Lisinopril and Lung Cancer?

Understanding Literature about Assessing Harms

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Disclosures

- Paid Editorial Role JAMA’s The Rational Clinical Examination
- No other disclosures or conflicts of interest
Different Kind of Disclosures

1. Copyrighted “Sheri’s Quotes”
   - A ratio is a ratio is a ratio
   - Hazard ratio is a risk ratio wearing a watch
     (total # events and timing of each event)

2. I am not a statistician

3. No offense is intended to hazard ratios or other statistical concepts
Learning Objectives

- To demonstrate how to assess and apply literature regarding HARM.
- To practice critical appraisal of a cohort study for a question of HARM that is relevant to GIM practice today.
- To understand how to handle prognostic imbalance.

Medications: Lisinopril 40 mg daily, diltiazem CD 180 daily, Atorvastatin 20 mg daily, ibuprofen as needed for pain

Hypertension history: on lisinopril for about 6 years. Recent difficulty in controlling BP. A trial of HCTZ was not tolerated in the setting of BPH and urinary frequency with a single episode of bladder outlet obstruction. Prior use of amlodipine was associated with ankle swelling.
Hypertension history: Lisinopril dose maximized to 40 mg and addition of diltiazem CD 180 now BPs are controlled (~130/70-80). He checks BPs at home and is very diligent with his health. He has never smoked; alcohol intake is a few glasses or wine or beer per week (less than 1 alcoholic beverage per day). No family history of lung cancer.

He asks if we should be concerned about his lisinopril because of something his read on the internet about association with lung cancer.
ENC Health Currents: Blood Pressure Drugs Linked To Increased Lung Cancer Risk

If you're among the 25 percent of adults in North Carolina who were told by a health professional that you have hypertension, chances are you've been prescribed blood pressure medication. An October 2018 study published in the British Medical Journal now links certain blood pressure drugs with an increased risk of lung cancer.

Blood pressure drug linked to possible small increased risk of lung cancer

Thursday October 25 2018

Page contents

- Where did the story come

“Blood pressure pills taken by millions may raise risk of lung cancer,” reports The Daily Telegraph.
Real Life Happens

- Within the next 24 hours two work colleagues (physicians in the practice) forward you this article stating that it has been in the press and patients may ask us about this article.

- What should we say?
Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study

Blánaid M Hicks,¹,²,³ Kristian B Filion,¹,²,⁴ Hui Yin,¹ Lama Sakr,⁵ Jacob A Udell,⁶,⁷ Laurent Azoulay¹,²,⁸

ABSTRACT
OBJECTIVE
To determine whether the use of angiotensin converting enzyme inhibitors (ACEIs), compared with use of angiotensin receptor blockers, 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 1 January 1995 and 31 December 2015 was identified and followed until 31 December 2016.

MAIN OUTCOME MEASURES

and peaking after more than 10 years of use (1.31, 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 people using ACEIs for more than five years. Additional studies, with long term follow-up, are needed to investigate the effects of these drugs on incidence of lung cancer.

Introduction
Angiotensin converting enzyme inhibitors (ACEIs) are effective drugs used in the treatment of hypertension.¹ Although these drugs have been shown to be relatively
Outline

- Read Abstract
- Understanding Study Design: Cohort study
  - Risk of Bias in Cohort Study (Q 1,2,3)
  - How to deal with prognostic imbalance?
- What are the Results (Q 4,5)
- Application (Q6,7,8,9,10)
Systematic Reviews & Meta-Analyses
Critically-Appraised Topics [Evidence Syntheses]
Critically-Appraised Individual Articles [Article Synopses]
Randomized Controlled Trials (RCTs)
Cohort, Descriptive, Qualitative Studies
Case-Control Studies, Case Reports, Case Series
Background Information

In general: Risk of Bias Decreases as we go up

Filtered Information

Unfiltered Information
Prospective Cohort Study

Exposure Present

Exposure Absent

Outcome Yes

Outcome No

Measure HERE

YEAR 2020

TIME

YEAR 2030
Retrospective Cohort Study

Exposure
- Present
- Absent

Outcome
- Yes
- No

Year
- 2000
- 2010

Time
Outline

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- Understanding Study Design: Cohort study
- Risk of Bias in Cohort Study (Q 1,2,3)
- How to deal with prognostic imbalance?
- What are the Results (Q 4,5)
- Application (Q6,7,8,9,10)
Buzz Groups

- Discuss questions 1-3 in the paper (Use the mark-ups in the margins to quickly direct you to where you will find the answers)

  #1: Similar for prognostic factors / adjustment to level playing field?

  #2: Circumstances and methods similar?

  #3: Was follow up sufficiently complete?
#1: Similar Prognostic (p.4)?

Table 1 | Baseline demographic and clinical characteristics of cohort and stratified by drug use at cohort entry. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire cohort</th>
<th>Antihypertensive drug use at cohort entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACEIs (21.0)</td>
</tr>
<tr>
<td>Total</td>
<td>992,061</td>
<td>208,353</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>55.6 (16.6)</td>
<td>57.8 (13.1)</td>
</tr>
<tr>
<td>Male sex</td>
<td>459,064 (46.3)</td>
<td>133,091 (63.9)</td>
</tr>
<tr>
<td>Alcohol related disorders</td>
<td>71,605 (7.2)</td>
<td>18,199 (8.7)</td>
</tr>
<tr>
<td>Smoking status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>215,098 (21.7)</td>
<td>41,595 (20.0)</td>
</tr>
<tr>
<td>Past</td>
<td>227,504 (22.9)</td>
<td>58,683 (28.2)</td>
</tr>
<tr>
<td>Never</td>
<td>484,831 (48.9)</td>
<td>99,820 (47.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>64,428 (6.5)</td>
<td>8,255 (4.0)</td>
</tr>
<tr>
<td>Body mass index:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>303,311 (30.6)</td>
<td>45,164 (21.7)</td>
</tr>
<tr>
<td>25-30</td>
<td>304,699 (30.7)</td>
<td>71,655 (34.4)</td>
</tr>
<tr>
<td>≥30.0</td>
<td>224,888 (22.7)</td>
<td>67,353 (32.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>159,163 (16.0)</td>
<td>24,181 (11.6)</td>
</tr>
<tr>
<td>Mean (SD) duration of treated hypertension, years</td>
<td>0.2 (1.5)</td>
<td>0.3 (1.8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22,403 (2.3)</td>
<td>5027 (2.4)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2399 (0.2)</td>
<td>474 (0.2)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>78,669 (7.9)</td>
<td>16,152 (7.8)</td>
</tr>
<tr>
<td>Statins</td>
<td>164,891 (16.6)</td>
<td>73,510 (35.3)</td>
</tr>
<tr>
<td>Mean (SD) total No of unique drug classes</td>
<td>4.1 (4.1)</td>
<td>4.1 (4.1)</td>
</tr>
<tr>
<td>0</td>
<td>150,293 (15.2)</td>
<td>35,384 (17.0)</td>
</tr>
<tr>
<td>1</td>
<td>147,609 (14.9)</td>
<td>31,022 (14.9)</td>
</tr>
<tr>
<td>2</td>
<td>135,085 (13.6)</td>
<td>27,027 (13.0)</td>
</tr>
<tr>
<td>3</td>
<td>115,121 (11.6)</td>
<td>22,157 (10.6)</td>
</tr>
<tr>
<td>≥4</td>
<td>443,953 (44.8)</td>
<td>92,763 (44.5)</td>
</tr>
</tbody>
</table>
2. Circumstances and Methods for detecting outcome similar?

3. Was follow up sufficiently complete?
Outline

- Read Abstract
- Understanding Study Design: Cohort study
- Risk of Bias in Cohort Study (Q 1, 2, 3)
- How to deal with prognostic imbalance?
- What are the Results (Q 4, 5)
- Application (Q 6, 7, 8, 9, 10)
Prognostic Imbalance

- Understand Prognostic and Confounding Variables
- How to deal with prognostic imbalance in randomized trials or observational studies – adjusted analysis
- Credit: Gordon originated slides in this section
Why do we randomize?

Goal of randomization: three components
- Similarity of groups
- Similar known and unknown prognostic factors
- Similar prognosis for outcome of interest
Bad Luck Investigators

- Treatment
  - 80 young
  - 20 old

- Control
  - 20 young
  - 80 old

- Treated group does better

- What are possible explanations?

- What to do?
Solution: Level the Playing Field

- Young
  - Trt vs control
- Old
  - Trt vs control
- pool across groups
More complicated problem

- **Treatment**
  - 80% young
  - 10% diabetics

- **Control**
  - 20% young
  - 20% diabetics
Same Solution: Level Playing Field

- Young diabetics
  - Trt vs control
- Old diabetics
  - Trt vs control
- Young non-diabetics
  - Trt vs control
- Old non-diabetics
  - Trt vs control
- Pool across four groups
Quantitative example

- True treatment effect: RR = 1
- Old event rate 40%
- Young event rate 10%
### Unadjusted

**Treatment**
- 80 young: 8 events
- 20 old: 8 events

**Control**
- 20 young: 2 events
- 80 old: 32 events

<table>
<thead>
<tr>
<th>Groups</th>
<th>Description</th>
<th>Number</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Young</td>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Old</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>Control</td>
<td>Young</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Old</td>
<td>80</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
<td>34</td>
</tr>
</tbody>
</table>

**Total**
- Old event rate: 40%
- Young event rate: 10%

**Relative risk**
### Unadjusted

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=100)</th>
<th>Control (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 young</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>20 old</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

**Old event rate** 40%

**Young event rate** 10%

**Relative risk** $\frac{16}{34} = 0.47$
<table>
<thead>
<tr>
<th></th>
<th>Young patients</th>
<th>Risk (%)</th>
<th>Old patients</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
<td></td>
<td>Relative risk</td>
<td></td>
</tr>
</tbody>
</table>
Young patients
Treatment: 10%
Control: 10%
Relative risk

Old patients
Treatment: 10%
Control: 10%
Relative risk
<table>
<thead>
<tr>
<th>Young patients</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>10%</td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Old patients</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>10%</td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
</tr>
<tr>
<td>Patient Group</td>
<td>Risk (%)</td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Young patients</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>10%</td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Old patients</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
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</tbody>
</table>

Adjusted
<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young patients</td>
<td>10%</td>
<td>10%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Old patients</td>
<td>40%</td>
<td></td>
<td></td>
<td>Risk (%)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young patients</td>
<td>Risk (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tbody>
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<td>Control</td>
<td>40%</td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
</tr>
<tr>
<td>Young patients</td>
<td>Risk (%)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td>Treatment</td>
<td>10%</td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Relative risk</strong></td>
<td><strong>1.0</strong></td>
</tr>
</tbody>
</table>
Adjusted Analysis: Example #1

- Incidental appendectomy
Should we be doing incidental appendectomies?

Some surgeons take out the appendix even if non-diseased in course of cholecystectomy
- good thing or bad?

Retrospective Cohort
- Administrative Data from Ontario hospitals 1981 - 90
- 7,846 cholecystectomy patients with appendectomy
- 191,599 controls
Incidental Appendectomy

- **Mortality**
  - with appendectomy 0.27%
  - without 0.73%
  - odds ratio 0.37, p < 0.001

- Incidental appendectomy saves lives!
Predictors of Mortality / Unequal Distribution

- Men 1.25%, women 0.5%
- Under 60 0.22%; 61 to 60 0.74%, over 70 3.7%
- No co-morbidity 0.32%; co-morbidity 4.3%
- elective 0.22%; urgent 1.32%; emergent 1.9%

Adjusted OR 0.98

- incidental appendectomy doesn’t effect mortality
Example #2: Relation Between Funding & Conclusions (JAMA 2003; 290:921)

- Observational study of 370 randomized drug trials included in Cochrane reviews
- Eligible studies were drug trials with binary outcomes (e.g. dead/alive, MI/ no MI) with no less than 5 individual studies and with at least some trials reporting methodologic factors
- Used logistic regression with adjustment for treatment effect.
6-point scale to “grade” conclusion

- 6 = experimental intervention should be “highly preferred”
- 1 = control should be “highly preferred”

Association between funding and conclusion was adjusted for:

- Treatment effect (how big was the effect)
- Adverse events
- Confounding factors: Methodologic quality, control intervention, sample size, publication year, publication place
<table>
<thead>
<tr>
<th>Funding</th>
<th># of Trials</th>
<th>Median Score (IQR)+</th>
<th># (%) of Trials Scoring 6 Points+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonprofit organizations</td>
<td>67</td>
<td>4 (3-5)</td>
<td>11 (16.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>106</td>
<td>5 (3-6)</td>
<td>32 (30.1)</td>
</tr>
<tr>
<td>Nonprofit and for-profit organizations</td>
<td>51</td>
<td>5 (4-6)</td>
<td>18 (35.2)</td>
</tr>
<tr>
<td>For-profit organizations</td>
<td>146</td>
<td>6 (5-6)</td>
<td>74 (50.6)</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
<td>5 (4-6)</td>
<td>135 (36.4)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

*Conclusions in trials were assessed by a 1-6 point scale. If the conclusions recommended the experimental drug as the treatment of choice without disclaimers, 6 points was assigned, and if not, 1-5 points was assigned.

+p<.001, using Kruskal-Wallis test (medians) or X² test (proportions)
Possible conclusions

- Published studies warrant endorsement
  - For-profit larger effects
  - For-profit better done studies
  - Publication bias – withholding negative studies

- Published studies don’t warrant endorsement
  - Biased interpretation

- Solution?
Results

- Logistic regression found 3 significant predictors of drug recommendations
  - Effect Size: Bigger effect size, more likely strong recommendation
  - Methodologic Quality: Double Blinding, more likely strong recommendation
  - Funding source (for profit versus others)
Solution: Level the Playing Field

- Large effect, high quality
  - For-profit versus others
- Small effect, high quality
  - For-profit versus others
- Large effect, low quality
  - For-profit versus others
- Small effect, low quality
  - For-profit versus others
- Pool across four groups
Results

- After adjustment for effect size and blinding:
  - industry funding, odds ratio 5.3 (95% CI 2.0 to 14.4)

- Conclusion: industry funded trials may be more positive due to biased interpretation of trial results. “Please review carefully whether conclusions in RCTS are supported by data”
Randomization aims to equally distribute prognostic factors between groups

If prognostic factors are unequally distributed, they are confounding factors

Adjusted analysis help level the playing field

- Aim to create prognostically homogeneous groups
- Calculate effect in each homogenous group
- Pool across groups
- Deals – partly – with prognostic imbalance
- Cannot adjust for unknown prognostic imbalances
Outline

- Read Abstract
- Understanding Study Design: Cohort study
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- Application (Q6,7,8,9,10)
### Question 4 and 5

**Table 2 | Crude and adjusted hazard ratios for association between the use of ACEIs and risk of lung cancer**

<table>
<thead>
<tr>
<th>Exposure*</th>
<th>Events</th>
<th>Person years</th>
<th>Incidence rate (95% CI)†</th>
<th>Hazard ratio (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crude</td>
<td>Adjusted‡</td>
<td></td>
</tr>
<tr>
<td>ARBs</td>
<td>266</td>
<td>213 557</td>
<td>1.2 (1.1 to 1.4)</td>
<td>1.00</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>ACEIs</td>
<td>3186</td>
<td>1 977 139</td>
<td>1.6 (1.6 to 1.7)</td>
<td>1.32</td>
<td>1.14 (1.01 to 1.29)</td>
</tr>
</tbody>
</table>

**Cumulative duration of ACEI use (years)**

<table>
<thead>
<tr>
<th>Cumulative duration of ACEI use (years)</th>
<th>Events</th>
<th>Person years</th>
<th>Incidence rate (95% CI)†</th>
<th>Hazard ratio (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>2084</td>
<td>1 440 232</td>
<td>1.4 (1.4 to 1.5)</td>
<td>1.24</td>
<td>1.10 (0.96 to 1.25)</td>
</tr>
<tr>
<td>5.1-10</td>
<td>905</td>
<td>457 309</td>
<td>2.0 (1.9 to 2.1)</td>
<td>1.44</td>
<td>1.22 (1.06 to 1.40)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>197</td>
<td>79 598</td>
<td>2.5 (2.1 to 2.8)</td>
<td>1.63</td>
<td>1.31 (1.08 to 1.59)</td>
</tr>
</tbody>
</table>

**Time since first ACEI use (years)**

<table>
<thead>
<tr>
<th>Time since first ACEI use (years)</th>
<th>Events</th>
<th>Person years</th>
<th>Incidence rate (95% CI)†</th>
<th>Hazard ratio (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>1617</td>
<td>1 158 441</td>
<td>1.4 (1.3 to 1.5)</td>
<td>1.24</td>
<td>1.11 (0.97 to 1.27)</td>
</tr>
<tr>
<td>5.1-10</td>
<td>1155</td>
<td>647 103</td>
<td>1.8 (1.7 to 1.9)</td>
<td>1.33</td>
<td>1.14 (0.99 to 1.30)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>414</td>
<td>1 715 96</td>
<td>2.4 (2.2 to 2.7)</td>
<td>1.62</td>
<td>1.29 (1.10 to 1.51)</td>
</tr>
</tbody>
</table>

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.

*Use of other antihypertensive drugs (including use of both ACEIs and ARBs) was considered in model but not shown in table; these generated 4500 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 before cohort entry (including pneumonia, tuberculosis, and chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and total number of unique drug classes in year before cohort entry.
Outline

- Read Abstract
- Understanding Study Design: Cohort study
- Risk of Bias in Cohort Study (Q 1,2,3)
- How to deal with prognostic imbalance?
- What are the Results (Q 4,5)
- Application (Q6,7,8,9,10)
How can I apply the results to my patient care?

- Study patients similar to patients in my practice?
- Was follow up sufficiently long?
- Is the exposure similar to what might occur in my patient
**Magnitude of Risk Q# 9 (p. 5)**

### #1,4,5,9: Association
- **Precision**
- **Risk Magnitude**
- **Adjustment**

### Risk Magnitude

**ARB**
- 266 events
- 29,008 people
- **92 events / 10,000**

**ACE-I**
- 3186 events
- 335,135 people
- **95 events / 10,000**

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**Table 2 | Crude and adjusted hazard ratios for association between the use of ACEIs and risk of lung cancer**

<table>
<thead>
<tr>
<th>Exposure*</th>
<th>Events</th>
<th>Person years</th>
<th>Incidence rate (95% CI)†</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs</td>
<td>266</td>
<td>213,557</td>
<td>1.2 (1.1 to 1.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>ACEI</td>
<td>3186</td>
<td>1,977,139</td>
<td>1.6 (1.6 to 1.7)</td>
<td>1.32</td>
</tr>
</tbody>
</table>

**Cumulative duration of ACEI use (years)**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Person years</th>
<th>Incidence rate (95% CI)†</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>2084</td>
<td>1,440,232</td>
<td>1.4 (1.4 to 1.5)</td>
<td>1.24</td>
</tr>
<tr>
<td>5.1-10</td>
<td>905</td>
<td>457,309</td>
<td>2.0 (1.9 to 2.1)</td>
<td>1.44</td>
</tr>
<tr>
<td>&gt;10</td>
<td>197</td>
<td>79,598</td>
<td>2.5 (2.1 to 2.8)</td>
<td>1.63</td>
</tr>
</tbody>
</table>

**Time since first ACEI use (years)**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Person years</th>
<th>Incidence rate (95% CI)†</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>1617</td>
<td>1,158,441</td>
<td>1.4 (1.3 to 1.5)</td>
<td>1.24</td>
</tr>
<tr>
<td>5.1-10</td>
<td>1155</td>
<td>647,103</td>
<td>1.8 (1.7 to 1.9)</td>
<td>1.33</td>
</tr>
<tr>
<td>&gt;10</td>
<td>414</td>
<td>171,596</td>
<td>2.4 (2.2 to 2.7)</td>
<td>1.62</td>
</tr>
</tbody>
</table>

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.
*Use of other antihypertensive drugs (including of use of both ACEIs and ARBs) was considered in model but not shown in table.
†Per 1000 person years.
‡Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol related disorders, history of lung diseases before cohort entry (pneumonia, tuberculosis, and chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and anti-hypertensive classes in year before cohort entry.

Diuretics showed null associations overall (hazard ratio 0.93, 0.82 to 1.06) and by cumulative duration of use (supplementary table I).

Short durations of follow-up (median 3.5 [range 1.3-5.1] years), the lack of sufficient follow-up to assess longer-term outcomes such as cancer. This is partly...
Q#10

In Summary, for those who took anti-hypertensives:

**Benefits in NNT**
- 1 in 125 were helped (prevented death)
- 1 in 67 were helped (prevented stroke)
- 1 in 100 were helped (prevented heart attack*)

*Fatal and non-fatal myocardial infarction and sudden or rapid cardiac death

**Harms in NNT**
- 1 in 10 were harmed (medication side effects, stopping the drug)

NNT: 125 death, 67 stroke, 100 MI

NNH: 10 for side effect to d/c drug

Source:
- Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure avg- eraging 90 through 114 mm Hg. JAMA. 1970 Aug 17;213(7):1143-52.
- Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures avg- eraging 115 through 129 mm Hg. JAMA. 1967 Dec 11;202(11):1028-34.

Efficacy Endpoints: Mortality, heart attack, stroke

Harm Endpoints: Adverse medication effects leading to drug stoppage

**Narrative:** Hypertension (elevated blood pressure) is associated with an increased risk of cardiovascular events and mortality. However, numerous studies have shown a number of medications when given to reduce BP can reduce the risk of developing cardiovascular problems like heart attacks and strokes.
Back My Patient & My Colleagues

- Should I stop the ACE-I for my patient?
- What should I say to my colleagues?
Well designed population based cohort with strong methods; adjustment partly addresses confounding but bias may remain

Magnitude of possible harm is small to any individual, may be moderate applied to a population

Additional long term studies will be useful

In the meantime, must consider the significant benefit to ACE-I and individualize treatment decisions.