The Use of Real-World Data and Real-World Evidence in Drug Development

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies. The author have no conflicts of interest to disclose.

Outline

- Overview of Real-World Data/Real-World Evidence
- Things to Consider in Conducting an observational study
- Illustration of an Observational Study with Case Study
  - Clarithromycin and CV risk
- Concluding Remarks

Definition

- Real-World Data (RWD): data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources
  - Electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices
- Real-World Evidence (RWE): the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD
  - RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, such as large simple trials, pragmatic trials, and *observational studies (prospective and/or retrospective*)

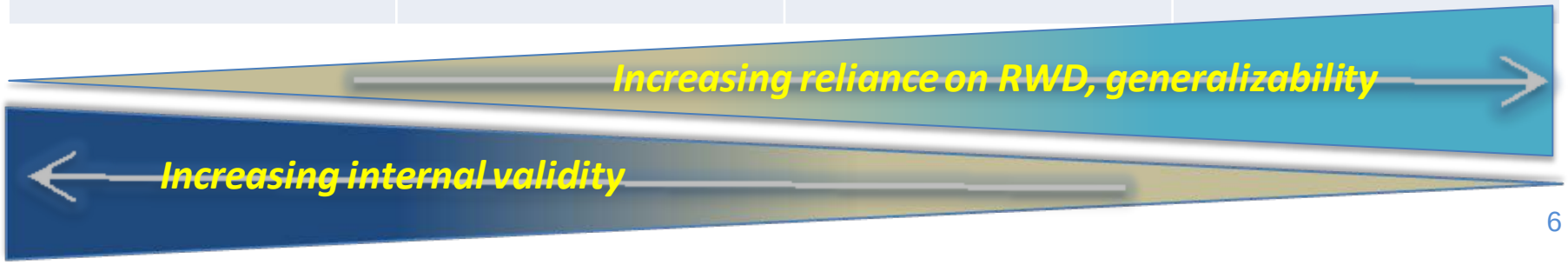
Source: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Background

- 21st Century Cures Act (2016)
  - Designed to accelerate drug development and bring new innovation and advances faster and more efficiently to the patients
  - FDA shall establish a program to evaluate the potential use of real-world evidence (RWE) to support:
    - Approval of new indication for a drug already approved
    - Post-approval study requirements
- PDUFA VI Commitment Letter (2017)
  - Enhance use of RWE in regulatory decision making
    - Initiate appropriate activities (e.g., pilot studies or methodology development projects) to address key issues in the use of RWE for regulatory decision-making purposes
    - Publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions (e.g., supplemental applications, post-marketing applications)
- Guidance "Framework for FDA's Real-World Evidence Program" (2018)
  - FDA's RWE program will focus on exploring the potential use of RWD/RWE to support regulatory decisions about product effectiveness
    - Specifically, changes to labeling about drug product effectiveness including adding or modifying an indication such as change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information

From Traditional Clinical Trials To Observational Study

Randomized, Interventional Clinical Trial		Non-randomized, Interventional Clinical Trial	Non-randomized, non-interventional study
Traditional Clinical Trial	Large Simple Trial, Pragmatic Trial	Single-arm Trial	Observational Study
• Single or double blind • Supported by a research infrastructure that is largely separate from routine clinical practice • Designed to control variability and maximize data quality • Have restrictive eligibility criteria • Strict follow-up	• Conduct ***in routine practice setting*** • Minimal eligibility criteria • Less strict follow-up	• Typically, in rare disease or oncology • External control from historical data or RWD	• Treatment or drug is given based on physician's decision • Depending on data collection method: retrospective study vs. prospective study • Retrospective study: study population is defined using existing RWD data • Prospective study: data is collected prospectively and follow patients in routine clinical setting



Example of RWD

- Electronic Health Record (EHR): an individual patient record created in physician's office during routine care
  - Include medical history, diagnosis, lab and diagnostics test, treatment history, pharmacy records, radiology images
- Medical claims data: generated through paid claims in administrative system
  - Include information necessary for reimbursement of medical services such as diagnosis, procedure, dispensed prescription medication
- Registry data: organized system that uses observational study methods to collect data to evaluate particular disease, condition or exposure
  - Cancer registry, pregnancy registry, transplant registry

Note: these are not intended for research or regulation purpose.
These are not under the control of FDA-regulated entities such as pharmaceutical company

Misuse of RWD: Hydroxychloroquine Controversy

FDA issues emergency authorization of anti-malaria drug for coronavirus care

The drugs have been championed by President Donald Trump for treatment despite scant evidence.

FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems

Does not affect FDA-approved uses for malaria, lupus, and rheumatoid arthritis

[4-24-2020] FDA Drug Safety Communication

Trump says he's taking hydroxychloroquine, despite scientists' concerns

The anti-malarial drug has not been shown to be effective in treating Covid-19, the disease caused by the novel coronavirus.

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study period and met the inclusion criteria. Of these, 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6·1%; 2·369, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; 3·561, 2·760–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation.

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The New York Times | https://nyti.ms/3ey8clU

Scientists Question Validity of Major Hydroxychloroquine Study

Experts demanded verification of data and methods used in a study of drugs to treat Covid-19. The study suggested the drugs might have increased deaths.

By Roni Caryn Rabin

Published May 29, 2020 Updated May 30, 2020

THE LANCET

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COMMENT | VOLUME 395, ISSUE 10240, P1820, JUNE 13, 2020

Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra • Frank Ruschitzka • Amit N Patel

updates

Surgisphere: governments and WHO changed Covid-19 policy based on suspect data from tiny US company

Surgisphere, whose employees appear to include a sci-fi writer and adult content model, provided database behind Lancet and New England Journal of Medicine hydroxychloroquine studies

Melissa Davey *in Melbourne and* **Stephanie Kirchgaessner** *in Washington and* **Sarah Boseley** *in London*

Wed 3 Jun 2020 14.47 EDT

The New York Times | https://nyti.ms/2Au654f

F.D.A. Revokes Emergency Approval of Malaria Drugs Promoted by Trump

The agency said that a review of some studies showed that the drugs' potential benefits in treating Covid-19 did not outweigh the risks.

By Katie Thomas

June 15, 2020

Goal of RWD/RWE

- Increase the diversity of populations and clinical settings that reflect actual use in practice
- Improve study efficiency by larger sample size, lower resource intensity and making use of existing data
- **While maintaining current <u>evidentiary standards</u>**

Substantial Evidence of Effectiveness

A. Statutory standard

In 1962, Congress required for the first time that drugs be shown to be effective as well as safe A drug's effectiveness must be established by "substantial evidence," which is defined as:

> "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[5]

The 1998 guidance was issued in response to the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115), which stated that the substantial evidence requirement for effectiveness, which had generally been interpreted as calling for two adequate and well-controlled trials, could also be met by a single trial[2] plus confirmatory evidence. The

https://www.fda.gov/media/133660/download

Characteristics of Adequate & Well-Controlled Study (21CFR314.126)

1. Clear objectives, summary of methods & results
2. Design permits a valid comparison with a control (concurrent and historical controls)
3. Adequate selection of patients
4. Assigning patients to treatment and control groups minimizes bias
5. Adequate measures to minimize biases on subjects, observers, and analysts
6. Well-defined and reliable assessment of subjects' responses
7. Adequate analysis to assess drug results

randomization

blinding

Key question: non-traditional RCT or observational study can meet these characteristics?

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126

Activities within FDA

- Sentinel initiative
  - https://www.sentinelinitiative.org/
- FDA regulatory science projects
  - Pharmacoepidemiologic studies in collaboration with other Federal partners
  - RCT DUPLICATE initiative
    - https://healthpolicy.duke.edu/events/evaluating-rwe-observational-studies-regulatory-decision-making-lessons-learned-trial
  - Grant awards for projects exploring the use of Real-World Data to generate Real-World Evidence in regulatory decision making in 2020
    - https://www.fda.gov/drugs/science-and-research-drugs/fda-announces-4-grant-awards-projects-exploring-use-real-world-data-generate-real-world-evidence
- Development of guidances
  - https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Procedural

237309153ft.docx

Real-World Data: Assessing Electronic Health Records and Medical Claims Data for Regulatory Purposes

Coming soon

Guidance for Industry

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Current Status of RWD/RWE in Drug Development

- In drug safety,
  - RWD has been widely used in postmarket drug safety setting even before 21st Century Cures Act
- In drug efficacy,
  - Focus of FDA's RWE program
  - Historical control has been used mainly in rare disease and oncology drug development
  - Still limited number of approved drug for new indication using RWD as a *primary evidence*
  - Number of IND submissions using RWD is expected to increase

Example: IBRANCE® (Indication expansion)

- Palbociclib (Ibrance): approved for the treatment of estrogen receptor-positive, HER2-negative advanced breast cancer in women in combination with letrozole in 2015 (accelerated approval)
- In 2019, supplemental NDA was approved to expand the indications to male patients with breast cancer
- Data: One RCT and Two observational studies
  - PALOMA-2: Randomized clinical trial
    - Updated results in women with breast cancer were reviewed and used as the primary evidence
  - A5481097: retrospective cohort study with administrative claims data
    - This study was not considered for approval because of limitations
  - Flatiron health study: retrospective cohort study with EHR data
    - This study was used for supportive evidence of efficacy of palcocicib for male patients with breast cancer

Source: FDA's review, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/207103Orig1s008.pdf

Benefit and Risk Assessment of IBRANCE®

	Evidence	Conclusion
Benefit	• Based upon results from Study PALOMA-2 in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated, the estimated median PFS in the palbociclib plus letrozole arm was 27.6 months (95% CI = 22.4, 30.3) compared to 14.5 months (95% CI: 12.3, 17.1) in the placebo plus letrozole arm (HR = 0.563 95% CI: 0.461, 0.687; p< 0.001). • Based upon the results of the Flatiron Health Study, male patients with breast cancer who received palbociclib in combination with endocrine therapy (aromatase inhibitors or fulvestrant) tolerated this therapy and experienced tumor responses.	• Treatment with palbociclib plus letrozole demonstrates a statistically significant and clinically meaningful improvement in PFS. • Updated results based upon additional follow-up in the PALOMA-2 trial show persistent benefit of treatment with palbociclib plus letrozole therapy. • Electronic health record data provide supportive evidence of the use and activity of palbociclib in male patients with breast cancers.
Risk and Risk Management	• Limited data were provided for support a comprehensive evaluation of safety in male patients with breast cancer. However, no new safety signals have been identified in this population based upon review of postmarketing reports, the review of cases in Pfizer global safety database and in two phase 1 studies with palbociclib monotherapy which enrolled male patients with solid tumor malignancies and mantle cell lymphoma.	• The safety profile of palbociclib is acceptable for the intended population, and manageable with current labeling and routine oncology care. • No new safety signals have been identified in male patients receiving palbociclib.

Source: FDA's review, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/207103Orig1s008.pdf

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Things To Consider in Conducting an Observational Study

Focused on Retrospective Observational Study

Revisit: Characteristics of Adequate & Well-Controlled Study (21CFR314.126)

1. Clear objectives, summary of methods & results
2. Design permits a valid comparison with a control (concurrent and historical controls)
3. Adequate selection of patients
4. Assigning patients to treatment and control groups minimizes bias
5. Adequate measures to minimize biases on subjects, observers, and analysts
6. Well-defined and reliable assessment of subjects' responses
7. Adequate analysis to assess drug results

Key to success for using observational study

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126

Key Components in Designing Observational Study

Study Objective	**Data Source**	**Type of study**	**Study population: inclusion/ exclusion criteria**
Exposure: strategy to capture accurate exposure information and to avoid misclassification	**Outcome: method for adjudication or validation of outcome**	**Sample size estimation**	**Statistical Method** **•Confounding adjustment method** **•Primary Outcome model** **•Potential sensitivity analysis**

This should be all pre-specified in study protocol or statistical analysis plan

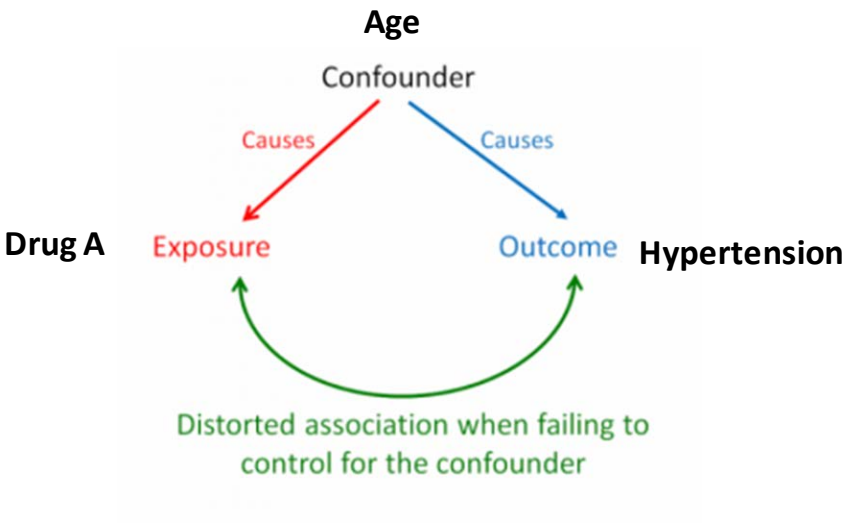
Causal Inference

- Association is not necessarily causation
  - Causal inference aims to draw causal conclusion on the effect of drug on the outcome based on data
- Randomized clinical trial: gold-standard for causal inferences
  - Treatment assignment is random
  - In theory, baseline characteristics between groups are similar
  - Difference in the outcome can be considered as a causal treatment effect
- Observational study
  - Treatment selection is NOT random
  - Difference in the outcome is not the causal effect of treatment *due to measured and unmeasured confounders*
  - *Goal: to mimic RCT*

Major challenge in observational study : treatment groups are not comparable!

Confounders

Hypothetical example: effect of drug A on treating hypertension compared to a comparator



- When the distribution (such of mean) of age is not balanced between drug A and comparator (drug A has more younger patients), the effect of drug on hypertension will be confounded by age
- How to deal with unbalanced age variable
  - Adjust age variable in the outcome model
  - Matching on age
  - Weighting
- It may not be feasible when there are many confounders
  - Solution: propensity score method

Propensity Score Method

What is it?	How is it estimated?	What do we do with it?
• Probability of treatment assignment conditioned on measured covariates • Summary measure of multiple confounders • Supported by solid statistical foundation	• Statistical model such as logistic regression • Need assumptions such as consistency, positivity, no unmeasured confounders and correct model specification • Machine learning technique can be used to relax the assumption of correct model specification	• Matching • Inverse probability of treatment weighting (IPTW) • Stratification

Propensity Score Method

- *Goal of observational study is to mimic RCT*
- Goal of PS analysis is to make comparable treatment groups like RCT
- PS analysis should be performed before conducting outcome analysis
  - Even in retrospective study, you should be blinded to the outcome when conducting PS analysis
- Diagnostics should be always considered in PS analysis
  - Overlap of PS distribution between treatment groups
  - Covariates balance diagnostics before and after PS application
    - Statistical testing such as chi-square test or t-test is not recommended for large sample size
    - Standardized mean difference based on ±10% has been well accepted
  - This also should be done before outcome analysis

Other Sources of Potential Biases

- Drug exposure misclassification
- Outcome misclassification
- Selection bias
- Residual confounding
- Unmeasured confounders

Sensitivity analyses are always recommended

Case Study of Conducting Observational Study

Clarithromycin – CV risk

FDA initiated project

This work has been published by American Journal of Epidemiology
: https://www.ncbi.nlm.nih.gov/pubmed/29036565

Study Overview

- Objective: To evaluate risks of cardiovascular events and all-cause mortality in adult patients by use of clarithromycin
- Design: A retrospective cohort study of two new user cohorts in the U.K. Clinical Practice Research Datalink (CPRD), from January 1, 2000 through December 31, 2013
  - All indication cohort (Main cohort)
    - Clarithromycin (CLA) was compared to Doxycycline (DOXY) and Erythromycin (ERY)
  - *H. pylori* indication cohort
    - A triple therapy with and without clarithromycin
      - A proton pump inhibitor (PPI)+amoxicillin +clarithromycin(PPI+AMOX+CLA)
      - PPI + amoxicillin + metronidazole (PPI+AMOX+MET)
- Outcomes: A composite outcome defined as any first occurrence of AMI, stroke and all-cause mortality / All-cause mortality

Statistical Method

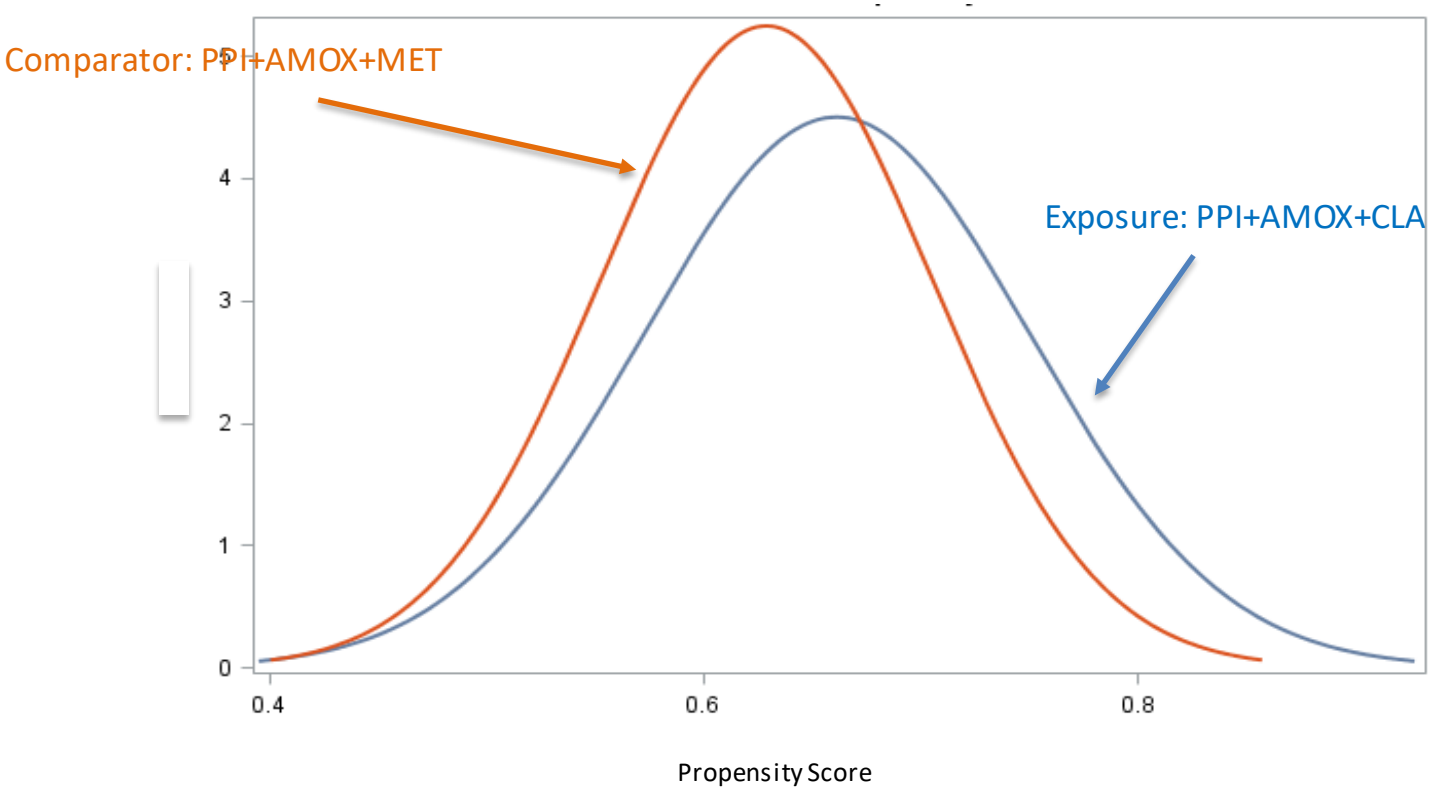
- Confounding adjustment method: Inverse probability of treatment weighting (IPTW) based on propensity score
  - Propensity score was estimated by logistic regression by adjusting 40 potential confounders
  - Weight for each subject was calculated by inverse of propensity score
- Primary outcome model: Weighted Cox proportional hazard model

Baseline Characteristics

	Before PS weighting			After PS weighting		
Characteristic	**% patients**			**% patients**		
	Clarithromycin	Doxycycline	Erythromycin	Clarithromycin	Doxycycline	Erythromycin
AGE (yr)						
40-64	62.0	70.7	67.2	65.8	66.9	67.2
65-74	21.1	18.0	18.5	19.4	18.9	18.8
75-85	16.9	11.3	14.3	14.8	14.2	14.0
Indication						
Unknown	26.9	31.3	29.9	29.5	29.7	30.0
Pneumonia and Influenza	1.1	0.6	0.7	0.8	0.8	0.8
COPD/chronic pulmonary	2.6	1.9	1.5	2.0	1.8	1.8
Acute bronchitis and bronchiolitis	22.1	9.7	15.9	16.3	15.3	15.4
Acute respiratory tract infection and disease	12.7	34.0	19.1	20.7	22.0	22.0
Respiratory symptoms	17.7	11.7	12.8	14.1	13.7	13.5

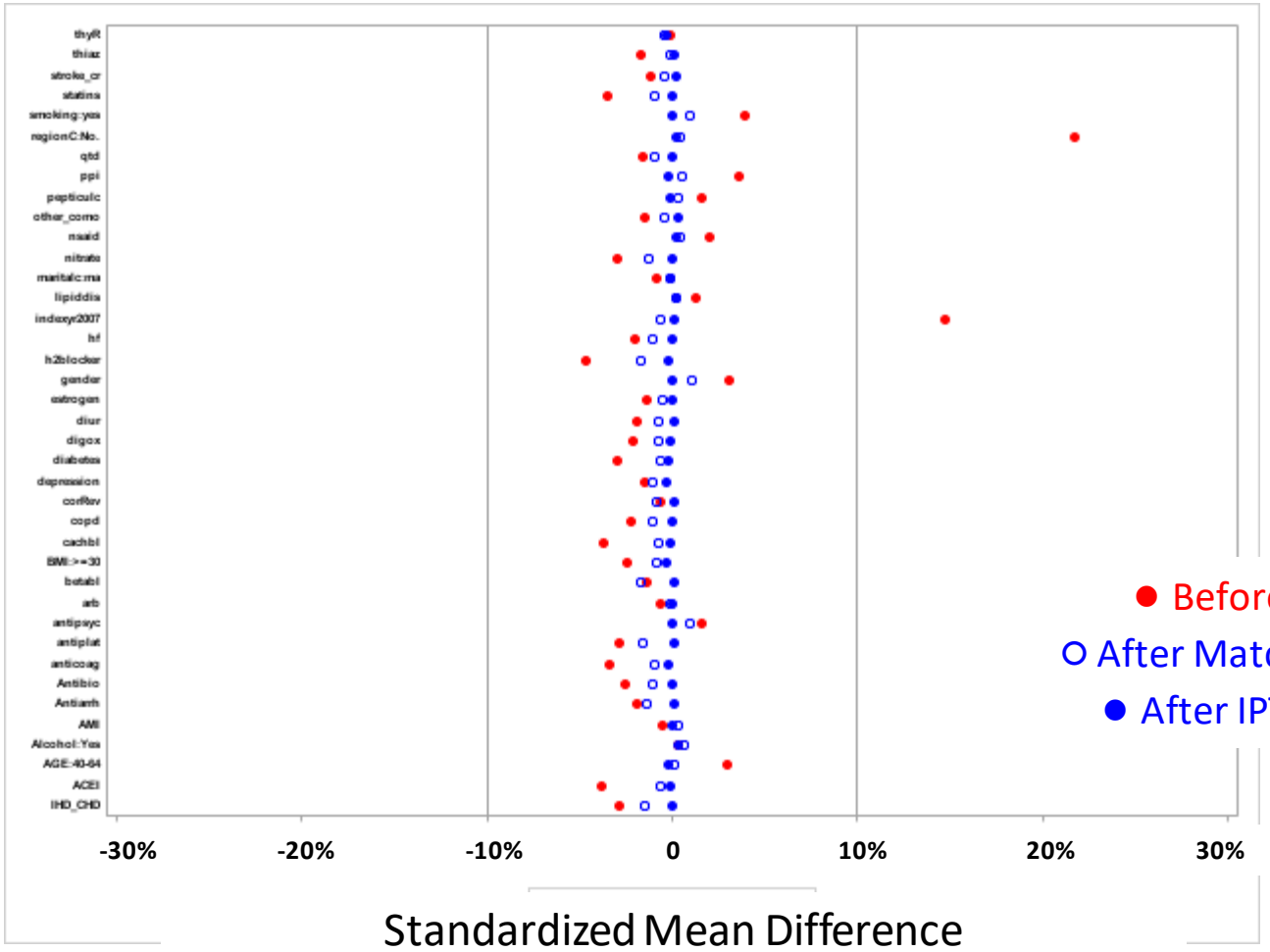
Selected covariates

Distribution of PS Shows Good Overlap



For illustration purpose, this is from h.pylori cohort with two groups for comparison

Balance Checking



For illustration purpose, this is from h.pylori cohort with two groups for comparison.

Study Conclusion

- In main cohort, use of clarithromycin showed statistically significant increased risk of all-cause mortality compared to both doxycycline and erythromycin
  - The risk was dose-dependent
  - Clarithromycin group also showed slight increased risk of AMI and stroke compared to both doxycycline and erythromycin
- In *H.pylori* eradication cohort, mortality slightly increased with clarithromycin containing triple therapy, which was not statistically significant
  - Possibly due to lack of study power
- Study findings were incorporated in update of Drug Safety Communication (DSC) in 2018

Closing Remarks

- 21st century cures act opened a new door in drug development
- Still require high standard to meet regulatory requirement
  - Major challenge in non-intervention/non-randomized studies is to overcome potential biases from multiple sources
  - Should make extra efforts in designing the study
- Early communication with FDA is key to success

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Question to
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