

Bias and Confounding

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December 10, 2023



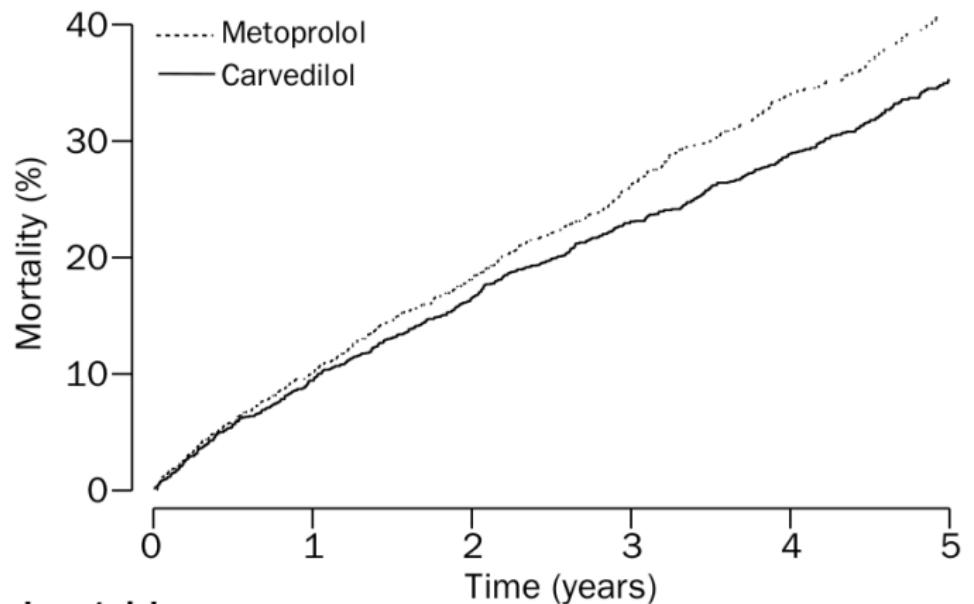
Why - How - What

- ▶ A protocol provides motivation and hopefully is approved by donors, regulators and universities
- ▶ A protocol includes an analysis section which is generally superficial
- ▶ An ideal analysis plan supplements with every decision that needs to be made to transform the data to a final report
- ▶ An analysis plan forms a relevant document for methodological discussions
- ▶ An analysis plan is not a protocol and does not need to include motivations
- ▶ For observational studies the analysis plan needs to be revised during calculations

Preparing the question

- ▶ For a randomised trial everything is controlled and the question formulated in advance
- ▶ For an observational study the data needs to be interrogated.
- ▶ In a randomised study the sample size is well defined to ensure that p-values calculated are relevant
- ▶ In many observational studies the sample size is defined by circumstances and the statistics evaluated require thought.

Carvedilol or Metoprolol for heart failure

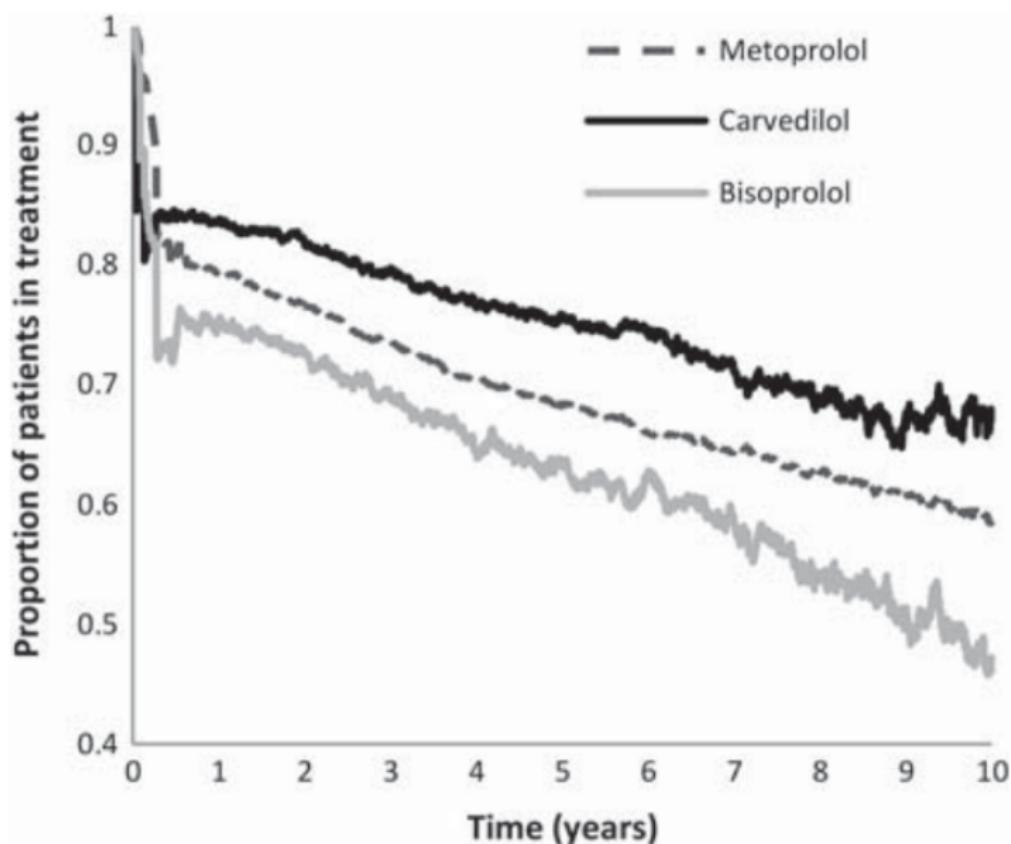


Number at risk

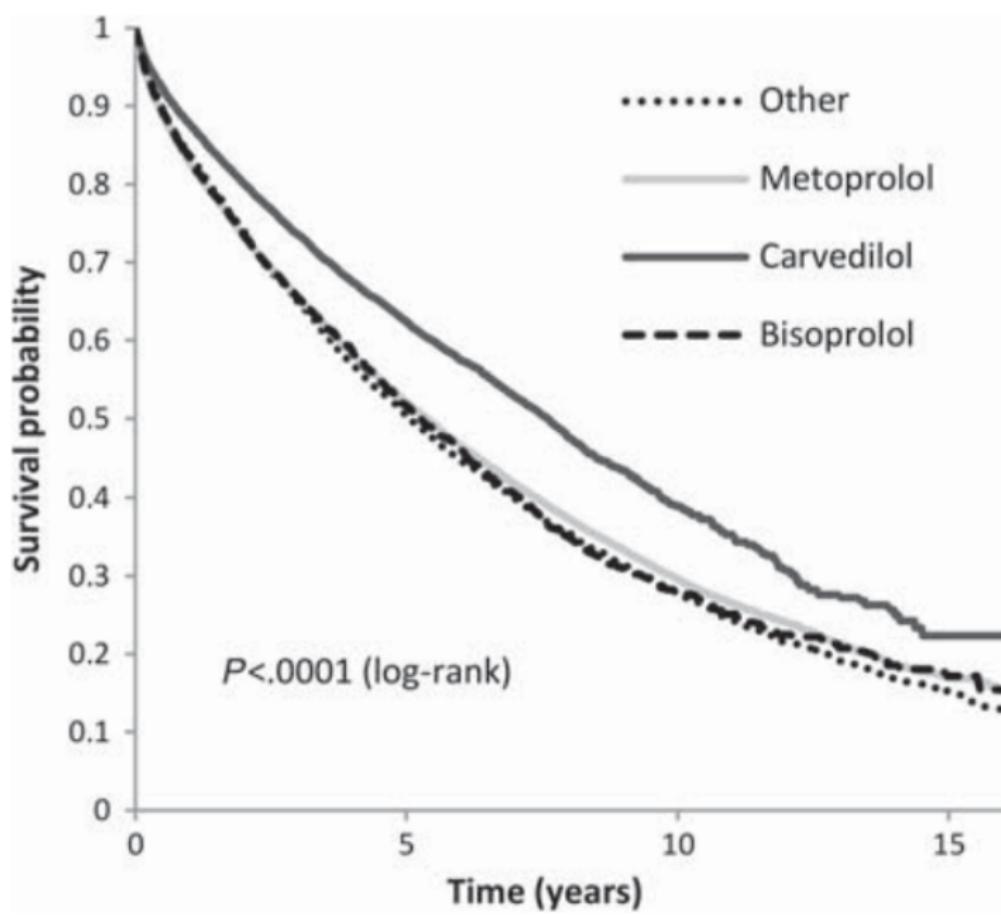
Carvedilol	1511	1366	1259	1155	1002	383
Metoprolol	1518	1359	1234	1105	933	352

COMET trial, Lancet 2003

How are beta blockers used?



Univariable comparison



Cox model

Drug/time	Dose	Mean dose	St. dev.	N	Risk	Low	High	P
3 months								
Metoprolol	<100 mg/day	64.4	25.88	26,688	1.038	0.98	1.1	0.2046
	101–199 mg/day	144.3	10.5	5,239	1.056	0.987	1.13	0.1157
	>200 mg/day	200	0	3,182	1	1	1	-
Carvedilol	<12.5 mg/day	10.2	3	4,178	1.084	1.005	1.169	0.0377
	12.6–49 mg/day	26.4	6	3,376	0.931	0.857	1.012	0.0936
	>50 mg/day	55	11.4	2,097	0.873	0.789	0.966	0.0084
Bisoprolol	<5 mg/day	4.5	1	1,811	1.06	0.971	1.157	0.1955
	6–9 mg/day	7.5	0.3	364	1.048	0.892	1.232	0.5674
	>10 mg/day	14.3	4.2	887	1.125	1.004	1.261	0.0416

Target trial emulation

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

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Initially submitted December 9, 2014; accepted for publication September 8, 2015.

Hernan Robins, American Journal of Epidemiology, 2016

Protocol Component	Description
Eligibility criteria	Postmenopausal women within 5 years of menopause between the years 2005 and 2010 and with no history of cancer and no use of hormone therapy in the past 2 years.
Treatment strategies	Refrain from taking hormone therapy during the follow-up. Initiate estrogen plus progestin hormone therapy at baseline and remain on it during the follow-up unless you are diagnosed with deep vein thrombosis, pulmonary embolism, myocardial infarction, or cancer.
Assignment procedures	Participants will be randomly assigned to either strategy at baseline and will be aware of the strategy to which they have been assigned.
Follow-up period	Starts at randomization and ends at diagnosis of breast cancer, death, loss to follow-up, or 5 years after baseline, whichever occurs first.
Outcome	Breast cancer diagnosed by an oncologist within 5 years of baseline.
Causal contrasts of interest	Intention-to-treat effect, per-protocol effect
Analysis plan	Intention-to-treat effect estimated via comparison of 5-year cancer risks among individuals assigned to each treatment strategy. Per-protocol effect estimation requires adjustments for pre- and postbaseline prognostic factors associated with adherence to the strategies of interest. All analyses will be adjusted for pre- and postbaseline prognostic factors associated with loss to follow-up (57). This analysis plan implies that the investigators prespecify and collect data on the adjustment factors.

Critical Steps

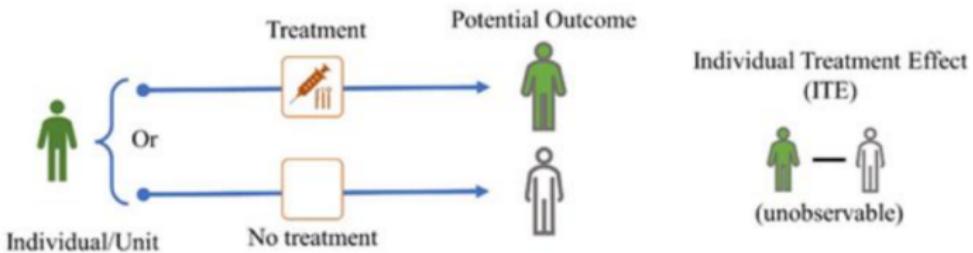
- ▶ Eligibility
 - ▶ Inclusion and Exclusion criteria - new user!
- ▶ Treatment Strategy
 - ▶ Starting treatment - Continuous treatment - Treatment rules
- ▶ Assignment
- ▶ Follow up
- ▶ Causal contrast of interest
- ▶ Analysis
 - ▶ Adjustment for baseline differences
 - ▶ Adjustment for covariate effect on outcome
 - ▶ Double robust methods

Results

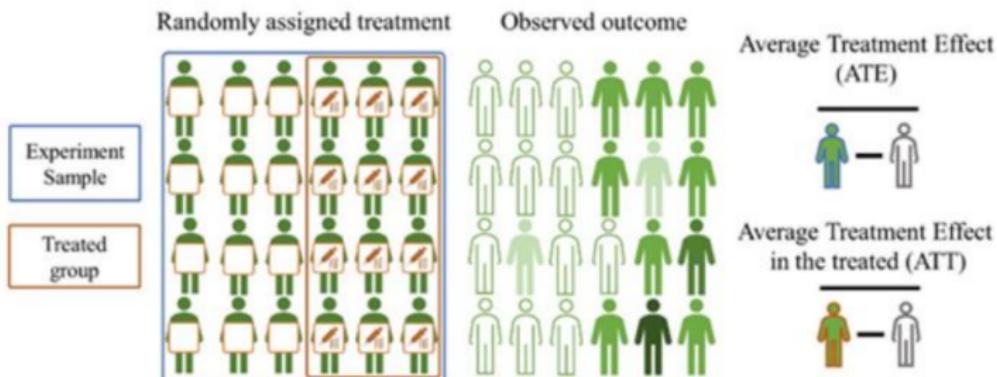
- ▶ Hazard Ratio
- ▶ Average treatment effect
- ▶ Average treatment effect of the treated
- ▶ Intention to treat

ATE ATT

A



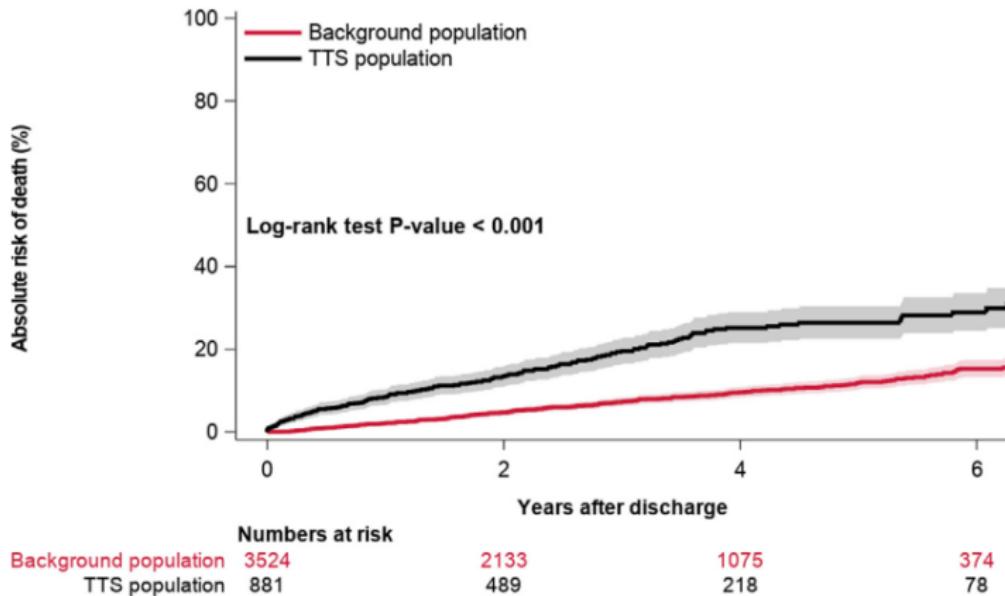
B



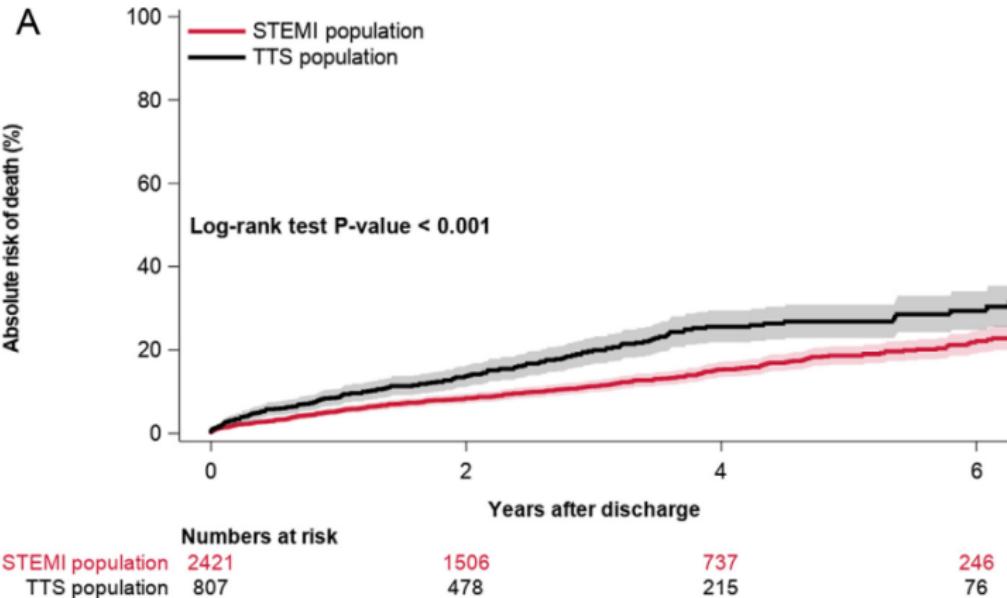
Dominico Veneziano



What if exposure is not a treatment?



Butt, J. Cardiac Failure 2022



Analysis plan

- ▶ Descriptive analyses to define possibilities
- ▶ Define population, exposure, follow-up, outcome, analysis
- ▶ Be ready to adjust analysis plan as study develops
- ▶ Consider putting analysis plan in repository



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