Sharing experience and the preliminary experience from on-going international OHDSI study:
Comparative risk of the incidence cancer between histamine-2 receptor antagonists

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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

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

\[\text{Zeng et al., Carcinogenesis 2016}\]

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

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

SCYou  Seng Chan You  4d
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.

Sharing the study protocol

- 35-page long protocol includes details of statistical analytic plan and outcome definitions with reference
- It has been registered to EU PAS

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

• Study population
  – Exposure to one of the H\textsubscript{2} Receptor Antagonists (H\textsubscript{2}RAs) of interest longer than 30 days with allowing gaps between the treatment
  – Without use of other H\textsubscript{2}RAs except the treatment of interest during a previous year
  – Without previous cancer

• Target group: Ranitidine user

• Comparator group: Other H\textsubscript{2}RA
  – Nizatidine, Roxatidine, Famotidine, Lafutidine
  – Cimetidine user was excluded from the comparator group since feasibility study shows no empirical equipoise between ranitidine and cimetidine users.

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

• Primary outcome: Overall cancer except non-melanoma skin cancer
• Secondary outcomes: Overall cancer, cancer death, and 16 types of cancer
• 119 negative control outcomes
• The hazard ratio of the outcomes between ranitidine versus other H$_2$RA users will be estimated by using propensity score model

https://github.com/ohdsi-studies/RanitidineCancerRisk
Three assumptions to draw causal inference (Neyman-Rubin Causal model)

- **Stable Unit Treatment Value Assumption (SUTVA)**
  - The potential outcomes for any unit do not vary with the treatment assigned to other units
  - For each unit, there are no different forms or versions of each treatment level, which lead to different potential outcomes

- **Strong ignorability**
  - Ignorability (Unconfoundedness)
    - Given the background variable, $X$, treatment assignment $T$ is independent to the potential outcomes
  - **Positivity (Overlap)**
    - For any value of $X$, treatment assignment is not deterministic

Rosenbaum and Rubin, Biometrika, 1983
Holland, Am Stat Assoc, 1986
Three assumptions to draw causal inference (Neyman-Rubin Causal model)

- **Stable Unit Treatment Value Assumption (SUTVA)**
  - The potential outcomes for any unit do not vary with the treatment assigned to other units
  - For each unit, there are no different forms or versions of each treatment level, which lead to different potential outcomes
  - Appropriate phenotyping

- **Strong ignorability**
  - **Ignorability (Unconfoundedness)**
    - Given the background variable, X, treatment assignment $T$ is independent to the potential outcomes
    - Check balance of more than 10,000 covariates between two groups (S.Diff<0.1)
  - **Positivity (Overlap)**
    - For any value of X, treatment assignment is not deterministic
    - Determine empirical equipoise if majority of patients have preference score between 0.3 and 0.7

Rosenbaum and Rubin, Biometrika, 1983  Holland, Am Stat Assoc, 1986
Treatment strategies:
- Ranitidine
- Other H$_2$RAs

Should be prescribed or longer than 30 days allowing gap of 30 days

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect

Eligibility criteria:
- Adult (≥ 19 yr)
- Without previous cancer
- Without other H$_2$RAs within one year

Outcome:
Overall cancer except non-melanoma skin cancer

Index: Time zero
Follow-up duration
1,175,689 adults (≥20 years old) who exposed to H2RAs longer than 30 days without history of cancer

905,607 Ranitidine users

270,082 Other H2RAs users

1:1 Propensity-score matching

676,998 Patients not matched

78,049 Patients meeting eligibility criteria from the Asian databases (NHIS-NSC, AUSOM, HUMIC, KDH)

758,683 Patients meeting eligibility criteria from the American databases (IQVIA AmBER, CUIMC, STARR)

338,957 Patients meeting eligibility criteria from the European databases (SIDIAP, IMRD, IQVIA DA Ger)

Patients not matched

228,609 Ranitidine users matched

228,609 Other H2RAs users matched

Diagnostics

11,203 Patients did not pass the diagnostics

217,406 Ranitidine users in the primary analysis

217,406 Other H2RAs users in the primary analysis
Empirical equipoise (overlap)

IQVIA AmbEMR

CIUMC

SIDIAP

NHIS-NSC

Ranitidine  Other HRAs

Density

Preference score

0.00  0.25  0.50  0.75  1.00

80.0% is in equipoise

69.6% is in equipoise

55.5% is in equipoise

89.1% is in equipoise
Number of covariates: 18,882
After matching max(absolute): 0.04

IQVIA
AmbEMR

Number of covariates: 19,045
After matching max(absolute): 0.06

CIUMC

Number of covariates: 9,870
After matching max(absolute): 0.10

SIDIAP

Number of covariates: 11,021
After matching max(absolute): 0.04

NHIS-NSC
Preliminary result: Survival curves

IQVIA Ambulatory EMR_Overall cancer except skin cancer

CUIMC_Overall cancer except skin cancer

SIDIAP_Overall cancer except skin cancer

NHIS-NSC_Overall cancer except skin cancer

Cumulative Incidence

Follow-Up Duration (Days)

P = 0.996

P = 0.609

P = 0.042

P = 0.015

Number at risk
Ranitidine
Other H2RAs

190,614 153,572 121,097 94,903 72,495 54,112 38,796 26,405 21,879 190,614 151,944 120,817 94,349 71,876 53,284 36,365 29,021 21,617

Number at risk
Ranitidine
Other H2RAs

10,813 9,411 8,038 6,836 5,695 4,726 3,856 3,133 2,575 10,813 9,341 8,053 6,718 5,486 4,439 3,602 2,889 2,362

Number at risk
Ranitidine
Other H2RAs

3,177 2,994 2,748 2,556 2,372 2,162 2,003 1,848 1,679 3,177 2,990 2,769 2,580 2,387 2,178 2,003 1,848 1,676

Number at risk
Ranitidine
Other H2RAs

12,602 11,551 10,502 9,186 8,231 7,281 6,444 5,594 4,794 12,602 11,557 10,391 9,122 8,194 7,204 6,327 5,457 4,680
Preliminary result: Survival curves
Preliminary result: Meta-analysis using all results

<table>
<thead>
<tr>
<th>Source</th>
<th>Ranitidine Total</th>
<th>Ranitidine Event</th>
<th>Other HRAs Total</th>
<th>Other HRAs Event</th>
<th>HR</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQVIA Ambulatory EMR</td>
<td>190,814</td>
<td>7,459</td>
<td>190,814</td>
<td>7,412</td>
<td>1.00</td>
<td>[0.97; 1.03]</td>
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<tr>
<td>CUIMC</td>
<td>10,813</td>
<td>635</td>
<td>10,813</td>
<td>631</td>
<td>0.97</td>
<td>[0.87; 1.08]</td>
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<tr>
<td>STARROMOP</td>
<td>3,294</td>
<td>149</td>
<td>3,294</td>
<td>157</td>
<td>0.94</td>
<td>[0.75; 1.17]</td>
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<tr>
<td>SIDIAP</td>
<td>3,177</td>
<td>409</td>
<td>3,177</td>
<td>353</td>
<td>1.16</td>
<td>[1.01; 1.34]</td>
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<tr>
<td>imrd1903</td>
<td>633</td>
<td>59</td>
<td>633</td>
<td>64</td>
<td>0.97</td>
<td>[0.68; 1.39]</td>
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<tr>
<td>IQVIA DA Germany</td>
<td>2,974</td>
<td>487</td>
<td>2,974</td>
<td>468</td>
<td>1.05</td>
<td>[0.93; 1.19]</td>
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<tr>
<td>NHIS-NSC</td>
<td>12,602</td>
<td>1,267</td>
<td>12,602</td>
<td>1,125</td>
<td>1.11</td>
<td>[1.02; 1.20]</td>
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<tr>
<td>AUSOM</td>
<td>1,937</td>
<td>116</td>
<td>1,937</td>
<td>119</td>
<td>0.93</td>
<td>[0.72; 1.20]</td>
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<tr>
<td>HUMIC</td>
<td>1,456</td>
<td>91</td>
<td>1,456</td>
<td>78</td>
<td>1.21</td>
<td>[0.89; 1.64]</td>
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<tr>
<td>KDH</td>
<td>909</td>
<td>27</td>
<td>909</td>
<td>32</td>
<td>0.84</td>
<td>[0.50; 1.41]</td>
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<tr>
<td>Meta-analysis</td>
<td>228,609</td>
<td>10,699</td>
<td>228,609</td>
<td>10,439</td>
<td>1.03</td>
<td>[0.98; 1.08]</td>
<td></td>
</tr>
</tbody>
</table>

Overall: 457,218 21,398 457,218 20,878 1.03 [0.99; 1.06]

Heterogeneity: $I^2 = 19.6\%$
Preliminary result: Meta-analysis using results passing diagnostics

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<th>Other HRAs</th>
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<td>1,267</td>
<td>12,602</td>
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<tr>
<td>Overall</td>
<td>217,406</td>
<td>9,770</td>
<td>217,406</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 67.0\%$
Thank You for your time