Transporting the effects of a randomized trial to a new target population: an example using the TASTE trial

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Outline

- **Motivation**
- Theory & assumptions
- Example with TASTE
- Methods
- Results
- Discussion

Motivation

- Randomized trials are the established gold standard to estimate causal effects in medicine

- Well designed trials return internally valid estimate of treatment effects for a specific group of individuals

Motivation

- We hope to be able to use trial results to learn about the effects of different treatment choices in routine settings
- But for who ?
- Different decision makers are interested in the result of the trial, but applied to different populations (target populations)

Motivation

- For example, health boards or regional health services may be interested in the results of the trial applied to their specific patient population
- Care-givers may be interested in the effect in the individual patients they see
- Patients may be interested in the effect of treatment on themselves

Motivation

- Randomized trials define one possible target population via their eligibility criteria
- e.g. patients with ST-elevated MI, over 18 years old, with the ability to perform the intervention
- But there are issues we face when trying to translate results from a trial into practice, for such a group of patients

Motivation

- To precisely estimate the effect of the intervention, trials often use strict protocols
- Such strict protocols may not reflect routine use of the treatment
- Multiple versions of the treatment may exist, such as different delivery mechanisms, or surgical techniques

Motivation

- Patients enrolled in a trial may benefit from increased contact with physicians
- This may result in additional care, or recommendations that would not happen otherwise

Motivation

- Adherence to treatment may also not reflect the routine setting
- Patients may be more motivated to stay on treatment, or may receive encouragement during visits

Motivation

- Finally, not all patients in meeting the eligibility criteia will enrol in the trial with equal probability

- This can cause imbalances in important effect modifiers that can shift the measured treatment effect

Motivation

- All of these points can have an impact on the measured treatment effect in the population
- What can we do if we want to estimate the average effect in the target population ?
- Many of these issues can be releived by conducting pragmatic trials, nested inside registries

Motivation

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

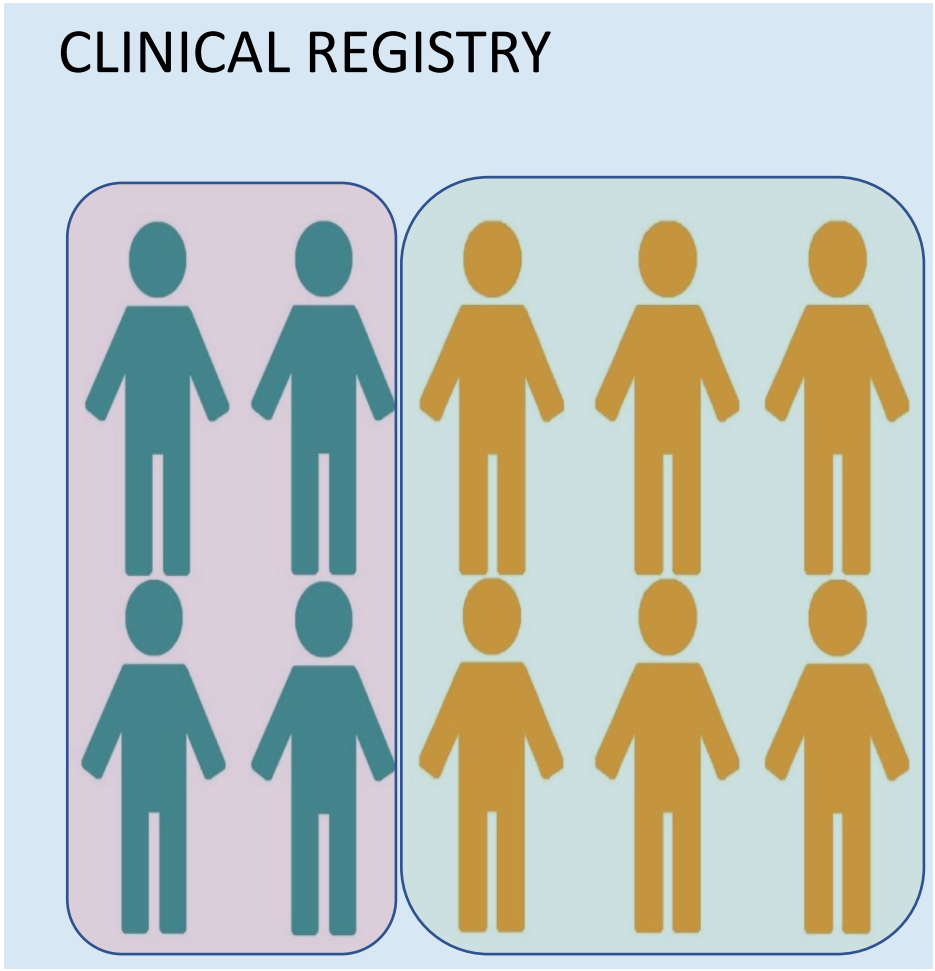
Related article, p. 1587

- Pragmatic trials typically compare standards of care, non-blinded, and allow some physician input
- Registry structures allow easy data collection and followup
- The trial resembles routine care as closesly as possible

N Engl J Med 2013; 369:1579-1581

Motivation

- Patients still need to opt-in, and provide consent
- There will still be systemic groups of patients who will not participate
- We can still make use of their data in the registry



Motivation

Published in final edited form as:
J R Stat Soc Ser A Stat Soc. 2001 April 1; 174(2): 369–386. doi:10.1111/j.1467-985X.2010.00673.x.

The use of propensity scores to assess the generalizability of results from randomized trials

Elizabeth A. Stuart[2], **Stephen R. Cole**[3], **Catherine P. Bradshaw**[4], and **Philip J. Leaf**[4]

- Developments in methods have how we can combine observational and trial data to asses a trials external validity
- We can use these data to standardise, or weight, our trial population to look like a target population
- Randomized registry trials are the perfect setting for these types of analyses

- Motivation
- **Theory & assumptions**
- Example with TASTE
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Some notation

- S indicates trial participation (0 or 1)
- X is some vector of covariates
- Y indicates outcome (0 or 1)
- Z indicates treatment assignment (0 or 1)

- For these examples I assume full adherence, no measurement error or missing data, and no loss to followup in the trial

Theory

- Hypothetical intervention to **scale up trial participation to the target population**, and **assign treatment in the target population**
- Practically, this involves transforming the trial data to look like the data from the target population
- We can do this, if we make several strong assumptions

Assumptions required

Assumption	
Exchangeability	Participants in the study are exchangeable with individuals in the target population, conditional on X
Consistency	
Positivity	

Assumptions required

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Exchangeability	Participants in the study are exchangeable with individuals in the target population, conditional on X
Consistency	Treatment versions should not differ between the trial and target population.
Positivity	

Lesko CR, Buchanan AL, Westreich D, Edwards JK, Hudgens MG, Cole SR. Generalizing Study Results: A Potential Outcomes Perspective. Epidemiology. 2017 Jul;28(4):553-561.

Assumptions required

Assumption	
Exchangeability	Participants in the study are exchangeable with individuals in the target population, conditional on X
Consistency	Treatment versions should not differ between the trial and target population
Positivity	All individuals in the target population have a non-zero probability of participating in the trial

Lesko CR, Buchanan AL, Westreich D, Edwards JK, Hudgens MG, Cole SR. Generalizing Study Results: A Potential Outcomes Perspective. Epidemiology. 2017 Jul;28(4):553-561.

Estimators

- If assumptions are satisfied, we can use IPW or g-formula estimators to obtain the treatment effect in the target population

- This gives an estimate of the effect, had everyone in our target population enrolled in the trial

Estimators

- If assumptions are satisfied, we can use IPW or g-formula estimators to obtain the treatment effect in the target population

- These give an estimate of the absolute risk under either treatment, had everyone in our target population enrolled in the trial

- IPW estimator $\frac{1}{n}\sum_{i=1}^{n}\frac{I(Z=z)\times S\times Y}{\Pr(S=1|X)}$

- G-formula estimator $\frac{1}{n}\sum_{i=1}^{n}E[Y|X,S=1,Z=z]$

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Example - The TASTE trial

ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., et al.

N Engl J Med 2013; 369:1587-1597

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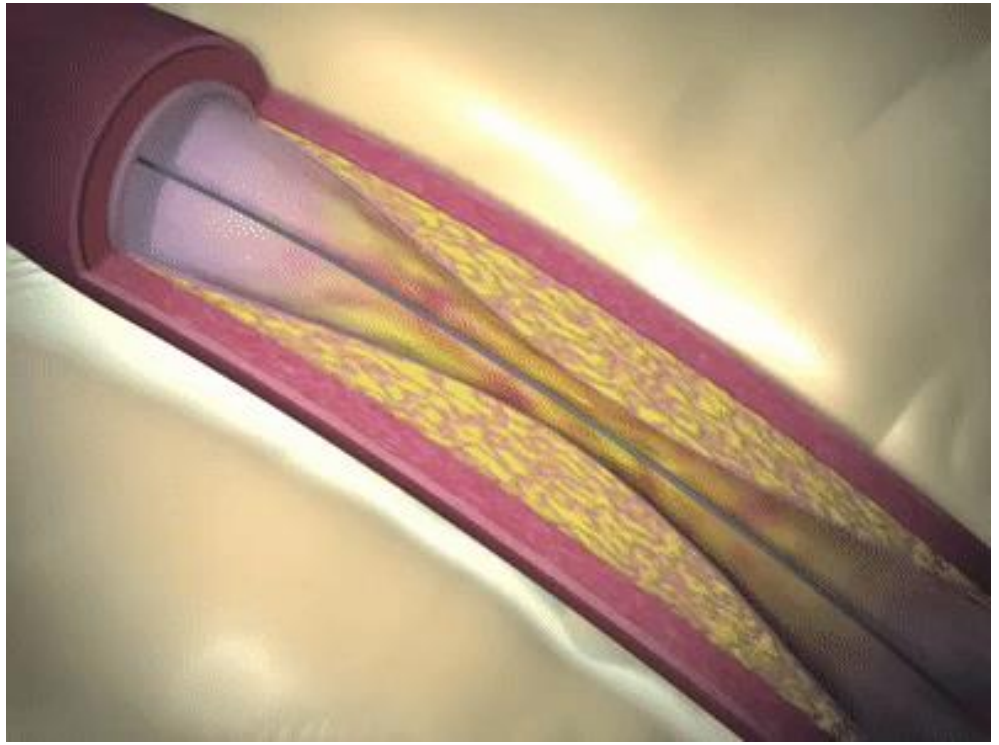
Clinical context

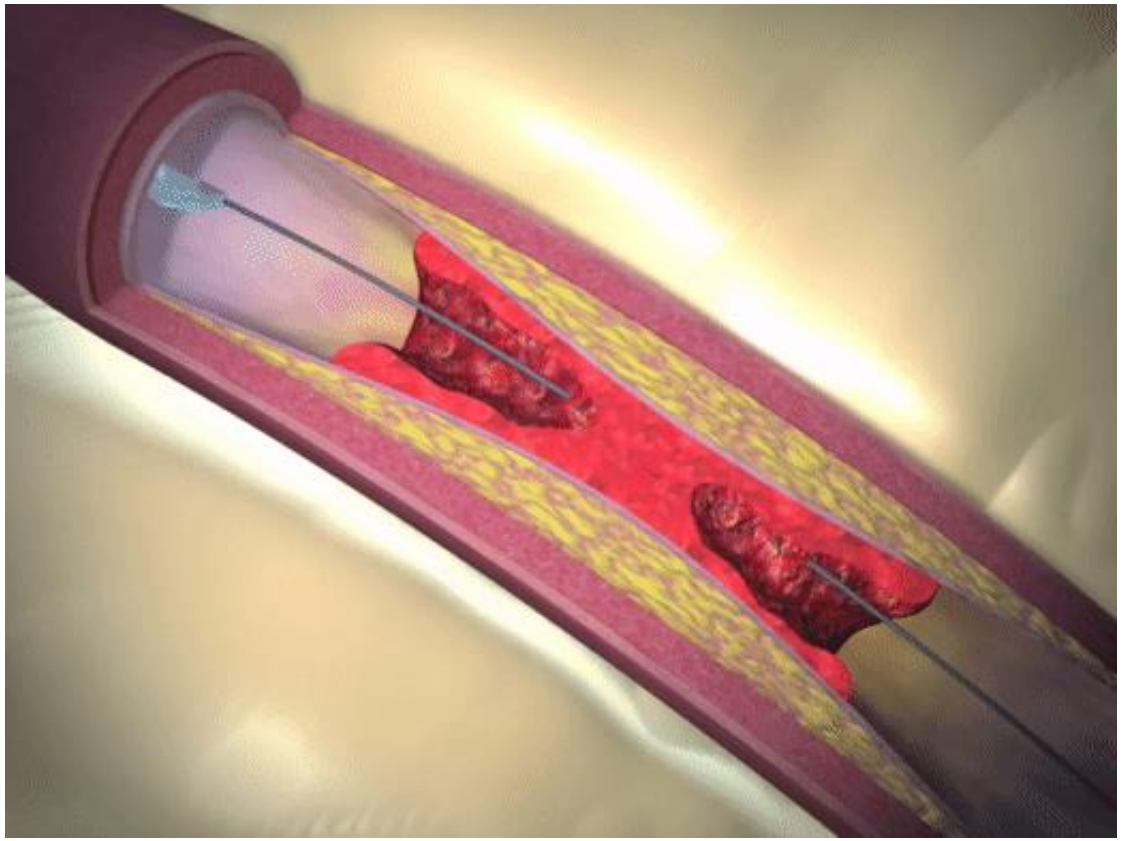
- ST Elevated MI (STEMI) is a severe type of heart attack, and major cause of death
- Commonly treated by PCI (balloon + stent)



PCI procedure, NEJM group

Thrombus aspiration in Myocardial Infarction

- Removal of thrombus prior to PCI may improve outcomes post PCI
- Thrombus aspiration – vacuum to suck out the thrombus
- Supported by observational data, but before TASTE no large trials



Thrombus aspiration, NEJM group

The TASTE trial - Design

- Multicenter, randomized, open-label trial assessing PCI + thrombus aspiration vs PCI alone
- Conducted across 29 PCI centers in Sweden, 1 in Denmark, 1 in Iceland, from 2010-13
- In Sweden, **embedded in SCAAR clinical registry**

The TASTE trial - Design

- SCAAR, web-based interface of **all patients** undergoing angiography & angioplasty in Sweden
- Baseline data collected for **all patients**
- SCAAR used for patient ID, data collection, and randomization

The TASTE trial – Outcomes & Followup

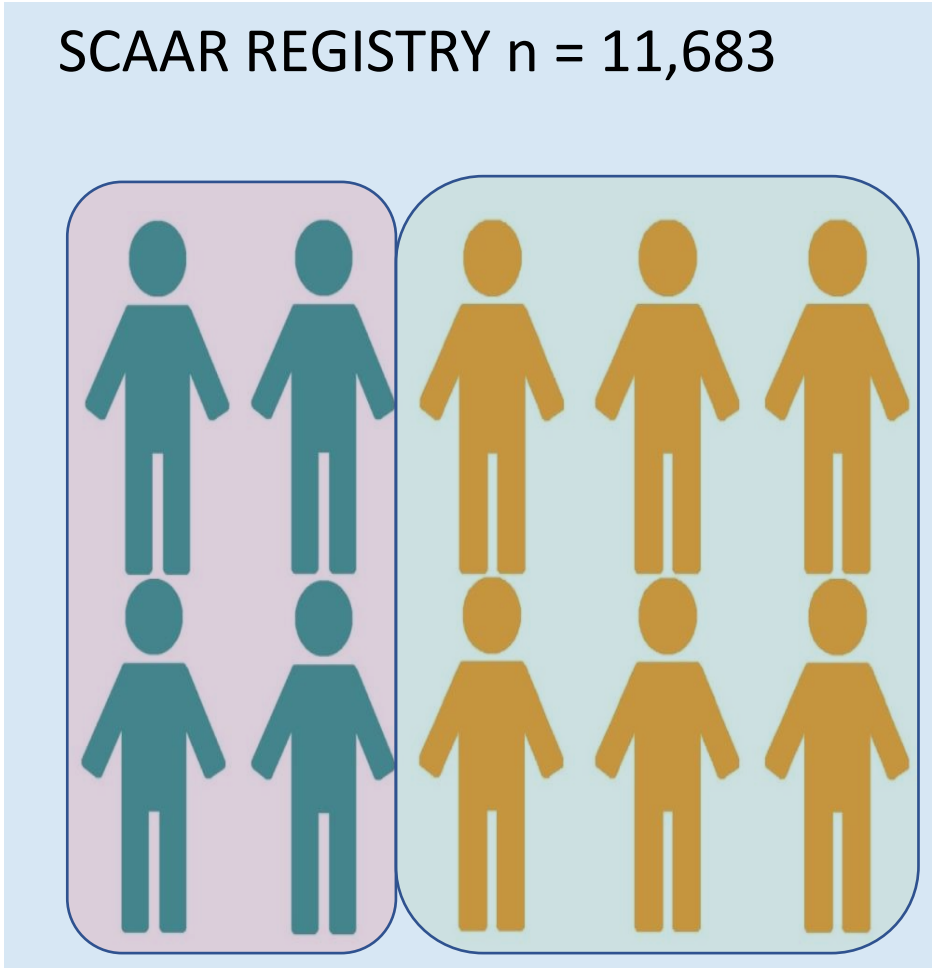
- Outcomes: death, recurrent MI, stent thrombosis at one-year
- Outcomes obtained from national health registries
- No study-specific clinical follow-up

The TASTE trial – Inclusion & Exclusion

Inclusion	Exclusion
Referred for PCI due to STEMI	Need for emergency CABG
Correspondance between ECG & culprit artery pathology	Unable to provide consent
50 % stenosis of culprit artery	< 18 years
Deemed possible to perform thrombus aspiration	Previous randomisation

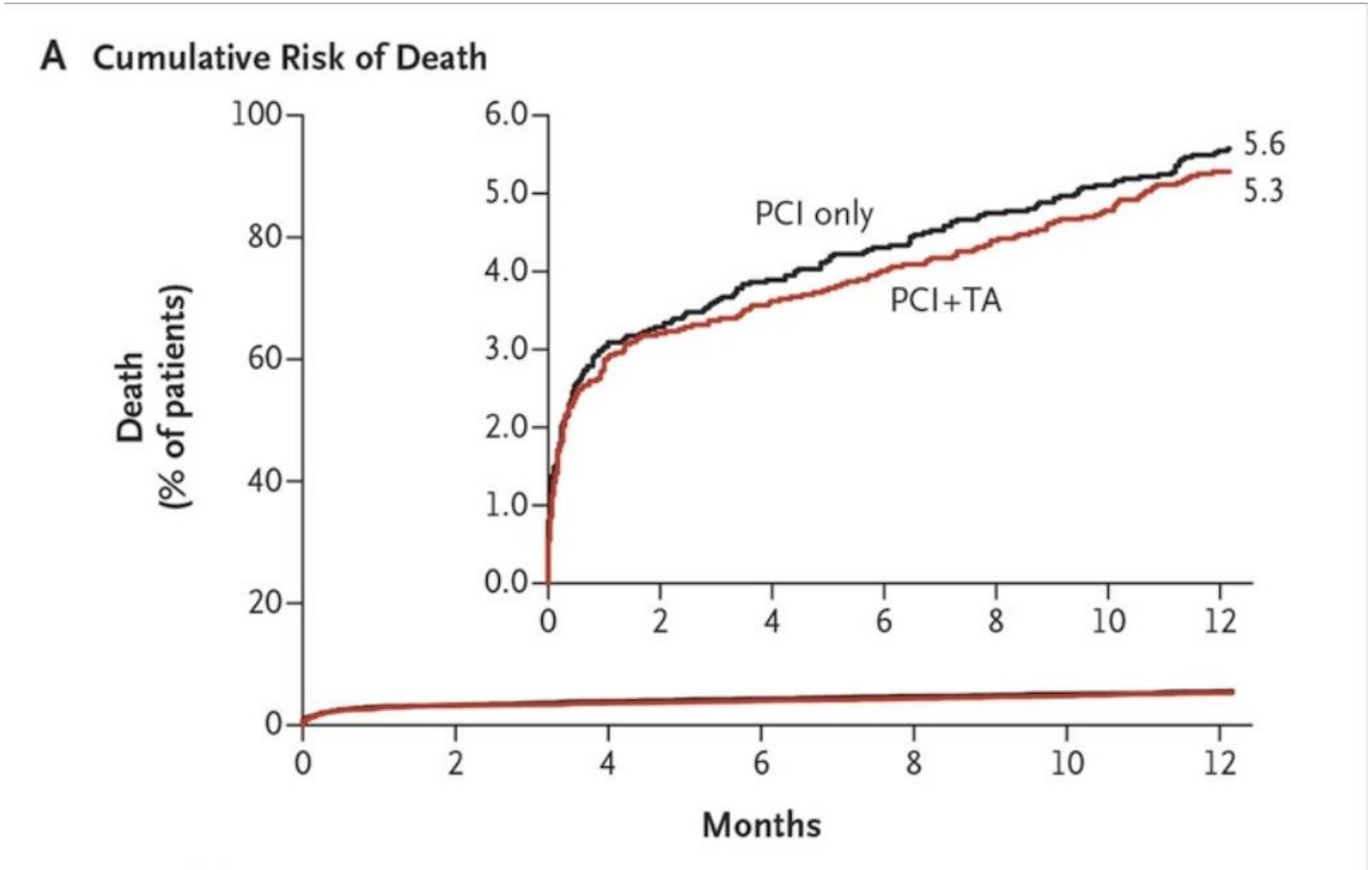
The TASTE trial - Results

- In Sweden, 11,683 patients were referred for PCI due to MI
- 7088 (61%) of these patients were recruited into the trial
- Among the enrolled ~ 75 % male, BMI ~ 27kg/m2, severe MI ~ 5 %



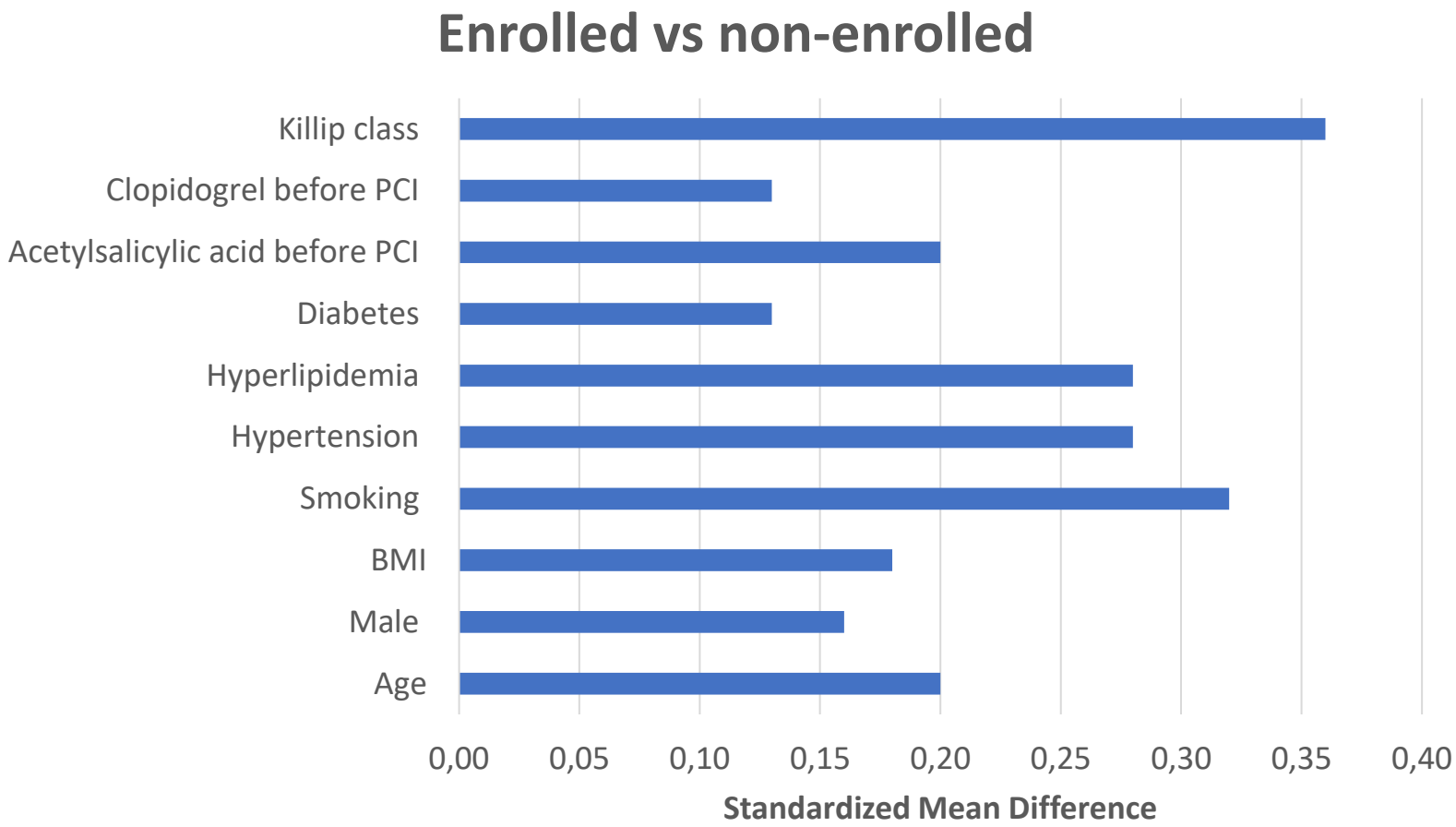
The TASTE trial - Results

- No effect of treatment in the TASTE trial



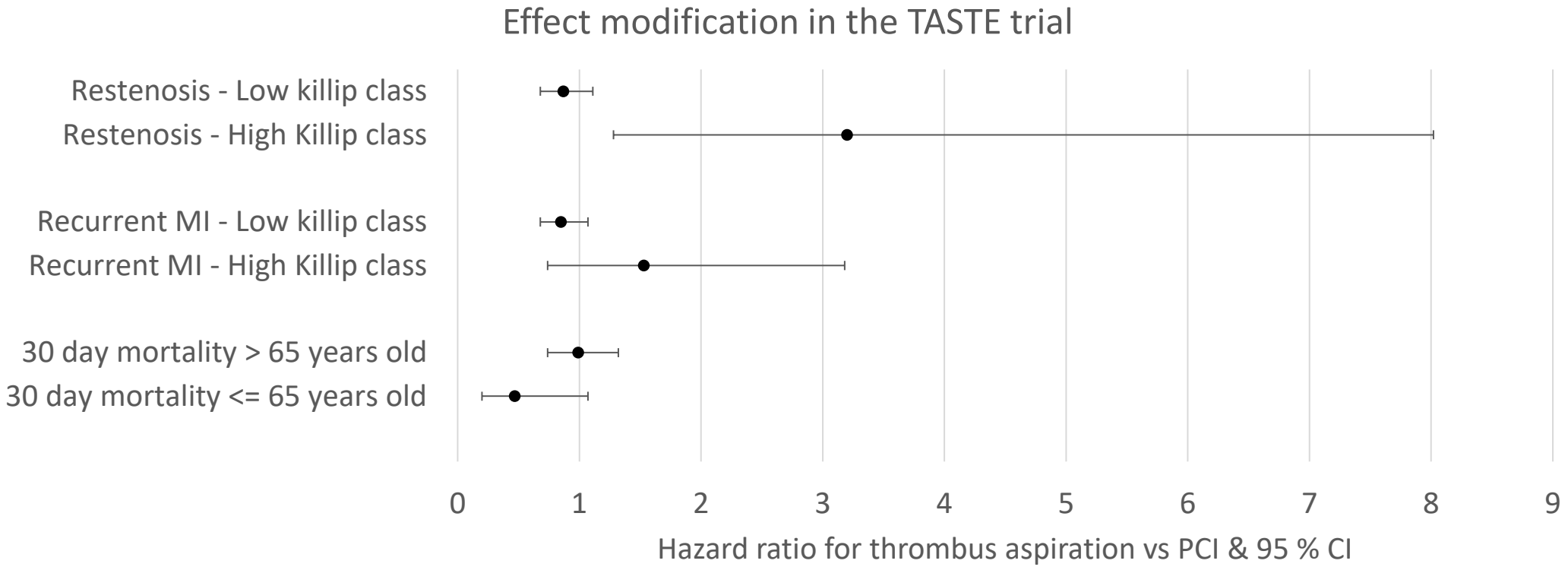
The TASTE trial – who participated ?

- Enrolled were generally *'healthier'*
- Differences known to be related to risk of death



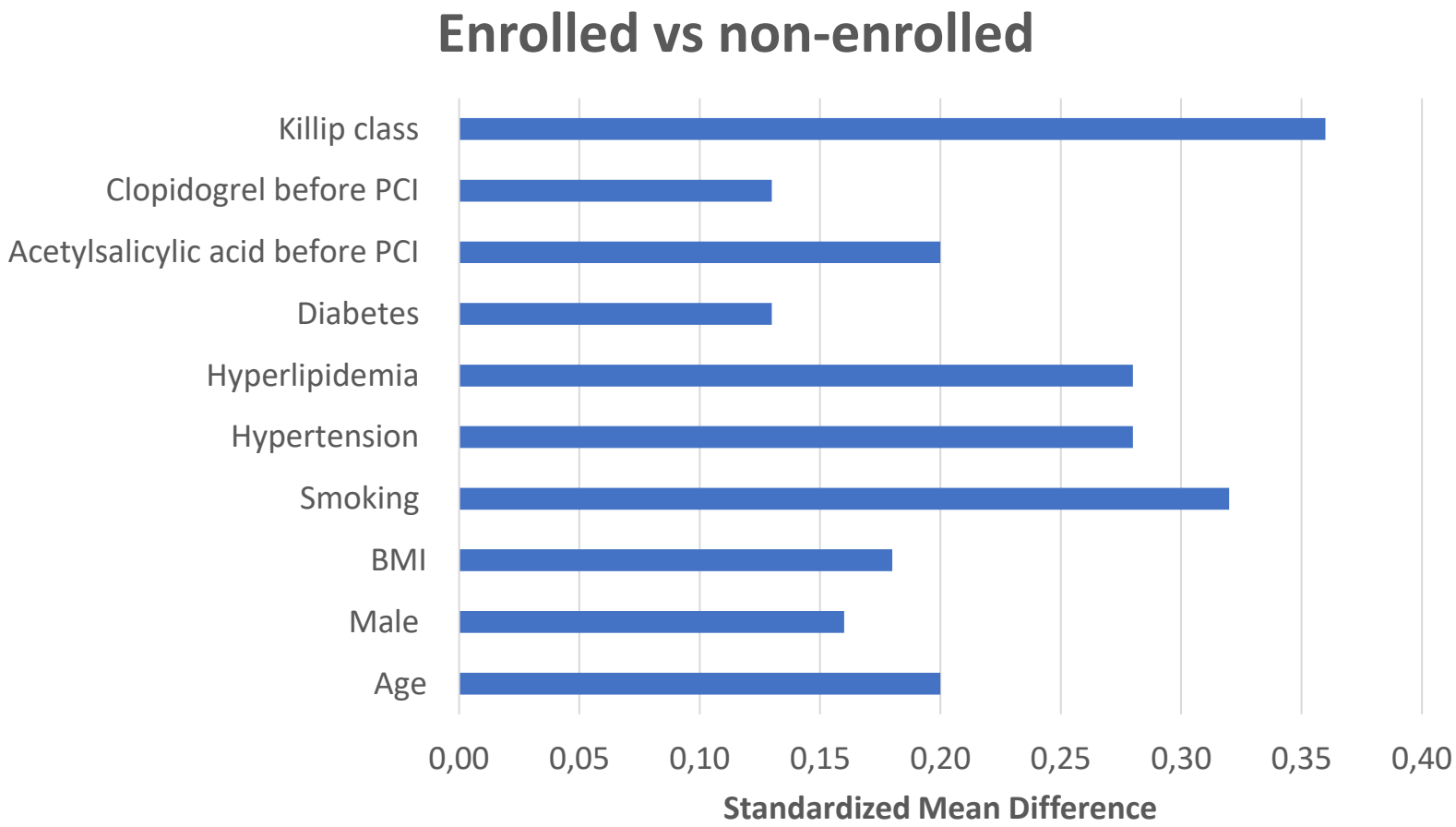
Effect modification in the TASTE trial

- Potential effect modification in TASTE from **Killip class (MI severity)** and **age**



The TASTE trial – who participated ?

- Could this shift in covariates affect average treatment effect?
- What would the result have been if everybody participated?



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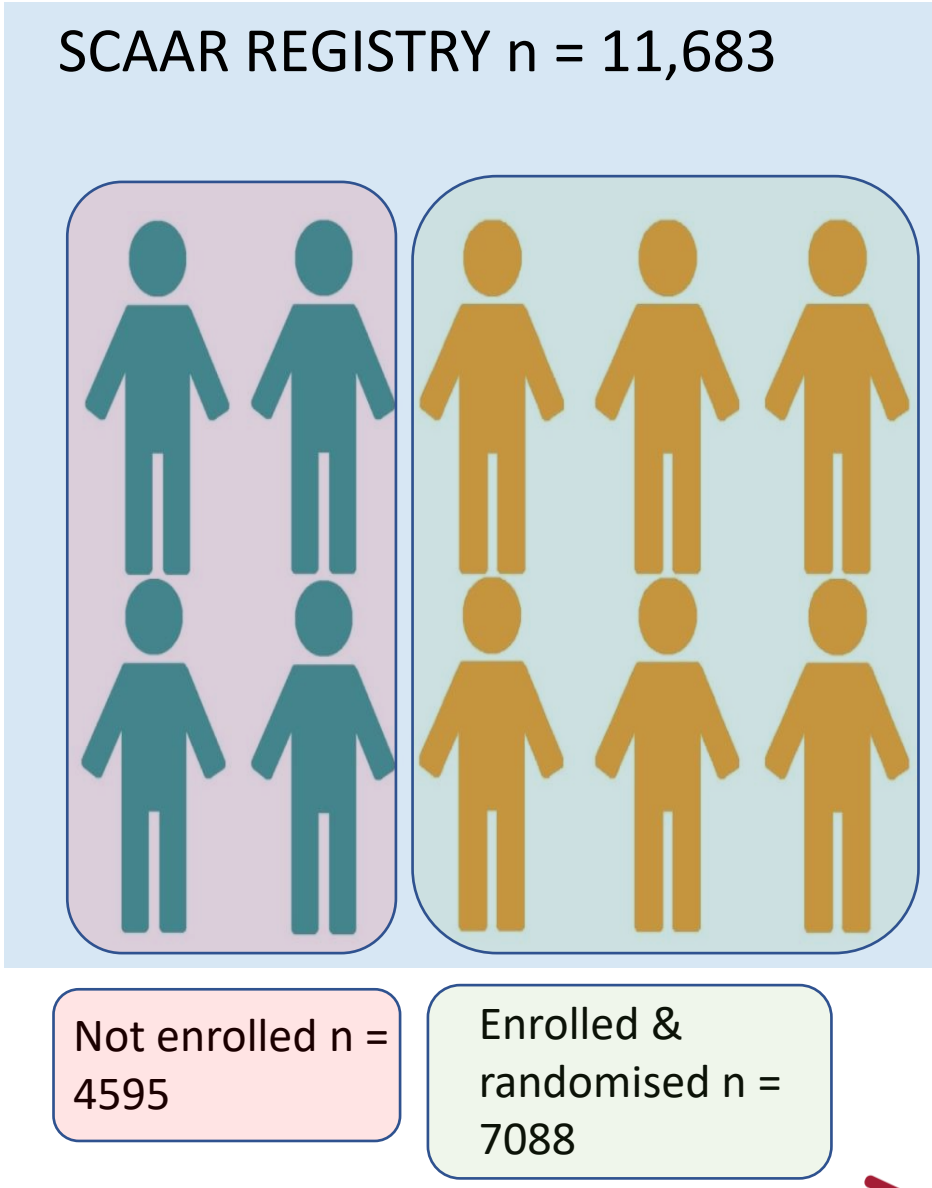
Methods – Transportability

- Currently (from the trial) we know : $E[Y^{z=1}|s=1]$, $E[Yz^{=0}|s=1]$
- We want to know $E[Y^{z=1}]$, $E[Y^{z=0}]$ i.e. the expected outcomes under each treatment if everyone had participated in the trial
- **Method** : Inverse probability weights based on trial participation & g-formula to estimate $E[Y^{z=1}]$, $E[Y^{z=0}]$

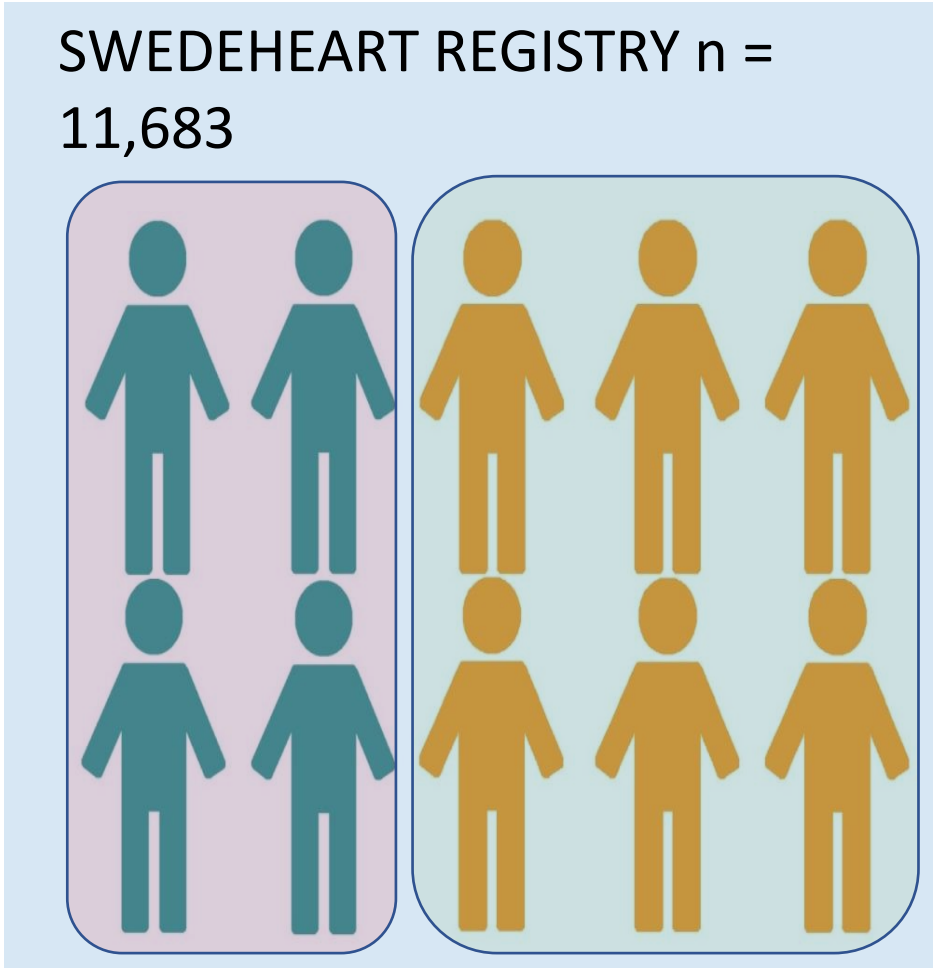
Methods – Assumptions

- **Consistency** : Same distribution of treatments regardless of enrolment in the trial
- **Exchangeability** : Can identify factors affecting trial participation in the registry
- **Positivity** : We can assess the probability of trial inclusion



Methods – Additional benefits

- The population in the registry underlying the trial forms a natural target population
- Covariates should have been recorded in the same manner, regardless of trial enrolment



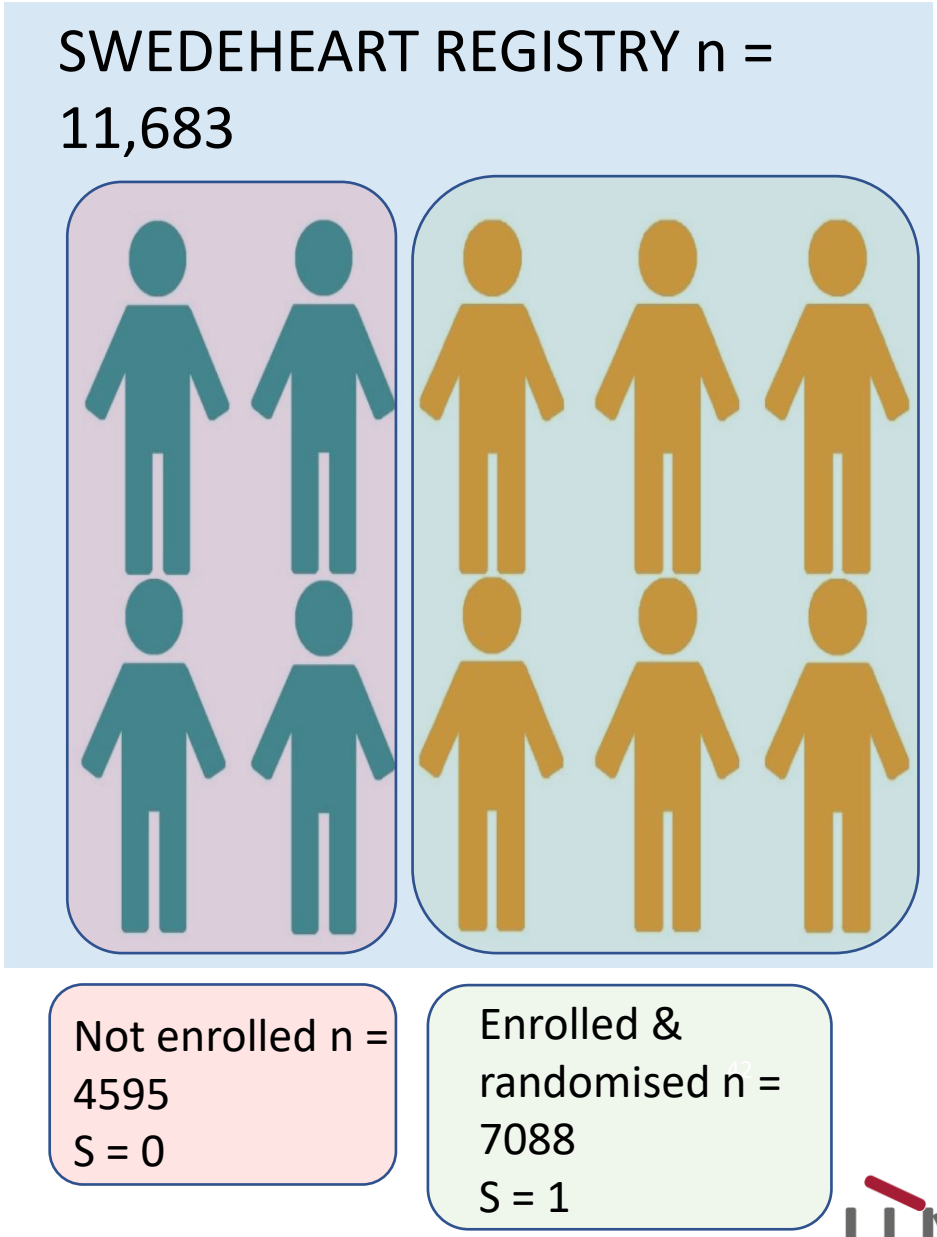
Methods – Inverse probability weighting based estimator

Methods – Weights and models

Step 1 :

Calculate weights based on the inverse probability of trial participation (conditional on *age, sex, bmi, killip class*) and treatment assignment (for efficiency)

i.e. weights = $\frac{S}{\Pr(S=1|X)}$

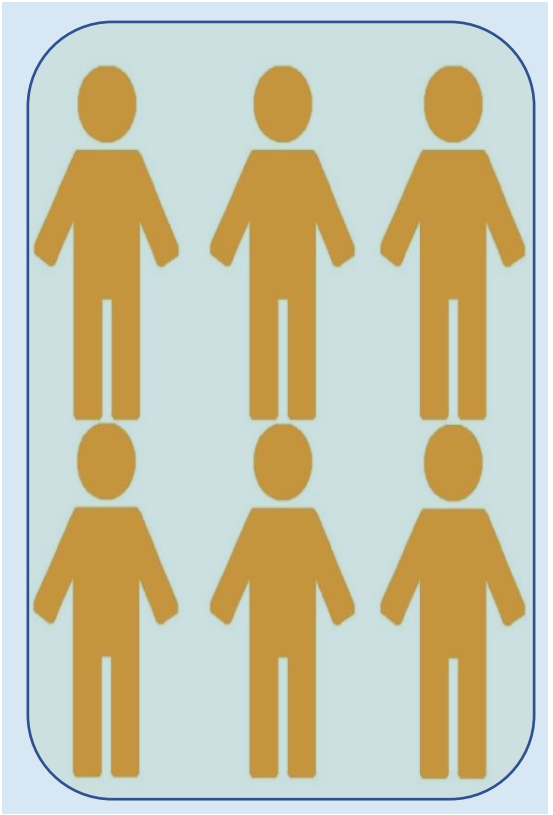


Methods – Weights and models

Step 2 :

Fit **weighted** logistic regression for the outcome, conditional on treatment, among trial participants

i.e. model for Pr(Y=1|Z, S=1)



Enrolled & randomised n = 7088

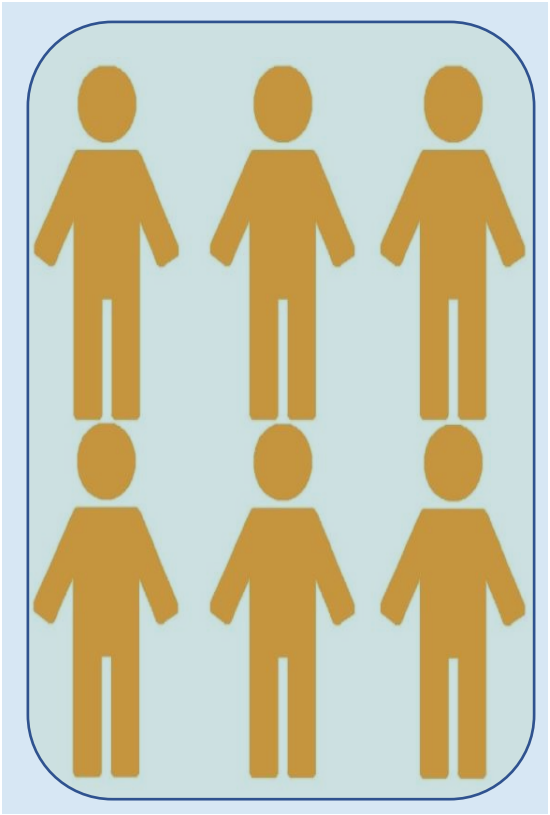
Methods – Weights and models

Step 2 :

Fit weighted logistic regression for the outcome, conditional on treatment, among trial participants

Step 3:

Use the predictions from this model to obtain the risk under each treatment, and RD or RR



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Methods – Weights and models

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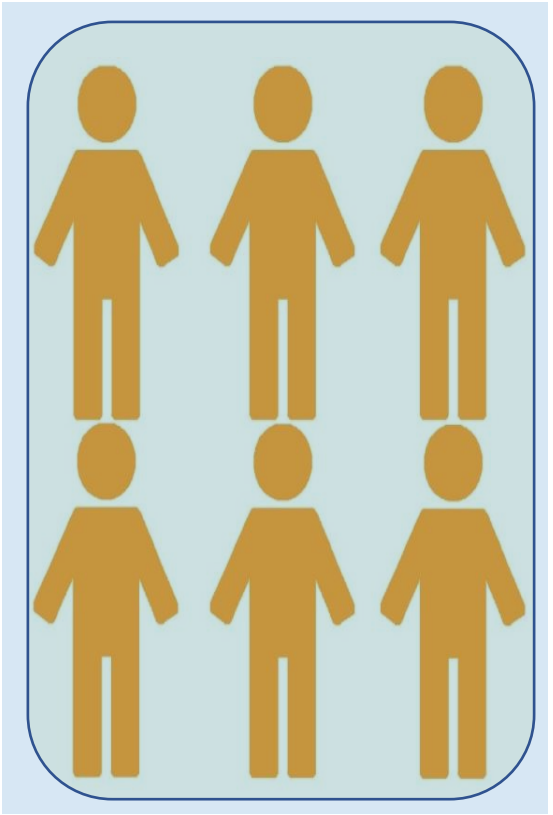
Step 4:

95 % CI by boostrapping this process



Enrolled & randomised n = 7088

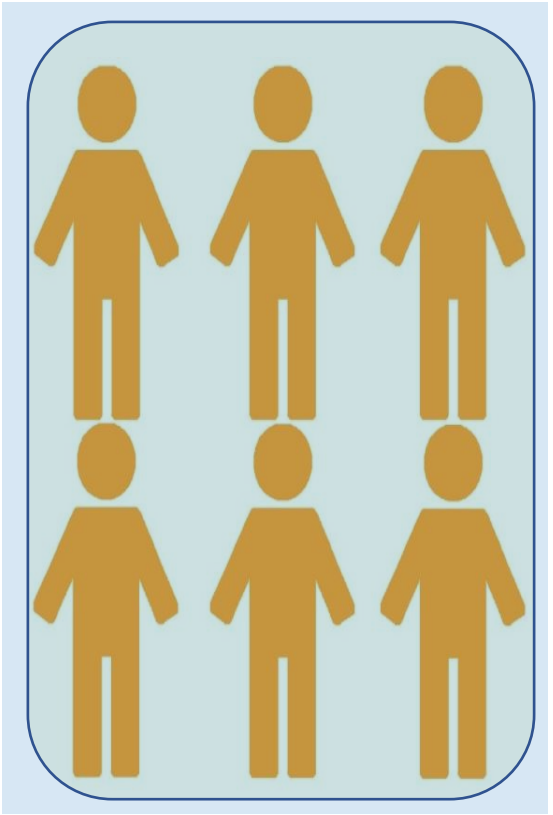
Methods – G-formula based estimator

Methods – Outcome modelling

Step 1 :

Fit a logistic regression model for the outcome, conditional on treatment and covariates among participants the randomized trial

i.e. model for Pr(Y=1|Z, X, S=1)

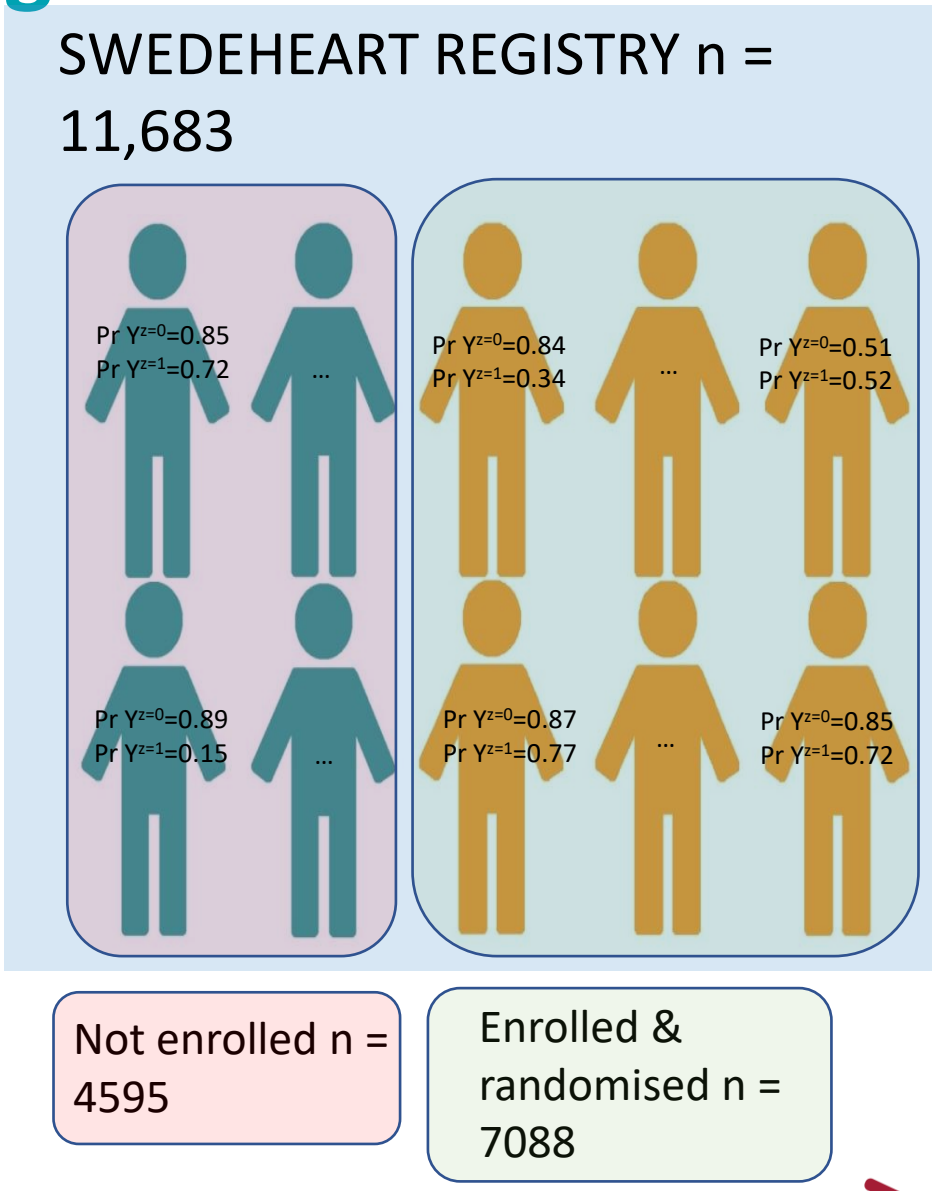


Enrolled & randomised n = 7088

Methods – Outcome modelling

Step 2 :

Use this model to predict the outcomes under each treatment for each individual in the target pop



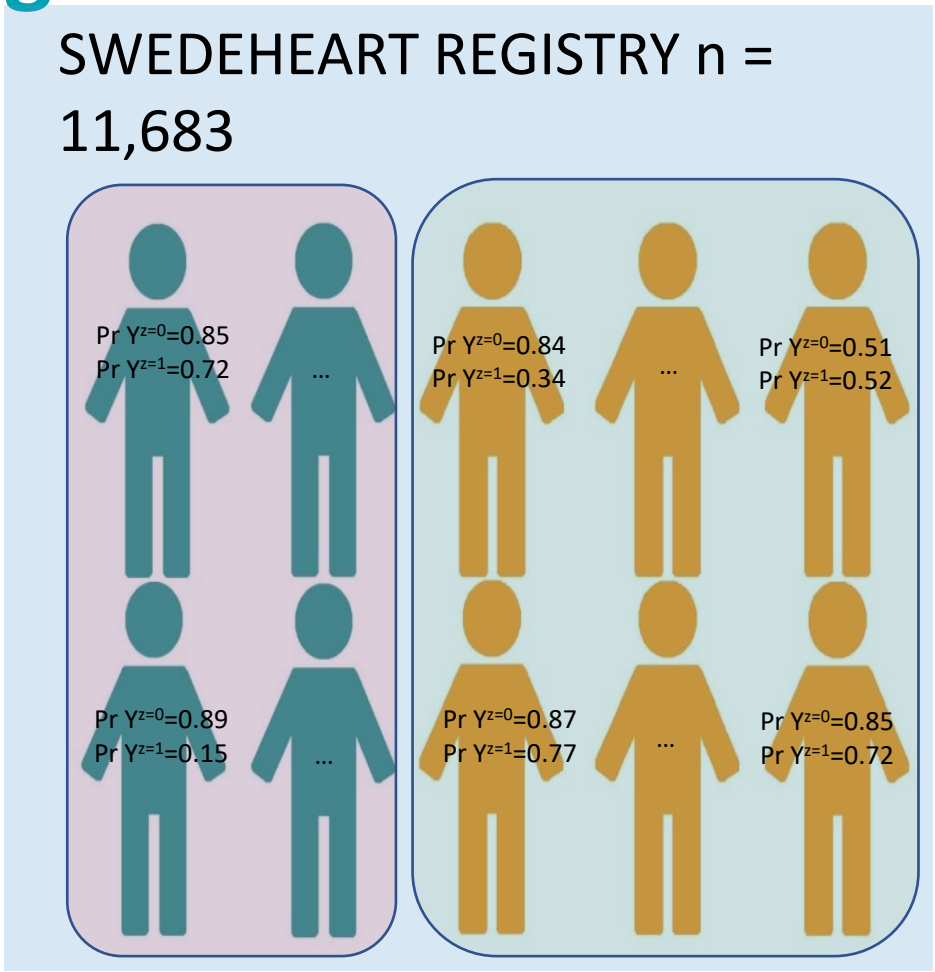
Methods – Outcome modelling

Step 2 :

Use this model to predict the outcomes under each treatment for each individual in the target pop

Step 3 :

Take the average of these predictions for each treatment, and calculate the risk-difference



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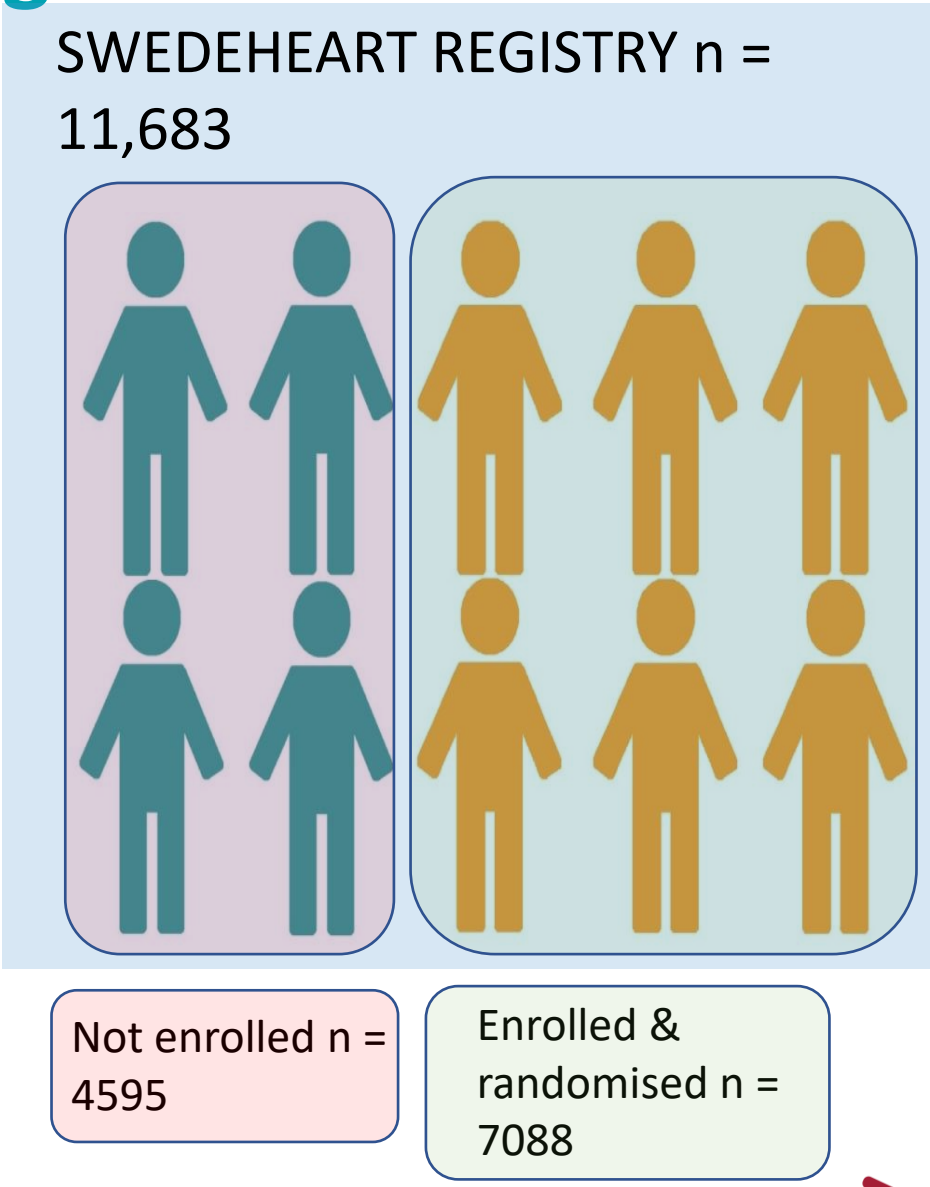

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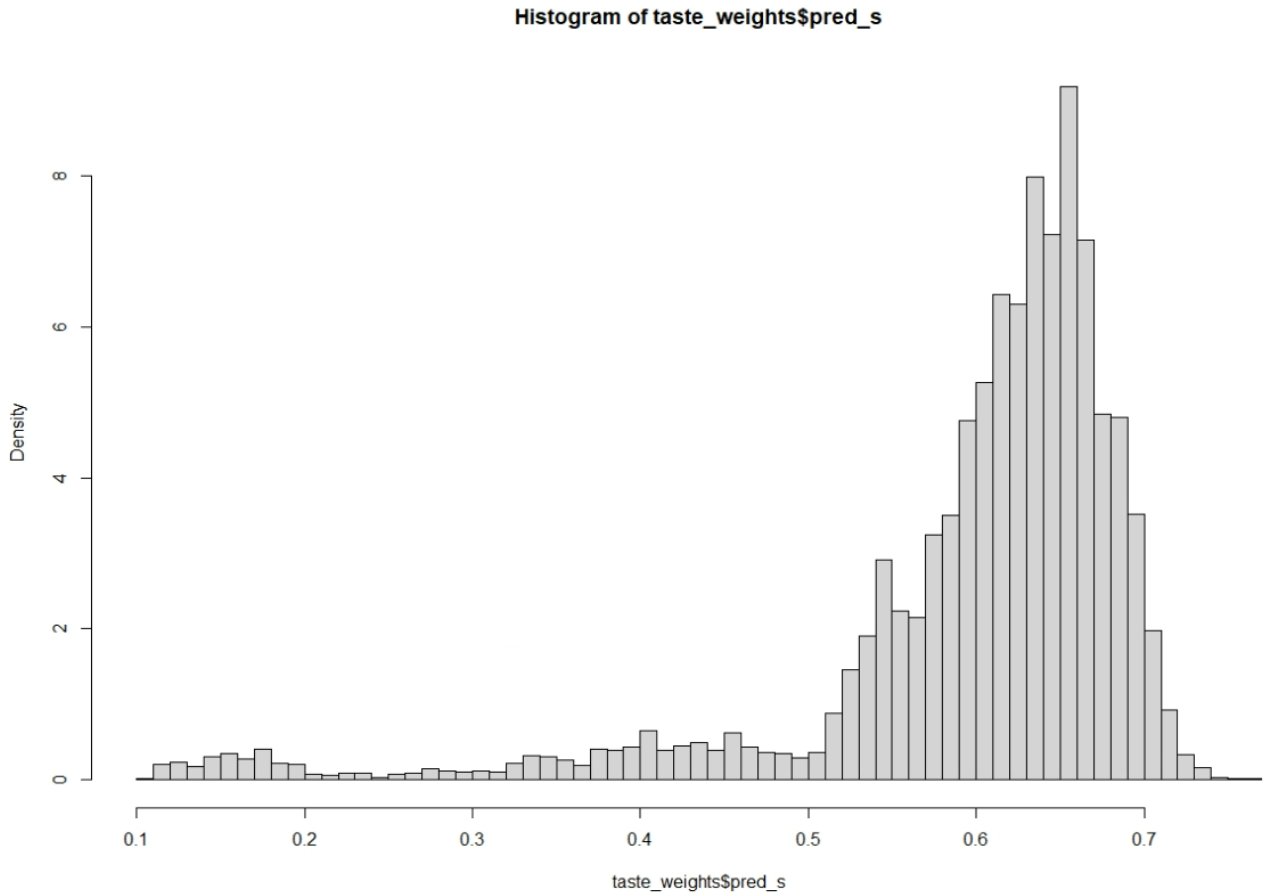
- **Preliminary results**
- Discussion

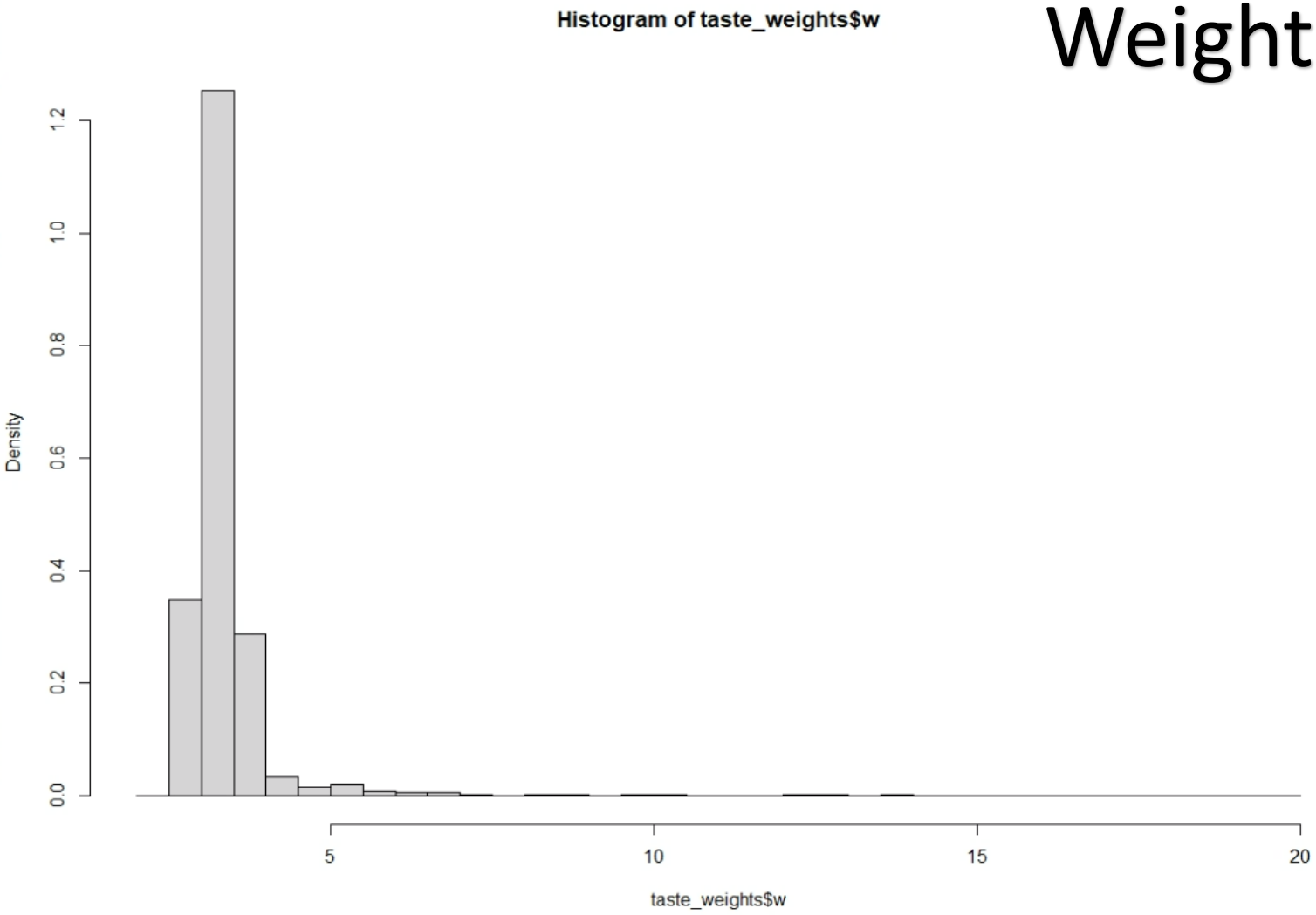
Preliminary results – Probability of trial inclusion & weights

Probability of participation



Preliminary results – Probability of trial inclusion & weights

Weights



Preliminary results – transport analysis, effect of assignment

Death at one year	Risk under PCI alone	Risk under PCI + TA	Risk difference
Trial population *	5.6	5.3	0.2
Target – g formula	7.8 [7.0: 8.8]	8.2 [7.3: 9.3]	0.4 [-0.7: 1.8]
Target – IPW	7.5 [6.6: 9.0]	7.6 [6.6: 9.0]	0.1 [-1.5: 1.9]

- We observe no effect of treatment, on average, when we include these patients
- As expected, higher absolute risk of death on average when including sicker patients
- *No CI presented in original TASTE publication for absolute risk

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What do the results mean ?

- Both methods used treatment and outcome data from the trial only – **no confounding**
- The results in the target population also reflect any trial specific effects
- If there are trial engagement effects, these might be transported too

Why TASTE ?

- We don’t expect there to be strong trial engagement effects
- Treatments are likely the same regardless of enrolment
- Covariate data should be collected identically regardless of enrolment
- In pragmatic, registry nested trials, we have the idea setting to use trial and observational data together

G-formula or IPW ?

G-formula

- Simple to implement
- Trial and target data don’t need to be stacked
- Conceptually hard to understand

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IPW

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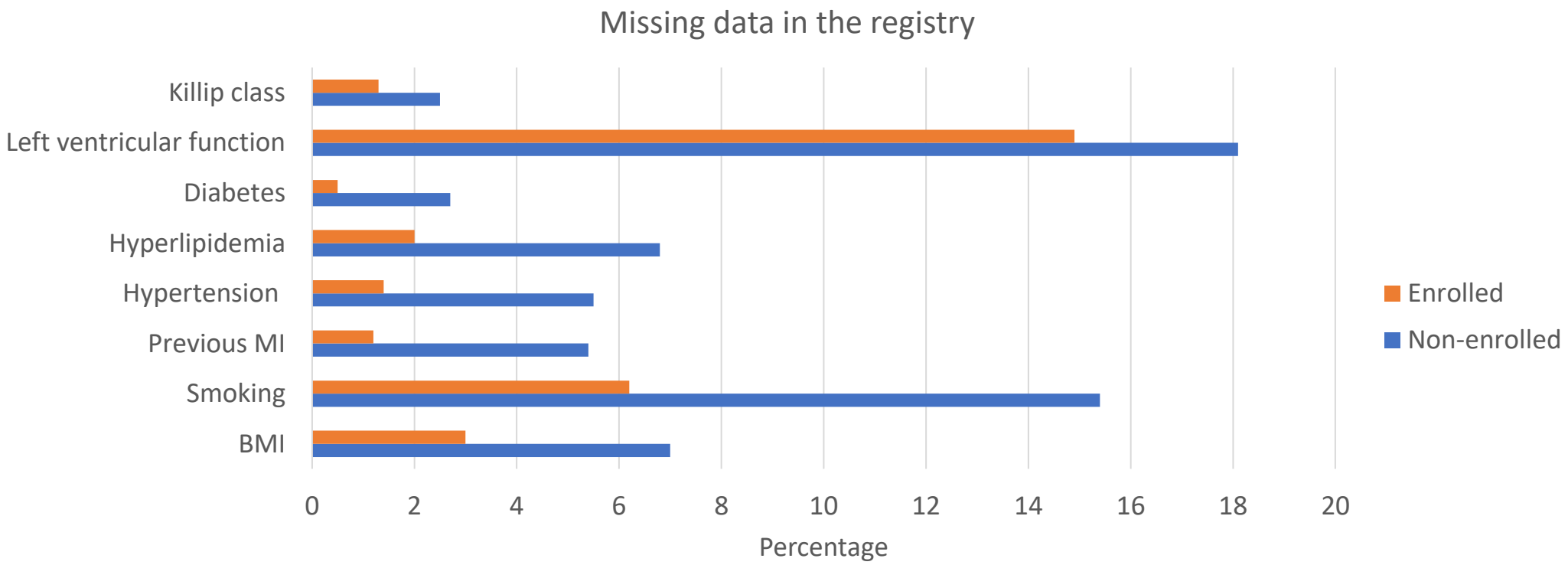
Both models must be correctly specified

Some other issues & difficulties

Missing data

- Missing data differed depending on trial inclusion



Definition of the target population

- Some criteria are difficult to recreate using the observational data
- Particularly, it is hard to obtain data on these softer criteria

Inclusion	Exclusion
Referred for PCI due to STEMI	Need for emergency CABG
Correspondance between ECG & culprit artery pathology	**Unable to provide consent**
50 % stenosis of culprit artery	< 18 years
Deemed possible to perform thrombus aspiration	Previous randomisation

Adherence to treatment assignment

- In reality, not everyone will receive their assigned treatment
- What about transporting other effects, such as the per-protocol effect?

Conclusions

- Pragmatic randomized registry trials such as TASTE are ideal for learning about treatment effects in wider populations, using novel methods
- We can do lots of interesting things with combined data, here I showed how to estimate the effects in a new population
- Registry design allows identification of factors associated with enrollment
- Remaining issues as to non-adherence, selection into the trial & missing data patterns

Thank you

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