



ASSOCIATION OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR USE AND LUNG CANCER

Angiotensin converting enzyme inhibitors (ACEIs) are used extensively for the treatment of hypertension. Although short-term use is not associated with life-threatening adverse effects, long-term use may be associated with lung cancer. The possible explanation for an increased risk of lung cancer with ACEI use is due to the accumulation of bradykinin in the lung that may stimulate the growth of lung cancer. In addition, substance P is also increased in patients receiving ACEIs and has been associated with tumor growth. This issue of *CLIPs* reviews a population-based cohort study of ACEIs and the risk of lung cancer. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

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.

Introduction

- Previous studies have not found much evidence of an increased cancer incidence with ACEIs; however, the majority of the studies were of short duration and had small sample sizes.
- Observational studies have reported mixed results.
- Overall cancer risk was evaluated in previous studies and the effect on ACEIs on lung cancer was not assessed.
- Potential confounders may have affected the results of previous studies.

Study objective

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

Methods

- The data source used was the UK Clinical Practice Research Datalink (CPRD).
- CPRD includes data from approximately 700 general practices with more than 15 million patients.
- The following data was included in the database: demographic information, anthropometric data (e.g., BMI), lifestyle information, medical diagnoses and procedures, and prescription data.
- Patients included in the sample were at least 18 years and were newly treated with an antihypertensive drug between 1 January 1988 and 31 December 2015. All patients had one year of medical history in the CPRD before receiving antihypertensive therapy.
- Patients were excluded if they had a previous diagnosis of any cancer and those who had received treatment for cancer before entry into the study.
- Patients were followed up for one year after cohort entry until lung cancer diagnosis.
- Exposure was determined by categorizing patients as receiving ACEI, ARB, or other antihypertensive therapy.
- Potential confounders included age, sex, year of cohort entry, body mass index, smoking status, alcohol-related disorders, and history of lung diseases. All of these were adjusted based on these variables.
- Secondary analyses included: whether a duration-response relation existed between cumulative duration of ACEI use and incidence of lung cancer; association between time since starting ACEIs and risk of lung cancer; and cumulative duration of use and time since initiation.

Results

- A total of 992,061 patients were followed for a mean of 6.4 years beyond the one year post-cohort entry latency period.
- A total of 336,135 patients were treated with ACEIs, 29,008 with ARBs, and 101,637 with both ACEIs and ARBs. The most commonly used ACEIs were ramipril (26%); lisinopril (12%); and perindopril (7%).
- A total of 7952 patients developed lung cancer during the 6350584 person years of follow up (crude incidence rate 1.3% (95% CI, 1.2 to 1.3) per 1000 person years).
- ACEIs were associated with a 14% greater risk of lung cancer (1.6 vs 1.2 per 1000 person years; HR, 1.14; 95% CI, 1.01 to 1.29).
- Use of ACEIs for less than 5 years with an increased risk of lung cancer (HR, 1.10; 95% CI, 0.96 to 1.25). The HR was increased with 5-10 years of use HR, 1.22 (95% CI, 1.06 to 1.40) and continued to increase with more than 10 years of use (1.31, 95% CI, 1.08 to 1.59).
- Compared to thiazide diuretics, ACEIs were associated with a 6% increased risk of lung cancer (HR, 1.06; 95% 1.00 to 1.13). Increasing use of ACEIs were associated with an increased risk of lung cancer, with a peak of more than 10 years of use (HR,1.23; 95%, 1.04 to 1.44).
- This study had several benefits including the large number of patients included and mechanisms to reduce biases were used.
- Socioeconomic status, diet, exposure to cancer-causing agents, and family history of lung cancer were not included.
- Detection bias may have occurred due to the known adverse effect of coughing with ACEI use.

Conclusions

- Use of ACEIs were associated with an elevated risk of lung cancer.
- The absolute increase in lung cancer is small; however, large populations may be at risk for lung cancer because of the large numbers of patients who are receiving ACEIs.