Extending Randomized Trial Estimates to Different Target Populations

An application to a nested trial comparing anticoagulant regimens for percutaneous coronary intervention

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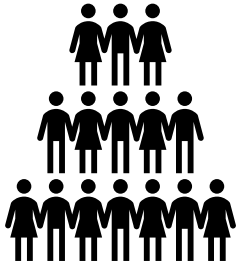
Motivation

Trial Population



Randomized Trial → Evidence → Approvals / Guidelines

Target Population

Evidence generation

To whom evidence is applied

The population the evidence is generated from *differs* from the population the evidence is applied to

- Underrepresentation: Not everyone who was eligible enrolled in the trial
- Excluded: Not everyone who is a candidate for treatment was eligible for the trial

Generalizability

Transportability

Extending Inference from Trials

If characteristics that differ between the populations modify the treatment effect, then:

$$Effect\ from\ Trial\ \neq Effect\ in\ Target\ Population$$

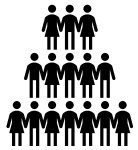
Methods to Extend Inference

1. Generalizability: the target population is a subset of the trial-eligible population

2. Transportability: the target population includes individuals who were not eligible for the trial

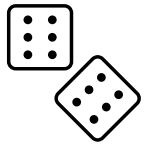
Today's Aim
Extending inferences from the VALIDATE trial

Registry-based randomized clinical trial (RRCT): VALIDATE



Patients with myocardial infarction (MI) undergoing percutaneous coronary intervention (PCI)

Nested in nationwide SWEDEHEART quality registry, linked to several other registers



Bivalirudin vs Heparin monotherapy (treatment)

Composite outcome of death, MI, major bleeding @ 180 days
HR: 0.96 (0.84, 1.10)

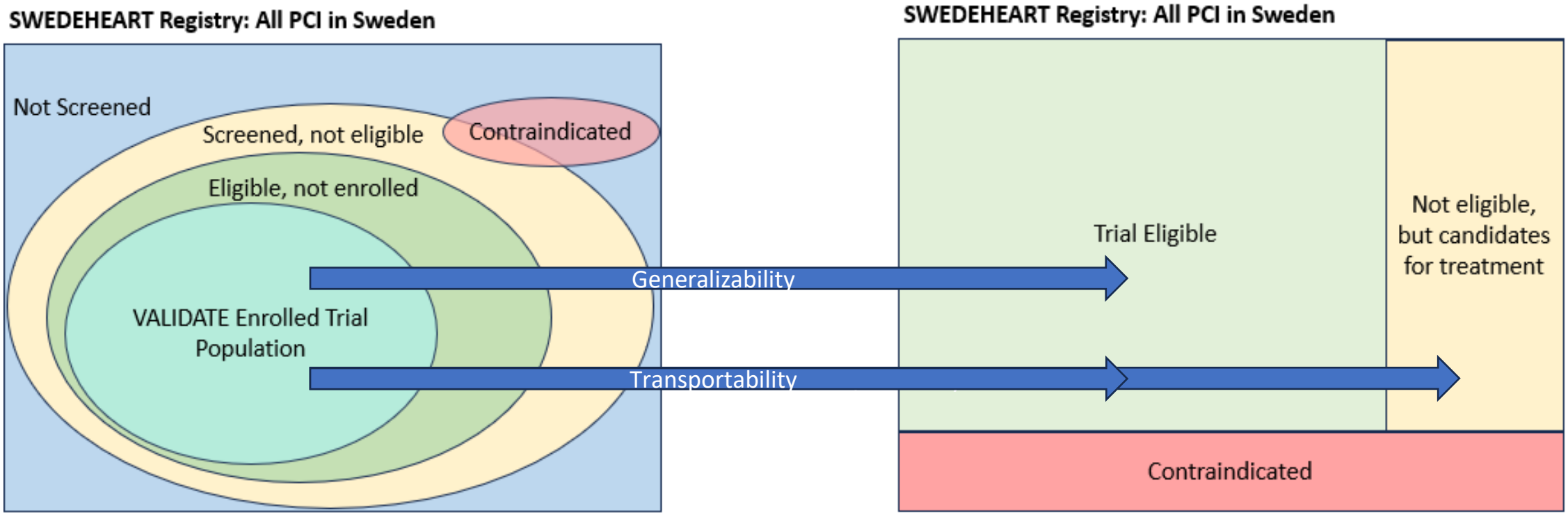
Extend to 2 target populations:

1) All trial-eligible patients in Sweden (Generalizability)

2) All treatment-eligible patients in Sweden– regardless of if they were eligible for VALIDATE (Transportability)

Erlinge et al. NEJM 2017

VALIDATE and Target Populations



Analysis Steps

- Compare baseline characteristics between:
  - VALIDATE enrolled vs. Trial-eligible Target vs Treatment-eligible Target
- Estimation of assigned treatment effect in VALIDATE
  - Logistic regression model for the outcome
- Estimation of assigned treatment effect in the trial-eligible and the treatment-eligible target populations
  - Logistic regression model with baseline covariates.
  - Standardize risk estimates to baseline covariate distribution of each target population

Assumptions

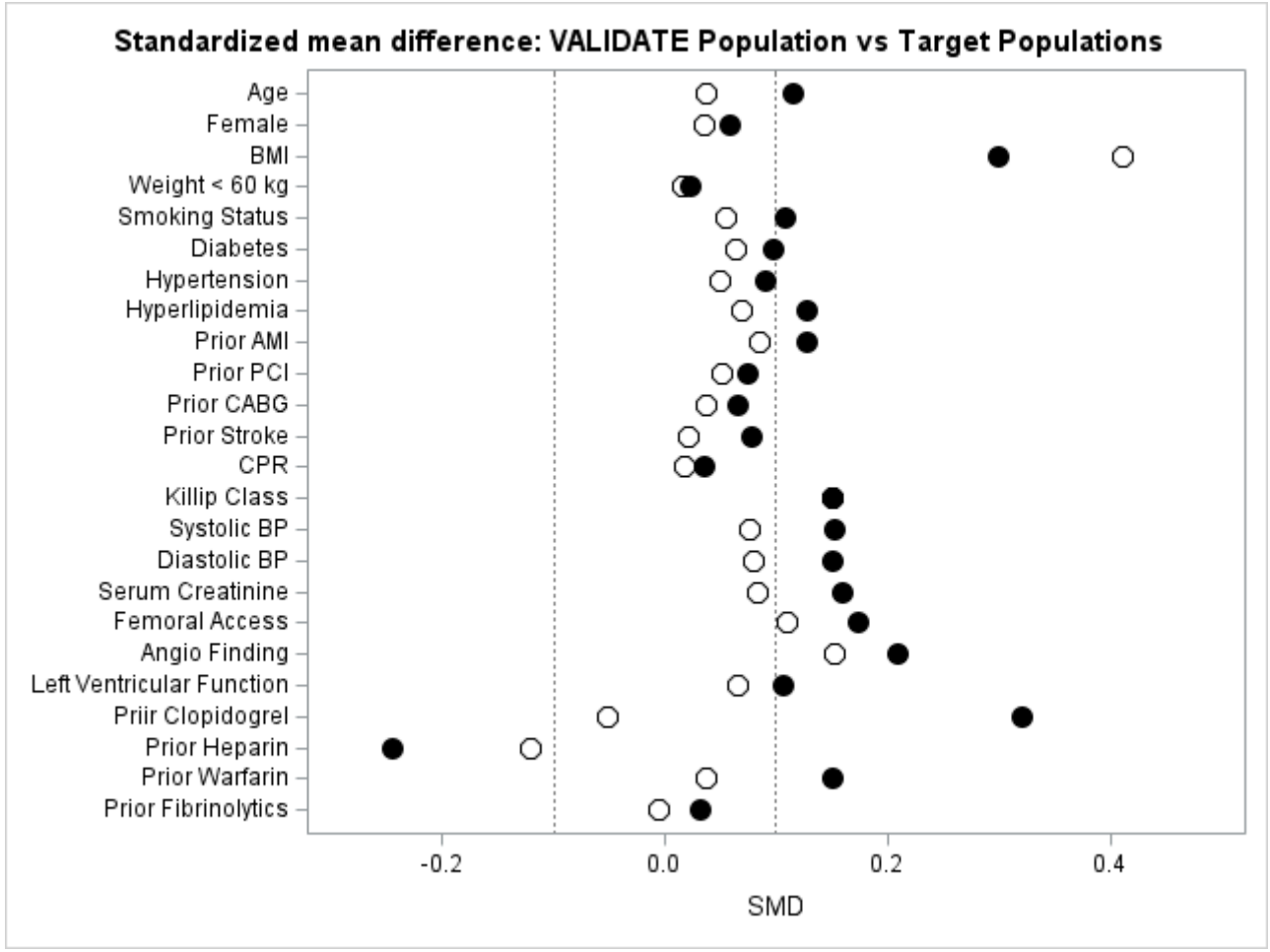
- Assumptions needed to make valid causal inferences within the trial:
  - Consistency (well-defined interventions)
  - Conditional exchangeability (across treatment arms)
  - Positivity (positive Pr of receiving each treatment)

By design, these hold in VALIDATE

- Additional assumptions for extending inference:
  - Consistency (same versions of treatment used in and out of the trial)
  - Conditional exchangeability (of trial participation)
  - Positivity of trial participation (positive Pr of trial participation conditional on EMMs)

Plausibility of these may differ across aims: Generalize to trial eligible vs. transport to treatment eligible

Results – Baseline Comparisons



Results – Estimated Treatment Effects

Population	Treatment	# of individuals	# of events	Risk	Risk Difference	Risk Ratio
VALIDATE	Heparin	2964	383	12.9 (11.7, 14.1)		
	Bivalirudin	2968	368	12.4 (11.2, 13.6)	-0.5 (-2.2, 1.2)	0.96 (0.84, 1.10)
Target Population 1: Trial-Eligible Population	Heparin			14.2 (12.8, 15.5)		
	Bivalirudin			13.2 (11.9, 14.5)	-1.0 (-3.2, 1.1)	0.93 (0.79, 1.08)
Target Population 2: Treatment-Eligible Population	Heparin			14.5 (12.8, 16.5)		
	Bivalirudin			13.7 (12.5, 14.9)	-0.9 (-3.4, 1.5)	0.94 (0.79, 1.11)

≈ **HR: 0.96 (0.84, 1.10)** from the published trial

Erlinge et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. NEJM 2017

Main findings and Discussion

- Different decision makers may have different target populations
  - Clinical trialists: All trial-eligible patients
  - Guideline makers: All treatment-eligible patients
- Ideal setting with original trial nested in registry and nationwide population registries
  - Differences existed, but not large enough to translate to meaningful clinical difference
- Consistent with published VALIDATE trial, no difference at 180 days between treatments compared in either target population
- Higher risk in both target populations – expected consequence of trial recruiting healthier individuals
- Next step, include a wide range of socioeconomic factors from registers

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