

# ASSOCIATION OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS WITH LUNG CANCER AMONG A U.S. COHORT: A REAL WORLD APPROACH



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## OBJECTIVES

This analysis aims to reproduce a U.K. based study investigating whether there is a risk between angiotensin converting enzyme inhibitors (ACEIs) and lung cancer, among a cohort of U.S. patients, using a real world approach. Prior biological studies have suggested that ACEIs increase lung cancer risk through bradykinin accumulation in the lungs.<sup>1,2,3</sup>

## METHODS

Real world data, composed of electronic medical records from approximately 57.2 million U.S. patients were analyzed. Two unique cohorts were defined, with the first comprising of patients treated with ACEIs and the second with patients who were treated with angiotensin receptor blockers (ARBs) (Figure 1). The age of the population was restricted to patients aged 18 years or older. Those who had a medical history of less than five years and had treatment (ARBs or ACEIs in their medical history for less than 3 years were excluded (Figure 1). In addition, patients who had lung cancer prior to the initiation of ACEIs or ARBs were excluded from the analysis, as well as those who had ever had any other cancers in order to rule out secondary lung cancers (Figure 1). The index event was defined as initiation of either ACEIs or ARBs anytime on, or after January 1st, 2000. Medications were defined using the RxNorm codes, *CV800 ACE inhibitors* and *CV805 Angiotensin II receptor blocker*. The ICD-10 code C34 was used to define the primary outcome, lung cancer, with an observation period between 1 day to anytime after medication initiation. Measures of association, which include a risk difference, a risk ratio and an odds ratio were calculated and propensity score matching was used to balance cohorts and adjust for 110 of the most likely confounders (Table 2). Confounders that were matched on include age and sex, as well as ICD-10 diagnosis codes for nicotine dependence, alcohol use, BMI, pneumonia, family history of lung cancer and exposure to asbestos (table 2). Propensity scores matched 1:1 using a nearest neighbor greedy matching algorithm with a caliper of 0.25 times the standard deviation.

Table 2. Propensity score matching characteristics

ICD-10 Code	Description	ICD-10 Code	Description
AI	Age at Index	F10.15	Alcohol abuse with alcohol-induced psychotic disorder
F	Female	F10.159	Alcohol abuse with alcohol-induced psychotic disorder, unspecified
M	Male	F10.28	Alcohol dependence with other alcohol-induced disorders
F17	Nicotine dependence	F10.25	Alcohol dependence with alcohol-induced psychotic disorder
F17.2	Nicotine dependence	F10.27	Alcohol dependence with alcohol-induced persisting dementia
F17.20	Nicotine dependence, unspecified	F10.959	Alcohol use, unspecified with alcohol-induced psychotic disorder, unspecified
F17.200	Nicotine dependence, unspecified, uncomplicated	F10.950	Alcohol use, unspecified with alcohol-induced psychotic disorder with delusions
J44	Other chronic obstructive pulmonary disease	F10.980	Alcohol use, unspecified with alcohol-induced anxiety disorder
Z87.891	Personal history of nicotine dependence	F10.929	Alcohol use, unspecified with intoxication, unspecified
Z68-Z68	Body mass index [BMI] (Z68)	F10.280	Alcohol dependence with alcohol-induced anxiety disorder
J18	Pneumonia, unspecified organism	F10.288	Alcohol dependence with other alcohol-induced disorder
F10	Alcohol related disorders	F10.281	Alcohol dependence with alcohol-induced sexual dysfunction
F10.1	Alcohol abuse	F10.259	Alcohol dependence with alcohol-induced psychotic disorder, unspecified
F10.10	Alcohol abuse, uncomplicated	K70.9	Alcoholic liver disease, unspecified
F10.2	Alcohol dependence	K70.0	Alcoholic fatty liver
F10.20	Alcohol dependence, uncomplicated	K72.91	Hepatic failure, unspecified with coma
J15	Bacterial pneumonia, not elsewhere classified	K72.1	Chronic hepatic failure
F10.23	Alcohol dependence with withdrawal	K72.10	Chronic hepatic failure without coma
K70	Alcoholic liver disease	J13	Pneumonia due to Streptococcus pneumoniae
K72	Hepatic failure, not elsewhere classified	J17	Pneumonia in diseases classified elsewhere
F10.22	Alcohol dependence with intoxication	J14	Pneumonia due to Hemophilus influenzae
F10.229	Alcohol dependence with intoxication, unspecified	Z77.090	Contact with and (suspected) exposure to asbestos
F10.21	Alcohol dependence, in remission	F17.220	Nicotine dependence, chewing tobacco, uncomplicated
K72.0	Acute and subacute hepatic failure	F17.290	Nicotine dependence, other tobacco product, uncomplicated
K72.00	Acute and subacute hepatic failure without coma	F17.291	Nicotine dependence, other tobacco product, in remission
K70.3	Alcoholic cirrhosis of liver	F17.213	Nicotine dependence, cigarettes, with withdrawal
K70.30	Alcoholic cirrhosis of liver without ascites	F17.219	Nicotine dependence, cigarettes, with unspecified nicotine-induced disorders
A15	Respiratory tuberculosis	F17.209	Nicotine dependence, unspecified, with unspecified nicotine-induced disorders
F17.21	Nicotine dependence, cigarettes	F17.203	Nicotine dependence unspecified, with withdrawal
K70.1	Alcoholic hepatitis	Z77.22	Contact with and (suspected) exposure to environmental tobacco smoke (acute) (chronic)
K70.10	Alcoholic hepatitis without ascites	F10.97	Alcohol use, unspecified with alcohol-induced persisting dementia
F10.9	Alcohol use, unspecified	F10.94	Alcohol use, unspecified with alcohol-induced mood disorder
Z80.1	Family history of malignant neoplasm of trachea, bronchus and lung	F10.129	Alcohol abuse with intoxication, unspecified
K72.9	Hepatic failure, unspecified	F10.121	Alcohol abuse with intoxication delirium
K72.90	Hepatic failure, unspecified without coma	F10.182	Alcohol abuse with alcohol-induced sleep disorder
J12	Viral pneumonia, not elsewhere classified	F10.19	Alcohol abuse with unspecified alcohol-induced disorder
F17.29	Nicotine dependence, other tobacco product	F10.14	Alcohol abuse with alcohol-induced mood disorder
F17.22	Nicotine dependence, chewing tobacco	F10.24	Alcohol abuse with alcohol-induced mood disorder
F17.228	Nicotine dependence, chewing tobacco, with other nicotine-induced disorders	F10.951	Alcohol use, unspecified with alcohol-induced psychotic disorder with hallucinations
F17.298	Nicotine dependence, other tobacco product, with other nicotine-induced disorders	F10.982	Alcohol use, unspecified with alcohol-induced sleep disorder
F17.210	Nicotine dependence, cigarettes, uncomplicated	F10.988	Alcohol use, unspecified with other alcohol-induced disorder
F17.218	Nicotine dependence, cigarettes, with other nicotine-induced disorders	F10.920	Alcohol use, unspecified with intoxication, uncomplicated
F17.211	Nicotine dependence, cigarettes, in remission	F10.921	Alcohol use, unspecified with intoxication delirium
F17.208	Nicotine dependence, unspecified, with other nicotine-induced disorders	F10.220	Alcohol dependence with intoxication, uncomplicated
F17.201	Nicotine dependence, unspecified, in remission	F10.221	Alcohol dependence with intoxication delirium
F10.95	Alcohol use, unspecified with alcohol-induced psychotic disorder	F10.282	Alcohol dependence with alcohol-induced sleep disorder
F10.99	Alcohol use, unspecified with unspecified alcohol-induced disorder	F10.250	Alcohol dependence with alcohol-induced psychotic disorder with delusions
F10.98	Alcohol use, unspecified with other alcohol-induced disorders	K70.31	Alcoholic cirrhosis of liver with ascites
F10.92	Alcohol use, unspecified with intoxication	K70.11	Alcoholic hepatitis with ascites
F10.96	Alcohol use, unspecified with alcohol-induced persisting amnesic disorder	K70.4	Alcoholic hepatic failure
F10.12	Alcohol abuse with intoxication	K70.40	Alcoholic hepatic failure without coma
F10.120	Alcohol abuse with intoxication, uncomplicated	K70.41	Alcoholic hepatic failure with coma
F10.18	Alcohol abuse with other alcohol-induced disorders	K72.11	Chronic hepatic failure with coma
F10.180	Alcohol abuse with alcohol-induced anxiety disorder	J16	Pneumonia due to other infectious organisms, not elsewhere classified
F10.188	Alcohol abuse with other alcohol-induced disorder		
F10.181	Alcohol abuse with alcohol-induced sexual dysfunction		
F10.15	Alcohol abuse with alcohol-induced psychotic disorder		

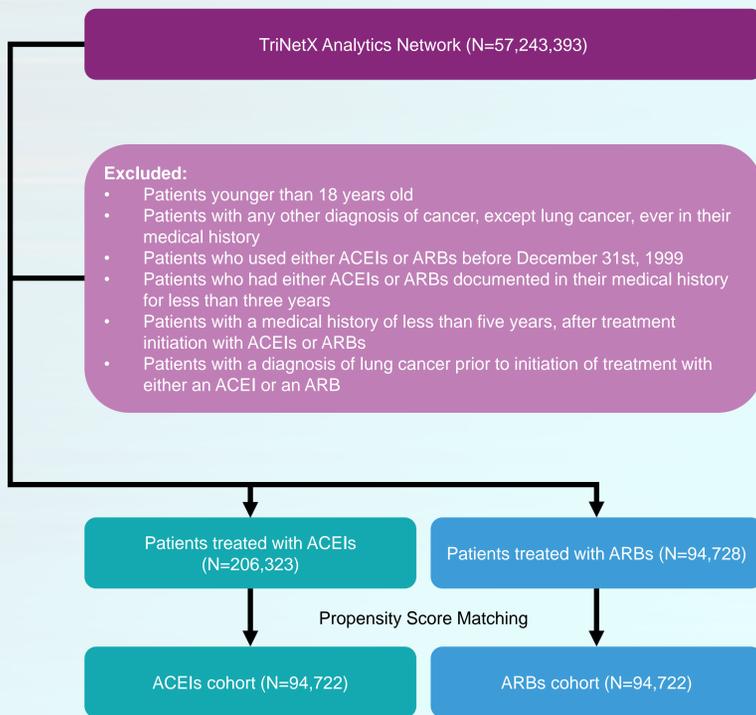


Figure 1. Study population

Table 1. Baseline demographics (Before propensity score matching)

	ACEIs (N=206,323)		ARBs (N=94,728)	
	Patient count	% of count	Patient count	% of count
<b>Age (years)</b>				
Age at index (mean + sd)	55.2 + 14.5		59.5 + 13.1	
<b>Sex</b>				
Male	113,815	55	41,607	44
Female	92,423	45	53,067	56
<b>Ethnicity</b>				
Hispanic or Latino	11,862	6	4,273	5
Not Hispanic or Latino	171,219	83	78,887	83
Unknown	23,242	11	11,862	12
<b>Race</b>				
White	153,444	74	68,403	72
Black or African American	33,144	16	14,846	16
Asian	3,425	2	2,637	2
Other	897	<1	364	<1
Unknown	15,413	8	8,478	9

## RESULTS

Baseline demographics for this cohort were obtained (Table 1). In the balanced cohort of 189,444 patients, use of ACEIs, compared with ARBs was associated with an increased risk for lung cancer RR (95% CI) 1.166 (1.001, 1.357) (table 3).

Table 3. Measures of association (ACEIs vs. ARBs)

	95% C.I.	P-value
Risk Difference	0.054 (0%,0.107%)	0.0478
Risk Ratio	1.166 (1.001,1.357)	-
Odds Ratio	1.166 (1.001,1.358)	-

## CONCLUSIONS

In this real world analysis of a cohort of U.S. patients, the use of ACEIs was associated with an increased risk for lung cancer, in comparison with use of ARBs. The results of this analysis were in accordance with the findings from the U.K. based study, conducted by Hicks et al.<sup>1</sup> Further analysis of this U.S. cohort could include analyzing risk for lung cancer over different time periods.

1. Hicks, B.M. et al.. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018; 363: k4209  
2. Triffitt A, Da Silva A, Gies JP. Kinins and respiratory tract diseases. Eur Respir. J1993;6:576-87.pmid:8387934  
3. Sethi T, Rozengurt E. Multiple neuropeptides stimulate clonal growth of small cell lung cancer: effects of bradykinin, vasopressin, cholecystokinin, galanin, and neurotensin. Cancer Res1991;51:3621-3.pmid:1711414