Comparative risk of incidence cancer between histamine-2 receptor antagonists: Preliminary results and lessons from the Feasibility test
In September 2019, FDA warned about probable carcinogen, N-nitrosodimethylamine (NMDA) in the most famous heartburn medication (ranitidine, zantac).

Subsequently, ranitidine has been voluntarily recalled from the market.

Background

• NDMA is classified as a probable human carcinogen (group 2A, a substance that could cause cancer) based on results from laboratory tests

• NDMA is a known environmental contaminant and found in water and foods, including meats, dairy products and vegetables
Background

• It was reported that oral intake of ranitidine increased urinary excretion of NMDA

• If this low-dose NMDA in ranitidine increases the cancer risk, we need to recommend vigilant cancer screening for ranitidine heavy users.

Zeng et al., Carcinogenesis 2016
Background: Valsartan case

- Valsartan also has been recalled due to presence of NMDA

FDA updates on voluntary valsartan recalls

The FDA has provided guidance on valsartan recalls that have been occurring recently, providing lists of drugs affected, and methods of impurity testing...
Background: Valsartan case

In fact, valsartan use was not associated with increased cancer risk in observational study

Pottegård et al., BMJ 2018
Background: Reason for Feasibility test in distributed observational research

The likelihood of transforming matter into energy is something akin to shooting birds in the dark in a country where there are only a few birds. Einstein, 1935

Ranitidine is an over-the-counter drug

- To understand how information of OTC drugs have been captured and stored in the OMOP-CDM databases across the various countries and healthcare system
- To understand real-world clinical patterns

Method

• Study population (Target and Comparator)
  – Exposure to one of the H2 Receptor Antagonists (H2RAs) of interest longer than 30 days with allowing gaps between the treatment
  – Without use of other H2RAs except the treatment of interest during a previous year
  – Without previous cancer

• List of H2RA
  – Ranitidine, Cimetidine, Nizatidine, Roxatidine, Ramotidine, Lafutidine

https://github.com/ohdsi-studies/RanitidineCancerRisk
Method

- Primary outcome: Overall cancer except thyroid cancer
- Secondary outcomes: Overall cancer, cancer death, and 16 types of cancer
- 99 negative control outcomes
- The hazard ratio of the outcomes for each pairwise comparison of H2RA uses will be estimated

https://github.com/ohdsi-studies/RanitidineCancerRisk
## Preliminary result

### Cohort size, outcome incidence

<table>
<thead>
<tr>
<th>Database</th>
<th>Target</th>
<th>Comparator</th>
<th>Number of subjects, n</th>
<th>Median follow-up duration, days</th>
<th>Incidence rate, per 1000 PY</th>
<th>MDRR</th>
</tr>
</thead>
<tbody>
<tr>
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<td>T</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td>NHIS-NSC</td>
<td>Ranitidine</td>
<td>Cimetidine</td>
<td>34,598</td>
<td>135,155</td>
<td>392</td>
<td>755</td>
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<tr>
<td></td>
<td></td>
<td>Famotidine</td>
<td>38,574</td>
<td>14,037</td>
<td>377</td>
<td>363</td>
</tr>
<tr>
<td>Ajou (EHR)</td>
<td>Ranitidine</td>
<td>Cimetidine</td>
<td>8,564</td>
<td>16,000</td>
<td>622</td>
<td>1,141</td>
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<tr>
<td></td>
<td></td>
<td>Famotidine</td>
<td>8,968</td>
<td>1,642</td>
<td>625</td>
<td>501</td>
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<tr>
<td>Kangdong (EHR)</td>
<td>Ranitidine</td>
<td>Cimetidine</td>
<td>4,993</td>
<td>1,432</td>
<td>870</td>
<td>858</td>
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<tr>
<td></td>
<td></td>
<td>Famotidine</td>
<td>5,051</td>
<td>486</td>
<td>870</td>
<td>133</td>
</tr>
<tr>
<td>CUMC (EHR)</td>
<td>Ranitidine</td>
<td>Cimetidine</td>
<td>19,113</td>
<td>220</td>
<td>950</td>
<td>1,063</td>
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<tr>
<td></td>
<td></td>
<td>Famotidine</td>
<td>18,461</td>
<td>18,119</td>
<td>956</td>
<td>918</td>
</tr>
</tbody>
</table>

[https://data.ohdsi.org/RanitidineCancerRisk/](https://data.ohdsi.org/RanitidineCancerRisk/)
Preliminary result (Survival curve):
Ranitidine vs Cimetidine

ITT

ITT with 1-year blanking period

https://data.ohdsi.org/RanitidineCancerRisk/
Violation of the proportional hazards assumption in Cox regression

- Cox proportional hazard model assumes that \textit{ratio} of hazards for any two individuals is constant over time.

Example of \textbf{Non}-proportional hazards
My experience: ranitidine vs cimetidine

ITT

ITT with 1-year blanking period

https://data.ohdsi.org/RanitidineCancerRisk/
Conclusion

- Feasibility test can
  - Validate the cohort definition
    - Previous outcome cohort definitions did not work against EHR data of Ajou university hospital ➔ We revised cohort definition
    - Estimate unadjusted outcome incidence and MDRR
    - Estimate how many negative control outcomes are usable (only one third)
  - Assess the real-world clinical pattern
    - The duration of drug continuation is much longer than I expected
    - The medication patterns was different between US and Korea
  - Assess the feasibility of overall study design
    - It seems feasible to investigate evidence for this OTC drug
    - Identify the violation of proportional hazards assumption

- It is easy to implement of feasibility test in current OHDSI ecosystem
- I recommend to implement feasibility test step in all future OHDSI PLE studies
Join the study!

Comparative risk of the incident cancer between histamine-2 receptor antagonists 📝

Researchers

SCYou  Seng Chan You

Dear all,

The new network study is launched to compare the risk of incident cancer between histamine-2 receptor antagonists.

Comparative risk of the incident cancer between histamine-2 receptor antagonists

Abstract: Dietary N-nitrosodimethylamine (NDMA) has been shown to be carcinogenic in animals, however, evidence from population-based studies is inconclusive. The U.S. Food and Drug Administration has issued a statement on ranitidine because they may contain unacceptable levels of NDMA in 2019. To date, there have been several studies regarding association between NDMA exposure and risk of cancer, however, real-world evidence of cancer risk in relation with ranitidine is scarce. We aim to evaluate the comparative risk of incident cancer in patients exposed to various H2 receptor antagonists (H2RAs). We will conduct systematic, multinational study to estimate the relative risk of primary outcome (overall cancer except thyroid cancer) and secondary outcomes (overall cancer, 16 types of cancer, and cancer mortality) in ranitidine cohort. We will compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model after propensity score adjustment.

The package for feasibility test is available at the OHDSI-Studies Repo 2

You can see the more detailed protocol here 3.

Currently, We are searching for collaborators to join this network study and to execute feasibility test of this study. Please follow the instruction 2, and please send me the result from the feasibility test first before running execute function.

https://github.com/ohdsi-studies/RanitidineCancerRisk
Thank You
for your time