Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Use of ACE (Angiotensin-Converting Enzyme) Inhibitors and Risk of Lung Cancer

A Nationwide Nested Case-Control Study

Kasper Bruun Kristensen, MD
Blánaid Hicks, PhD
Laurent Azoulay, PhD
Anton Pottegård, PhD

BACKGROUND: Use of angiotensin-converting enzyme inhibitors (ACEIs) was associated with increased risk of lung cancer in a cohort study from the United Kingdom. We aimed to replicate these findings in a Danish population.

METHODS: We conducted a nested case-control study using data from 4 Danish national health and administrative registries. New users of ACEIs or angiotensin II receptor blockers in Denmark from January 1, 2000 were followed until December 31, 2015, incident lung cancer, death, or emigration. Each lung cancer case was matched with up to 20 controls on age, sex, duration of follow-up, and year of cohort entry using risk-set sampling. Conditional logistic regression was used to estimate odds ratios (ORs) for incident, histologically verified lung cancer with high use of ACEIs defined as a cumulative dose above 3650 defined daily doses. We examined different cumulative doses of ACEI (≤1800, 1801–3650, >3650 defined daily doses), examined whether the association varied with lung cancer histology, and repeated the analyses using thiazides as active comparator.

RESULTS: We included 9652 lung cancer cases matched to 190 055 controls. High use of ACEIs was associated with lung cancer (adjusted OR, 1.33 [95% CI, 1.08–1.62]). Lower cumulative doses showed neutral associations (≤1800 defined daily doses OR, 1.01 [95% CI, 0.94–1.09]; 1801–3650 defined daily doses OR, 1.03 [95% CI, 0.90–1.19]). CIs were wide and included the null when stratifying on histology. Using thiazides as active comparator yielded comparable results (OR, 1.34 [95% CI, 0.96–1.88]).

CONCLUSIONS: Use of high cumulative ACEI doses was associated with modestly increased odds of lung cancer although use of lower doses showed neutral associations. The established benefits of ACEIs should be considered when interpreting these findings.

Key Words: angiotensin-converting enzyme inhibitor ■ angiotensin receptor antagonists ■ lung neoplasms ■ pharmacoepidemiology ■ registries

https://www.ahajournals.org/journal/circoutcomes

WHAT IS KNOWN

- A recent study reported that use of ACE (angiotensin-converting enzyme) inhibitors (ACEIs) was associated with lung cancer (hazard ratio, 1.14 [95% CI, 1.01–1.29]) compared with angiotensin receptor blockers. The risk increased with increasing duration of use with a hazard ratio of 1.31 (95% CI, 1.08–1.59) for >10 years of ACEI use.
- Given the widespread use of ACEIs, it is important to replicate these findings in other populations.

WHAT THE STUDY ADDS

- We examined whether long-term use of ACEIs was associated with increased lung cancer risk in a nationwide Danish study.
- We found a modestly increased risk of lung cancer associated with use of high cumulative doses of ACEIs (odds ratio, 1.33 [95% CI, 1.08–1.62]). However, associations for lower doses of ACEIs were neutral.
- Further research is needed and a meta-analysis of data (published and unpublished) from randomized controlled trials assessing the risk of lung cancer with ACEI use is warranted.

ACE (angiotensin-converting enzyme) inhibitors (ACEIs) are widely used as first-line antihypertensive drugs, have been shown to improve survival in heart failure, and have renoprotective effects in patients with diabetes.[1] Recently, concerns that ACEIs increase the risk of lung cancer were raised in a cohort study that reported an increased risk of lung cancer associated with ACEIs compared with angiotensin receptor blockers (ARBs), particularly for 10 or more years of use (hazard ratio, 1.31 [95% CI, 1.08–1.59]).[2] There is biological evidence to support this finding, as use of ACEIs could promote lung cancer development through accumulation of bradykinin and substance P in lung tissue, both of which may play a role in carcinogenesis.[3,4] With the high prevalence of ACEI use, even a modest relative risk increase potentially translates into a large absolute number of patients at excess risk of lung cancer. Thus, there is a need for the findings of the recent cohort study of patients from the United Kingdom to be replicated in other settings, particularly among patients exposed to ACEIs for longer durations. We examined the association between ACEIs and lung cancer using the Danish health registries and further examined whether the association varied with lung cancer histology.

METHODS

We conducted a population-based, nationwide study to examine whether use of high cumulative ACEI doses was associated with an increased risk of lung cancer in a Danish setting. We used a nested case-control study design with a source population of new users of ACEIs or ARBs in Denmark during 2000 to 2015. In this population, we identified incident lung cancer cases and matched each case to up to 20 controls using risk-set sampling. Using conditional logistic regression, we obtained odds ratios (ORs) for lung cancer associated with ACEI use compared with ARB use.

Data Sources

We used individual level data from Danish civil and health registries. Vital status, date of birth, sex, and migration was obtained from the Danish Civil Registration System.[5] Information on drug use is recorded in the Danish National Prescription Registry with data on all prescriptions filled at community pharmacies in Denmark since 1995 including date of dispensing, anatomic therapeutic chemical code, pack size, and strength.[6] We identified incident lung cancers using the Danish National Cancer Registry.[7] The completeness of lung cancer diagnoses in the Danish Cancer Registry has been validated in 2006 with a sensitivity of 98%.[8] Comorbid conditions were identified using the Danish National Patient Registry with diagnoses from all inpatient contacts since 1978 and all emergency department and outpatient contacts since 1995.[9]

Because of the sensitive nature of the Danish administrative and health registry data, individual level data cannot be shared by the authors and is only accessible via the Danish Health Data Authority or Statistics Denmark. The statistical code is available upon request to the corresponding author.

Study Population

The source population was new users of ACEIs or ARBs in Denmark between 2000 and 2015. To ensure inclusion of new users only, patients who had filled a prescription for ACEIs or ARBs during 1995 to 1999 were not eligible. Cohort entry was defined as the date of the first prescription. We excluded individuals aged 18 years or below at cohort entry, individuals who migrated within 1 year before cohort entry and individuals with any history of cancer (except nonmelanoma skin cancer) before cohort entry (Figure 1).[10] Follow-up began at cohort entry and continued until censoring at the time of incident lung cancer, migration, death, or end of the study period (December 31, 2015). For latency considerations, only case patients with at least 1 year of follow-up between cohort entry and diagnosis of lung cancer were included. We used risk-set sampling to select controls from the same cohort of new users of ACEIs or ARBs. At the time of each case defining event, we sampled 20 controls from the cohort that were still at risk of lung cancer to each case. Controls were matched on age, sex, year of cohort entry, and duration of follow-up and were assigned an index date corresponding to the date of diagnosis of their case. The cumulative exposure assessment window began at cohort entry and continued until 1 year before the date of diagnosis for cases and their matched controls (ie, a 1-year lag period was applied).

We chose a nested case-control study design because of the long follow-up period and multiple time-varying exposure definitions, where the case-control analysis is computationally efficient and, with risk-set sampling, produces odds ratios that are unbiased estimators of the hazard ratios from the cohort study.[11]

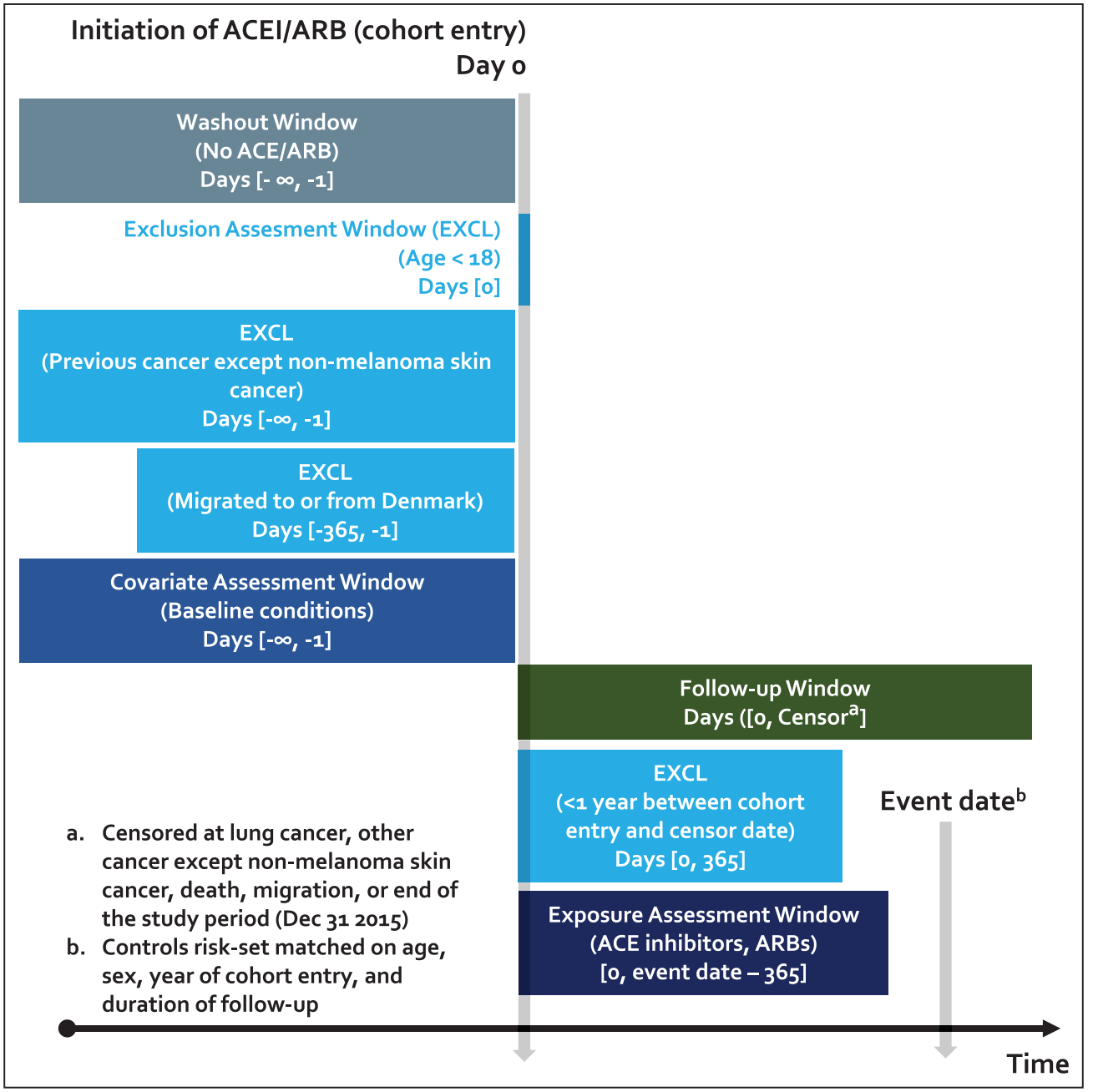

Figure 1. Study timeline.
ACEI indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and EXCL, exclusion criteria.

Exposure

We defined the main exposure of interest as use of a cumulative ACEI dose above 3650 defined daily doses (DDD). The DDD is a measure of the daily maintenance dose for a drug when used for its main indication in adults.[12] Under these assumptions, a cumulative dose of 3650 corresponds to ≈10 years of treatment. The main exposure was defined based on previous findings that long-term ACEI use was associated with increased lung cancer risk.[2] We classified cases and controls into the following mutually exclusive groups: use of ACEIs alone; use of ARBs alone; and use of both ACEIs and ARBs. We compared use of ACEIs alone with use of ARBs alone and allowed the reference category of ARBs alone to change with increasing ACEI dose, that is, a cumulative ACEI dose above 3650 DDDs was compared with a cumulative ARB dose above 3650 DDDs. Because recent drug use is unlikely to affect lung cancer risk and to minimize reverse causation (initiation of antihypertensive therapy may be associated with early symptoms of cancer),[13] we disregarded drug use in the year preceding the index date.

Outcome

The primary outcome was all histologically confirmed lung cancers. Furthermore, we examined individual types of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, other nonsmall cell carcinomas) based

on morphology codes from the International Classification of Diseases for Oncology version 3 (Methods in the Data Supplement).[14]

Potential Confounders

All covariates were measured before cohort entry to avoid adjusting for on-treatment covariates. We adjusted for age, sex, year of cohort entry, and follow-up duration by design. In adjusted models, we included the following covariates defined by ambulatory or discharge diagnoses and/or 2 or more filled drug prescriptions: alcohol related disorders, lung diseases (pneumonia, tuberculosis, chronic obstructive lung disease); use of statins, total number of filled prescriptions for unique drug classes the year before cohort entry as a measure of comorbidity and highest achieved education as a proxy of socioeconomic status (Methods in the Data Supplement).

Statistical Analyses

We calculated ORs for lung cancer associated with high use of ACEIs compared with high use of ARBs using conditional logistic regression. To examine dose-response, we categorized ACEI dose (≤1800, 1801–3650, 3651 and above DDDs) and used the corresponding cumulative ARB dose as reference in conditional logistic regression models. Additionally, we modeled cumulative dose as a continuous variable using restricted cubic splines with 3 knots located at the 10th, 50th, and 90th percentile.[15] We further included duration of use as a continuous variable in a linear unconditional logistic regression model restricted to ever-users of ACEIs where the matching variables age, sex, calendar time, and year of first ACEI/ARB prescription were included as covariates.

We evaluated the potential for effect measure heterogeneity or effect measure modification from sex, age, a diagnosis of heart failure, ischemic heart disease, or diabetes before initiation of ACEI/ARB therapy and clinical stage by including these as interaction terms in the adjusted model. To test for effect heterogeneity or effect measure modification, we conducted likelihood ratio tests of the model without interaction terms nested in the model with interaction terms.

We calculated E-values to quantify the minimum strength of association between an unmeasured confounder such as smoking and the exposure/outcome for unmeasured confounding to explain away the main result.[16]

Sensitivity and Supplementary Analyses

To examine whether reverse causation could influence the results, we varied the lag period from 0 to 4 years in sensitivity analyses. In an additional sensitivity analysis, we used ever use of ARBs as the reference category for all cumulative dose categories of ACEI, corresponding to the analysis in the study we aimed to replicate.[2]

To account for patients who used both ACEI and ARBs during the study period, we allowed for switching between these drugs by including moderate users (cumulative dose below 365 defined daily doses) of ARBs in the ACEI group and vice versa. In the primary analysis, covariates were measured before cohort entry. In supplementary analyses, we allowed the covariates to change during follow-up by measuring covariates in a time-dependent manner until 1 year before the index date. Last, to examine the robustness of our findings with regard to the choice of active comparator, we repeated the study with thiazides as active comparator instead of ARBs. To this end, we identified cases and sampled controls from a source population of new users of ACEIs or thiazides from 2000 onward using a washout period of 1995 to 1999 with the same analytic methods as in the main analyses with ARBs as active comparator.

RESULTS

We identified 14872 new users of ACEIs/ARBs diagnosed with lung cancer during 2000 to 2015. Of these, 9652 cases were eligible for study inclusion and matched to 190055 controls (Figure 2). The mean age (SD) of cases was 71 (9) years and 55% were male (Table 1). The mean duration (SD) of follow-up from cohort entry to lung cancer diagnosis was 5.6 (3.2) years. The dominant type of lung cancer was adenocarcinoma (42%), followed by squamous cell carcinoma (24%), other nonsmall cell carcinoma (17%), and small cell carcinoma (17%). Most patients (52%) presented with metastatic disease (TNM stage IV) at time of diagnosis. Among cases, 915 (9.5%) were high users of ACEIs with no use of ARBs and 151 (1.6%) were high users of ARBs with no use of ACEIs.

High use of ACEIs was associated with a 33% increased risk of lung cancer (adjusted OR, 1.33 [95% CI, 1.08 to 1.62]; Table 2). This association was not observed with cumulative doses between 1 and 1800 and 1801 and 3650 DDDs (OR, 1.01 [95% CI, 0.94–1.09] and 1.03 [95% CI, 0.90–1.19], respectively). When including cumulative dose of ACEI as a continuous variable using restricted cubic splines, the increased risk was apparent with ACEI doses above ≈4000 DDDs and continued to increase hereafter (Figure 3). When cumulative dose was included as a continuous variable in a linear logistic regression model, the risk increased with increasing dose (P<0.001). Small cell carcinomas, other nonsmall cell carcinomas, and squamous cell carcinomas showed the strongest association with ORs of 1.54 (95% CI, 0.90–2.62), 1.48 (95% CI, 0.85–2.59), and 1.45 (95% CI, 0.96–2.19), respectively (Table 2). The ORs were closer to unity for adenocarcinomas of the lung (OR, 1.15 [95% CI, 0.86–1.55]). However, in these subgroup analyses, the number of events were small and the CIs were wide, precluding evaluation of effect heterogeneity by lung cancer type. There was no evidence of effect measure modification by sex, age, heart failure, ischemic heart disease, diabetes, or clinical stage (Table 3).

When varying the lag period, the OR was 1.19 (95% CI, 1.00–1.42) for no lag period and increased to 1.37 (95% CI, 1.07–1.74) applying a 2-year lag period (Figure 4). Increasing the lag period to 3 and 4 years yielded similar point estimates but with less precision, for

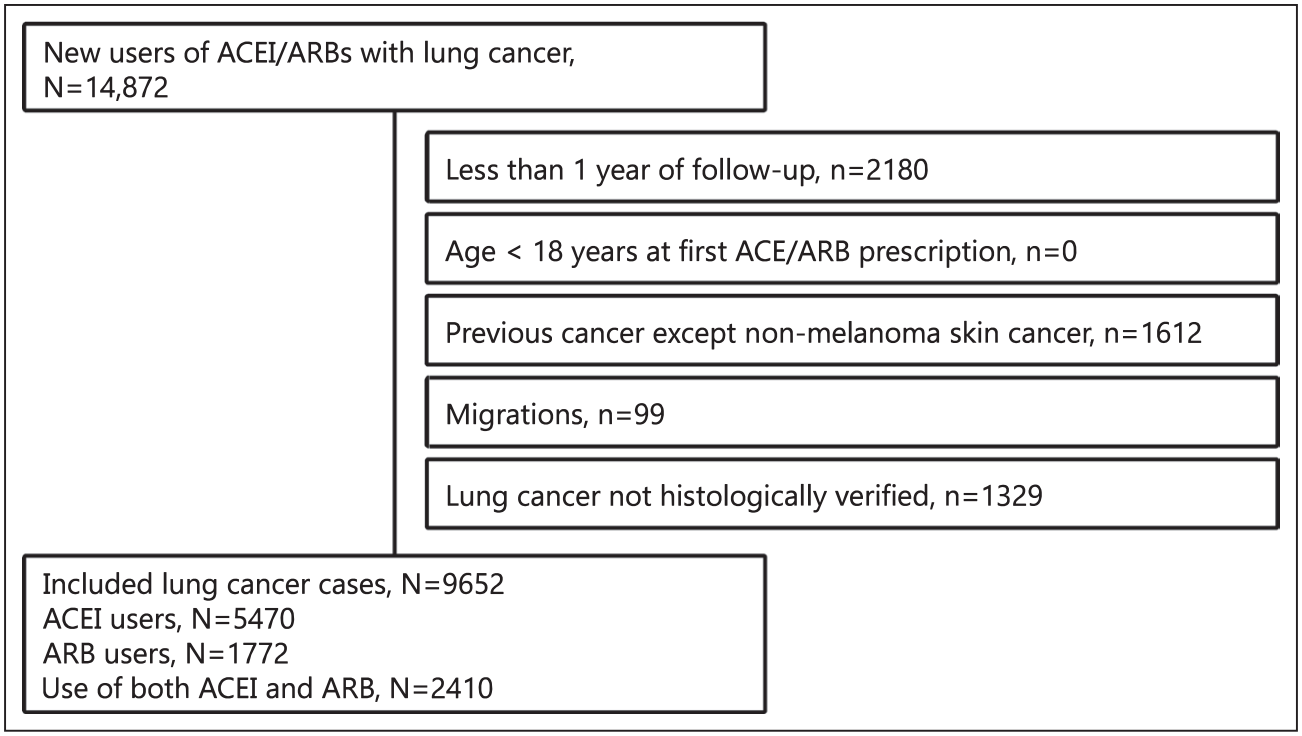

Figure 2. Flowchart of selection of cases.
ACE indicates angiotensin-converting enzyme; ACEI, ACE inhibitor; and ARB, angiotensin receptor blocker.

example, the OR for a 4-year lag period was 1.23 (95% CI, 0.86–1.75).

With ever-use of ARBs as reference throughout all categories of cumulative ACEI doses, the ORs were comparable to the main analyses (Figure 4, Table I in the Data Supplement).

Allowing for switching between ACEIs and ARBs did not change the observed association with high use of ACEIs and lung cancer considerably (OR, 1.24 [95% CI, 1.06–1.45]; Figure 4, Tables II and III in the Data Supplement).

The analyses where the included covariates were measured in a time-dependent manner during follow-up did not change the main results with an OR of 1.28 (95% CI, 1.04–1.57) for high use of ACEI and 1.02 (95% CI, 0.96–1.08) for ever-use of ACEIs.

When repeating the study with thiazides as active comparator, the study population consisted of 11 091 cases that were matched to 219 295 controls (Figure I in the Data Supplement, Table IV in the Data Supplement). The adjusted OR for high use of ACEIs compared with high use of thiazides was 1.34 (95% CI, 0.96–1.88). When stratifying by lung cancer histology, the association was most marked for adenocarcinomas 1.72 (95% CI, 1.00–2.94) while the OR for small cell carcinoma was close to unity (OR, 0.97 [95% CI, 0.43–2.15]; Table V in the Data Supplement).

The E-value, that is, the minimum strength of association on the risk ratio scale required for an unmeasured confounder associated with the exposure as well as the outcome to explain away the association, was 1.99 (Figure 5).

DISCUSSION

We examined whether high use of ACEIs was associated with increased risk of lung cancer and whether the association varied with lung cancer histology. Use of a high cumulative ACEI dose was associated with a 33% increased risk of lung cancer. The increased risk was confined to high cumulative doses of ACEIs and not apparent with doses below ≈3650 DDDs. We did not observe strong evidence that the increased risk was linked to a specific histological type of lung cancer.

Our main findings are compatible with the findings of the study we aimed to replicate, where a hazard ratio of 1.31 (95% CI, 1.08–1.59) for more than 10 years of ACEI use was reported.[2] However, while we found no associations with ever-use and lower cumulative doses, the previous study reported a HR of 1.14 (95% CI, 1.01–1.29) for ever-use of ACEIs. We included 915 lung cancer patients with exposure to high cumulative ACEI doses compared with 197 exposed lung cancer patients in the UK study. As the previous study, we had a long follow-up, included only new users of ACEIs or ARBs minimizing the risk of prevalent user bias, and used an active comparator to minimize confounding by indication. Further, applying a risk-set sampling scheme avoided time-window biases and allowed for time-varying exposure. Previous observational studies have produced

Table 1. Characteristics of Lung Cancer Cases and Matched Controls

Patient characteristic*	Cases (n=9652)	Controls		
		All controls (n=190 055)	ACEI exposed† (n=104 860)	ARB exposed‡ (n=36 474)
Basic characteristics				
Male, n (%)	5341 (55.3%)	105 059 (55.3%)	61 683 (58.8%)	18 723 (51.3%)
Female, n (%)	4311 (44.7%)	84 996 (44.7%)	43 177 (41.2%)	17 751 (48.7%)
Age, mean (SD), y	71.2 (8.6)	71.4 (8.2)	71.4 (8.3)	70.7 (8.4)
Follow-up, mean (SD), y	5.6 (3.2)	5.6 (3.2)	5.1 (3.0)	5.2 (3.2)
Lung cancer histology, n (%)				
Adenocarcinoma	4048 (41.9%)	…	…	…
Squamous cell carcinoma	2321 (24.0%)	…	…	…
Small cell carcinoma	1637 (17.0%)	…	…	…
Other nonsmall cell carcinoma	1646 (17.1%)	…	…	…
Clinical stage of lung cancer, n (%)				
Stage IA-IIB	1923 (19.9%)	…	…	…
Stage III	2138 (22.2%)	…	…	…
Stage IV	4987 (51.7%)	…	…	…
Unknown	604 (6.3%)	…	…	…
Use of other antihypertensive drugs, n (%)§				
Alpha blockers	102 (1.1%)	2241 (1.2%)	1265 (1.2%)	481 (1.3%)
β blockers	2413 (25.0%)	45 093 (23.7%)	24 243 (23.1%)	8892 (24.4%)
Calcium channel blockers	1580 (16.4%)	29 966 (15.8%)	15 337 (14.6%)	6575 (18.0%)
Centrally acting antihypertensives	24 (0.2%)	470 (0.2%)	210 (0.2%)	121 (0.3%)
Thiazides	2621 (27.2%)	54 687 (28.8%)	29 263 (27.9%)	10 410 (28.5%)
Renin inhibitors	(n<5)	23 (0.0%)	8 (0.0%)	14 (0.0%)
No. of unique drug classes used, n (%)§				
0	1160 (12.0%)	26 224 (13.8%)	15 284 (14.6%)	4639 (12.7%)
1	1016 (10.5%)	24 564 (12.9%)	13 918 (13.3%)	4704 (12.9%)
2	1072 (11.1%)	24 921 (13.1%)	13 938 (13.3%)	4656 (12.8%)
3	1036 (10.7%)	23 321 (12.3%)	12 859 (12.3%)	4474 (12.3%)
≥4	5368 (55.6%)	91 025 (47.9%)	48 861 (46.6%)	18 001 (49.4%)
Medical history, n (%)§				
Lung diseases (COPD, pneumonia, tuberculosis)	1702 (17.6%)	16 915 (8.9%)	10 216 (9.7%)	2836 (7.8%)
Alcohol-related conditions	657 (6.8%)	6401 (3.4%)	3971 (3.8%)	1047 (2.9%)
Statin use	1914 (19.8%)	32 880 (17.3%)	19 078 (18.2%)	5753 (15.8%)
Education, n (%)				
Short	4772 (49.4%)	79 924 (42.1%)	45 801 (43.7%)	14 130 (38.7%)
Medium	3463 (35.9%)	69 843 (36.7%)	38 024 (36.3%)	13 431 (36.8%)
Long	1025 (10.6%)	31 772 (16.7%)	16 171 (15.4%)	7238 (19.8%)
Unknown	392 (4.1%)	8516 (4.5%)	4864 (4.6%)	1675 (4.6%)

ACE indicates angiotensin-converting enzyme; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; and COPD, chronic obstructive pulmonary disease.

*Characteristics were measured at the time of diagnosis or sampling (index date) unless mentioned otherwise.

†Exposed controls defined as ever-users of ACEIs with no use of ARBs.

‡Unexposed controls defined as ever-users of ARBs with no use of ACEIs.

§Measured before cohort entry, that is, initiation of ACEIs or ARBs.

conflicting findings with increased[17–19] as well as neutral risks[20–23] for ACEIs associated with lung cancer. Of these studies, only one was designed specifically to assess the association with ACEIs and lung cancer and reported a neutral association. This study had a maximum follow-up of 5 years, thus the lack of an association reported

Table 2. ORs for Lung Cancer Associated With Use of ACEIs Compared With ARBs

	Cases exposed to ACEI/ARB	Controls exposed to ACEI/ARB	Unadjusted OR*	Adjusted OR†
Lung cancer overall				
Ever use of ACEI	5470/1772	104 860/36 474	1.08 (1.02–1.15)	1.04 (0.98–1.10)
High use of ACEI (>3650 DDD)‡	915/151	16 110/3446	1.37 (1.12–1.68)	1.33 (1.08–1.62)
Cumulative dose of ACEI (DDD)				
≤1800	3500/1224	67 823/24 813	1.06 (0.98–1.13)	1.01 (0.94–1.09)
1801–3650	1055/397	20 931/8215	1.06 (0.92–1.22)	1.03 (0.90–1.19)
3651-	915/151	16 106/3446	1.37 (1.12–1.68)	1.33 (1.08–1.62)
Test for trend	5470	104 860	*P*<0.001	*P*<0.001
Adenocarcinoma				
Ever use of ACEI	2225/777	43 334/15 141	1.00 (0.92–1.10)	0.97 (0.89–1.06)
High use of ACEI (>3650 DDD)‡	388/74	6946/1517	1.19 (0.89–1.59)	1.15 (0.86–1.55)
Cumulative dose of ACEI (DDD)				
≤1800	1390/518	27 589/10 143	0.98 (0.88–1.10)	0.95 (0.85–1.06)
1801–3650	447/185	8799/3481	0.98 (0.80–1.20)	0.94 (0.76–1.16)
3651	388/74	6946/1517	1.19 (0.89–1.59)	1.15 (0.86–1.55)
Test for trend	2225	43 334	*P* value: 0.19	*P* value: 0.22
Squamous cell carcinoma				
Ever use of ACEI	1351/394	25 633/8413	1.14 (1.01–1.29)	1.08 (0.96–1.22)
High use of ACEI (>3650 DDD)‡	244/37	4171/873	1.57 (1.05–2.35)	1.45 (0.96–2.19)
Cumulative dose of ACEI (DDD)				
≤1800	836/274	16 188/5548	1.06 (0.92–1.23)	1.00 (0.86–1.16)
1801–3650	271/83	5276/1992	1.15 (0.86–1.53)	1.13 (0.84–1.52)
3651-	244/37	4169/873	1.57 (1.05–2.35)	1.45 (0.96–2.19)
Test for trend	1351	25 633	*P* value: 0.025	*P* value: 0.014
Small cell carcinoma				
Ever use of ACEI	949/287	17 866/6328	1.19 (1.04–1.37)	1.14 (0.99–1.32)
High use of ACEI (>3650 DDD)‡	145/20	2540/516	1.58 (0.94–2.65)	1.54 (0.90–2.62)
Cumulative dose of ACEI (DDD)				
≤1800	631/199	11 910/4393	1.22 (1.02–1.45)	1.18 (0.99–1.40)
1801–3650	173/68	3417/1419	1.15 (0.82–1.62)	1.08 (0.76–1.53)
3651-	145/20	2539/516	1.58 (0.94–2.65)	1.54 (0.90–2.62)
Test for trend	949	17 866	*P* value: 0.15	*P* value: 0.18
Other nonsmall cell carcinoma				
Ever use of ACEI	945/314	18 027/6592	1.10 (0.96–1.26)	1.06 (0.92–1.21)
High use of ACEI (>3650 DDD)‡	138/20	2453/540	1.47 (0.85–2.53)	1.48 (0.85–2.59)
Cumulative dose of ACEI (DDD)				
≤1800	643/233	12 136/4729	1.08 (0.92–1.27)	1.05 (0.89–1.24)
1801–3650	164/61	3439/1323	1.10 (0.77–1.56)	1.11 (0.77–1.59)
3651-	138/20	2452/540	1.47 (0.85–2.53)	1.48 (0.85–2.59)
Test for trend	945	18 027	*P* value: 0.058	*P* value: 0.062

ACE indicates angiotensin-converting enzyme; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; DDD, defined daily dose; and OR, odds ratio.

*Adjusted for age, sex, calendar time, year of initiation of ACEI/ARB and follow-up duration by design (matching)

†Adjusted for alcohol related conditions, lung diseases (pneumonia, tuberculosis, chronic obstructive lung disease), use of statins, total number of filled prescriptions for unique drug classes the year before cohort entry, and the highest achieved education.

‡High use of ACEIs was the predefined main exposure of interest.

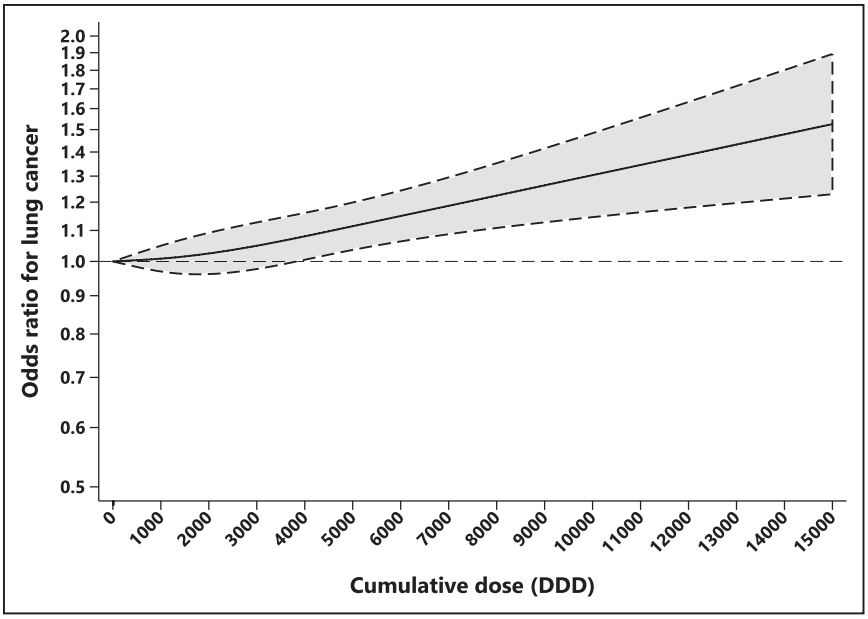

Figure 3. Association between cumulative dose of ACE (angiotensin-converting enzyme) inhibitors in defined daily doses (DDD) and lung cancer.

in that study is not incompatible with our findings of no association with low cumulative doses.[23] Evidence from randomized controlled trials (RCTs) is sparse. Two meta-analyses have assessed whether ACEIs increase overall cancer risk and reported neutral risk ratios of 1.01 (95% CI, 0.95–1.07)[24] and 1.00 (95% CI, 0.92–1.09).[25] Of note, the mean follow-up for the included RCTs was 3.5 years. To our knowledge, there is currently no published meta-analyses of RCTs regarding the risk of lung cancer specifically. Although the limited follow-up and relatively small sample size of RCTs render it difficult to detect rare events presenting with long latency, a meta-analysis of RCT data on ACEIs and lung cancer is warranted considering the available observational evidence.

There is a biologic rationale that ACEIs could promote development of lung cancer. Inhibition of the ACE results in accumulation of bradykinin in the lung.[26] Bradykinin receptors are present in human lung cancer tissue[3,27] and may stimulate growth of lung cancer through release of vascular endothelial growth factor promoting angiogenesis and activation of matrix metalloproteinases.[28,29] Further, ACEIs result in accumulation of substance P associated with tumor proliferation and angiogenesis.[4] Both ARBs and ACEIs act on the renin-angiotensin-aldosterone system; however, unlike ACEIs, ARBs do not cause accumulation of bradykinin in lung tissue. Other biological studies show that the ACEI captopril inhibited tumor growth and metastasis in mice[30]; thus, the biological evidence is conflicting with regard to the potential carcinogenic effect of ACEIs on lung cancer.

In the present study, the OR was the highest for small cell carcinomas; however, the CIs were wide when stratifying by lung cancer type and when using thiazides as active comparator, the ORs for small cell carcinoma associated with ACEIs were close to unity. Further, we are not aware of biological mechanisms that would explain an increased risk of small cell carcinomas in favor of other lung cancer types. Rather, bradykinin receptors are expressed in both small cell carcinoma and nonsmall cell carcinomas of the lung.[27]

We were not able to adjust for smoking and BMI. Thus, residual confounding is possible, however, substantial imbalance in the prevalence of smoking between users of ACEIs and ARBs is not likely. For example, there was little difference in the prevalence of smokers between ACEI users (48%) and ARB users (42%) in the study we replicated.[2] Assuming that the prevalence of smoking is distributed similarly in the Danish population (corresponding to a relative risk of 1.14 for smoking associated with ACEI use compared with ARBs) smoking alone would not be able to explain away the association entirely even with implausibly strong associations between lung cancer and smoking.[31] The E-value can be used to assess whether confounding by, for example, smoking may explain the observed association. To fully explain the observed OR of 1.33, a confounder would have to be associated with both ACEI use and with lung cancer, each by a risk ratio of 1.99 or more, in addition to the confounders we were able to measure and adjust for. Other possible confounders include diet, radon exposure, and family history of lung cancer. Considering the modest relative risk increase from our main analyses, we acknowledge that residual confounding and potentially several confounders acting together to explain the observed association is difficult to rule out with confidence.

ACEIs commonly cause dry cough that may lead to increased diagnostic workup and increased likelihood of detection of lung cancer. If detection bias were to explain our findings, we would expect that the association would be strongest with no lag period and disappear with

Table 3. ORs for Lung Cancer Associated With High Use of ACE Compared With High Use of ARBs by Patient Characteristics

Subgroup	Cases exposed to ACEI/ARB	Controls exposed to ACEI/ARB	Unadjusted OR*	Adjusted OR†	*P* value‡
Sex					0.59
Male	571/73	10 392/1802	1.44 (1.10–1.90)	1.40 (1.06–1.84)	
Female	344/78	5718/1644	1.29 (0.96–1.73)	1.25 (0.93–1.68)	
Age					0.94
<65 y	151/22	2543/479	1.29 (0.75–2.21)	1.21 (0.70–2.10)	
65–75 y	438/64	7719/1624	1.39 (1.02–1.89)	1.36 (0.99–1.85)	
≥75 y	326/65	5848/1343	1.38 (1.02–1.87)	1.34 (0.99–1.81)	
Medical history					
No heart failure	815/148	14 684/3402	1.36 (1.11–1.66)	1.32 (1.08–1.63)	0.33
No ischemic heart disease	688/135	12 754/3175	1.33 (1.08–1.65)	1.28 (1.03–1.59)	0.96
No diabetes	770/134	13 373/3058	1.39 (1.12–1.72)	1.34 (1.08–1.67)	0.86
Clinical stage					0.65
Stage IA-IIB	203/34	3542/791	1.39 (0.91–2.12)	1.35 (0.88–2.07)	
Stage III	200/42	3646/791	1.14 (0.76–1.69)	1.08 (0.72–1.62)	
Stage IV	474/72	8351/1750	1.46 (1.10–1.94)	1.42 (1.06–1.89)	
Unknown	38/(n<5)	571/114	(…)	(…)	

ACE indicates angiotensin-converting enzyme; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; and OR, odds ratio.
*Adjusted for age, sex, calendar time, year of initiation of ACEI/ARB and follow-up duration by design (matching).
†Adjusted for alcohol-related conditions, lung diseases (pneumonia, tuberculosis, chronic obstructive lung disease), use of statins, total number of filled prescriptions for unique drug classes the year before cohort entry, and the highest achieved education.
‡*P* value from a likelihood ratio test of the model without interaction terms nested in the model with interaction terms corresponding to the subgroup of interest.

increasing lag periods. Further, a previous study reported that initiators of ACEIs had slightly more chest X-rays taken compared with ARB initiators during the first 6 months after initiation but found no evidence of differential workup with regards to computed tomography scans, magnetic resonance imagings, or bronchoscopies.[23]

The lag time analyses showed slightly attenuated associations when no-lag time was applied, while the point estimates were robust when the lag-time was increased to 3 and 4 years. This finding could be due to random error given the width of the CIs or could indicate that recent use is not likely to affect cancer risk and inclusion of such exposure will dilute the obtained effect estimates. Identification of lung cancer cases was based on the Danish Cancer Registry with a high sensitivity in capturing lung cancer diagnoses. The specificity with regards to lung cancer has not been reported. However, the Danish Cancer Registry requires histological verification of all reported cancers and has complete and accurate data in general.[7]

We chose ARBs as active comparator as this drug class to some extent have the same indications as ACEIs. In Denmark, the first ACE inhibitor, captopril, was introduced in 1982 and the first ARB, losartan, was introduced in 1995. The uptake of ARBs happened gradually and was initially recommended only for patients with side effects to other antihypertensives or treatment resistant hypertension.[32] ARBs were increasingly recommended as first-line agents along with ACEIs from 2004 and onward.[33] Prices of ARBs in Denmark dropped significantly in 2008 where generic competition was introduced. Thus, there may be unmeasured factors, especially early in the study period, which channeled patients toward either ACEIs or ARBs. We adjusted for

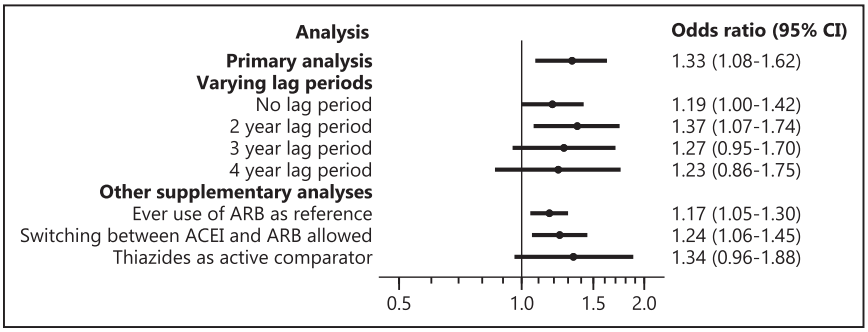

Figure 4. Association between use of high cumulative doses of ACE (angiotensin-converting enzyme) inhibitors (ACEIs) and risk of lung cancer in supplementary analyses.
ARB indicates angiotensin receptor blocker.

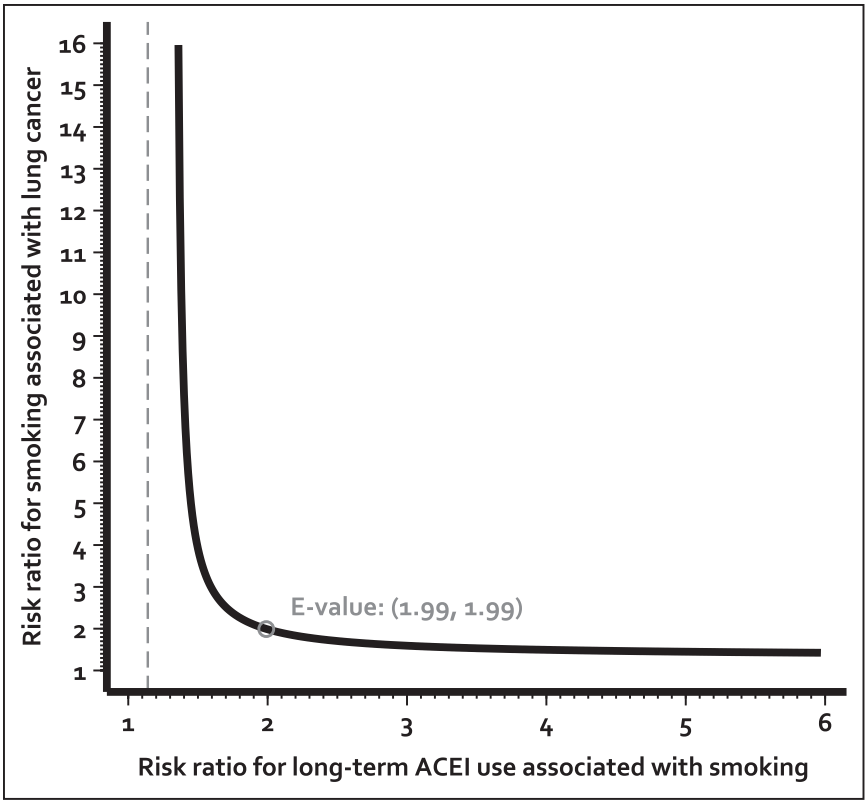

Figure 5. Joint values of the minimum strength of association between smoking and ACE (angiotensin-converting enzyme) inhibitors (ACEIs) and smoking and lung cancer to fully explain away the observed point estimate of 1.33.
The dashed vertical line indicates the expected imbalance between smokers and nonsmokers for ACEI users compared with angiotensin receptor blocker (ARB) users.

the highest achieved education as a proxy for socioeconomic status and during the entire study period, both ACEIs and ARBs were eligible for reimbursement with a maximal self-payment of medicine costs of ≈600 USD each year. Further, the fact that we observed similar point estimates using thiazides as active comparator speaks against these potential confounding factors as having influenced the results. Thiazides are low-priced, were available in Denmark before ACEIs, and are also first-line agents for treatment of hypertension.

A potential issue with ARBs as an active comparator is that their association with lung cancer is unclear. Two meta-analyses of RCTs reported an ≈25% increased risk of lung cancer in patients assigned to ARBs compared with placebo or other antihypertensives.[24,34] However, another meta-analysis of 15 RCTs did not report an increased risk of lung cancer with ARBs reporting a risk ratio of 1.01 (0.90–1.14).[35] In July 2018, it was reported that some valsartan products were contaminated with the carcinogenic substance N-nitrosodimethylamine from 2012 and onward. This is unlikely to have influenced on our findings, as valsartan has a small market share compared with other ARBs in Denmark,[36] and since no associations with lung cancer was found in a Danish cohort study comparing users of contaminated valsartan to uncontaminated valsartan.[37]

In conclusion, this study adds to the evidence of an association between use of high cumulative doses of ACEIs and modestly increased risk of lung cancer. Given the small effect sizes, bias from confounding is difficult to rule out with certainty. Thus, these findings need further replication and a meta-analysis of RCTs to evaluate risk of lung cancer with long-term ACEI use would be important. Further, the long-established benefits of ACEI therapy should be considered when interpreting these findings.

ARTICLE INFORMATION

Received March 12, 2020; accepted October 23, 2020.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCOUTCOMES.120.006687.

Correspondence

Kasper Bruun Kristensen, MD, Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, J.B. Winsløwsvej 19, 2, 5000, Odense C, Denmark. Email kaskristensen@health.sdu.dk

Affiliations

Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Denmark (K.B.K., A.P.). Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, United Kingdom (B.H.). Department of Epidemiology, Biostatistics and Occupational Health, Gerald Bronfman Department of Oncology, McGill University and Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada (L.A.).

Acknowledgments

Dr Azoulay holds a Chercheur-Boursier Senior Award from the Fonds de la Recherche du Québec—Santé and is the recipient of a William Dawson Scholar Award from McGill University. Dr Hicks hold a Cancer Research UK Population Research Postdoctoral Fellowship and a Vice Chancellor's Fellowship from Queen's University Belfast. Ethical approval: according to Danish law, studies based solely on anonymized registry data do not require ethical approval.

Sources of Funding

This work was supported by a grant from Independent Research Fund Denmark (grant 8020-00176B) and the Research Fund of the Region of Southern Denmark (grant 17/33580) to Dr Kristensen. The funding sources had no influence on the study design; on the collection, analysis and interpretation of data; or on the writing of the report; and the decision to submit the article for publication

Disclosures

Dr Azoulay served as a consultant for Janssen and Pfizer for work unrelated to this study. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Supplemental Figure I
Supplemental Tables I–V

REFERENCES

1. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? *J Am Coll Cardiol*. 2018;71:1474–1482. doi: 10.1016/j.jacc.2018.01.058
2. Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. *BMJ*. 2018;363:k4209. doi: 10.1136/bmj.k4209
3. Golias Ch, Charalabopoulos A, Stagikas D, Charalabopoulos K, Batistatou A. The kinin system–bradykinin: biological effects and clinical implications. Multiple role of the kinin system–bradykinin. *Hippokratia*. 2007;11:124–128.
4. Muñoz M, Coveñas R. Involvement of substance P and the NK-1 receptor in human pathology. *Amino Acids*. 2014;46:1727–1750. doi: 10.1007/s00726-014-1736-9
5. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi: 10.1007/s10654-014-9930-3
6. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46:798–798f. doi: 10.1093/ije/dyw213
7. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health*. 2011;39(7 Suppl):42–45. doi: 10.1177/1403494810393562
8. Friis S, Jørgensen T, Mellemkjær L, Olsen JH. Validation of The Danish Cancer Registry and selected Clinical Cancer Databases. 2012. Available from: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/cancerregisteret. Accessed March 12, 2020.
9. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi: 10.2147/CLEP.S91125
10. Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, Dal Pan G, Goettsch W, Murk W, Wang SV. Graphical depiction of longitudinal study designs in health care databases. *Ann Intern Med*. 2019;170:398–406. doi: 10.7326/M18-3079
11. Suissa S. The Quasi-cohort approach in pharmacoepidemiology: upgrading the nested case-control. *Epidemiology*. 2015;26:242–246. doi: 10.1097/EDE.0000000000000221
12. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment 2019*. World Health Organization. 2018.
13. Pottegård A, Hallas J. New use of prescription drugs prior to a cancer diagnosis. *Pharmacoepidemiol Drug Saf*. 2017;26:223–227. doi: 10.1002/pds.4145
14. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S (Eds.) *International Classification of Diseases for Oncology*. 3rd ed. First Revision. Geneva: World Health Organization; 2013.
15. Harrell FE. *Regression Modeling Strategies: with Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. 2nd ed. Springer International Publishing; 2015.
16. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–274. doi: 10.7326/M16-2607
17. Azoulay L, Assimes TL, Yin H, Bartels DB, Schiffrin EL, Suissa S. Long-term use of angiotensin receptor blockers and the risk of cancer. *PLoS One*. 2012;7:e50893. doi: 10.1371/journal.pone.0050893
18. Pasternak B, Svanström H, Callréus T, Melbye M, Hviid A. Use of angiotensin receptor blockers and the risk of cancer. *Circulation*. 2011;123:1729–1736. doi: 10.1161/CIRCULATIONAHA.110.007336
19. Bhaskaran K, Douglas I, Evans S, van Staa T, Smeeth L. Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. *BMJ*. 2012;344:e2697. doi: 10.1136/bmj.e2697
20. Friis S, Sørensen HT, Mellemkjaer L, McLaughlin JK, Nielsen GL, Blot WJ, Olsen JH. Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based cohort study in Denmark. *Cancer*. 2001;92:2462–2470. doi: 10.1002/1097-0142(20011101)92:9<2462::aid-cncr1596>3.0.co;2-l
21. Hallas J, Christensen R, Andersen M, Friis S, Bjerrum L. Long term use of drugs affecting the renin-angiotensin system and the risk of cancer: a population-based case-control study. *Br J Clin Pharmacol*. 2012;74:180–188. doi: 10.1111/j.1365-2125.2012.04170.x
22. Chang CH, Lin JW, Wu LC, Lai MS. Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. *J Clin Oncol*. 2011;29:3001–3007. doi: 10.1200/JCO.2011.35.1908
23. Gokhale M, Girman C, Chen Y, Pate V, Funk MJ, Stürmer T. Comparison of diagnostic evaluations for cough among initiators of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf*. 2016;25:512–520. doi: 10.1002/pds.3977
24. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol*. 2010;11:627–636. doi: 10.1016/S1470-2045(10)70106-6
25. Bangalore S, Kumar S, Kjeldsen SE, Makani H, Grossman E, Wetterslev J, Gupta AK, Sever PS, Gluud C, Messerli FH. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *Lancet Oncol*. 2011;12:65–82. doi: 10.1016/S1470-2045(10)70260-6
26. Campbell DJ, Kladis A, Duncan AM. Effects of converting enzyme inhibitors on angiotensin and bradykinin peptides. *Hypertension*. 1994;23:439–449. doi: 10.1161/01.hyp.23.4.439
27. Bunn PA Jr, Chan D, Dienhart DG, Tolley R, Tagawa M, Jewett PB. Neuropeptide signal transduction in lung cancer: clinical implications of bradykinin sensitivity and overall heterogeneity. *Cancer Res*. 1992;52:24–31.
28. Ishihara K, Hayash I, Yamashina S, Majima M. A potential role of bradykinin in angiogenesis and growth of S-180 mouse tumors. *Jpn J Pharmacol*. 2001;87:318–326. doi: 10.1254/jjp.87.318
29. Stewart JM. Bradykinin antagonists as anti-cancer agents. *Curr Pharm Des*. 2003;9:2036–2042. doi: 10.2174/1381612033454171
30. Rosenthal T, Gavras I. Angiotensin inhibition and malignancies: a review. *J Hum Hypertens*. 2009;23:623–635. doi: 10.1038/jhh.2009.21
31. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15:291–303. doi: 10.1002/pds.1200
32. Kampmann JP, Thirstrup S. Angiotensin II antagonister: Sjældent indiceret. 2000. Available from: https://www.sst.dk/da/rationel-farmakoterapi/maanedsbladet/2000/~/media/1986B4974276110901 91BB9488D7509C.ashx. Accessed March 12, 2020.
33. Elung-Jensen T, Feldt-Rasmussen B. ACE-hæmmere vs. AT-II-antagonister – hvilken behandling skal man vælge? 2004. Available from: https://www.sst.dk/da/rationel-farmakoterapi/maanedsbladet/2004/~/media/DE71FF9583E2168A23519F163F9C1D18.ashx. Accessed March 12, 2020.
34. FDA medical review: NDA 207620, LCZ696 (Entresto), Novartis. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000MedR.pdf. Accessed March 12, 2020.
35. The ARB Trialists Collaboration. Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138 769 individuals. *J Hypertens*. 2011;29:623–635. doi: 10.1097/HJH.0b013e328344a7de
36. Based on calculations of data from the Danish online drug use statistics medstat.dk. Available from: http://www.medstat.dk/. Accessed March 12, 2020.
37. Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. *BMJ*. 2018;362:k3851. doi: 10.1136/bmj.k3851