers (female group) produced results consistent with those of the primary analyses, with a clear dose-response association, providing reassurance that residual confounding through smoking did not considerably affect our findings. In addition, stratified analysis showed that other lung cancer types such as lung SQC and SCLC were not associated with ARB and ACEI use. The association between ACEI or ARB use and lung SQC and SCLC risks indirectly proved the role of ACEI and ARB in lung ADC. Fourth, because all patients with hypertension included in this study were Asians, the corresponding ethnic susceptibility is unclear; hence, our results should be cautiously extrapolated to non-Asian populations. Fifth, the sample size of patients with large-cell lung carcinoma was considerably small; hence, we did not analyze the association of ACEI or ARB use with the risk of large-cell lung carcinoma. Sixth, the comorbidities were diagnosed solely according to International Classification of Diseases, Ninth Revision, Clinical Modification codes. However, the Bureau of National Health Institute randomly reviews charts and interviews patients to verify diagnosis accuracy. Thus, hospitals with outlier chargers or practices may undergo an audit and subsequently receive heavy penalties if malpractices or discrepancies are identified. Therefore, a large-scale randomized trial of carefully selected patients receiving suitable treatments is essential to obtain crucial information on population specificity and disease occurrence. Considering the magnitude and statistical significance of the observed outcomes in this study, these limitations are unlikely to have affected the conclusions.

Conclusions

ACEI and ARB at high cumulative doses might be associated with lung ADC risk.

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Disclosure of conflict of interest

None.

Abbreviations

ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; OR, odds ratio; CI, confidence interval; NHIRD, National Health Insurance Research Database; TCR, Taiwan Cancer Registry; ADC, adenocarcinoma; SQC, squamous cell carcinoma; SCLC, small cell lung carcinoma; CCI, Charlson comorbidity index; AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; AT1R, angiotensin II type-1 receptor; AT2R, angiotensin II type-2 receptor; MI, myocardial infarction; RCTs, randomized controlled trials.

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Table S1. Univariate and multivariate ORs for different types of lung cancer patients according to the doses of ACEI or ARB used

All types of lung cancer risk	Crude OR		*P* value	Adjusted OR		*P* value
	OR	(CI)		OR	(CI)	
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.032	(0.99, 1.08)	0.161	1.045	(0.99, 1.1)	0.085
Dose ≥ 1095 DDD	1.066	(1.02, 1.11)	0.002	1.069	(1.02, 1.12)	0.003
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.973	(0.92, 1.03)	0.319	0.991	(0.93, 1.06)	0.791
Dose ≥ 1095 DDD	1.037	(0.98, 1.10)	0.242	1.066	(0.99, 1.14)	0.079
Lung adenocarcinoma risk						
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.104	(1.02, 1.19)	0.010	1.073	(1.01, 1.14)	0.025
Dose ≥ 1095 DDD	1.086	(1.02, 1.16)	0.016	1.106	(1.05, 1.17)	2.74E-04
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.965	(0.89, 1.05)	0.414	0.989	(0.91, 1.07)	0.795
Dose ≥ 1095 DDD	1.023	(0.94, 1.11)	0.577	1.095	(1.01, 1.19)	0.033
Lung small cell lung cancer risk						
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.006	(0.88, 1.16)	0.929	1.033	(0.89, 1.2)	0.674
Dose ≥ 1095 DDD	0.992	(0.87, 1.13)	0.897	0.996	(0.87, 1.14)	0.956
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.086	(0.92, 1.28)	0.329	1.074	(0.88, 1.31)	0.473
Dose ≥ 1095 DDD	0.936	(0.74, 1.18)	0.579	0.984	(0.76, 1.28)	0.900
Lung squamous cell carcinoma risk						
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.974	(0.89, 1.07)	0.574	0.977	(0.88, 1.08)	0.647
Dose ≥ 1095 DDD	1.009	(0.93, 1.10)	0.827	1.004	(0.92, 1.1)	0.924
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.963	(0.86, 1.08)	0.523	0.967	(0.84, 1.11)	0.631
Dose ≥ 1095 DDD	1.023	(0.89, 1.18)	0.754	1.018	(0.86, 1.2)	0.829

All the aforementioned variables were used in the multivariate analysis. ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; OR, odds ratio; CI, confidence interval.

Table S2. Univariate and multivariate ORs for female with different types of lung cancer patients according to the doses of ACEI or ARB used

Female all types of lung cancer risk	Crude OR		*P* value	Adjusted OR		*P* value
	OR	(CI)		OR	(CI)	
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.084	(1.01, 1.16)	0.026	1.117	(1.03, 1.22)	0.011
Dose ≥ 1095 DDD	1.085	(1.02, 1.16)	0.012	1.101	(1.02, 1.19)	0.011
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.964	(0.89, 1.04)	0.367	1.023	(0.92, 1.14)	0.679
Dose ≥ 1095 DDD	0.993	(0.92, 1.07)	0.860	1.040	(0.94, 1.15)	0.430
Female lung adenocarcinoma risk						
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.058	(1.00, 1.12)	0.043	1.153	(1.05, 1.26)	0.002
Dose ≥ 1095 DDD	1.098	(1.05, 1.15)	1.49E-04	1.108	(1.02, 1.20)	0.010
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.961	(0.90, 1.03)	0.228	1.012	(0.90, 1.13)	0.835
Dose ≥ 1095 DDD	1.048	(0.98, 1.12)	0.183	1.090	(1.03, 1.21)	0.018
Female lung small cell lung cancer risk						
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.784	(0.277, 1.09)	0.220	0.889	(0.35, 1.28)	0.141
Dose ≥ 1095 DDD	0.941	(0.66, 1.34)	0.734	0.995	(0.67, 1.48)	0.978
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.985	(0.63, 1.55)	0.950	1.284	(0.73, 2.25)	0.381
Dose ≥ 1095 DDD	0.604	(0.36, 1.02)	0.061	0.616	(0.32, 1.17)	0.139
Female lung squamous cell carcinoma risk						
Total cumulative doses of ARB (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	1.100	(0.85, 1.42)	0.464	1.021	(0.75, 1.39)	0.897
Dose ≥ 1095 DDD	1.135	(0.90, 1.43)	0.280	1.096	(0.84, 1.43)	0.499
Total cumulative doses of ACEI (ref: < 365 DDD)						
365 DDD ≤ Dose < 1095 DDD	0.944	(0.71, 1.26)	0.692	1.062	(0.73, 1.54)	0.750
Dose ≥ 1095 DDD	0.817	(0.61, 1.09)	0.164	0.726	(0.50, 1.05)	0.087

All the aforementioned variables were used in the multivariate analysis. ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; OR, odds ratio; CI, confidence interval.