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Angiotensin Converting Enzyme Inhibitors and the Risk of Lung Cancer: population-based cohort study

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ABSTRACT

Objective: To determine whether the use of angiotensin converting enzyme inhibitors (ACEIs), when compared with use of angiotensin receptor blockers (ARBs), is associated with an increased risk of lung cancer.

Design: Population-based cohort study.

Setting: United Kingdom Clinical Practice Research Datalink.

Participants: A cohort of 992,061 patients newly-treated with antihypertensive drugs between January 1, 1995 and December 31, 2015 was identified and followed until December 31, 2016.

Main outcomes and measures: Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident lung cancer associated with the time-varying use of ACEIs, when compared with use of ARBs, overall, by cumulative duration of use, and by time since initiation.

Results: The cohort was followed for a mean of 6.4 years (standard deviation 4.7), generating 7952 incident lung cancer events (crude incidence 1.3 (95% CI 1.2 to 1.3) per 1000 person years). Overall, use of ACEIs was associated with an increased risk of lung cancer (incidence rate: 1.6 vs 1.2 per 1000 person-years; HR: 1.14, 95% CI: 1.01 to 1.29), when compared with use of ARBs. HRs gradually increased with longer durations of use, with an association evident after 5 years of use (HR, 1.22; 95% CI, 1.06 to 1.40) and peaking after more than 10 years of use (HR 1.31, 95% CI: 1.08 to 1.59). Similar findings were observed with time since initiation.

Conclusions: In this population-based cohort study, the use of ACEIs was associated with an increased risk of lung cancer. The association was particularly elevated among those using ACEIs for over 5 years. Additional studies, with long-term follow-up, are needed to investigate the effects of these drugs on lung cancer incidence.

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) are effective drugs used in the treatment of hypertension.[1] While these drugs have been shown to be relatively safe in the short-term, there have been concerns that their long-term use may be associated with an increased risk of cancer. These concerns have been subject to debate, with observational studies producing mixed findings,[2–4] including with respect to lung cancer.[2,4] Indeed, there is some biological evidence for a possible association between ACEIs and lung cancer risk. The use of ACEIs causes an accumulation of bradykinin in the lung,[5] which has been reported to stimulate growth of lung cancer.[5,6] Moreover, ACEI use also results in accumulation of substance P, which is expressed in lung cancer tissue and has been associated with tumour proliferation and angiogenesis.[7]

While meta-analyses of randomized controlled trials (RCTs) found no evidence of an increase in cancer incidence with ACEIs, most had relatively small sample sizes and short durations of follow-up (median 3.5 years).[8,9] To date, the few observational studies that have investigated the association between ACEI use and lung cancer reported mixed findings.[10–17] However, most of these studies were designed to assess the risk of cancer overall, and not lung cancer specifically.[10–16] Additionally, several of these studies had a number of methodological shortcomings, including short duration of follow-up (e.g., median of 0.7 years),[17] failure to account for cancer latency,[12,13,15,17] and immortal time bias.[15] Furthermore, results of some studies may have been influenced by the use of an inappropriate comparator group, introducing potential confounding by indication,[14] and the inclusion of prevalent users of antihypertensives.[15]

Thus, to address the conflicting and limited evidence from both pre-clinical and observational studies, we conducted a large, population-based study to determine whether the use of ACEIs, compared with use of angiotensin receptor blockers (ARBs), is associated with an increased risk of lung cancer.

METHODS

Data source

This study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The CPRD includes data from approximately 700 general practices comprising over 15 million patients; these have been shown to be representative of the UK population.[11] The CPRD records demographic information, anthropometric data (such as body mass index [BMI]), lifestyle information (such as smoking status and alcohol use), medical diagnoses and procedures (coded using the Read code classification[19]), and prescription data (coded according to the UK Prescription Pricing Authority Dictionary[20]) which have been shown to be valid and of high quality.[12,13] Furthermore, lung cancer diagnoses recorded in the CPRD have been shown to be highly concordant (>93%) with those recorded in the UK National Cancer Data Repository.[14]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 16_255R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study population

We identified a base cohort of all patients, at least 18 years of age, who were newly-prescribed an antihypertensive drug (including beta-adrenoceptor blockers, alpha-adrenoceptor blockers, ACEIs, ARBs, calcium channel blockers (CCBs), vasodilators, centrally-acting antihypertensives, diuretics, ganglion blockers, and renin inhibitors) between January 1, 1988 and December 31, 2015. All patients were required to have at least one year of medical history in the CPRD before their first-ever antihypertensive drug prescription. This was necessary to ensure

the inclusion of new-users of antihypertensive drugs, thus minimizing the possibility of prevalent user bias.[24]

From the base cohort defined above, we identified a study cohort of all patients who initiated a new antihypertensive drug class on or after January 1, 1995 (the first year where both ACEIs and ARBs were available in the UK) until December 31, 2015. These patients included those newly-treated with an antihypertensive drug class (i.e., first-ever antihypertensive prescriptions) as well as those who added-on or switched to an antihypertensive drug class not previously used in their treatment history. Cohort entry was defined as the date of this first prescription. Patients with a previous diagnosis of any cancer (other than non-melanoma skin cancer) or those who previously received cancer treatments (chemotherapy or radiotherapy) at any time before cohort entry were excluded. This was to ensure the identification of incident cases of lung cancer during follow-up, and to avoid the inclusion of patients with metastatic lesions to the lung from other cancer sites. Finally, patients with less than one year follow-up after cohort entry were excluded for latency considerations and to ensure the identification of incident events during follow-up.

All patients meeting the study inclusion criteria were followed up starting one year after cohort entry and until a diagnosis of incident lung cancer (identified on the basis of Read codes; **Supplementary Table 1**) or censored upon death from any cause, end of registration with the general practice, or the end of the study period (December 31, 2016), whichever occurred first.

Exposure assessment

We used a time-varying exposure definition where each person-day of follow-up was classified into one of three mutually-exclusive exposure categories: ACEIs (alone or in

combination with other antihypertensive drugs, but no previous use of ARBs), ARBs (alone or in combination with other non-ACEI antihypertensive drugs), and other antihypertensive drugs. The latter category also included patients who switched from an ACEI to an ARB, and vice versa; these may represent an atypical group where switching may have been motivated by side effects, such as cough in the case of ACEIs, which may in turn lead to increased lung cancer detection.[24] A one-year exposure lag period was introduced to account for a minimum latency time window and to minimize reverse causality. Thus, patients initiating an antihypertensive drug were considered unexposed until one year after the date of the first prescription and considered exposed thereafter. The reference category were ARBs, as these drugs are recommended at the same disease stage, thereby minimizing potential confounding by indication.[25]

Potential confounders

All models were adjusted for the following variables measured at cohort entry: age, sex, year of cohort entry, BMI (modelled as a continuous variable using a restricted cubic spline with five interior knots), smoking status (current, former, never), alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), and history of lung diseases (including pneumonia, tuberculosis, chronic obstructive pulmonary disease [COPD]); all measured at any time before cohort entry. In addition, models included duration of treated hypertension (defined as the time between first-ever prescription for an antihypertensive drug and cohort entry) and use of statins at any time before cohort entry. Finally, the models were adjusted for the total number of unique drug classes prescribed in the year before cohort entry, as a general measure of comorbidity.[26]

Statistical analyses

Crude incidence rates of lung cancer and 95% confidence intervals (CIs), based on the Poisson distribution, were calculated for each exposure group. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs of lung cancer associated with the use of ACEIs compared with the use of ARBs, using multiple imputation for variables with missing values. [27,28] Ordinal logistic regression and linear regression models were used to impute variables with missing information (for smoking and BMI, respectively) with explanatory variables and cumulative hazard (as recommended [29] and ACEI use at cohort entry), along with all confounders mentioned previously. Five imputations were conducted, and the results combined using Rubin's rules.[30]

Secondary analyses

We performed three secondary analyses. First, we assessed whether there was a duration-response relation between ACEI cumulative duration of use and lung cancer incidence. For this time-dependent analysis, HRs were estimated in a time-dependent manner for three predefined duration categories: ≤5 years, 5.1-10 years, and >10 years. Second, we also investigated the association between time since initiation of ACEIs and lung cancer risk, estimating HRs for three predefined categories: ≤5 years, 5.1-10 years, and >10 years. We also modelled cumulative duration of use and time since initiation as continuous variables, using restricted cubic spline models with five knots to produce a smooth curve of the HR as a function of duration.[31,32] To investigate possible effect modification by smoking status, we included an interaction term between the exposure and smoking status variables. Additionally, the primary and secondary analyses were repeated among non-smokers.

Sensitivity analyses

Three sensitivity analyses were conducted to assess the robustness of our findings. First, given uncertainties related to the length of the latency time window, we varied the length of the exposure lag period to two and three years. Second, as an alternate means to control for confounding, we repeated the analysis by stratifying the model on disease risk score deciles (**Supplementary Methods 1**).[33,34] Finally, we repeated the analysis using a marginal structural Cox proportional hazards model using inverse-probability-of-treatment and censoring weighting; a method designed to adjust for time-dependent confounding associated with time-varying exposures (**Supplementary Methods 2**).[35,36]

Ancillary analyses

We conducted two ancillary analyses to address the possibility that ARBs may be associated with a decreased risk of lung cancer incidence.[37] The first compared ACEIs with thiazide diuretics, as the latter have not been previously associated with lung cancer incidence. For this analysis, exposure was redefined hierarchically into four mutually-exclusive categories: ACEIs (alone or in combination with other antihypertensive drugs, but no previous use of thiazide diuretics or ARBs), thiazide diuretics (alone or in combination with other non-ACEI or non-ARB antihypertensive drugs), ARBs (alone or in combination with other non-ACEI or non-thiazide antihypertensive drugs), and other antihypertensive drugs. The second analysis compared ARBs to thiazide diuretics to assess whether the former are indeed associated with a decreased risk of lung cancer. For this analysis, exposure was redefined hierarchically as ARBs (alone or in combination with other antihypertensive drugs, but no previous use of thiazide diuretics or ACEIs), thiazide diuretics (alone or in combination with other non-ACEI or non-

ARB antihypertensive drugs), ACEIs (alone or in combination with other non-ARB or non-thiazide antihypertensive drugs), and other antihypertensive drugs. For both analyses, we assessed the association overall and by cumulative duration of use. All analyses were conducted with SAS version 9.4 (SAS institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

Patient and Public involvement

Our study was a secondary data analysis and did not include patients as study participants. No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results, nor will we disseminate results directly to patients, beyond our general media communications plan.

RESULTS

The cohort included 992,061 patients (**Figure 1**) followed for a mean (standard deviation) of 6.4 (4.7) years beyond the one-year post-cohort entry latency period. During the follow-up period, 335,135 patients were prescribed ACEIs, 29,008 ARBs, and 101,637 both ACEIs and ARBs. The three most commonly used ACEIs were ramipril (26%; 257,420 patients) lisinopril (12%; 120,641 patients) and perindopril (7%; 70,955 patients). Overall, 7952 patients were newly-diagnosed with lung cancer during 6,350,584 person-years of follow-up, generating a crude incidence rate of 1.3 (95% CI: 1.2 to 1.3) per 1000 person-years.

Table 1 presents baseline characteristics of the entire cohort, and by use of ACEIs, ARBs and other antihypertensive drugs at cohort entry. Compared with ARB users, ACEI users were more likely to be male, more likely to have alcohol-related disorders, to be current smokers, and to have a higher BMI. Additionally, ACEI users had a shorter duration of treated hypertension and were more likely to have used statins and other prescription drugs. Both ACEI and ARB users had a similar history of pneumonia, tuberculosis, and COPD.

The results from primary and secondary analyses are presented in **Table 2**. Compared with ARBs, ACEIs were associated with an overall 14% increased risk of lung cancer (1.6 vs 1.2 per 1000 person-years; HR, 1.14; 95% CI, 1.01 to 1.29). In secondary analyses, the use of ACEIs for less than 5 years was not associated with an increased risk of lung cancer (HR, 1.10; 95% CI, 0.96 to 1.25). However, the HR was elevated with 5 to 10 years of use (HR, 1.22; 95% CI, 1.06 to 1.40), and continued to increase with more than 10 years of use (HR, 1.31; 95% CI, 1.08 to 1.59). Similar associations were observed with time since ACEI initiation, with HRs increasing with longer times since initiation, peaking at >10 years since initiation (HR, 1.29; 95% CI, 1.10 to 1.51). Similar patterns were observed in analyses using restricted cubic splines

(**Supplementary Figures 1 & 2**). Smoking status did not significantly modify the association between ACEI use and lung cancer risk (p-interaction=0.40; **Supplementary Table 2**). Analyses conducted within non-smokers are presented in **Supplementary Table 3**. Overall, the results were consistent with those of the primary analyses, with the HR increasing with longer cumulative durations of use (> 10 years cumulative use HR, 1.64 95%CI, 1.02 to 2.64).

Sensitivity analyses

Results of sensitivity analyses are summarized in **Figure 2** and **Supplementary Tables 4-7.** Overall, these yielded consistent results, generating HRs ranging between 1.13 and 1.22. The latter estimate was from the marginal structural model that controlled for potential time-dependent confounding.

Ancillary analyses

Compared with the use of thiazide diuretics, the use of ACEIs was associated with a 6% increased risk of lung cancer (HR, 1.06; 95% CI, 1.00 to 1.13) (**Supplementary Table 8**). Similar to the main analysis, use of ACEIs for less than 5 years was not associated with an increased risk of lung cancer, while HRs were elevated with increasing use, peaking with more than 10 years of use (HR, 1.23; 95% CI, 1.04 to 1.44). Analysis comparing ARBs to thiazide diuretics revealed null associations overall (HR, 0.93; 95% CI, 0.82 to 1.06) and by cumulative duration of use (**Supplementary Table 9**).

DISCUSSION

In this large population-based study of nearly one million patients, the use of ACEIs was associated with an overall 14% increased risk of lung cancer. Associations were evident after 5 years of use and increased with longer durations of use, particularly among those who used ACEIs for more than 10 years (31% increased risk). While the magnitudes of the observed associations are modest, it is important to note that ACEIs are one of the most widely prescribed drug classes; in the UK 70.1 million antihypertensives are dispensed each year, of which approximately 32% are ACEIs.[38,39] Thus, small relative effects could translate into large absolute numbers of patients at risk for lung cancer. Given the potential impact of our findings, it is imperative that they are replicated in other settings, particularly among patients exposed for longer durations.

Comparison with previous studies

While meta-analyses of RCTs found no evidence of an association between the use of ACEI with cancer overall, or lung cancer specifically,[8,9] these RCTs were not powered or designed to assess these outcomes. Moreover, with relatively short durations of follow-up (median duration of 3.5 years; range between 1.3 to 5.1 years), these RCTs did not have the sufficient follow-up to assess long-term adverse events such as cancer.[8,9] This particularly important given that an association between ACEI use and lung cancer risk became evident after 5 years of use in our study. To our knowledge, while several observational studies reported on the association between ACEIs and lung cancer incidence,[10–16] only one study was specifically designed to investigate this association.[17] In this well-conducted study, the use of ACEIs was not associated with an increased risk of lung cancer (HR, 0.99; 95% CI, 0.84 to 1.16), when

compared with ARBs. However, as this study had a maximum follow-up of 5 years, its conclusion is not incompatible with our finding suggesting no association in the first 5 years of use (HR, 1.10; 95% CI, 0.96 to 1.25). While other observational studies investigated this association, their findings were part of secondary analyses and thus should be interpreted with caution. Overall, these studies produced mixed results, with some reporting increased risks,[10,11,16] others null associations,[12–14] and one study reporting a 66% decreased risk.[15] However, the latter study may have suffered from immortal time bias, which resulted from the misclassification of unexposed person-time as exposed person-time.[40] The other studies had other limitations, such as the inclusion of prevalent users of antihypertensive drugs,[15] confounding by indication,[14] and not accounting for cancer latency in their analyses.[13,15,17]

The association between ACEIs and lung cancer is biologically plausible. In addition to angiotensin I, ACE also metabolizes bradykinin, an active vasodilator.[41] Thus, the use of ACEIs results in the accumulation of bradykinin in the lung.[5] Bradykinin receptors have been located on various cancer tissues including lung cancer,[5,42] and it has been reported that bradykinin may directly stimulate growth of lung cancer.[5,6] Bradykinin has been shown to stimulate the release of vascular endothelial growth factor, thus promoting angiogenesis,[43,44] as well as indirect effects on lung cancer by enhancing vascular permeability, via the activation of MMP, facilitating tumour invasion and metastases.[44] Moreover, ACEI use also results in accumulation of substance P which is expressed in lung cancer tissue and is associated with tumour proliferation and angiogenesis.[7]

The results of this study also raise important questions regarding the new angiotensin-receptor/neprilysin inhibitor sacubitril/valsartan. Neprilysin inhibition results in increases in vasoactive and other peptides including bradykinin and substance P.[45] The recent PARADIGM-

HF trial reported clinical benefits for cardiovascular outcomes and death, however cancer events were not reported.[46] Therefore, it remains unknown whether these new renin-angiotensin system (RAS) inhibitors may also increase the risk of lung cancer in the long-term. Moreover, these results also raise questions regarding recent evidence suggesting that ACEIs may protect against radiation-induced pneumonitis in patients with lung cancer.[47] While limited studies have suggested improvements in survival in patients with lung cancer receiving renin-angiotensin system inhibitors and tyrosine kinase inhibitors or chemotherapy, the effect of ACEIs specifically on lung cancer progression remains uncertain.[48,49]

Strengths and Limitations

This study has several strengths. First, to our knowledge, with over 990,000 patients followed for an average of 6.4 years (beyond the one-year post-cohort entry lag period), this is the largest study to have been conducted to specifically assess this association. Second, we used a new-user design, thus minimizing biases related to the inclusion of prevalent users.[50] Third, we used a time-varying exposure definition that eliminated immortal time bias, while also accounting for cancer latency. Finally, the use of the CPRD allowed us to adjust the models for a number of potential important confounders, including smoking status, which was not available in some of the previous studies.[17]

This study has some limitations. First, while we were able to adjust for a number of important confounders, this study lacked information on other potential confounders such as socioeconomic status, diet, radon or asbestos exposure, and family history of lung cancer.[51,52] Additionally, despite adjusting for smoking status, we lacked detailed information on smoking duration and intensity which have been shown to be associated with lung cancer incidence.[51,52]

However, an analysis conducted within non-smokers revealed results consistent with those of the primary analyses; with a clear duration-response association, providing reassurance that residual confounding by smoking did not materially impact our findings. Second, prescriptions in the CPRD represent those written by general practitioners, and thus misclassification of exposure is possible if patients did not adhere to the treatment regimen or received prescriptions from specialists. However, since all patients entering the cohort were those newly-treated with antihypertensive drugs, misclassification due to non-adherence should be minimal and likely non-differential between ACEI and ARB users. Third, we compared ACEIs to ARBs, since the latter also act upon the RAS and are used at the same disease stage, but have not been associated with neuropeptide accumulation in the lung. However, it has been suggested that ARBs may also have an effect on lung cancer incidence,[53] including a meta-analysis of observational studies reporting a decreased risk with these drugs.[37] Studies included in this meta-analysis had a number of limitations, and several compared ARBs to ACEIs.[37] Thus, the apparent protective effect of ARBs may be the result of a deleterious effect of ACEIs on lung cancer incidence.[37] Nonetheless, our study was designed to address this possibility by comparing ACEIs to thiazide diuretics in ancillary analyses. Reassuringly, this analysis yielded consistent results, both in terms of overall association and by cumulative duration of use. Importantly, our analyses comparing ARBs to thiazide diuretics produced null associations for both overall and cumulative duration of use; this suggests that the observed increased risk with ACEIs is unlikely to be attributed to the purported antitumor effects of ARBs. Fourth, misclassification of the outcome is possible; however, lung cancer has been shown to be well recorded in the CPRD when compared with the UK National Cancer Data Repository (concordance rate of 93%).[23] Associations may also vary by lung cancer subtypes, but this information was not available within CPRD. Finally,

persistent cough is a common and well-known side effect of ACEIs, raising the possibility that the observed association could be due to detection bias. Indeed, it is possible that patients on ACEIs may be more likely to undergo diagnostic evaluations, such as computerized tomography of chest, leading to an increased detection of preclinical lung cancers. Information on chest workup is not well recorded in CPRD, and therefore it was not possible to account for this possibility in our analyses. However, a recent study found minimal evidence of differences in chest workup after ACEI and ARB initiation.[17] Moreover, an over-detection of lung cancer would be expected to be observed relatively soon after treatment initiation, which is one the reasons why our exposures were lagged by one year. Lengthening the exposure lag period to two and three year yielded consistent findings as those observed for the primary analysis. Furthermore, associations between ACEI use and lung cancer risk were evident only with increasing durations of use (at least after 5 years of use). Taken together, these results do not corroborate the hypothesis of an over-detection of lung cancer among ACEIs

Conclusions

In this large, population-based study, the use of ACEIs was associated with an elevated risk of lung cancer overall, along with evidence of a duration-response relation. While the magnitudes of the observed estimates are modest, these small relative effects could translate into large absolute numbers of patients at risk for lung cancer, and thus it is imperative that these findings are replicated in other settings.

What is already known on this subject

- Biological evidence suggests that angiotensin converting enzyme inhibitors may increase the risk of lung cancer via the accumulation of bradykinin and substance P in the lung.

- However, observational studies examining this association are limited and report inconsistent results.

What this study adds

- The use of angiotensin converting enzyme inhibitors was associated with a 14% increased risk of lung cancer.

- Associations were evident after 5 years of use and increased with longer durations of use, particularly among those who used ACEIs for more than 10 years.

- While the magnitudes of the observed estimates are modest, these small relative effects could translate into large absolute numbers of patients at risk for lung cancer, thus it is imperative that these findings are replicated in other settings.

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relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Details of Ethical Approval

The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 16_255R) and by the Research Ethics Board of Jewish General Hospital, Montreal, Quebec, Canada.

Data Sharing

No additional data available.

Transparency

The guarantor (LA) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explain.

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FIGURE LEGENDS

Figure 1   **Study flow diagram describing the construction of the base and study cohorts**

ARB indicates Angiotensin receptor blockers

Figure 2   **Forrest plot summarizing the results of the primary and sensitivity analyses**

assessing the association between ACEI use and lung cancer incidence.

HR indicates hazard ratio; CI , confidence interval

Table 1. Baseline Demographic and Clinical Characteristics of the Cohort and Stratified by Drug Use at Cohort Entry

Characteristic	Entire Cohort	Use at Cohort Entry		
		ACEIs	ARBs	Other Antihypertensives
Total	992,061	208,353 (21.0)	16,027 (1.6)	767,681 (77.4)
Age, years (mean, SD)	55.6 (16.6)	57.8 (13.1)	57.9 (13.2)	54.9 (17.5)
Male, n (%)	459,064 (46.3)	133,091 (63.9)	9591 (59.8)	316,382 (41.2)
Alcohol-related disorders, n (%)	71,605 (7.2)	18,199 (8.7)	1092 (6.8)	52,314 (6.8)
Smoking status, n (%)				
Current	215,098 (21.7)	41,595 (20.0)	2802 (17.5)	170,701 (22.2)
Past	227,504 (22.9)	58,683 (28.2)	3916 (24.4)	164,905 (21.5)
Never	484,831 (48.9)	99,820 (47.9)	8248 (51.5)	376,763 (49.1)
Unknown	64,628 (6.5)	8255 (4.0)	1061 (6.6)	55,312 (7.2)
Body mass index, n (%)				
< 25 kg/m^2	303,311 (30.6)	45,164 (21.7)	3602 (22.5)	254,545 (33.2)
25-30 kg/m^2	304,699 (30.7)	71,655 (34.4)	5447 (34.0)	227,597 (29.7)
≥30.0 kg/m^2	224,888 (22.7)	67,353 (32.3)	4724 (29.5)	152,811 (19.9)
Unknown	159,163 (16.0)	24,181 (11.6)	2254 (14.1)	132,728 (17.3)
Duration of treated hypertension, years (mean, SD)	0.2 (1.5)	0.3 (1.8)	0.5 (2.4)	0.2 (1.4)
Pneumonia, n (%)	22,403 (2.3)	5027 (2.4)	320 (2.0)	17,056 (2.2)
Tuberculosis, n (%)	2399 (0.2)	474 (0.2)	37 (0.2)	1888 (0.3)
Chronic obstructive pulmonary disease, n (%)	78,669 (7.9)	16,152 (7.8)	1180 (7.4)	61,337 (8.0)
Statins, n (%)	164,891 (16.6)	73,510 (35.3)	4092 (25.5)	87,289 (11.4)
Total number of unique drug classes, n (%)	4.1 (4.1)	4.1 (4.1)	3.8 (4.1)	4.2 (4.1)
0	150,293 (15.2)	35,384 (17.0)	3107 (19.4)	111,802 (14.6)
1	147,609 (14.9)	31,022 (14.9)	2603 (16.2)	113,984 (14.9)
2	135,085 (13.6)	27,027 (13.0)	2195 (13.7)	105,863 (13.8)
3	115,121 (11.6)	22,157 (10.6)	1740 (10.9)	91,224 (11.9)
≥4	443,953 (44.7)	92,763 (44.5)	6382 (39.8)	344,808 (44.9)

Abbreviations: SD, standard deviation ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers.

Table 2. Crude and Adjusted HRs for the Association Between the Use of ACEIs and the Risk of Lung Cancer

Exposure *	Events	Person-years	Incidence rate (95% CI) †	Crude HR	Adjusted HR (95% CI)‡
ARBs	266	213,557	1.2 (1.1 to 1.4)	1.00	1.00 [Reference]
ACEIs	3186	1,977,139	1.6 (1.6 to 1.7)	1.32	1.14 (1.01 to 1.29)
Cumulative duration of ACEI use (years)					
≤ 5	2084	1,440,232	1.4 (1.4 to 1.5)	1.24	1.10 (0.96 to 1.25)
5.1-10	905	457,309	2.0 (1.9 to 2.1)	1.44	1.22 (1.06 to 1.40)
> 10	197	79,598	2.5 (2.1 to 2.8)	1.63	1.31 (1.08 to 1.59)
					P for trend = <0.001
Time since first ACEI use (years)					
≤ 5	1617	1,158,441	1.4 (1.3 to 1.5)	1.24	1.11 (0.97 to 1.27)
5.1-10	1155	647,103	1.8 (1.7 to 1.9)	1.33	1.14 (0.99 to1.30)
> 10	414	171,596	2.4 (2.2 to 2.7)	1.62	1.29 (1.10 to 1.51)
					P for trend = <0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers
* Use of other antihypertensive drugs (including of use of both ACEI and ARBs) were considered in the model, but not presented in the table. These generated 4,500 lung cancer events and 4,159,887 person-years.
† Per 1000 Person-Years.
‡ Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders, history of lung diseases prior to cohort entry (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry