Causal Inference for Real-World Evidence: Propensity Score Methods and Case Study

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Disclaimer

This presentation reflects the view of the author and should not be construed to represent FDA's views or policies.

Course Outline

- Causal Inference for Real-World Evidence (RWE) : Propensity Score Methods and Case Study

- This short course will cover:
  - Causal inference framework
  - Propensity Score (PS) and PS-based methods
  - Associated target population and target estimand

Course Outline

- At the conclusion of this short course, participants should be able to:
  - Distinguish causation from association
  - Understand why the use of standard statistical models (including machine learning) is inadequate to estimate a causal effect
  - Understand causal inference framework and how to formally define a target causal estimand
  - Understand necessary conditions to infer a causal effect and inherent limitation of observational study
  - Understand methodologic basis of PS matching and weighting (including marginal structural model)
  - Weigh pros and cons of different methods to a causal inference problem
  - Use best practices of matching/weighting methods to a causal inference problem
  - Implement different causal methods and interpret findings accordingly

Course Outline

- Throughout, assume that we are interested in estimating the causal effect of a binary, point drug treatment setting:
  - Treatment (new drug) vs. control (active or placebo)
  - Patients take a drug at baseline (one time)
  - No censoring or loss to follow-up

Part 1

Introduction to Causal Inference

Introduction to Causal Inference: Association vs. Causation

- Standard statistical models describe associational relationship:

$$Y = \beta_0 + \beta_1 X + \varepsilon$$

- An associational concept: Bi-directional; any relationship that can be defined in terms of observed data

- A causal concept: Uni-directional; a relationship that CANNOT be defined from the observed data

Introduction to Causal Inference: When possible?

- When data attributes allow us to infer causal effect:
  - Data obtained from randomized trial
  - When outcome and covariate have a particular direction (time, space, etc.) in the absence of confounding
    - Central dogma: DNA -> RNA -> protein
    - RNA = $\beta_0 + \beta_1 \mathrm{DNA} + \varepsilon$

- Causal methods: aim to manipulate data so that it mimics (emulates) data from randomized trials

Introduction to Causal Inference: Randomized Trial vs. Observational Study

- Randomized clinical trial:
  - Treatment (intervention) assignment ← random
  - Two groups are similar on average
  - Difference in response ← treatment

- Observational study:
  - Treatment selection ← physician-patient preference
  - Difference in response ⇐ treatment only
  - Confounders: related to both treatment and outcome

Causal Inference

- Ideal solution: Conduct a randomized trial
- Even more ideal: The best way to obtain a causal effect of a drug T=0,1 on outcome Y from your sample
  - Observe Y under T=0 from everybody
  - Observe Y under T=1 from everybody

  } measured at the same time
  - Compare average of the two outcomes: $E(Y|T=0) - E(Y|T=1)$
- Requires to observe outcomes under treatment and control **simultaneously** from all subjects in the sample
- This problem leads to the notion of *"**potential outcome**"*
  - Some literature call it "*counterfactual*"

Potential Outcome: Hypothetical Example

- HIV/AIDS example
  - Treatment: Antiretroviral therapy (ART)
  - Observed outcome (Y): CD4 counts after taking or not taking ART, higher the better.
  - Truth: ART if beneficial ➔ Taking ART increases CD4 counts (improves immune system).
  - Confounding by age and sex: Older male (sicker) patients are more likely to take ART.

Patient	Age	Sex	ART?	Y	
1	45	male	1	500	
2	50	male	1	900	**Ave = 600**
3	55	male	1	600	
4	65	female	1	400	
5	23	male	0	800	
6	34	female	0	800	**Ave = 867**
7	40	female	0	1000	

Association
= 600 – 867 = -267 <0
→ Treatment is detrimental.

How potential outcomes relate to observed data

Patient	$Y(1)$	$Y(0)$	Causal effect	Received ART?	Y	
1	500	300	200	1	500	
2	900	200	700	1	900	**Ave = 600**
3	600	500	100	1	600	
4	400	100	300	1	400	
5	1200	800	400	0	800	
6	1000	800	200	0	800	**Ave = 867**
7	1300	1000	300	0	1000	
Average	843	529	314			

Association: $600 - 867 = \boxed{-267}$

Causation: $843 - 529 = \boxed{+314}$

Association and causation can be in completely opposite direction!

Defining Causal Estimands: Notation

- Focus on a binary point treatment setting:
  - i = 1,…, N : subject ID
  - Ti = 1 (treatment) or 0 (control): Treatment indicator for subject i
  - Yi(1): potential outcome for subject i when Ti=1
  - Yi(0): potential outcome for subject i when Ti=0
  - Yi: observed outcome for subject i
  - Ci: baseline confounder(s) for subject i

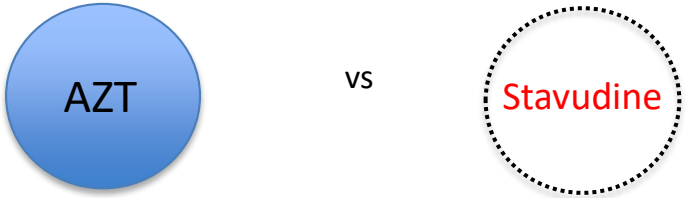
Defining Causal Estimands

- Individual-level causal effect: $Y_i(1) - Y_i(0)$
- Population-level causal effect = Average treatment effect (ATE)
  $= E\{ Y(1) - Y(0) \}$
- Subgroup-level causal effect
  - Average treatment effect among treated (ATT)
    $= E\{ Y(1) - Y(0) \mid T=1 \}$
- Can also define in terms of ratios, other sub-groups, etc.

Causal Estimands: ATE vs. ATT

Figure: Graphical representation of ATE and ATT

ATE: What happens if everybody had received AZT vs if everybody had received stavudine?



ATT: What happens if patient received AZT would have received stavudine?

Causal Inference: Limitations

- The fundamental **objective** of causal inference is to draw conclusions about potential outcomes from observed data.
- The fundamental **difficulty** is that potential outcomes are never fully observed.
- Deduce the relationship between treatment and potential outcomes given covariates ({Y(1), Y(0), T, C}) using partially observed data ({(Y, T, C)}. ➔ Need to make assumptions!

Causal Inference: Assumptions

1. Consistency: $Y = T * Y(1) + (1-T) * Y(0)$
   - $Y_i = Y_i(1)$ if subject i is treated ($T_i=1$)
   - $Y_i = Y_i(0)$ if subject i is untreated ($T_i=0$)
   - May not hold under poor treatment adherence, lost-to-follow-up, and interference

2. No unmeasured confounding: $T \perp \{Y(1), Y(0)\}|C$

   (a.k.a., strong ignorability, conditional exchangeability, exogeneity, etc.)

3. Positivity: $pr(T=t \mid C=c) > 0$ for all (t,c)

Limitations

- Why observational studies are criticized?
- No unmeasured confounding: $T \perp \{Y(1), Y(0)\} | C$
- Why randomized trials are valid? $T \perp \{Y(1), Y(0)\}$
- When would randomized trials be invalid? When causal assumptions are not satisfied.

Part 2

Causal Methods: Matching and IPW

Outline

- Propensity score (PS): Theory and implication
- PS Matching
- PS Weighting (including marginal structural model)
- Strength and limitation

Propensity Score

Propensity Score

- In a binary point treatment setting:
- Propensity score (PS) is defined by:

$$\Pr(T=1|C) = \pi(C)$$

- It refers to the probability of receiving treatment given observed covariates (patient/prescriber characteristics, etc.).

Key Result of PS Theory: Rosenbaum & Rubin (1983)[2]

- If no unmeasured confounding holds:

$$T \perp \{Y(1), Y(0)\} | C \quad \leftrightarrow \quad T \perp \{Y(1), Y(0)\} | \pi(C)$$

- If treatment is independent (= random) once conditioning on observed confounding information, treatment is also independent conditional on propensity score.

Key Result of PS Theory: Practical Implication

- If our data has all necessary confounding information C (i.e., if no unmeasured confounding assumption holds):
  - Having treatment vs. control groups that are similar on PS values

  ➔ having groups that are similar on the observed covariate values

- Instead of constructing groups w.r.t similar values of covariates: female, age<40, education level=1, BMI=18, ...

  ➔ Just create groups with similar PS values: e.g., 0.25<PS<0.35

- Basis of matching, stratification, and regression adjustment.

Matching

Matching: 1-to-1 Matching Example

1. Randomly select a subject from treatment group

2. Find a subject from control group who has exactly the same or **similar PS**: forms a matched pair

3. Iterate this process until no one left in treatment group or no match exists ➔ create final treatment and control groups

4. Examine covariate balance between treatment and control groups

5. Conduct final analysis to compare response between the two groups

1:1 Matching Example

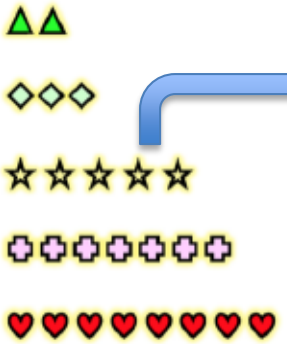
Treated Patients

Untreated Patients

Dr. Thomas Love, Professor of Medicine at Case Western Reserve University.
Pictures taken and modified from Dr. Love's short course material from ICHPS 2018.

1:1 Matching Example

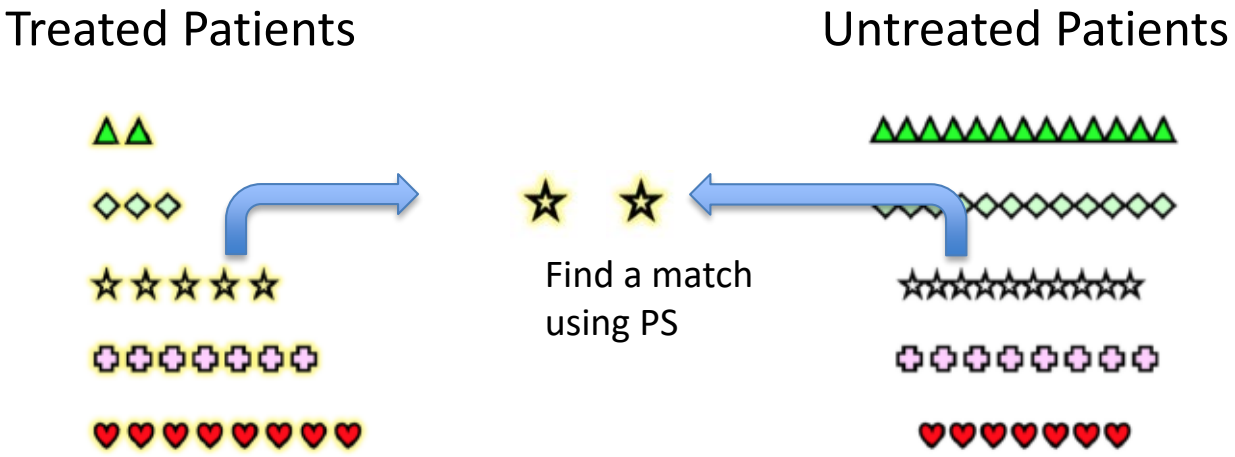
Treated Patients



Select a subject, perhaps at random

Untreated Patients

1:1 Matching Example



1:1 Matching Example

Treated Patients

A first matched pair!

Untreated Patients

1:1 Matching Example

Treated Patients

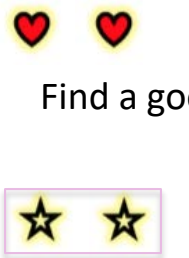
Untreated Patients

Select another treated subject.

1:1 Matching Example

Treated Patients

Find a good match.



Untreated Patients

1:1 Matching Example

Treated Patients

A second matched pair!

Untreated Patients

1:1 Matching Example

Treated Patients

Keep matching, until we find no more acceptable matches.

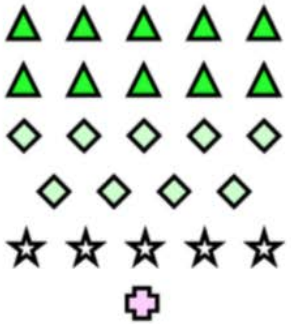
Untreated Patients

1:1 Matching Example

Treated Patients

Matched Set
(24 pairs)

Untreated Patients



Matching

- How many you want to match:
  - 1:1 matching, 1:m matching, variable-ratio matching, full matching…
- How close you want to match (maximum tolerated difference; **caliper**):
  - Exact matching, nearest neighbor matching (greedy, optimal, etc.), ….
- How to use subject:
  - Matching with replacement or without replacement.

Matching: Standard Error Estimation

- Matching without replacement: No further adjustment is needed
- Matching WITH replacement: The same subject was used multiple times
  - Give a weight: If a person is matched twice, give each a weight of ½
  - Robust standard error or bootstrap: caution when sample size is small.
- Areas of research: Should we account for variability in match?
  - Ignoring the matching step is asymptotically valid when matching is done without replacement. But could be problematic when it's done with replacement.

Matching: Implementation

- R package
  1. MatchIt: Most popular, does not do weighting (e.g., for full matching) explicitly. Updates coming very soon.
  2. twang: a very nice R package for weighting
  3. cobalt package and WeightIt: cobalt does some nice balance checks
- SAS: PSMATCH procedure (https://support.sas.com/documentation/onlinedoc/stat/142/psmatch.pdf)
- STATA: PSCORE for PS estimation and PSMATCH2 for PS matching
- See Dr. Joo-Yeon Lee's presentation for more details

Matching: Considerations

1. How many matches to get? 1:1 vs 1:m

- Some people reluctant to use small number for matched because it "throws away data." But sometimes it is a good thing, if that data not helpful.
- If lots of controls available, may make sense to get more than one match for each treated individual.
- Unusual to be able to do more than say 1:2 unless control pool MUCH larger than treatment group (Austin 2010[3]).
- Advice from E Stuart*: Work up from 1:1 to 1:2 to 1:3, etc.; keep increasing ratio until balance gets worse ➔ Clearly state the process in statistical analysis plan.
- Generally estimating ATT. So consider your target estimand first then choose a method accordingly.
- After that, it becomes a choice of caliper ➔ bias-variance trade-off problem.

**Dr. Elizabeth Stuart, Professor of Mental Health and Biostatistics at Johns Hopkins Bloomberg School of Public Health. Short course on PS methods at FDA, July 2017.*

Matching: Considerations

2. Choice of caliper

- Rosenbaum and Rubin (1985)[4] used 0.25 standard deviations (SD) of PS values based on the results of Cochran and Rubin (1973)[5]

  ➔ taken as a recommendation

- Austin (2011)[6] recommended reducing the caliper from 0.25 to 0.20 SD.

- The appropriate caliper depends on strength of confounding

  ➔ More confounding might require a tighter caliper

- Bias-variance trade-off: A tighter caliper can reduce bias but increase variance

Matching: Considerations

3. Greedy vs. Optimal algorithm?

- Greedy: goes through treated units one at a time and picks the best match from those available
- Greedy without replacement: order matches chosen may make a difference
- Optimal: allow earlier matches to be broken if overall bias will be reduced; optimizes global distance measure
- Often doesn't make a huge difference: Gu and Rosenbaum (1993)[7] "...optimal matching picks about the same controls as greedy matching but does a better job of assigning them to treated units."
- Note: Doesn't make a difference if matching with replacement
- Advice from E Stuart: Do optimal if it's easy but don't worry too much about this

Matching: Considerations

4. Full matching

- Fine stratification method: Full matching creates the subclasses automatically
- Creates lots of little subclasses, with either (1) 1 treated and multiple controls or (2) 1 control and multiple treated in each subclass
  - Treated individuals with lots of good matches will get lots of matches; those without many good matches won't get many
  - Can also do constrained full matching, which limits the ratio of treated:control in each subclass
  - Hansen (2004)[8], Stuart and Green (2008; has sample code)[9]
- Optimal in terms of reducing bias on propensity score
- Can estimate both ATE and ATT

Matching: Considerations

5. With or without replacement

- Without replacement can yield bad matches ➔ higher bias
- Without replacement is usually (matching) order dependent
- With replacement may yield less bias but higher variance
  - Keep track of how many times a control selected
  - Proper adjustment in standard error estimation (generally via weighting) is required
- Advice from E Stuart: Try without replacement, if not good balance then try with replacement

Matching: Considerations

6. Balance check

- Most common metric: Standardized mean difference (SMD)
  - Difference in means between two groups, divided by standard deviation (like an effect size)
  - SMD formula differ by type of variable (continuous, binary, etc.)

- Other possibilities: t-test, Wilcoxson test, Kolmogrov-Smirnov tests
- Have to be careful of hypothesis tests, p-values because of differences in power (Imai et al., 2008[10])

Matching: Considerations

7. Outcome analysis after matching (1)

- Adjust or not to adjust for covariates in analysis model?
  - Additional covariate adjustment is known to reduce bias and improve efficiency (Rubin and Thomas, 2000[11]).
- Some considerations on adjusted analysis:
  - Non-collapsibility for non-linear models: Odds Ratio, hazard Ratio
  - Population-level effect (ATE): Marginal, unconditional treatment effect

    ➔ additional step is needed to produce the marginal effect

    ➔ additional step is needed to estimate uncertainty of the effect estimate

Matching: Considerations

7. Outcome analysis after matching (2)

- Should we account for matched pair?
  - Matches generally pooled together into just “treated” and “control” groups.
  - We care only about average balance between treatment and control groups, not the balance within each pair.
  - Don’t need to account for individual pairings.
  - See Austin (2008)[12] and associated discussion and rejoinder for some debate.

Inverse Probability Weighting

Inverse Probability Weighting: Motivation

- If we can observe potential outcomes {Yi(1), Yi(0)} from everybody:

  ➔ unbiased estimator for ATE = $\frac{1}{N}\sum_{i=1}^{N}\{ Yi(1) - Yi(0)\}$

- However, …

- Missing data problem: Use inverse probability weighting (IPW) to account for missing potential outcome.

Idea Behind IPW: Survey Data Example

- Suppose that original (full) data is:

Group	A			B			C		
Response	1	1	1	2	2	2	3	3	3

➔ The average response = (1+1+1+2+2+2+3+3+3)/9 = 2

- Suppose that the missing data are:

Group	A			B			C		
Response	1	.	.	2	2	2	.	3	3

➔ The average response = (1+2+2+2+3+3)/6 = 2.17: **Biased!**

Idea Behind IPW: Survey Data Example

Missing data:

Group	A			B			C		
Response	1	.	.	2	2	2	.	3	3

- Group A: Probability of response = 1/3 ➔ IPW = 3
- Group B: Probability of response = 1 ➔ IPW = 1
- Group C: Probability of response = 2/3 ➔ IPW = 3/2

- Group A: Response 1 after weighting = 1*3 = 3
- Group B: Response 2 after weighting = 2*1 = 2
- Group C: Response 3 after weighting = 3*3/2 = 9/2

Weighted average

$$= \frac{(3*1 + 2*3 + 9/2*2)}{1*3 + 3*1 + 2*3/2} = 2$$

Number of responders in each group

Idea Behind IPW: Survey Data Example

Missing data:

Group	A			B			C		
Response	1	.	.	2	2	2	.	3	3

- Group A: Response 1 after weighting = 1*3 ➔ 3 = 1 + 1+ 1
- Group B: Response 2 after weighting = 2*1 ➔ 2 + 2 + 2 = 2 + 2 + 2
- Group C: Response 3 after weighting = 3*3/2 ➔ 3*3/2 + 3*3/2 = 3 + 3 + (3 *1/2 + 3*1/2)

After weighting:

Group	A			B			C		
Response	1	1	1	2	2	2	3	3	3

IPW eliminates bias by weighting “observed response” so that observed responses can represent not only themselves but also missing response from non-responders in the same group.

IPW: Extend The Survey Idea

- Analogy:
  - Responders vs. non-responders = Treated vs. untreated
  - Observed response = Observed outcome
  - Missing response = Unobserved part of potential outcome
  - Group info = confounder (patient-prescriber characteristics)
  - Missing at random = No unmeasured confounder

- Difference: Now each subject has two responses (potential outcomes under treatment and control) ➔ extend the idea of weighting and consider two different weighting – one for treated and the other for control.

Inverse Probability of Treatment Weighting

- Inverse probability of treatment weighting (IPTW)
  - Each subject has two potential outcomes: **Y(1)** and **Y(0)**
  - Among untreated, **Y(1)** is missing.

- Recover missing **Y(1)** using information from treated patients:
  - Weight observed outcomes from treated patients (T=1) using inverse probability of receiving treatment (= 1/PS) so that their outcomes not only represent themselves but also represent missing **Y(1)** from other similar individuals (in terms of C) who did **NOT** receive treatment.

Inverse Probability of Treatment Weighting

- The same principle applies to recover missing **Y(0)**
  - Each subject has two potential outcomes: **Y(1)** and **Y(0)**
  - Among treated, **Y(0)** is missing.

- Recover missing **Y(0)** using information from untreated patients:
  - Weight observed outcomes from untreated patients (T=0) using inverse probability of **NOT** receiving treatment (1/{1-PS}) so that their outcomes not only represent themselves but also represent missing **Y(0)** from other similar individuals (in terms of C) who **DID** receive treatment.

IPW: Before Weighting

Patient	$Y(1)$	$Y(0)$	Causal effect	Received ART?	Y	
1	500	300	200	1	500	
2	900	200	700	1	900	**Ave = 600**
3	600	500	100	1	600	
4	400	100	300	1	400	
5	1200	800	400	0	800	
6	1000	800	200	0	800	**Ave = 867**
7	1300	1000	300	0	1000	
Average	843	529	314			

IPW: After Weighting

Patient	$Y(1)$	$Y(0)$	Causal effect	Received ART?	Y	
1	500	300	200	1	500	
2	900	200	700	1	900	**Ave = 600**
3	600	500	100	1	600	
4	400	100	300	1	400	
5	1200	800	400	0	800	
6	1000	800	200	0	800	**Ave = 867**
7	1300	1000	300	0	1000	
Average	843	529	314			

Association: $600 - 867 = \boxed{-267}$

Causation: $843 - 529 = \boxed{+314}$

IPW: After Weighting

Patient	$Y(1)$	$Y(0)$	Causal effect	Received ART?	Y	
1	500	300	200	1	500	
2	900	200	700	1	900	**Ave = 600**
3	600	500	100	1	600	
4	400	100	300	1	400	
5	1200	800	400	0	800	
6	1000	800	200	0	800	**Ave = 867**
7	1300	1000	300	0	1000	
Average	843	529	314			

Association: $600 - 867 = \boxed{-267}$

Causation: $843 - 529 = \boxed{+314}$

Inverse Probability of Treatment Weighting

- In the weighted population, these is no missing potential outcome.

- HR call it “pseudo-population” where treatment is exchangeable, i.e., there is no confounding in the pseudo-population where treatment effect can be interpreted as causal.

IPW: Standard Error Estimation

- Common mistake: IPW artificially inflate sample size and inflate type-1 error.

- PS or 1-PS: always 0 – 1 (non-inclusive) ➔ weights are always >1

➔ individuals will be represented multiple times in the weighted sample

➔ the IPW induces within-subject correlation

- Standard error estimation should account for the weighting (Hernan et al. 2000[13]): Use **robust (sandwich) variance estimator** or bootstrap.

IPW: Standard Error Estimation

- Robust variance estimator is not adequate when sample size is small.
  - When n is small: tend to over-estimate true variance to protect model-misspecification
  - When n is very small: direction unknown, either under- or over-estimate true variance (estimation of the “meat” part is unstable)

- Rare disease: Robust variance estimator is not enough.

IPW: Implementation

- R package: A few available (eg, *ipw*), but no need to use a package
  1. Just run a regression model to estimate PS
  2. Add estimated PS to your data column
  3. Fit final analysis model using weight option
  4. Don't forget to specify a proper variance estimation option!

- SAS: same as R

- STATA: same as above. See also https://www.rand.org/content/dam/rand/pubs/presentations/PT100/PT147/RAND_PT147.binaryrts.pdf

- See Dr. Joo-Yeon Lee's presentation for more details

IPW: Considerations

1. Large weight

- PS or 1-PS: always 0 – 1 (non-inclusive) ➔ weights are always >1
- If PS or (1-PS) is close to 0 (near positivity violation) ➔ IPW can be very large
- Strategies:
  1) Stabilizing: multiply a stabilizing factor which is <1. Usually P[T=1] for treated, p[T=0] for untreated.
  2) Normalize weight, standardize, etc.
  3) Truncation: Replace large weight(s) with smaller weight (99^{th}, 97^{th}, 95^{th} percentile…)
  4) Trimming: Remove patients having large weight(s) from the sample.

IPW: Considerations

1. Large weight (continued)

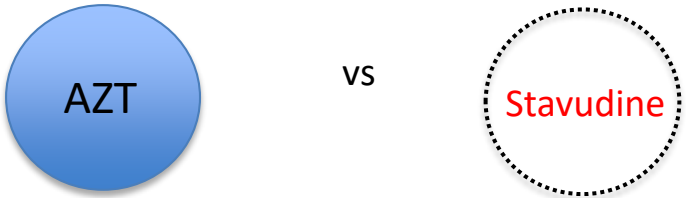
- Common misunderstanding:
  - Original, unstabilized IPW artificially inflate the sample size whereas stabilized IPW does not.
  - Stabilized IPW is better because treatment and control ratio is preserved.
- Goal of stabilizing: downweight extreme weights.
- Consequence of stabilizing: Proportion of treated and controls remains the same as in the original (unweighted) population.

IPW: Considerations

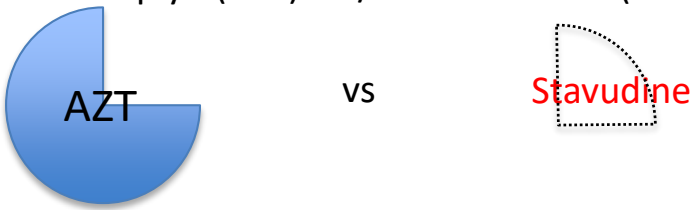
Figure: Graphical representation of ATE with and without stabilizing

ATE : What happens if everybody had received AZT vs if everybody had stavudine?

= ATE with unstabilized IPW



ATE with stabilized IPW: Multiply P(AZT) = 3/4 for AZT and P(stavudine)= ¼ for stavudine



IPW: Considerations

2. Type of estimand: ATE vs ATT

- ATE weight: $\frac{1}{\mathrm{PS}}$ for treated & $\frac{1}{1-\mathrm{PS}}$ for control
- ATT weight: treated patients are reference ➔ weight is 1 for treated

  ➔ equivalent to multiply ATE weight with PS

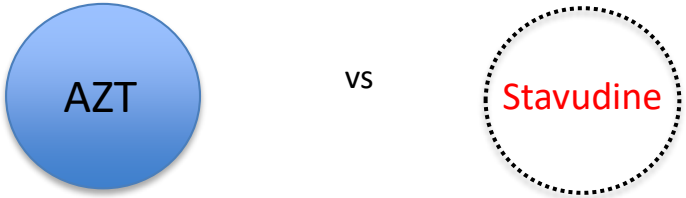
  ➔ weight =1 for treated & $\frac{\mathrm{PS}}{1-\mathrm{PS}}$ for control

- ATT weight: (somewhat) stabilized already where stabilizing factor = PS <1. In practice, extreme weights are rare with ATT unless there's a near positivity violation.

Causal Estimands: ATE vs. ATT

Figure: Graphical representation of ATE and ATT

ATE: What happens if everybody had received AZT vs if everybody had received stavudine?



ATT: What happens if patient received AZT would have received stavudine?

Inverse Probability Weighting – Marginal Structural Model

Marginal Structural Model (MSM)

- MSM: Simply, inverse-probability weighted models
- Implementation is straightforward:
  - Calculate PS and (1-PS)
  - For treated, weight their outcomes with 1/PS
  - For untreated, weight their outcomes with 1/(1-PS)
  - Fit a statistical model using treatment (T) as a sole covariate
- Idea: The weighted sample includes all Y(1) and Y(0). So you are modeling potential outcomes, not modeling observed outcomes!

MSM: Standard Error Estimation

- Again, the weighting induces within-subject correlation:

➔ Use robust variance estimator or bootstrap.

MSM: Origin of Its Name

- Hernan et al. (2001)[13] (actually Robins et al. 1997[14]):
  - IPW accounts for missing potential outcomes ➔ adjust for confounding
  - No confounding ➔ No need to adjust for them in the model
  - Model **marginal** mean of potential outcomes, not observed outcomes ➔ causal model (i.e., **structural** model)

- We can estimate causal risk difference, causal risk ratio, causal odds ratio, causal hazard ratio, etc., using weighted sample.

Causal and Associational Models

- Y(t): Potential outcome when treatment T=t (t=0,1)
- Y: Observed outcome

Causal Models (MSMs)	Associational Models
$E\{Y(t)\} = \alpha_0 + \alpha_1 t$	$E(Y) = \alpha_0^* + \alpha_1^* t$
$\log [E\{Y(t)\}] = \beta_0 + \beta_1 t$	$\log \{E(Y)\} = \beta_0^* + \beta_1^* t$
$\text{logit} [E\{Y(t)\}] = \delta_0 + \delta_1 t$	$\text{logit} \{E(Y)\} = \delta_0^* + \delta_1^* t$

Robins et al. (2000)[15]

- When $\alpha_1 = \alpha_1^*$, …? ➔ When treatment is uncounfounded (i.e., treatment is random).

Matching vs Weighting: Strength and Limitation

1:1 Matching Example

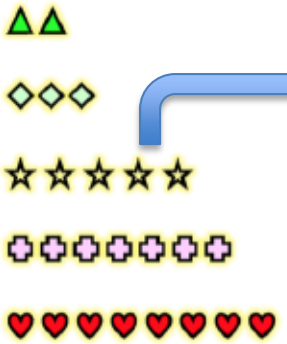
Treated Patients

Untreated Patients

Dr. Thomas Love, Professor of Medicine at Case Western Reserve University.
Pictures taken and modified from Dr. Love's short course material from ICHPS 2018.

1:1 Matching Example

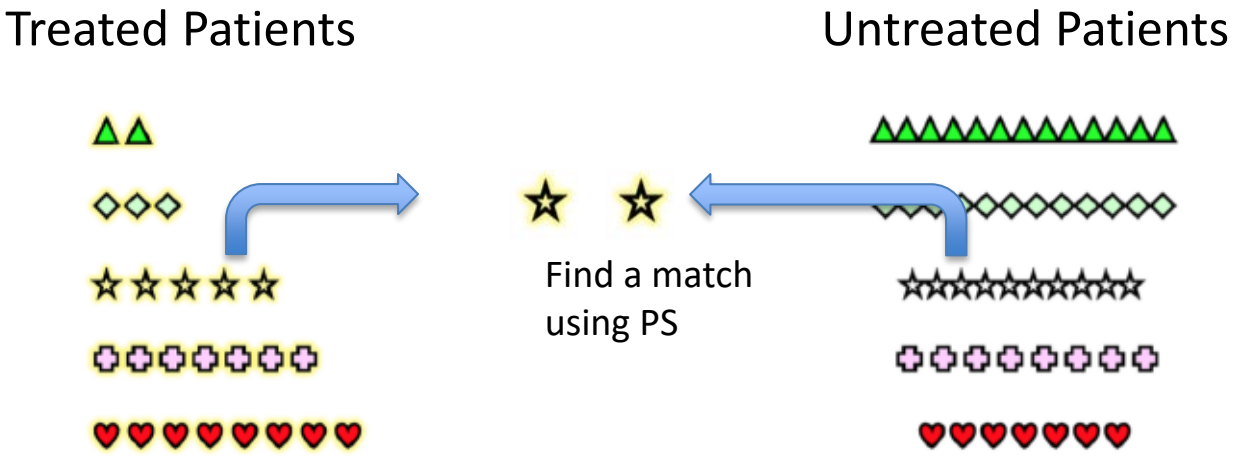
Treated Patients



Select a subject, perhaps at random

Untreated Patients

1:1 Matching Example



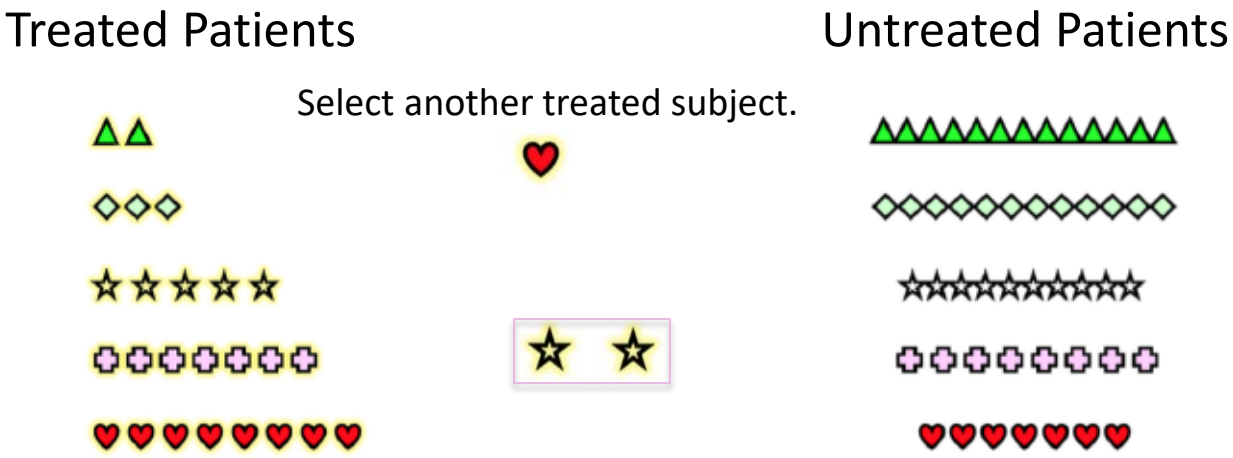
1:1 Matching Example

Treated Patients

A first matched pair!

Untreated Patients

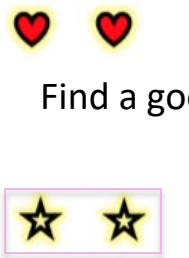
1:1 Matching Example



1:1 Matching Example

Treated Patients

Find a good match.



Untreated Patients

1:1 Matching Example

Treated Patients

A second matched pair!

Untreated Patients

1:1 Matching Example

Treated Patients

Keep matching, until we find no more acceptable matches.

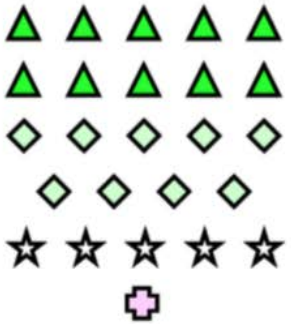
Untreated Patients

1:1 Matching Example

Treated Patients

Matched Set
(24 pairs)

Untreated Patients



IPW: ATT Weighting Example

Treated Patients: **IPW=1**

Untreated Patients

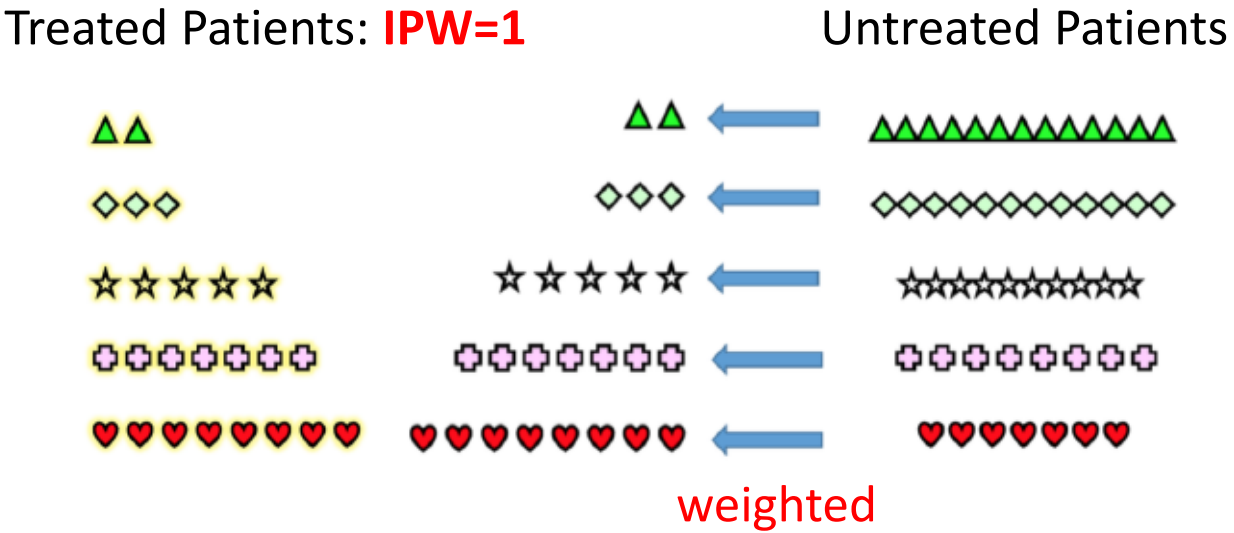
IPW: ATT Weighting Example

Treated Patients: **IPW=1**

weighted

Untreated Patients

IPW: ATT Weighting Example



IPW: ATT Weighting Example

Treated Patients: **IPW=1**

Untreated Patients: **weighted**

Weighted set: analysis sample

Strength and Limitation

Matching

- Strength: Very straightforward, easy to communicate with medical division

- Weakness:
  - May discard some observations that don't match

    ➔ Distort your target population: Matched sample might not representative of your target population anymore.

    ➔ Less efficient, lost in power
  - Some methods pre-determine your target estimand: Your estimand is ATT with 1:1 & 1:m matching.
  - Extension to longitudinal setting is limited.

Strength and Limitation

Weighting

- Strength:
  - Can utilize all observations in most cases ➔ more efficient, higher power
  - Easy to extend to longitudinal setting: use MSM to control for time-varying confounding

- Weakness:
  - Using all observations is not always a good thing.
  - Large weight can be problematic: distort your target population depending on how you deal with the large weight
  - Some misunderstandings about the method exist.

Strength and Limitation

Matching & Weighting

- Strength:
  - Clearly separate design from analysis compared to other PS methods (eg, PS regression adjustment) or (some) outcome regression-based methods (discussed later if time permits)

- Weakness:
  - Compared to outcome regression-based methods
    - PS methods require additional assumption: correctly specified PS model
    - (generally) less flexible

Matching & Weighting:

Statistical Analysis Plan

Statistical Analysis Plan

1. Specify target estimand

2. Specify design plan
   1) State a list of covariates (if not specified earlier) and a plan to check on covariate balance between two groups
   2) State a design plan to create comparable groups: matching or weighting
   3) State a diagnostic plan (for covariate balance)

3. Specify analysis plan
   1) State final analysis model for outcome stated in #1.
   2) State variance estimation strategy
   3) State sensitivity analysis (contingency) plan

Statistical Analysis Plan: 1. Estimand

1. Specify target estimand: Consider four attributes stated in ICH E9 (R1) addendum

1) **Population:** the patients targeted by the scientific question
2) **Variable (or endpoints):** an measurement of some kind obtained from/for each patient, that is required to address the scientific question
3) **Handling of intercurrent events:** specifies how to account for intercurrent events to reflect the scientific question of interest
4) **Population-level summary for the variable:** provides, as required, a basis for a comparison between treatment conditions.

Therefore, you should also provide description on population, exposure, outcome (endpoint), and a list of potential confounders in this step.

Statistical Analysis Plan: 2. Design Plan

1. Specify target estimand

2. Specify design plan
   1) State a list of covariates (if not specified earlier) and a plan to check on covariate balance between two groups
   2) State a design plan to create comparable groups: matching or weighting
   3) State a diagnostic plan (for covariate balance)

3. Specify analysis plan
   1) State final analysis model for outcome stated in #1.
   2) State variance estimation strategy
   3) State sensitivity analysis (contingency) plan

Statistical Analysis Plan: 2. Design Plan

- 2-1) Covariate balance: Provide a mock Table 1 or visuals (eg, PS distributions, SMD plot)

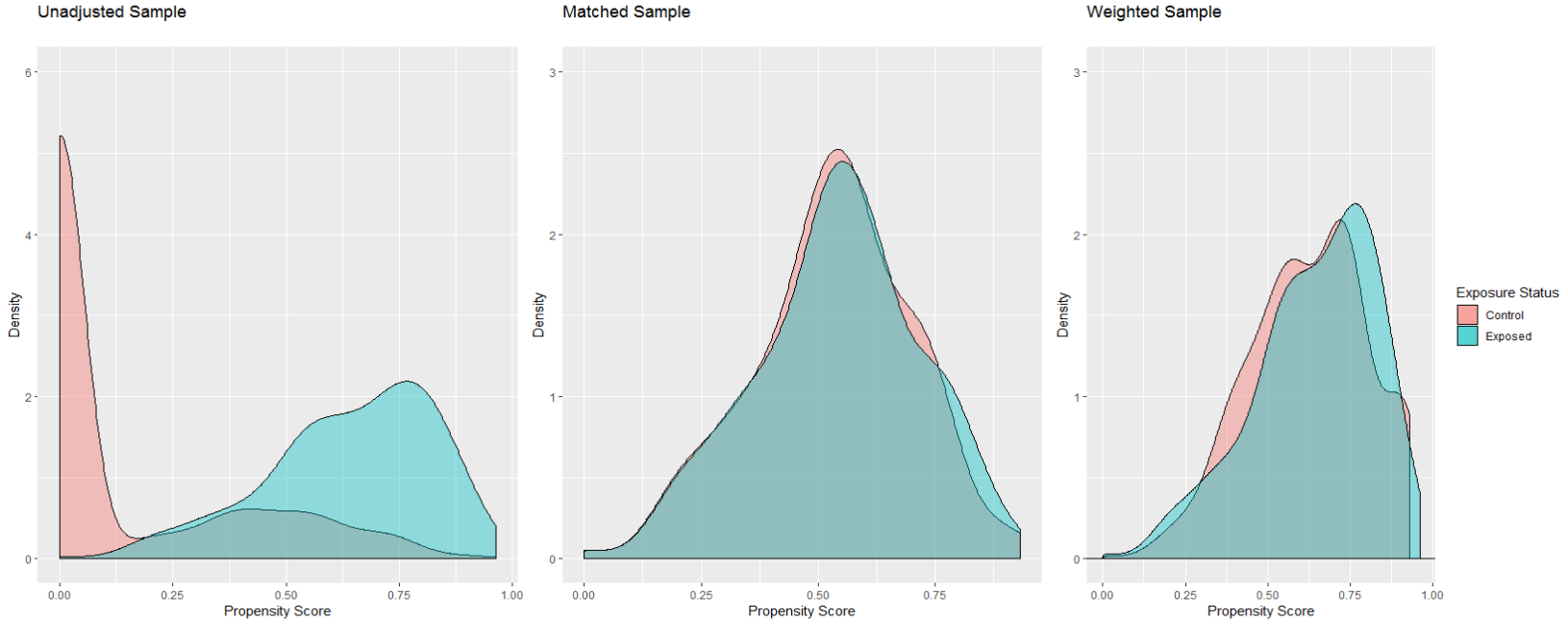
Table 1. Baseline and Exercise Characteristics According to Aspirin Use*

Variable	Aspirin (n = 2310)	No Aspirin (n = 3864)	*P* Value
Demographics			
Age, mean (SD), y	62 (11)	56 (12)	<.001
Men, No. (%)	1779 (77)	2167 (56)	<.001
Clinical history			
Diabetes, No. (%)	388 (17)	432 (11)	<.001
Hypertension, No. (%)	1224 (53)	1569 (41)	<.001
Tobacco use, No. (%)	234 (10)	500 (13)	.001
Prior coronary artery disease, No. (%)	1609 (70)	778 (20)	<.001
Prior coronary artery bypass graft, No. (%)	689 (30)	240 (6)	<.001
Prior percutaneous coronary intervention, No. (%)	667 (29)	148 (4)	<.001
Prior Q-wave MI, No. (%)	369 (16)	285 (7)	<.001
Atrial fibrillation, No. (%)	27 (1)	55 (1)	.04
Congestive heart failure, No. (%)	127 (6)	178 (5)	.12
Medication use			
Digoxin use, No. (%)	171 (7)	216 (6)	.004
β-Blocker use, No. (%)	811 (35)	550 (14)	<.001
Diltiazem/verapamil use, No. (%)	452 (20)	405 (10)	<.001
Nifedipine use, No. (%)	261 (11)	283 (7)	<.001
Lipid-lowering therapy, No. (%)	775 (34)	380 (10)	<.001
ACE inhibitor use, No. (%)	349 (15)	441 (11)	<.001

- When sample size is large: Do not use t-test or Wilcoxon test. Use SMD!

Statistical Analysis Plan: 2. Design Plan

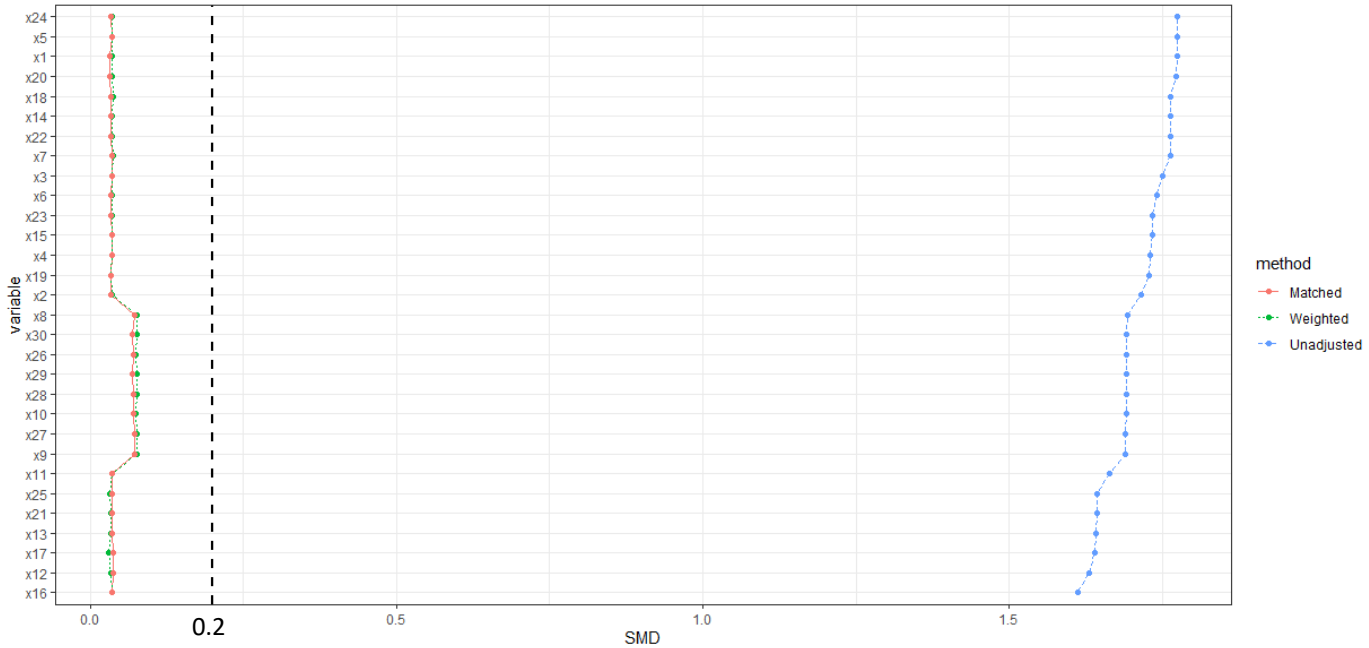
2-1) Covariate balance: PS distribution plot



**Figures generated by an FDA reviewer for an intramural project.*

Statistical Analysis Plan: 2. Design Plan

2-1) Covariate balance: SMD plot (LOVE plot)



**Figures generated by an FDA reviewer for an intramural project.*

Statistical Analysis Plan: 2. Design Plan

2-2) State a design plan:

a) State a method to create comparable groups (matching, weighting, etc.)

b) State a list of potential confounders if not stated in Step 1.

c) State a specific functional form of PS model:

- Main term logistic models using confounders listed in b).
- Machine-learning: Specify details including information on cross-validation.
- Regulatory setting emphasis is on pre-specification ➔ confounder selection based on unblinded data is discouraged

d) State details on matching/weighting:

- 1:1 matching, 1:m matching, full matching, caliper, etc.
- Specific weight: ATE vs ATT? Unstabilized vs stabilized weight? Trimming?

Statistical Analysis Plan: 2. Design Plan

2-3) State a diagnostic plan:

a) State a diagnostic plan after matching or weighting: tables or visuals

b) State a contingency plan if covariate balance is unsuccessful

- Use of another PS model including interaction terms
- Covariate adjustment in final analysis model using those still imbalanced

c) State a plan for poor PS overlap

- Note that not including unmatched treated subjects or removing those with large weights can distort your target population

  ➔ carefully think whether you can actually estimate what you stated as target estimand

Statistical Analysis Plan: 3. Analysis Plan

1. Specify target estimand

2. Specify design plan
   1) State a list of covariates (if not specified earlier) and a plan to check on covariate balance between two groups
   2) State a design plan to create comparable groups: matching or weighting
   3) State a diagnostic plan (for covariate balance)

3. Specify analysis plan
   1) State final analysis model for outcome stated in #1.
   2) State variance estimation strategy
   3) State sensitivity analysis (contingency) plan

Statistical Analysis Plan: 3. Analysis Plan

3-3) State sensitivity analysis

- Data quality: Is there any important covariate that was not captured in data? eg, smoking status in claims data
- Sensitivity analysis to explore robustness of findings under the (assumed) impact of unmeasured confounding
- Sensitivity analysis using different functional forms of PS model and outcome analysis model
- Inclusion/exclusion of large weights

Part 3

Target (Causal) Estimand

Target Estimand

- ICH E9 (R1) addendum: Estimands introduced with

"Central questions for drug development and licensing are to establish the existence, and to estimate the magnitude, of treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under alternative treatment (i.e. had they not received the treatment, or had they received a different treatment). An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarises at a population level what the outcomes would be in the same patients under different treatment conditions being compared."

Target Estimand

- While the main focus in the ICH E9(R1) is on randomized clinical trials (RCT), the principles are also applicable for single arm trials and observational studies as stated on page 5 of the ICH E9(R1).

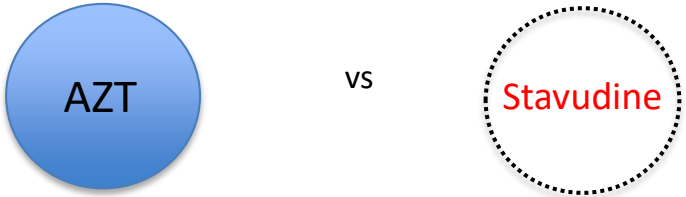
- However, when it comes to non-RCT setting, defining target estimand becomes more complicated and more considerations are needed.

- This is related to causal assumptions that we HAVE TO make to be able to infer causal effect of a treatment using observational data.

Causal Estimands: ATE vs. ATT

Figure: Graphical representation of ATE and ATT

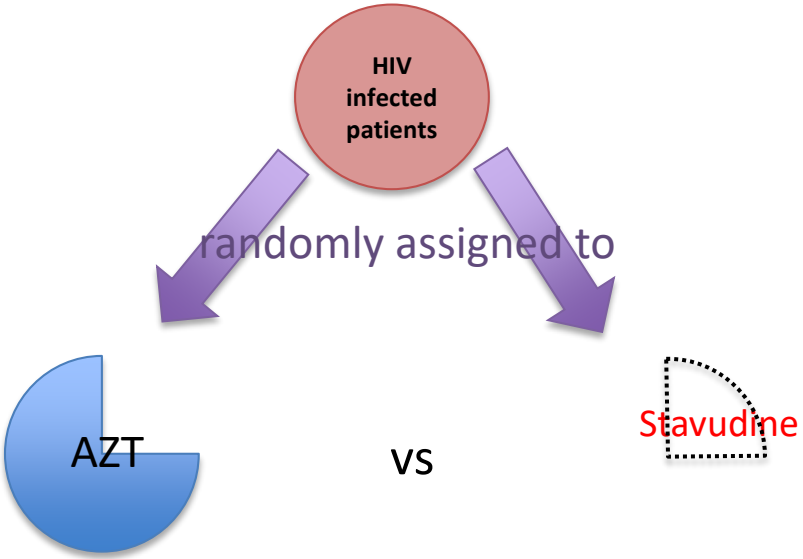
ATE: What happens if everybody had received AZT vs if everybody had received stavudine?



ATT: What happens if patient received AZT would have received stavudine?

Estimand in RCT

Figure: Graphical representation of ATE and ATT in RCT



ATE vs ATT

- This choice comes in when you use non-RCT data.
- ATE: population level treatment effect
- ATT: subgroup level treatment effect
- ATE = ATT under no treatment heterogeneity (for linear outcomes)
  - Eg, treatment effect among female = Treatment effect among male

  ➔ Treatment effect among female = Treatment effect among all

  - Treatment effect among treated = Treatment effect among control

  ➔ Treatment effect among treated/control = Treatment effect among all

ATE vs ATT: When ATT is of interest?

1. In the presence of treatment heterogeneity

2. Feasibility/Practicality

ATE vs ATT: When ATT is of interest?

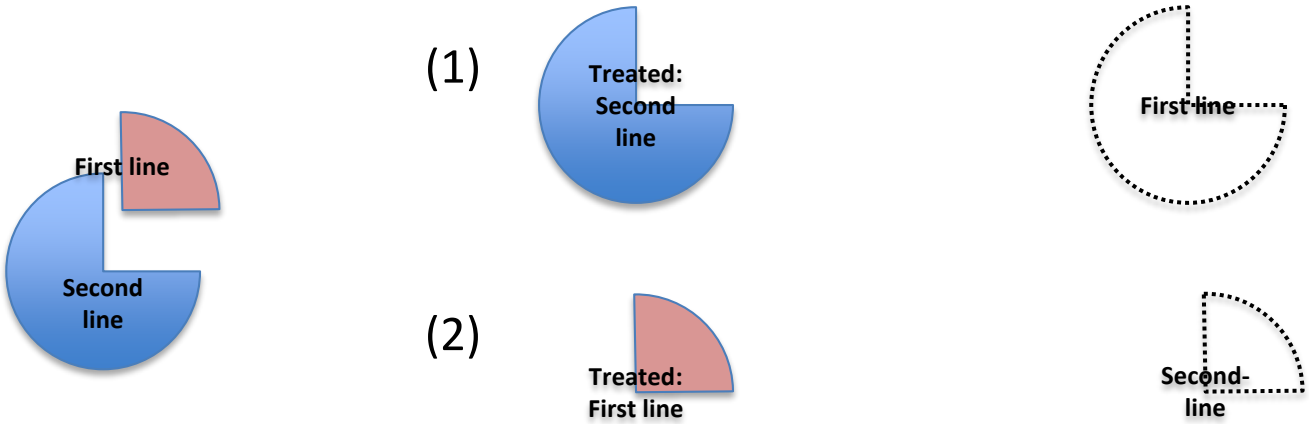
1. In the presence of treatment heterogeneity

Subject ID (n=8)	Treatment: Low dose (0) vs High dose (1)	Potential outcome under low dose Y(0)	Potential outcome under high dose Y(1)	Average Treatment Effect (ATE)	ATT for low dose group (ATT_Low)	ATT for high dose group (ATT_High)
1	0	1	1	0	0	NA
2	0	0	1	1	1	NA
3	0	0	1	1	1	NA
4	0	0	0	0	0	NA
5	1	0	0	0	NA	0
6	1	0	1	1	NA	1
7	1	1	1	0	NA	0
8	1	0	0	0	NA	0
Average				0.375	0.5	0.25

ATT_Low ≠ ATT_High ≠ ATE : Treatment heterogeneity

ATE vs ATT: When ATT is of interest?

1. In the presence of treatment heterogeneity: An aggressive treatment case



- Risk detected from (1) could be much lower then risk detected from (2)
- ATE may say there is no risk associated with the new treatment, but it should not be administered to those eligible for first line therapy.

ATE vs ATT: When ATT is of interest?

2. Feasibility/Practicality

- Second line chemotherapy regimen: potentially high barriers to participation and completion of the regimen
  - unrealistic to estimate the effect of the therapy if it were applied to all current cancer patients

- Instead, greater interest may lie in the effect of the second line therapy on those current cancer patients who elect to receive (or eligible for) the therapy

- Limit your target population to patients who elect to receive the second line therapy

ATE vs ATT: When ATT is of interest?

- ATT implies that we are interested in the effect of a treatment drug (compared to a control drug) on the clinical benefit (or risk of having adverse outcome) on **those who elect to take that drug** (from patient perspective) or on **those who are prescribed to that drug** (from prescribers perspective)

Estimand: Poor PS Overlap

- Population with good overlap: Clinical equipoise[16] or empirical equipoise[17] (in treatment)

- Unlike RCT, there could be poor overlap (w.r.t PS distribution) between treatment and control groups ➔ potential bias, high variance, modeling sensitivity

- Reason for poor overlap:
  - Violation of positivity assumption ➔ could be a data quality issue
  - PS model misspecification

Estimand: Poor Overlap

- Solutions:
  - Matching: changing caliper, changing method (from 1:1 to full)
  - IPW: Weight stabilizing, truncation, trimming, normalization[13]
  - Recent developments: overlap weights[16], matching weights[18], and entropy weights[19]
  - Adjustment of covariates with remaining imbalance in analysis model
  - Find alternative, better quality data

- Presence of poor overlap: Reconsider your target population ➔ Reconsider if your target estimand is something you can actually estimate given your data.

Questions or Comments?

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Case Study

The risk of cardiovascular outcome and all cause mortality with outpatient use of clarithromycin

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Disclaimer

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

Outline

- Background
- Study Overview
- Statistical Methods and Results
  - Two Treatment Arms Comparison (*H.Pylori* indication cohort)
  - Multiple Treatment Arms Comparison (All indication cohort)
- Software
- Summary

Clarithromycin

- A class of macrolide antibiotics
- Treatment for mild to moderate infections caused by designated, susceptible bacteria such as acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia etc
  - H.Pylori bacteria eradication: triple therapy with PPI and amoxicillin
- Since approval, there were mixed findings of risk of CV outcome or mortality

Drug Safety Communication

FDA Drug Safety Communication: FDA review finds additional data supports the potential for increased long-term risks with antibiotic clarithromycin (Biaxin) in patients with heart disease

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[02-22-2018]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is advising caution before prescribing the antibiotic clarithromycin (Biaxin) to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later. Our recommendation is based on our review of the results of a 10-year follow-up study[1] of patients with coronary heart disease from a large clinical trial[2] that first observed this safety issue.

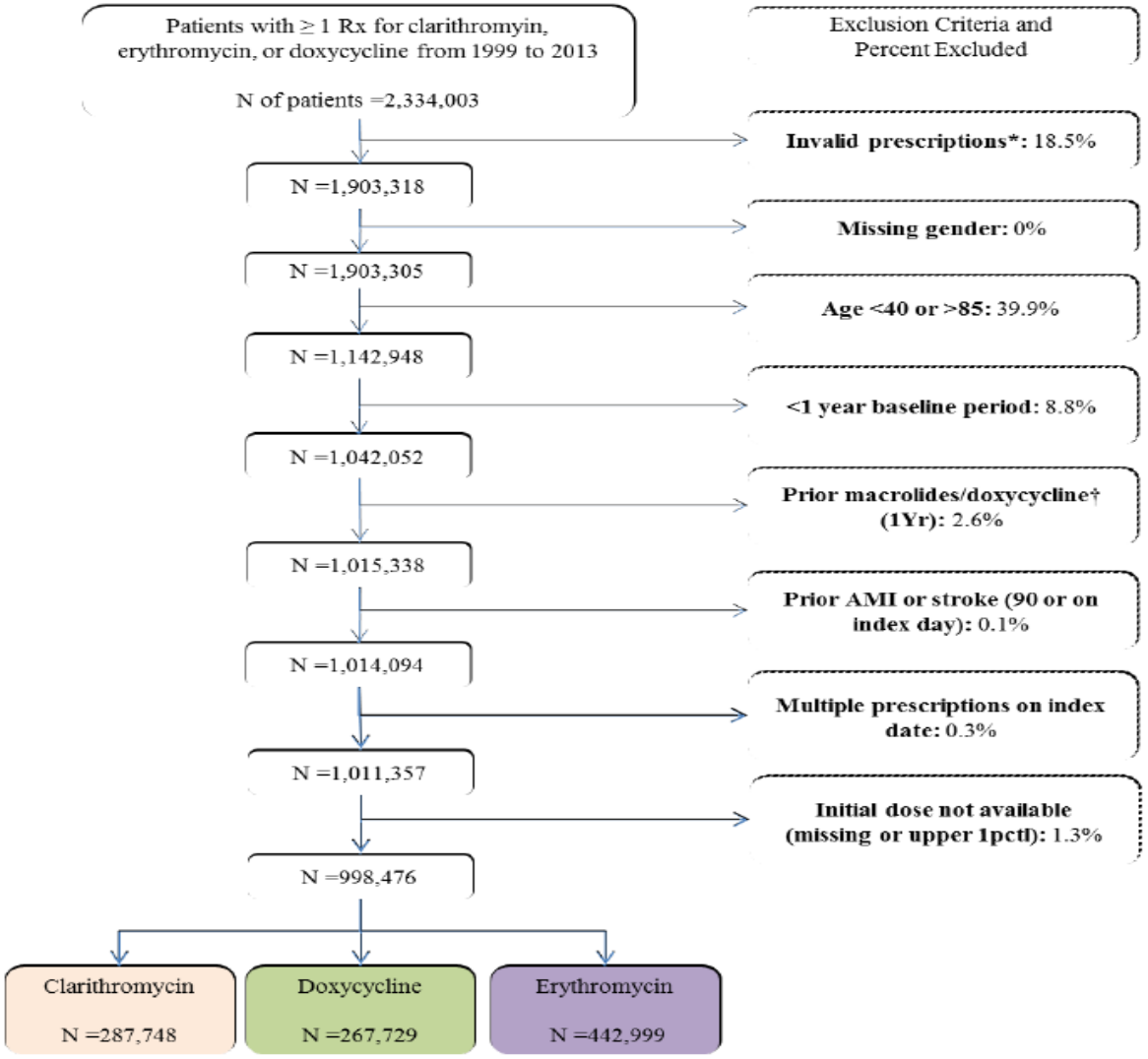
The large clinical trial, called the CLARICOR trial[2], observed an unexpected increase in deaths among patients with coronary heart disease who received a two-week course of clarithromycin that became apparent after patients had been followed for one year or longer. There is no clear explanation for how clarithromycin would lead to more deaths than placebo. Some observational studies also found an increase in deaths or other serious heart-related problems, while others did not. All the studies had limitations in how they were designed. Of the six observational studies published to date in patients with or without coronary artery disease, two found evidence of long-term risks from clarithromycin[3,4], and four did not[5,6,7,8]. Overall, results from the prospective, placebo-controlled CLARICOR trial provide the strongest evidence of the increase in risk compared to the observational study results. Based on these studies, we were unable to determine why the risk of death is greater for patients with heart disease.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-additional-data-supports-potential-increased-long

Study Overview

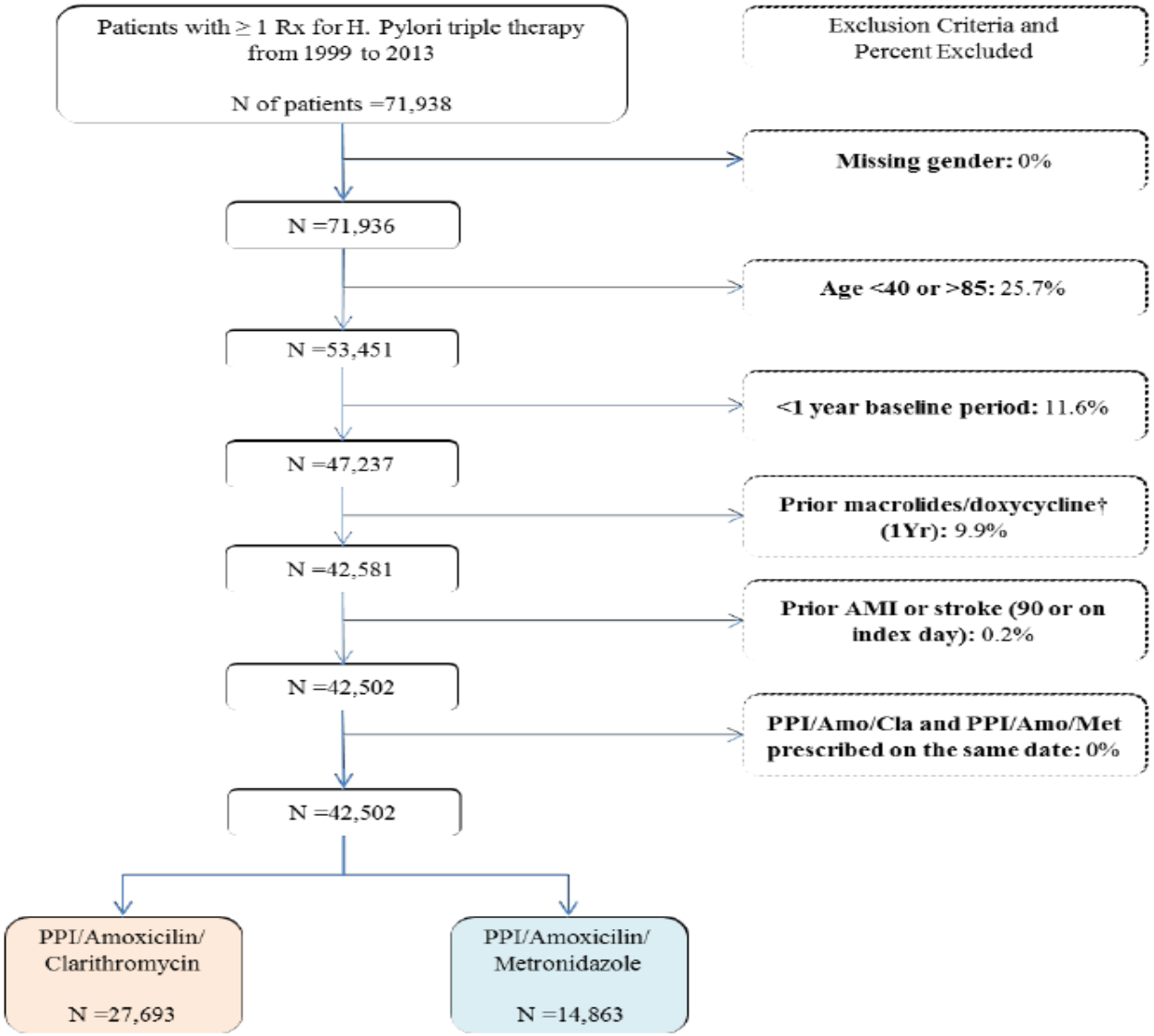
- Objective: To evaluate risks of cardiovascular events and all-cause mortality in adult patients by use of clarithromycin
- Design: A retrospective study of two new user cohorts in the U.K. Clinical Practice Research Datalink (CPRD), from January 1, 2000 through December 31, 2013
  - All indication 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)
- Endpoints:
  - Primary endpoint: All-cause mortality
  - Secondary endpoints: A composite outcome defined as any first occurrence of AMI, stroke and all-cause mortality

Patient Selection (All Indication)



* Drugs with intravenous, oral suspension, cutaneous, ocular, or other non-oral form were excluded from index drug. Patient's index Rx had to be oral pill.

Patient Selection (H.Pylori cohort)



H. pylori Indication Cohort with Two Treatment Arms

Confounding adjustment Method

- Inverse probability of treatment weighting (IPTW) based on propensity score (PS)
  - Propensity score was estimated by logistic regression by adjusting 40 potential confounders

$$log\frac{p(T=1|X)}{1-P(T=1|X)} = \beta_0 + \beta_1 X_1 + \ldots + \beta_{40} X_{40}$$

Where p(T=1|X) indicates the probability of treatment to PPI+AMOX+CLA group given 40 covariates

  - Stabilized weight for each individual was computed by

$$SW_i = \begin{cases} \frac{P(T=1)}{PS_{1,i}} : (PPI + AMOXICILIN + CLARITHROMYCIN) \\ \frac{1-P(T=1)}{PS_{2,i}} : (PPI + AMOXICILIN + METRONIDAZOLE) \end{cases}$$

Where PS indicates estimated PS from logistic regression and P(T=1) is the proportion of patients in PPI+AMOX+CLA group

    - Targeting to estimate ATE

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Why IPTW over Matching ?

Consideration of Sample Size

- *H. Pylori* cohort is small cohort compared to all indication cohort
  - There is less patients in comparator group
- The SS was reduced from a total of 42,502 pts to 29,726 pts by 1-1 matching
  - Before PS matching:
    - PPI/AMOX/CLA: 27,639 (65%)
    - PPI/AMOX/MET: 14,863 (35%)
  - After PS matching:
    - 14,863 for both group

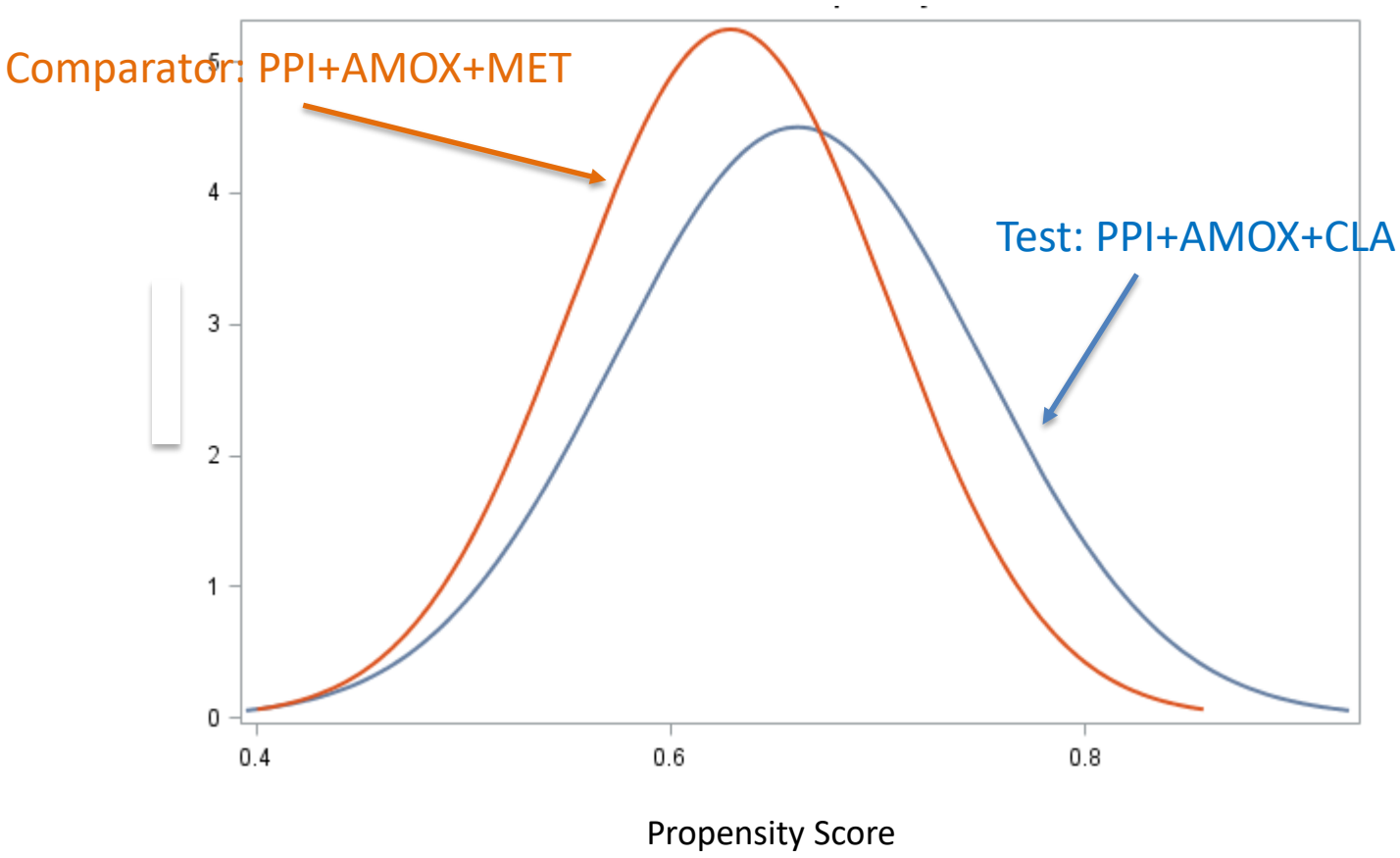
Consideration of Consistency in Method

- All indication cohort has multiple treatment arms
  - CLA, DOXY and ERY
- IPTW was preferred to matching in the case of multiple treatment arms comparison
  - Matching is computationally intensive
  - Matching can lose even more sample size for multiple arms

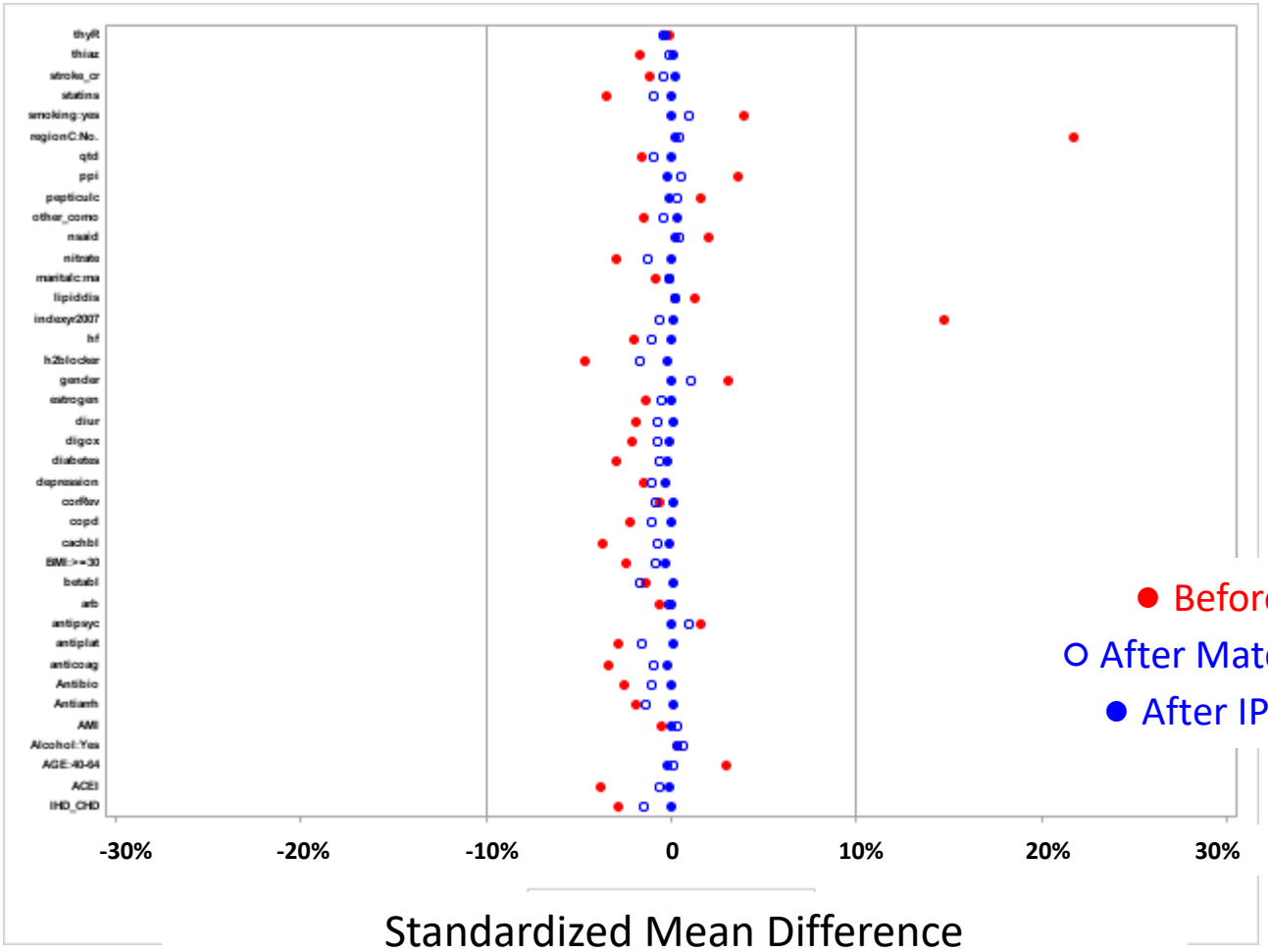
Diagnostics

- Distribution of PS
- Balance checking
- Distribution of weight

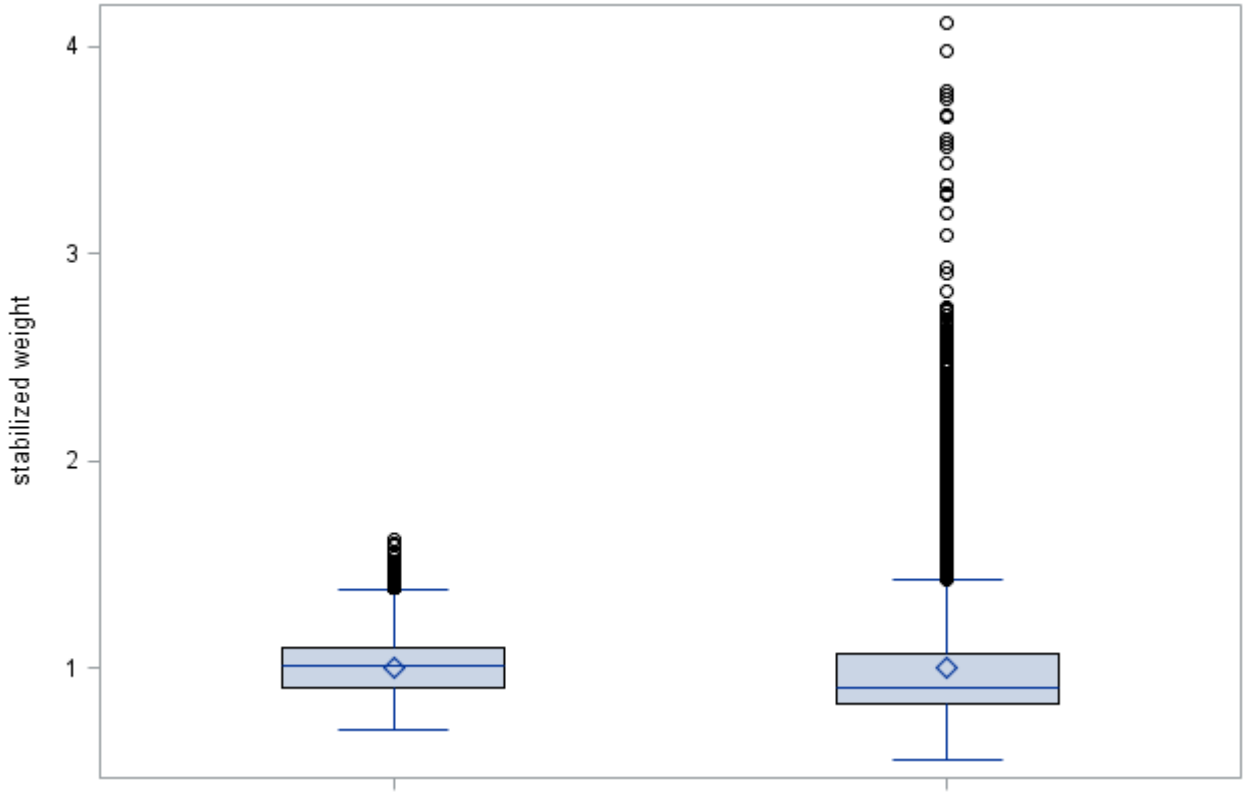
Distribution of PS shows good overlap



Balance Checking



Concern with weights?



There were no extreme weights in this cohort.

Primary Outcome Model

- Weighted Cox PH model
  - To assess the effect of repeated exposures, the cumulative number of index drug Rx was a time-varying covariate with two levels of exposure (1 or 2+ cumulative Rx)
  - Age variable (continuous) was doubly adjusted in the outcome model as well as PS model for any residual confounding.

$$h(t) = h_0(t)\exp(\beta_0 Trt + \beta_{1k} Cum(t) + \beta_{2k} Trt \bullet Cum(t) + \beta_3 Age)$$

Where Trt=1 if PPI+AMOX+CLA group, 0 otherwise

Cum(t) is # of RX at time t

Age is a patient age at baseline

  - Robust variance estimator was used for standard error

Subgroup Analysis

- Subgroup analysis was performed by statin use
  - Weight was re-calculated within each subgroup
  - Weighted Cox PH model was applied within subgroup

Primary Results:
HR of All-cause Mortality

		HR	95% confidence interval
Overall (n=27,639 CLA, 14,863 MET)		1.09	1.00, 1.18
	1 triple therapy	1.08	0.99, 1.18
	2+ triple therapies	1.25	0.77, 2.04

Main Cohort (All Indication Cohort) with Three Treatment Arms

(CLA vs. ERY / DOXY)

Propensity Score Methods for Multiple Treatment Arms

- Regression Adjustment (Imbens 2000, Spreeuwenberg 2010)
- Weighting (Imbens 2000, Rao et al. 2014)
- Stratification (Wang et al. 2001)
- Matching (Rassen et al. 2012)
- Note : Theoretical background remained same (2 groups vs. 3 groups) but there is practical complexity
  - Two groups : P(Trt=1)+P(Trt=2)=1
    - So we can care about only P(Trt=1) as other probability is redundant
  - Three groups : P(Trt=1)+P(Trt=2)+P(Trt=3)=1
    - We should care about two PSs out of Three

Regression Adjustment

1. Fit multinomial logistic regression
2. Predict PS1, PS2 and PS3 for each individual using the fitted multinomial Logistic regression model
3. Include two PSs out of three PSs in the outcome model and estimate the effect of main covariate of interest
   – Sum of three PS should be 1 so one PS is redundant in the model

Inverse Probability of Treatment Weighting (IPTW)

1. Fit a multinomial logistic regression and predict PS1, PS2 and PS3 for each individual

2. Calculate weights by taking inverse of PS or P(T=t)/PS for stabilized weight

3. Treatment effect is estimated using weighted regression model for outcome

Robust estimate of standard error should be used to account for within-subject correlation due to weighting

Stratification

1. Fit a multinomial logistic regression and Predict PS1, PS2 and PS3 for each individual using the fitted multinomial Logistic regression model
2. Make K strata based on percentiles of two of three PSs
   - Need to check the balance between groups within each stratum
   - If balance is not achieved, model may not be correct and need to refine the model
3. Overall treatment effect is weighted average over each stratum by sample size in each stratum

PS Matching for Three groups

Three different methods (next few slides)

- Pairwise matching
- Common reference group matching
- Three-way matching

Pairwise Matching

- Consider three contrast : Trt1 vs. Trt2, Trt1 vs. Trt3, Trt2 vs. Trt3
- Pairwise matching (3 cohorts)
  1. For each contrast estimate PS using **logistic** regression
  2. Match on PS using proper matching method (e.g. 1:1 nearest neighbor matching) for each contrast
  3. Estimate treatment effect of each contrast using matched cohort

Common Reference Group Matching

- Consider TRT 1 (such as clarithromycin group) to be a referent group
- Using **Trt 2 vs. Trt 1** and **Trt 3 vs. Trt1** *propensity-matched population from pairwise matching in the previous slide*
  1. Extract patients treated with Trt 2 or 3 who had a common match of a patient who was treated with Trt 1.
  2. Form a single cohort of these patients and their Trt 1 matches.

Produce generally smaller sample size

Three-way Matching

1. Fit multinomial logistic regression to estimate three propensity scores, PS1, PS2 and PS3
2. Find trio of patients – one receiving each of Trt1, 2 and 3 with the smallest within-trio distance d
   - One option, $d= (PS1_i-PS1_j)^2+(PS1_i-PS1_k)^2 +(PS1_j-PS1_k)^2 + (PS2_i-PS2_j)^2+(PS2_i-PS2_k)^2 +(PS2_j-PS2_k)^{2,}$

   where PS1, PS2 and PS3 are estimated PS score from multinomial logistic regression, i, j, k correspond to subjects who received treatment 1, 2 and 3

Computationally intensive

Statistical Methods

- A total of 998,476 patients are in cohort
  - Clarithromycin : 288,748 (28.8%)
  - Doxycycline : 267,729 (26.8%)
  - Erythromycin : 442,999 (44.4%)

- Propensity score model by multinomial logit model

$$log\frac{p(T=j|X)}{P(T=1|X)} = \alpha_j + \beta_1 X_1 + \ldots + \beta_{41} X_{41}$$

Where p(T=j|X) indicates the probability of treatment to CLA (j=1), DOXY(j=2) and ERY(j=3) given 41 covariates.

- Stabilized weight for each patient were calculated by

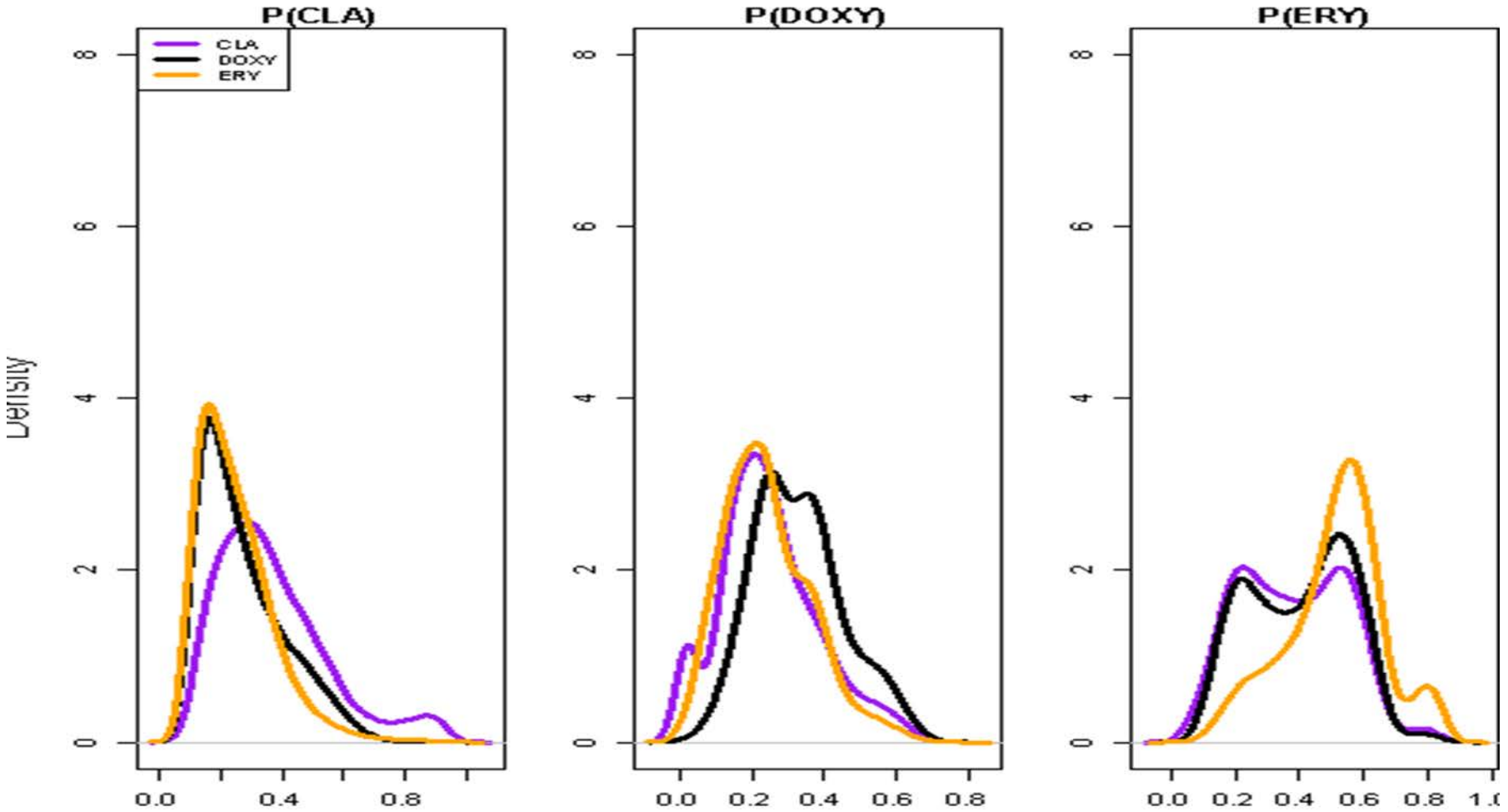
$$SW_i = \begin{cases} \frac{P(T=1)}{PS_{1,i}} : clarithromycin \\ \frac{P(T=2)}{PS_{2,i}} : Doxycyclin \\ \frac{P(T=3)}{PS_{3,i}} : Erythromycin \end{cases}$$

- Examined diagnostics for PS and weighting before analyzing outcome

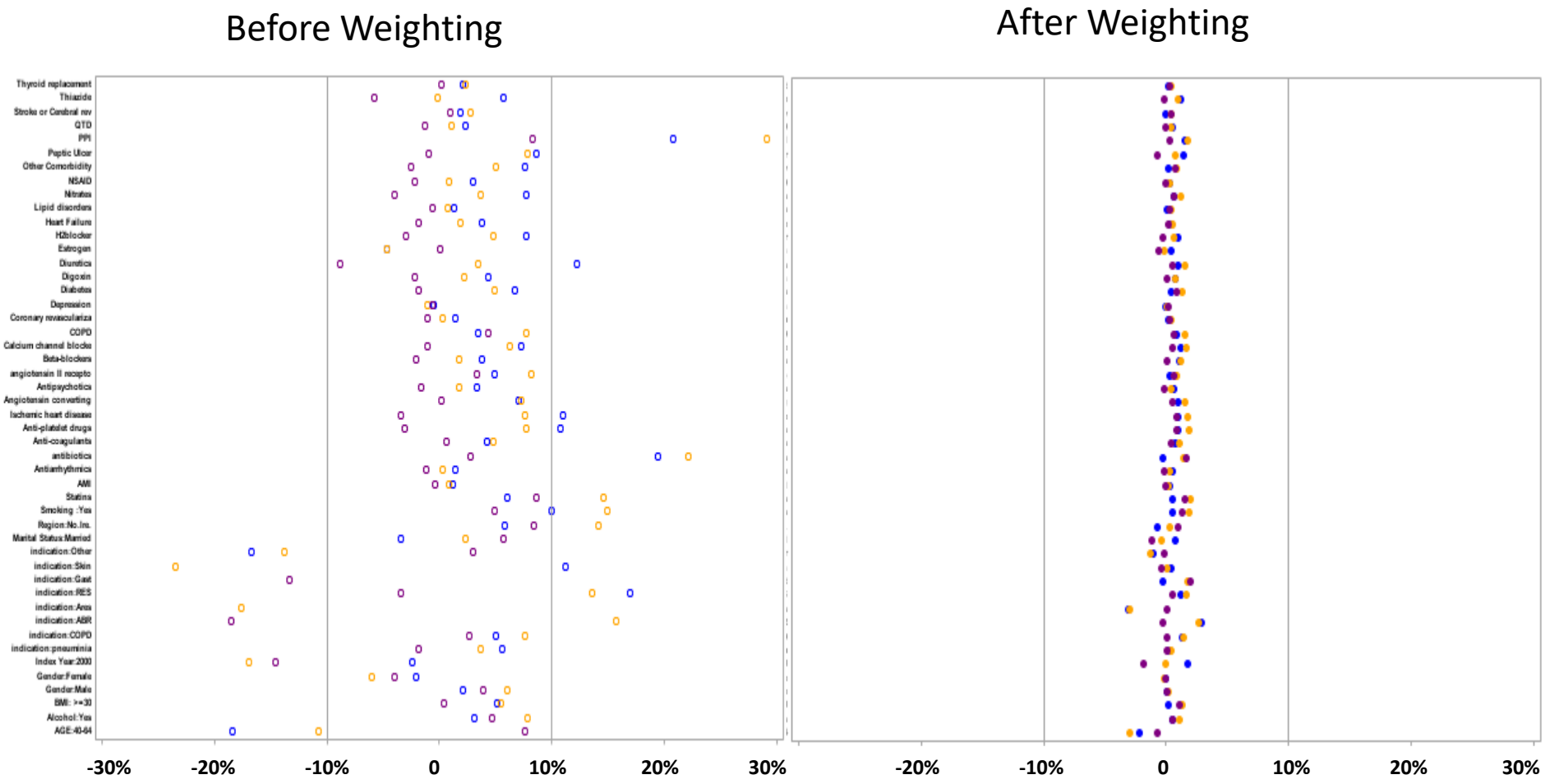
Statistical Methods (cont.)

- Primary outcome model: Weighted Cox PH regression
  - To assess the effect of repeated exposures, the cumulative number of index drug Rx was a time-varying covariate
  - *Indication* and age variables are doubly adjusted in the model
  - Robust variance estimator was used for standard error
- Subgroup analyses by age, statin use, calcium channel blocker use, indication of COPD and pneumonia, prior ischemic heart disease status at baseline
- Sensitivity analyses by setting large weights above 90th percentile to the ceiling of 90th percentile

Diagnostics #1: Distribution of PS

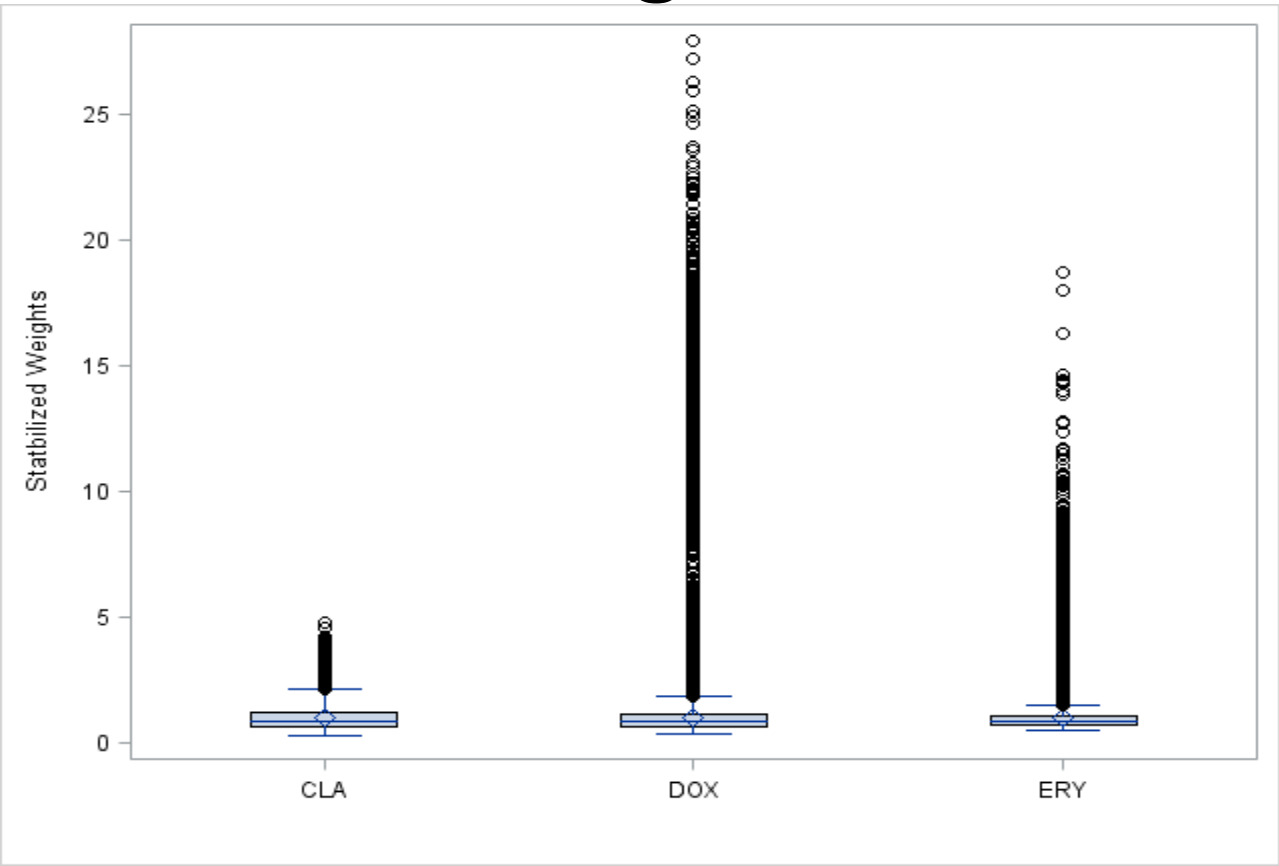


Diagnostics #2: Balance Checking



CLA vs. DOXY, CLA vs. ERY, DOXY vs. ERY

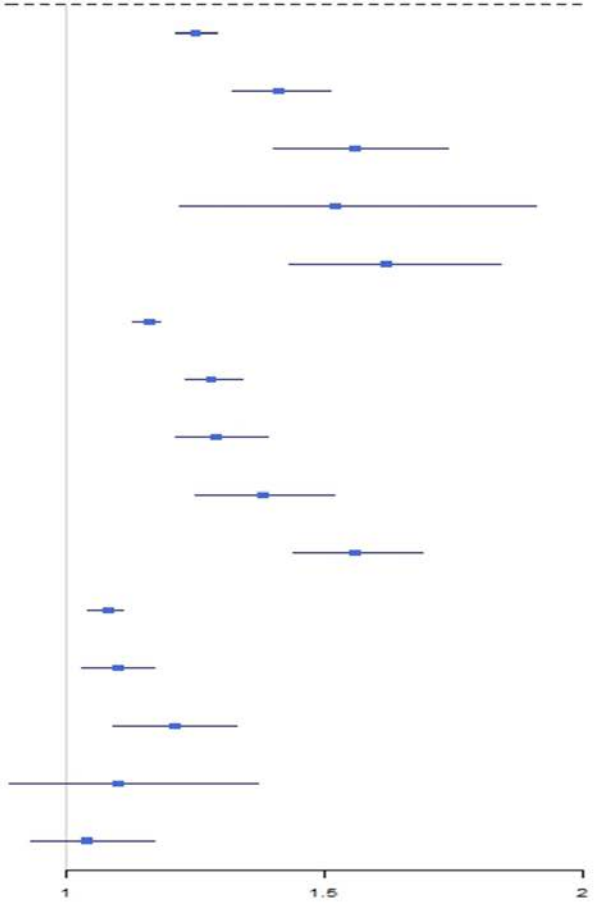
Diagnostics #3: The distribution of Weights



- It shows large weights for some patients so sensitivity analysis was performed to assess the impact of large weights on study conclusion.
- It didn't influence the primary study result.

Primary Results:
HR of All-cause Mortality

DRUG	# RX	HR	LCL	UCL
CLA vs.DOXY	1	1.25	1.21	1.29
	2	1.41	1.32	1.51
	3	1.56	1.4	1.74
	4	1.52	1.22	1.91
	5	1.62	1.43	1.84
CLA vs.ERY	1	1.16	1.13	1.18
	2	1.28	1.23	1.34
	3	1.29	1.21	1.39
	4	1.38	1.25	1.52
	5	1.56	1.44	1.69
ERY vs.DOXY	1	1.08	1.04	1.11
	2	1.1	1.03	1.17
	3	1.21	1.09	1.33
	4	1.1	0.89	1.37
	5	1.04	0.93	1.17



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SOFTWARE

Estimation of PS

/** SAS ***/**
proc logistic data = ps descending;
CLASS Exp X1.. X2;
MODEL exp (ref="1")=x1 x2… x40 /LINK=LOGIT; */** link=glogit for multinomial logit model **/*
OUTPUT OUT=ps_Score PRED=ps;
run;

/** R ****/**
/ TWO arms **/**
PS<-glm(exp~x1+x2+..+x40,data=, family="binomial")

/ THREE arms **/**
Library(nnet)
Data$exp<-relevel(data$exp,ref="1")
PS2<-multinom(exp~x1+x2+..x40, data=)

Weighted Cox PH model

/* SAS **/**

```
proc phreg data=all covs(aggregate);
ID subject;
CLASS exp(ref="0")  ;
WEIGHT sw;
model (start,stop)*out(0)=exp;
run;
```

/* R **/**

```
coxph(Surv(start, stop, out) ~ exp + cluster(id), weight=sw, data=)
```

Matching

/ *SAS macro */

%PSMatching(datatreatment=trt, datacontrol=con, method=caliper, numberofcontrols=1, caliper=0.2, replacement=no, out=psmatching_out);

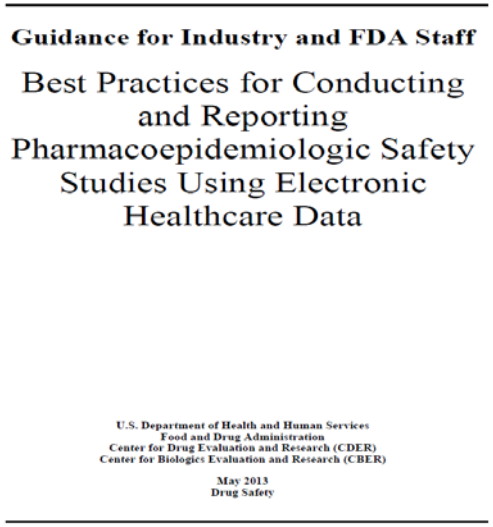
/* R */

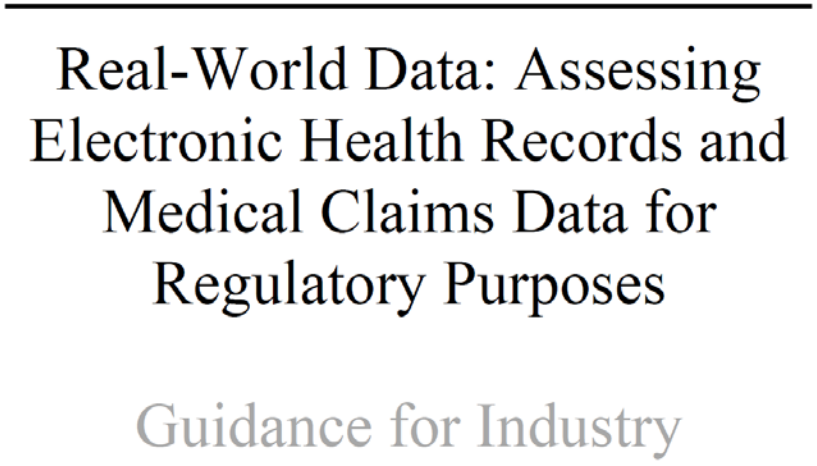
```
library(MatchIt)
psmatch <- matchit(exp ~x1+X2+..+x40,distance = "logit", method = "nearest", ratio =
1,replace = FALSE, caliper=0.2, data = data)
```

SUMMARY

IPTW DO'S AND DON'TS

Do # 1: Use Best Practices For Study Design





- Control for biases and confounding **by design** involve judicious choices of
  - Data source
  - Inclusion/exclusion criteria
  - Appropriate comparators
  - Outcome, exposure and covariate codes/algorithms

Do # 2: Prespecify Estimand of Interest in the Protocol or SAP

Estimand	Inference Population
Average Treatment Effect on the Treated (ATT)	All those indicated for drug T
Average Treatment Effect (ATE)	All those indicated for drugs T and C

- In IPTW, target estimand determines how weights are used in analysis. For example,
  - For target ATE all subjects are weighted
  - For target ATT (pairwise comparison), only control subjects are weighted

Do #3 Check Diagnostics

Diagnostics	Checking Point
Distribution of PS	To see overlap between treatment arms
Distribution of weights	To examine any large weights If Yes → conduct sensitivity analysis
SMD before and after weighting	To ensure balance of potential confounders between treatment arms is achieved

Do # 4: Use Robust Estimation or Bootstrap for Standard Errors

Do #5: Include Sensitivity Analysis to Large Weights

Lastly..

Do #6: Keep yourself blinded to outcome while performing PS analysis

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Thank You!