Emulating a randomized trial of statins in cancer patients
(Emilsson et al. *JAMA Oncology* 2018)

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Statins

Approved 1987

Cardiovascular prevention (primary and secondary)

Cholesterol-lowering

One of the most commonly prescribed drugs in the world

Binding and inhibition of HMG-CoA reductase enzyme

Side effects; Muscle pain and damage (common) , rhabdomyolysis, Liver damage (increased enzymes) & Increased blood sugar (type II diabetes) (uncommon)

Suggested effects of statins on cancer from preclinical research

Inhibition of proliferation

Induction of apoptosis & autophagy

Anti-invasion effect

Anti-migratory effect

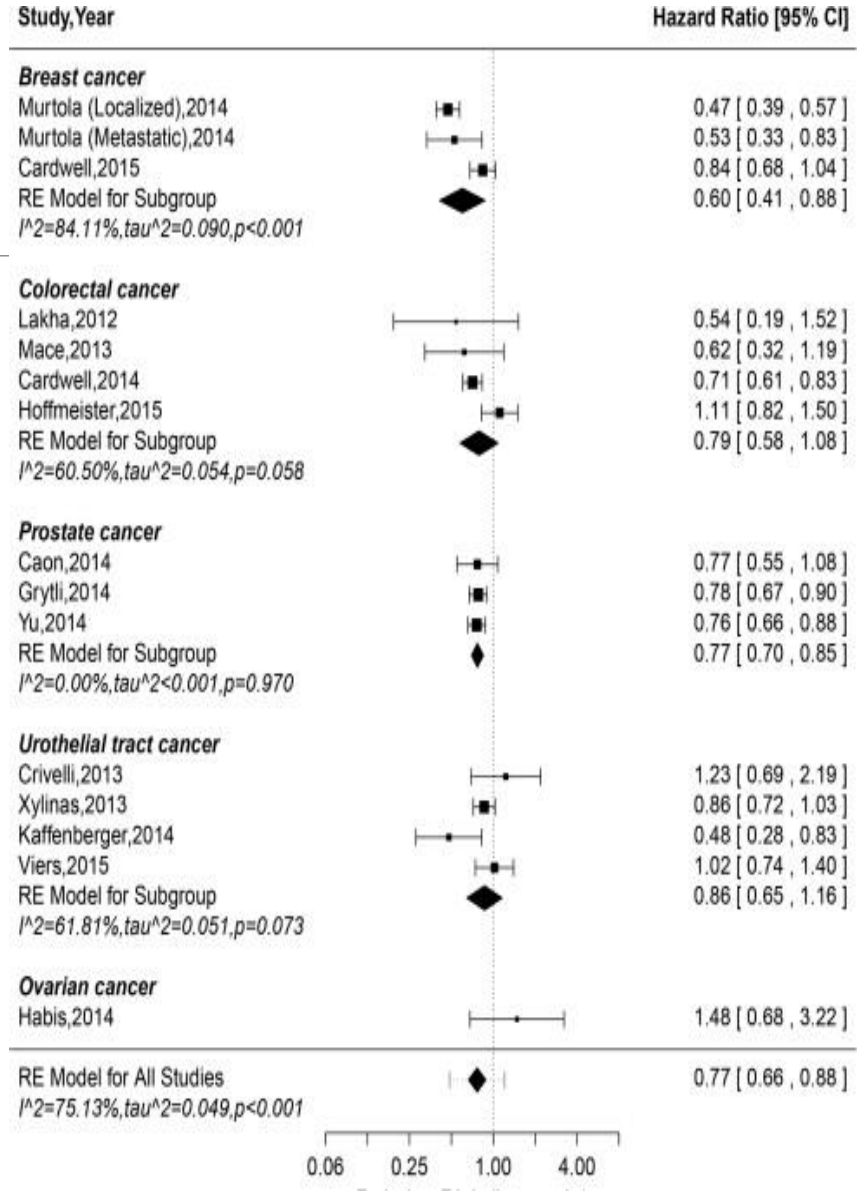
Overcoming classic chemotherapeutic drug resistance

Simona Pisanti, Paola Picardi, Elena Ciaglia, Alba D'Alessandro, Maurizio Bifulco, Novel prospects of statins as therapeutic agents in cancer, Pharmacological Research, Volume 88, October 2014, Pages 84-98, ISSN 1043-6618, http://dx.doi.org/10.1016/j.phrs.2014.06.013. (http://www.sciencedirect.com/science/article/pii/S1043661814001054)

Observational studies of statins and cancer

Meta-analysis of post-diagnostic statin use and cancer mortality

Overall HR 0.77 (CI 0.66-0.88)



Zhong, S. Cancer Treat Rev. 2015 Jun;41(6):554-67. doi: 10.1016/j.ctrv.2015.04.005. Epub 2015 Apr 11.

Randomized trials

Neutral risk of cancer compared to placebo

Mean follow-up 4.8 years

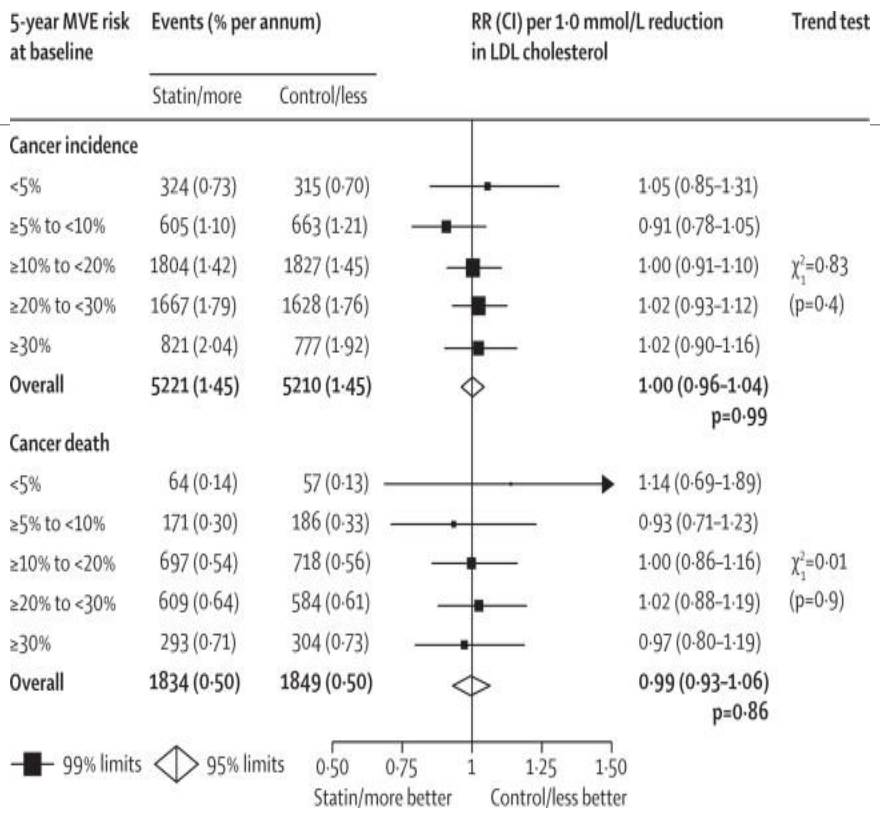


Figure 4. Effects on cancer incidence and cancer mortality per 1·0 mmol/L reduction in LDL cholesterol at different levels of risk MVE=major vascular event. RR=rate ratio. CI=confidence interval.

Cholesterol Treatment Trialists' (CTT) Collaborators, The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials, The Lancet, Volume 380, Issue 9841, 11–17 August 2012, Pages 581-590, ISSN 0140-6736, http://dx.doi.org/10.1016/S0140-6736(12)60367-5. (http://www.sciencedirect.com/science/article/pii/S0140673612603675)

Our approach has 2 steps

1. Specify the hypothetical randomized trial that we would like to conduct
   - Target Trial

2. Emulate the target trial

Specifying the target trial

Eligibility criteria

Diagnosis of colorectal, breast, prostate, or bladder cancer in 2007-2009

Enrolled in Medicare A and B during 12 months

No statins for at least 6 months

Treatment strategies

Initiation of any statin at any dose within six months after cancer diagnosis.

No initiation of statins.

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Specifying the target trial

Outcomes

Cancer-specific and all-cause mortality.

Follow-up

From cancer diagnosis until death, loss to follow-up (HMO enrollment), or 31 Dec 2011, whichever comes first

Per-protocol analysis

Censoring at deviation from assigned strategy

IP weighting to adjust for selection bias due to censoring

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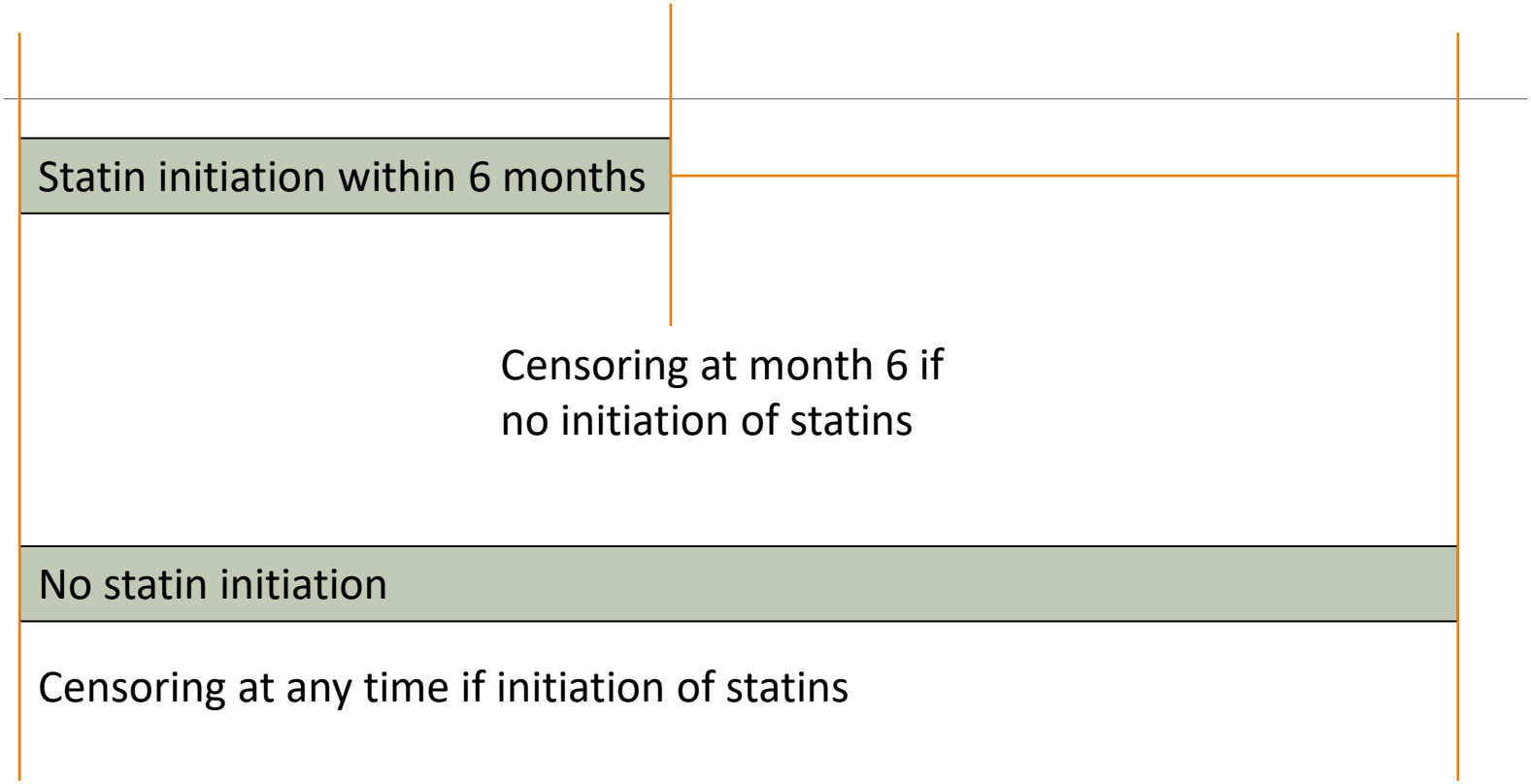
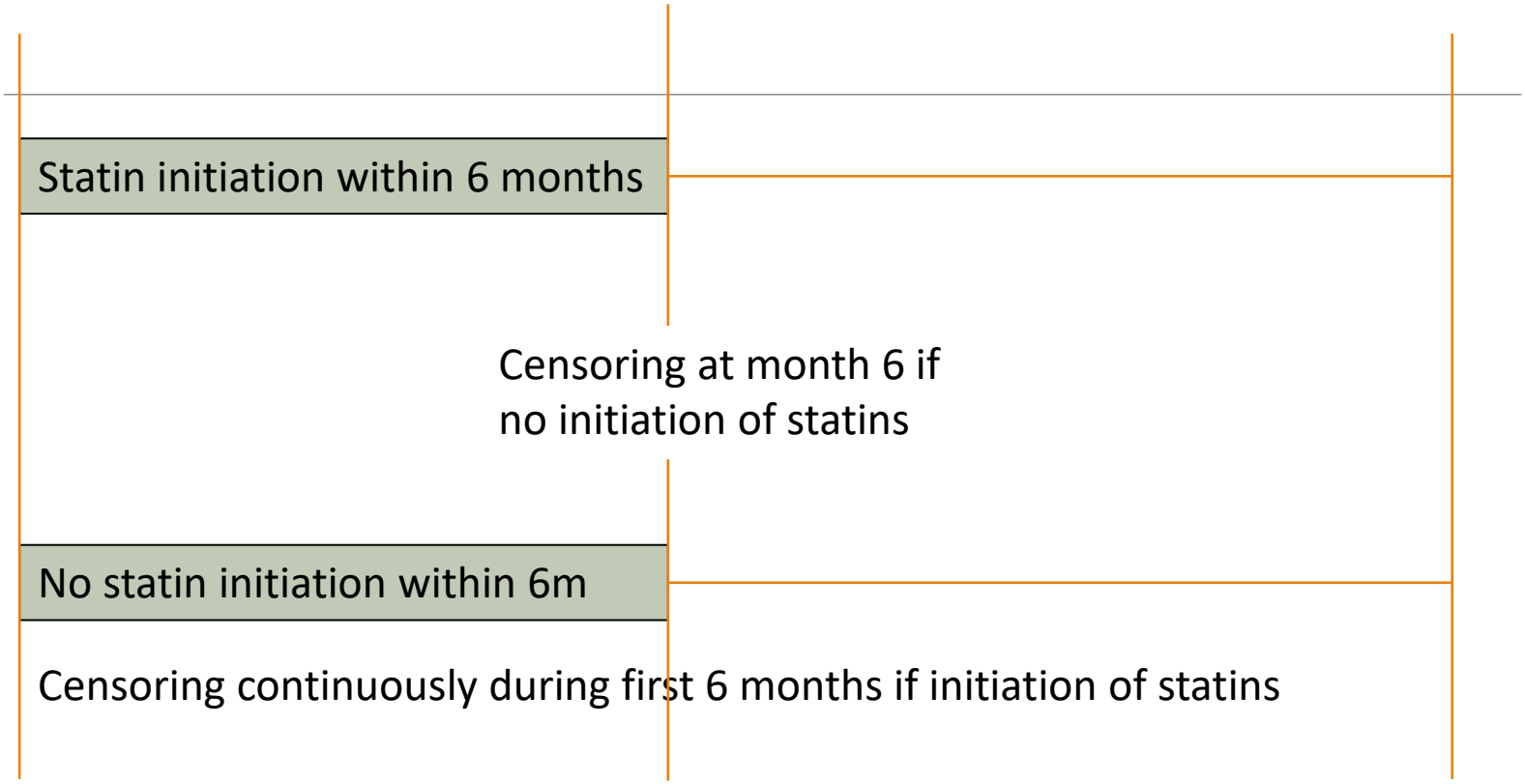
Censoring at non-adherence



IPW for statin initiation

Censoring at non-adherence



Start of follow-up
Cancer diagnosis

End of follow-up
Death, loss of follow-up, Event or administrative

IPW for statin initiation

Adjustment variables

Baseline

sex, age, cancer stage, race, year of diagnosis, marriage status, Charlson score, a composite measure of cardiovascular disease, tobacco use, obesity, depression, hyperlipidemia, hypertension and anemia

Post-baseline

surgery, radiotherapy, chemotherapy, Charlson score, a composite measure of cardiovascular disease, tobacco use, obesity, depression, hyperlipidemia, hypertension and anemia

Our approach has 2 steps

1. Specify the hypothetical randomized trial that we would like to conduct
   - Target Trial

2. Emulate the target trial

Emulating the target trial

Use same

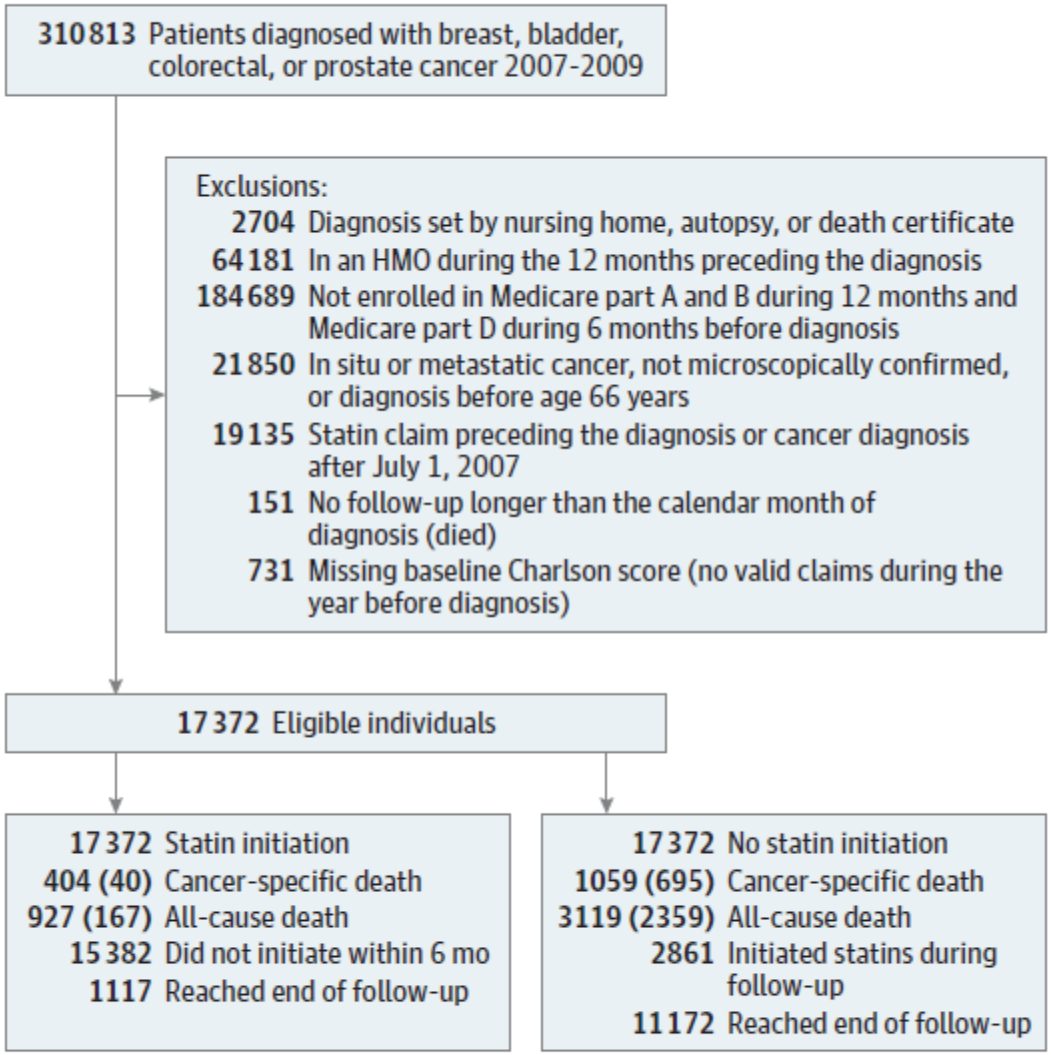
eligibility criteria, treatment strategies, outcome, follow-up, analysis

as the target trial

Cloning

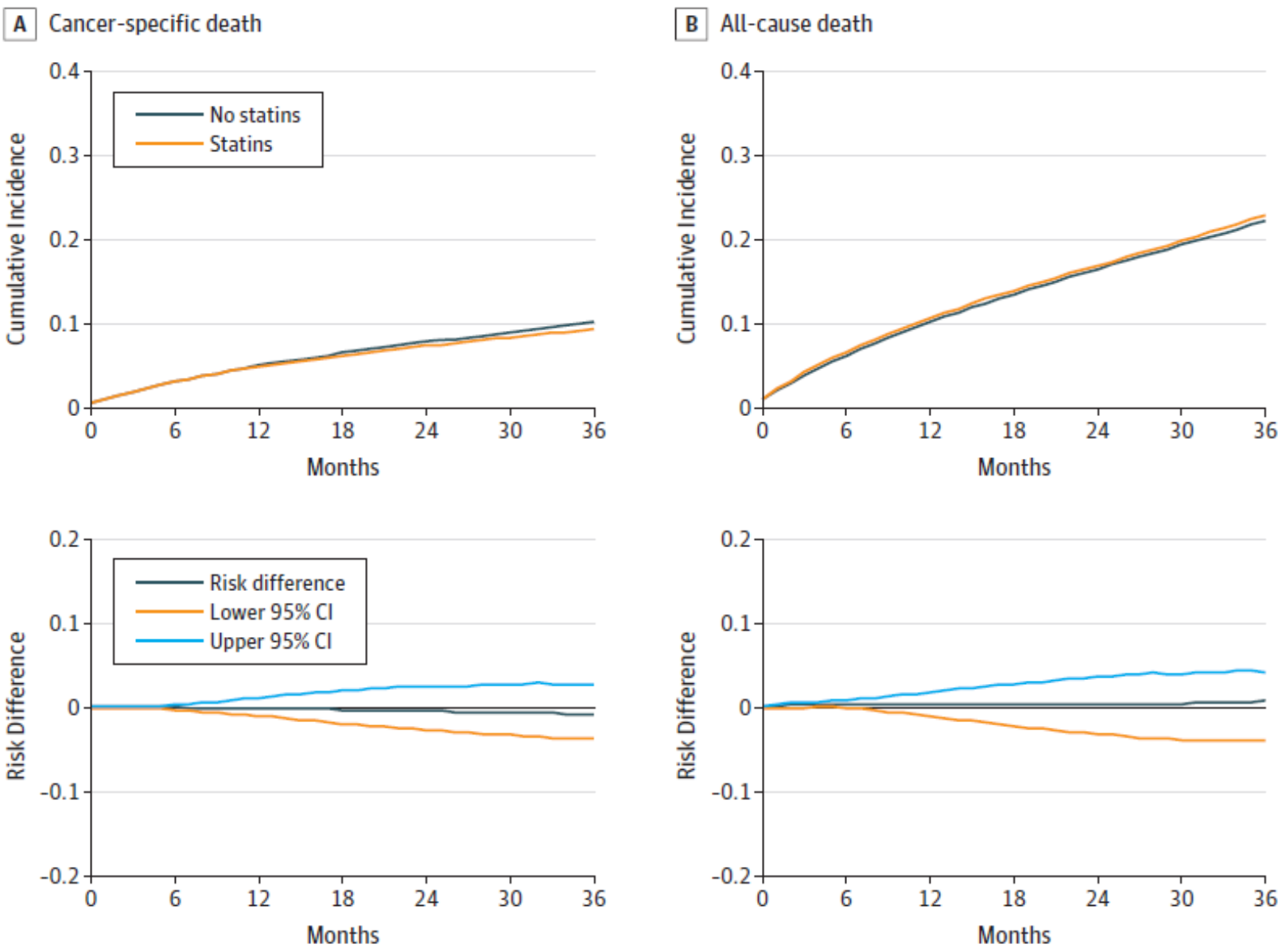
At baseline, all individuals are assigned to both strategies by replicating them in the database

Figure 1. Flowchart of Eligible Individuals, SEER-Medicare 2007-2009



Numbers in parentheses represent unique deaths. HMO indicates health maintenance organization; SEER, Surveillance, Epidemiology, and End Results database.

Figure 2. Three-Year Cumulative Incidence and Risk Differences, SEER-Medicare 2007-2009



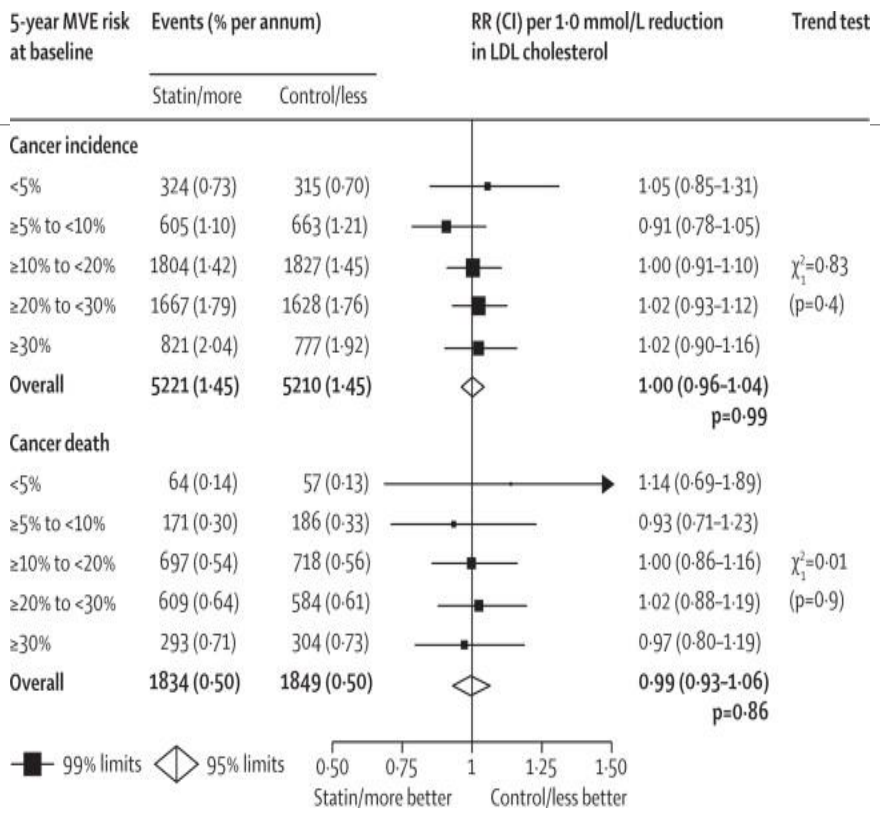
Hazard ratio (95% CI)

Cancer specific death	1.00 (0.88-1.15)
All-cause death	1.07 (0.93-1.21)

Randomized trials

Neutral risk of cancer compared to placebo

Mean follow-up 4.8 years



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Previous observational studies did not emulate a target trial

			HR (95% CI)	
Source	Publication Year	Cancer location	Cancer-Specific mortality	All-Cause Mortality
Category 1 Statin Users vs. Nonusers during Follow-up (Risk of Immortal-Time Bias)				
Murtola[28]	2014	Breast	0.35 (0.28-0.45)	0.39 (0.33-0.46)
Katz[38]	2010	Prostate (radical prostatectomy)	N/A	0.35 (0.21–0.58)
Katz[38]	2010	Prostate (radiation therapy)	N/A	0.59 (0.37–0.94)
Lakha[33]	2012	Colorectal	0.54 (0.19-1.50)	0.61 (0.26-1.41)
Pooled estimate			0.35 (0.27-0.44)	0.39 (0.33-0.45)
Category 2 Prevalent Statin Users vs. Non-Users at Cancer Diagnosis (Risk of Prevalent-User/ Selection Bias)				
Geybels[29]	2013	Prostate	0.19 (0.06, 0.56)	N/A
Desai[30]	2015	Breast	0.91 (0.60-1.37)	N/A
Brewer[31]	2013	Breast	0.95 (0.58-1.56)	1.00 (0.63-1.60)
Caon[32]	2014	Prostate	0.77 (0.55–1.08)	N/A
Lakha[33]	2012	Colorectal	0.60 (0.33-1.32)	0.59 (0.28-1.24)
Nielsen[34]	2012	All cancer forms	0.85 (0.82-0.87)	0.85 (0.83-0.87)
Siddiqui[35]	2009	Colorectal	N/A	0.7 (0.6-0.9)
Shao[36]	2015	Colorectal	0.77 (0.68-0.88)	0.82 (0.74-0.92)
Murtola[28]	2014	Breast	0.60 (0.46-0.77)	0.58 (0.49-0.70)
Da Silva [37]	2013	Bladder	1.04 (0.84-1.28)	N/A
Hoffmeister[39]	2015	Colorectal	1.11 (0.82-1.50)	1.10 (0.85-1.41)
Pooled estimate			0.77 (0.64-0.89)	0.78 (0.67-0.90)
Category 3 Mixed Prevalent and Incident Statin Users vs. Nonusers (Risk of Prevalent-user/ Selection Bias)				
Desai[30]	2015	Breast	0.59 (0.32-1.06)	N/A
Chan[40]	2015	Prostate	N/A	0.84 (0.71–0.99)
Pooled estimate			0.59 (0.32-1.06)	0.84 (0.71-0.99)
Overall pooled estimate			0.73 (0.58-0.88)	0.69 (0.55-0.84)

Hazard ratios using methods from previous observational studies

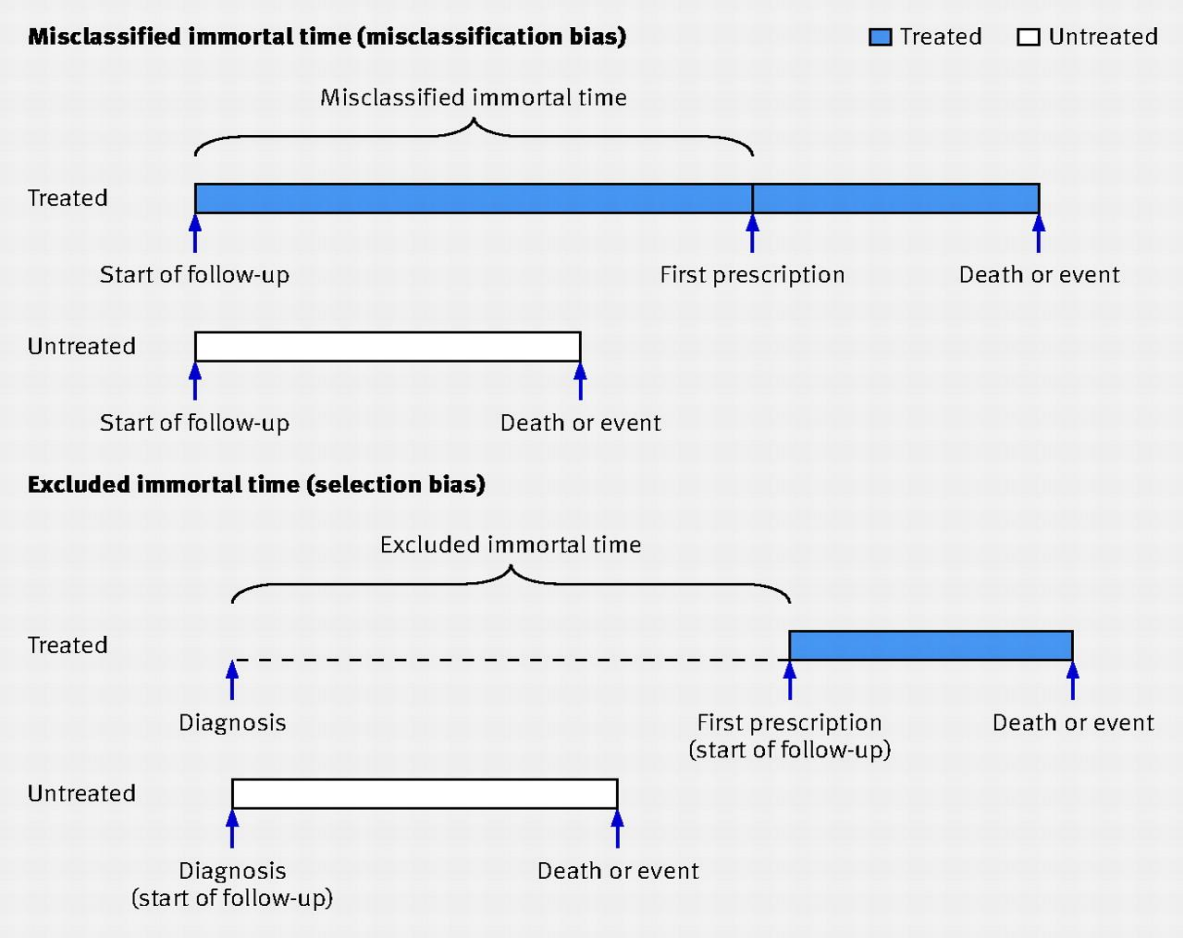
Prevalent users

Cancer mortality	0.83 (0.76-0.91)
All-cause mortality	0.83 (0.79-0.87)

Table 3. Mortality HRs for Statin Initiators vs Noninitiators When Statin Initiation Is Defined Within Increasingly Longer Periods Since Baseline, SEER-Medicare 2007-2009[a]

Time From Baseline of Statin Initiation, mo	Cancer-Specific Death		All-Cause Death	
	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
0-6	0.62 (0.45-0.85)	0.67 (0.49-0.93)	0.83 (0.71-0.97)	0.86 (0.74-1.01)
0-12	0.49 (0.38-0.65)	0.56 (0.42-0.73)	0.71 (0.63-0.81)	0.75 (0.66-0.86)
0-18	0.37 (0.28-0.48)	0.43 (0.33-0.56)	0.62 (0.55-0.69)	0.67 (0.60-0.76)
0-24	0.30 (0.23-0.39)	0.36 (0.28-0.47)	0.56 (0.50-0.63)	0.62 (0.55-0.69)
Ever during follow-up	0.25 (0.20-0.33)	0.31 (0.24-0.40)	0.51 (0.46-0.57)	0.57 (0.51-0.63)

Fig 1 Immortal time bias is introduced in cohort studies when the period of immortal time is either incorrectly attributed to the treated group through a time fixed analysis (top) or excluded from the analysis because the start of follow-up for the treated group is defined by the start of treatment and is, by design, later than that for the untreated group (bottom).



Linda E Lévesque et al. BMJ 2010;340:bmj.b5087

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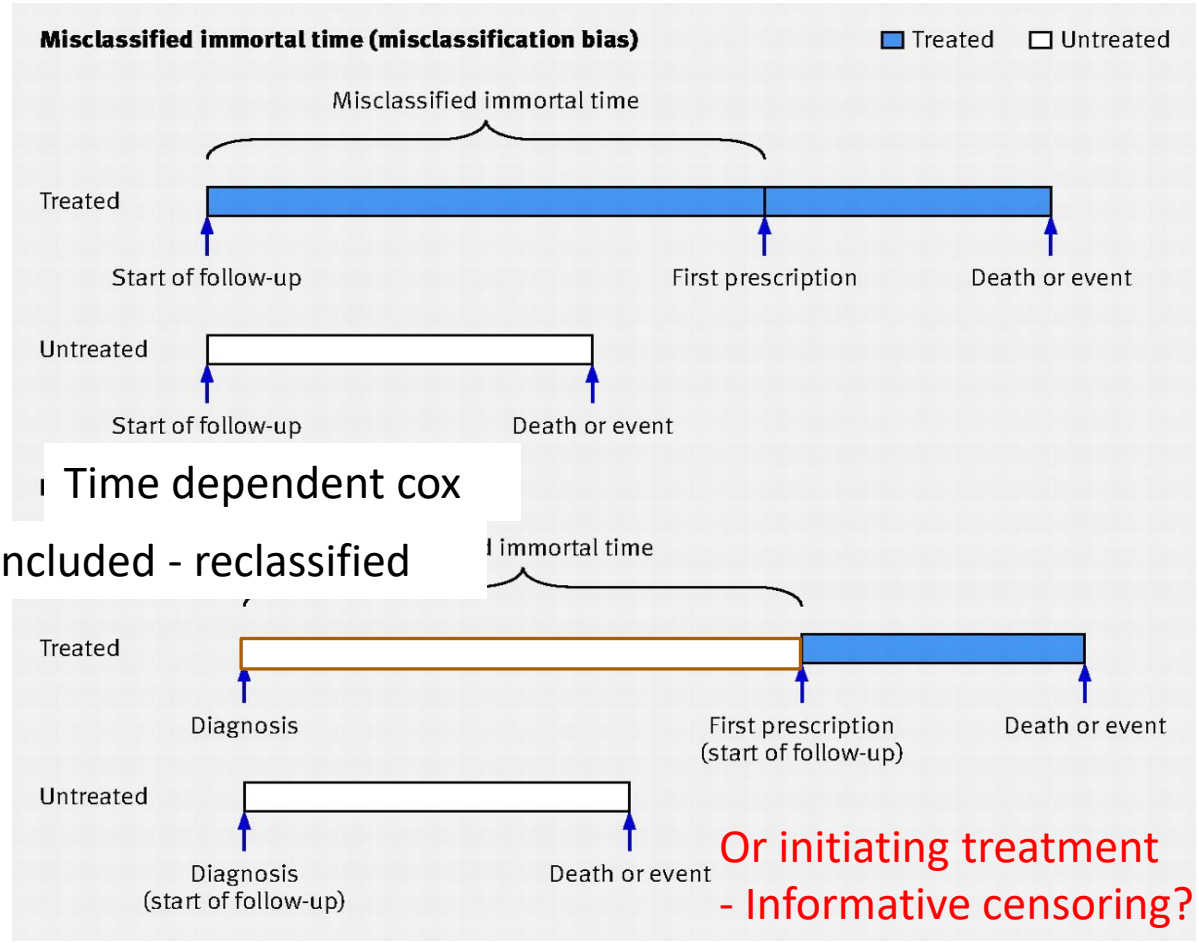

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Advantages of explicitly emulating a target trial

The intervention is well-defined (specifically in terms of initiation time)

No selection bias

- NO prevalent users vs non users at baseline

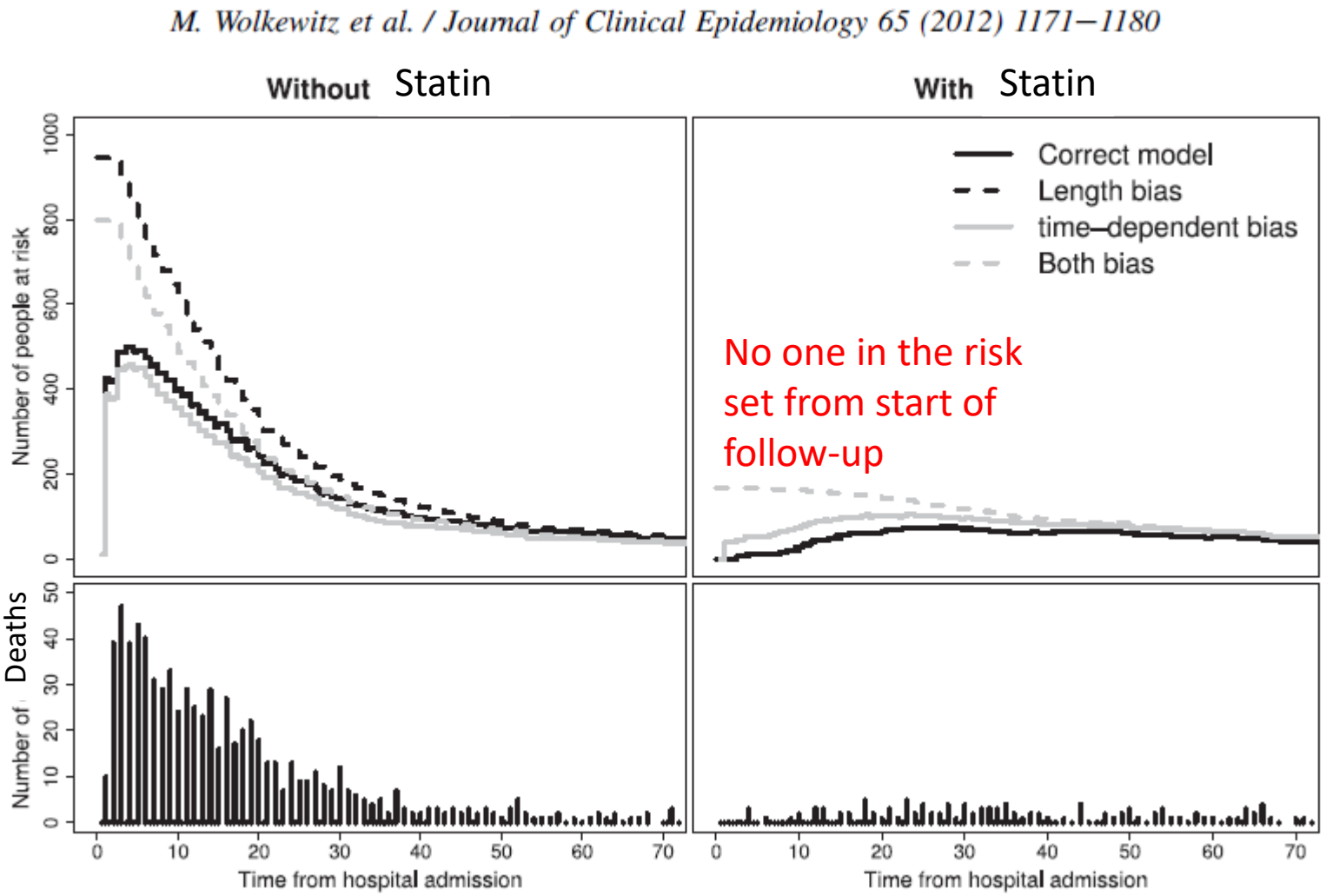
No immortal time bias

- NO initiators at some point during the follow-up (alive until initiation) vs non initiators

Assessment of survival from cancer diagnosis can generate absolute risks

- unlike time dependent & lag time methods

Risk sets in time dependent analyses



Limitations

Residual confounding?

- health-care seeking behavior associated with prescription and prognosis
- discontinuation of medication if poor prognosis (we assumed once initiated always user)

Positivity?

- everyone not being moribund with CVD will get statins

Short follow-up

The actual statistics

Database creation – longitudinal dataset based on months – each individual gets as many rows as they have month of observation -1

Pooled logistics regression shifting outcome one month back to ensure exposure proceeds outcome (T, At, Lt, Yt+1)

Weight P(initiation) regression including time-variant confounders for initiation restricted to those who have not yet initiated (creation of lag_treament variables)

Trimming of the weights (99.5 percentile) to compensate for heavy outlier effects

Outcome regression using only baseline confounders (no time dep)

Bootstrap whole process to obtain confidence intervals

Conclusion

Our model produced results similar to RCTs

Methodological flaws may explain previous observational associations

Statins does not improve short time (3-4 years) cancer survival

Appropriate statistical and epidemiological modelling is of paramount importance

Aspirin and colorectal cancer

More recent study with similar methodology:

Eur J Epidemiol. 2023 Oct;38(10):1105-1114. doi: 10.1007/s10654-023-01024-1. Epub 2023 Jun 15.PMID: 37322135

Background

1. Colorectal polyps = increased risk of colorectal cancer
2. Aspirin in the chemoprevention of CRC is hotly debated
3. No previous study of aspirin in individuals diagnosed with polyps
4. Aspirin (Sv. Trombyl/Acetylsalicylsyra) is a prescription drug in Sweden
5. Target trial emulation methodology avoids both immortal time and selection bias
6. Swedish nationwide registries offers reliable data on both cancers and cause of death for all residents
7. Swedish GI histopathology performed 1969-2017 has been collected by Prof. Jonas F. Ludvigsson for the ESPRESSO study

Our approach has 2 steps

1. Specify the hypothetical real world randomized trial that we would like to conduct
   - Target Trial (RCT)

2. Emulate the target trial using observational data

Ideal real world trial

Inclusion criteria:

Individuals aged 45-79 diagnosed with colorectal polyps in 2006-2016 in Sweden

Exclusion criteria:

1. Previous prescription of aspirin, warfarin or direct oral anticoagulant (DOAC)
2. Contraindications for preventive aspirin initiation (dementia, metastasized malignancy, hemorrhagic stroke, gastric ulcer, aortic aneurysms, liver cirrhosis)
3. Indication for aspirin, DOAC or warfarin (pulmonary emboli, myocardial infarction and cerebrovascular disease including TIA)
4. Any previous record of colorectal polyps or colorectal cancer.

Real world trial

Outcomes

CRC, cancer-specific and all-cause mortality.

Follow-up

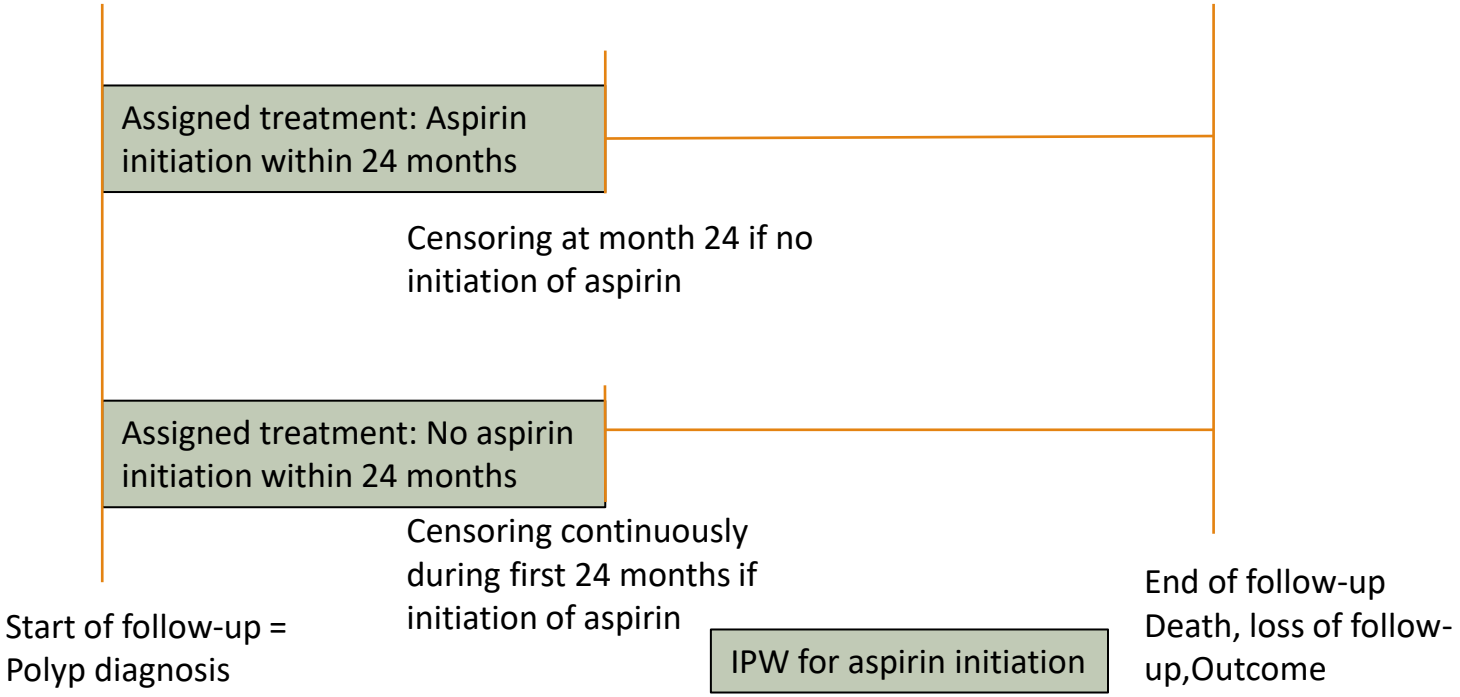
From polyp diagnosis until CRC, death, loss to follow-up (emigration), or End of study (31 Dec 2019), whichever comes first

Per-protocol analysis

Censoring at deviation from assigned strategy

IP weighting to adjust for selection bias due to censoring

Censoring at non-adherence



Emulating the target trial

Use same

eligibility criteria, treatment strategies, outcome, follow-up, analysis as the target trial

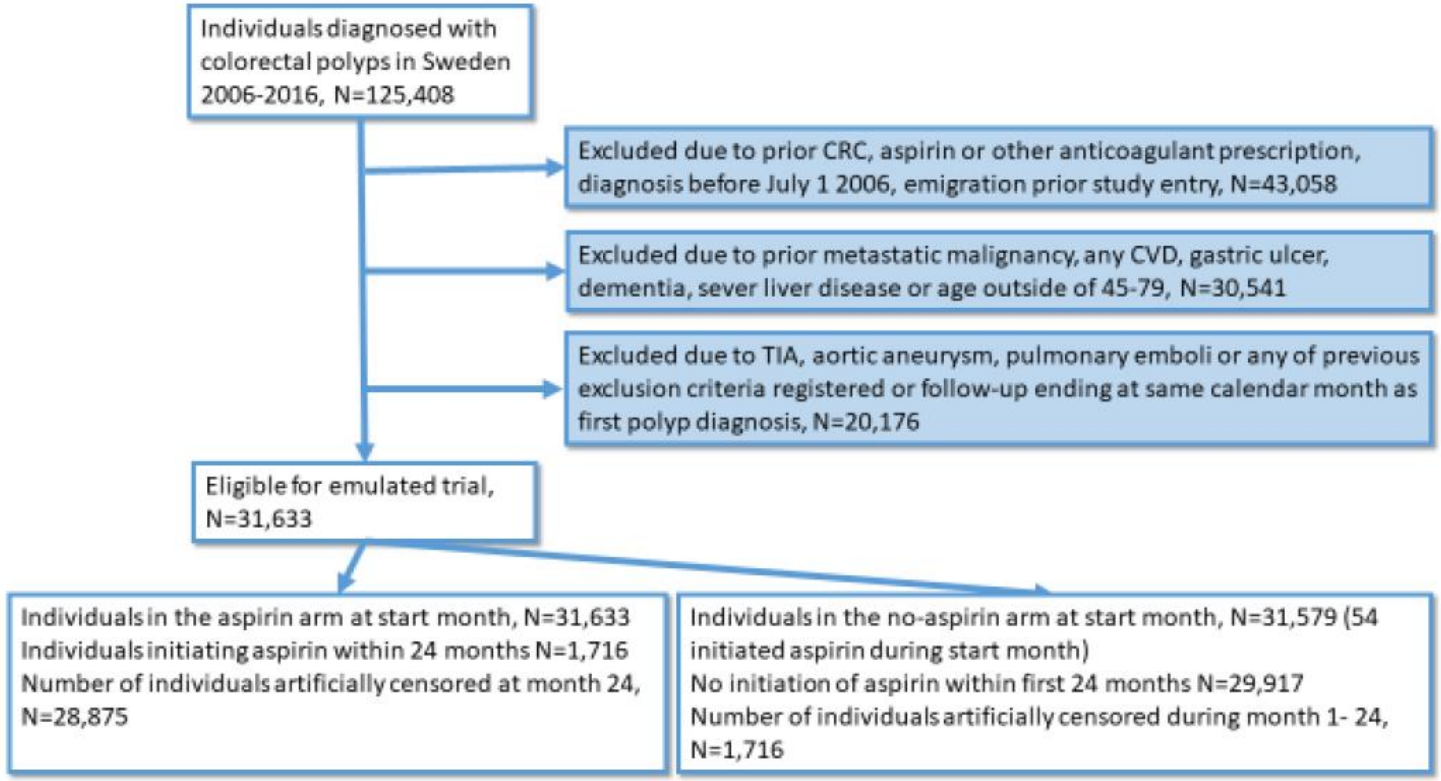
Cloning

At baseline, all individuals are assigned to both strategies by replicating them in the database

Flow chart

Inclusion and exclusion criteria = Same as target trial

Duplication at baseline and censoring when deviation from assigned treatment strategy

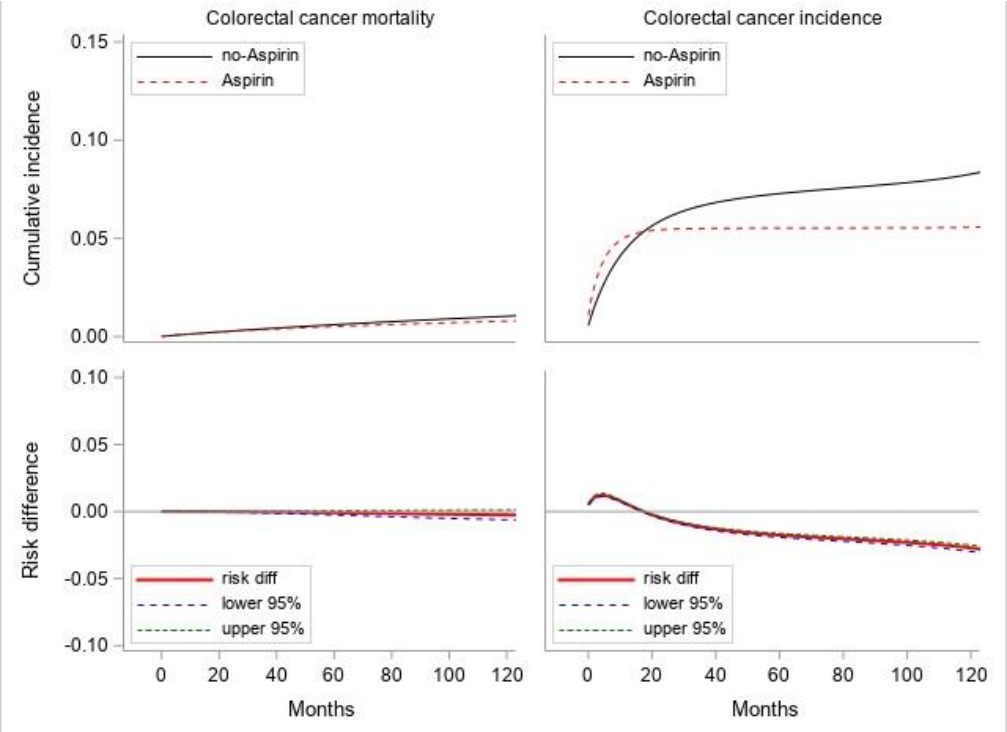


Results Colorectal Cancer

Median follow-up was 8.07 years.

The 10-year cumulative incidence in initiators vs. non-initiators
- 6% vs. 8% for CRC incidence
- 1% vs. 1% for CRC mortality

Corresponding hazard ratios
- 0.88 (95%CI, 95%CI=0.86-0.90) CRC
- 0.90 (95%CI=0.75-1.06) CRC mortality



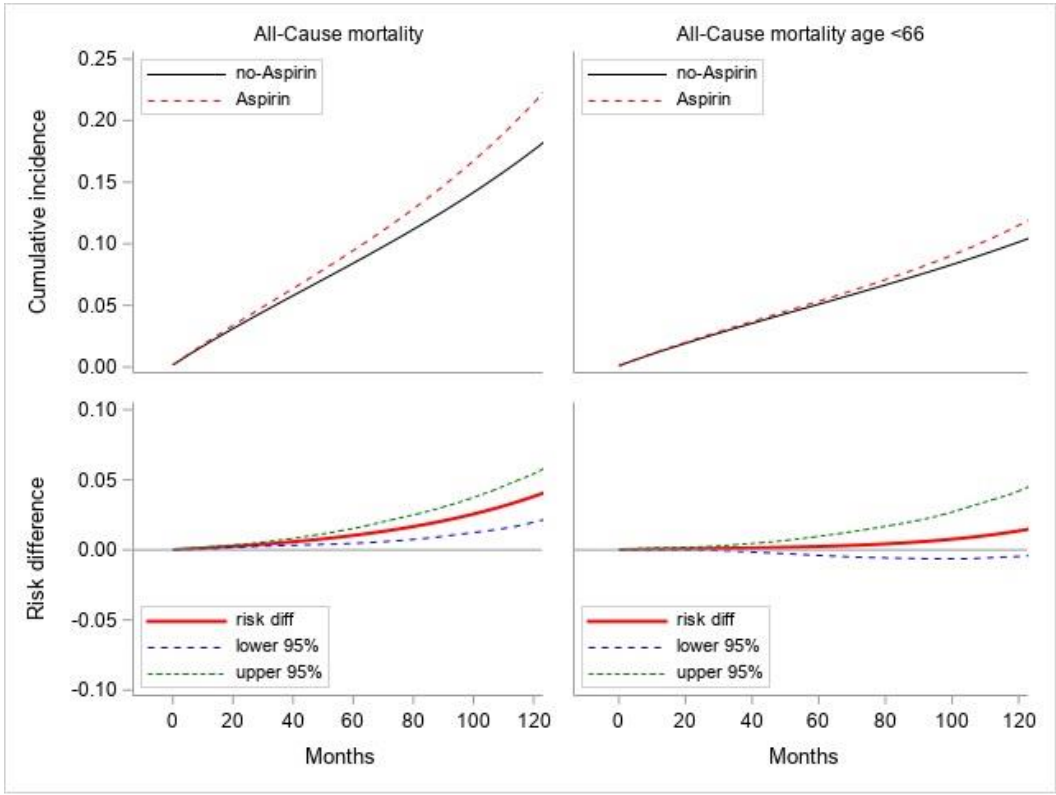
All-cause mortality

10 YR Cumulative Incidence
21% aspirin vs. 18% no aspirin
(11% vs. 10% in those <66yr)

Overall HR=1.18 (95%CI=1.12-1.24)

Risk difference
3.8% (2.0-5.4%)
1% (-0.05-4.2%) in those <66yr.

Bleeding-related cause of death
18 (1.1%) aspirin s. 166 (0.6%) non-aspirin
HR = 1.23 (0.89-1.73)



Advantages of a Target Trial

The intervention is well-defined

- Specifically in terms of initiation time

No selection bias

- NO prevalent users vs non users at baseline

No immortal time bias

- NO initiators at some point during the follow-up (alive until initiation) vs non initiators

Can generate absolute risks

- Unlike time dependent & lag time methods

Limitations

Residual confounding

- lacked information on the size and exact colonic location of polyps, smoking status (used COPD as a proxy measure for heavy smoking), body mass index, alcohol use, lifestyle risk factors and diet
- discontinuation of medication (we assumed once initiated always user)

Positivity

- Most individuals with MI/CVD events during follow-up initiated aspirin (but no true positivity violations occurred)

Conclusion

No net-benefit detected

Aspirin initiation within two years of first polyp diagnosis did not improve CRC mortality in individuals without CVD at baseline

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Karolinska Institutet

Region Värmland

Future

Current work with similar methodology:

Beta-blocker initiation within 24 months and colorectal cancer incidence and survival in Swedish polyp patients

Collaboration?!

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