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Department of Clinical Epidemiology and Biostatistics

Long-term Statin Use and Risk of Cancers: A Target Trial Emulation Study

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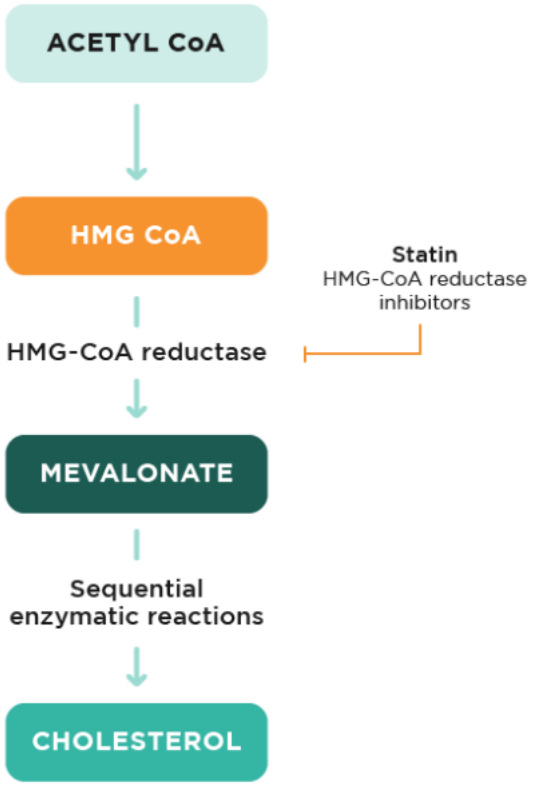
Background and Rationale

Background

- Statins are a group of drugs that lower the amount of cholesterol and certain fats in the blood
- Widely used lipid-lowering medications with demonstrated benefits in the primary and secondary prevention of cardiovascular disease
- Statins and cancer risks



Previous evidence

- RCTs and meta-analyses of RCTs demonstrated no significant association between statin use and overall cancer incidence
- Primary endpoints often not being cancer events, the rare number of events, and the relatively short follow-up periods

Previous evidence

- Observational studies have mixed findings reporting decreased incidence of colorectal, breast and prostate and others showing no association to increased risks
- Could be a resulted from potential selection and immortal time bias

Previous evidence

- A recent observational study employed a framework of target trial emulation to analyse electronic health records
- Aforementioned bias mitigated through synchronization of eligibility and treatment assignment with time zero
- Revealed no association of statin with cancer incidence

Rationale

- From the previous approach
  - Further improving the emulation process of statin indication in both treatment arms and
  - Balancing the baseline characteristics
- A long-term association of statin and cancer risk study was conducted

Material and methods

Description of database

- Electronic health records from the clinical management system (CMS) of the Hong Kong Hospital Authority (HA)
- CMS is an integrated clinical workstation that enables access to territory-wide electronic health records in all public health sectors.
- The database includes diagnosis records with high coding accuracy, detailed prescription data, and comprehensive information

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Target trial emulation

Eligible subjects

Pre-define indication of statin in each calendar month from January 2009 to December 2011

- Primary prevention
  - Cardiovascular disease (CVD) risk factors with low-density lipoprotein cholesterol (LDL-C) ≥4.1 mmol/L; or ≥2 CVD risk factors with LDL-C ≥3.4 mmol/L;
  - Coronary heart disease (CHD) risk equivalents such as diabetes mellitus or
  - Other target organ damage and LDL-C ≥2.6 mmol/L
- Secondary prevention
  - Established CVD and LDL-C ≥2.6 mmol/L.
- Acquired from local clinical guidelines to mirror real-life practice in statin prescription, similar to the guidelines of 2019 ESC and EAS for the Management of Dyslipidaemias

Exposure and Non exposure

- Statin initiators:
  - defined as the treatment with simvastatin, atorvastatin, luvastatin, rosuvastatin, lovastatin, pitavastatin, and pravastatin (or combination therapy that includes any of these drugs)
- Statin non-initiators: are those who do not initiate statins

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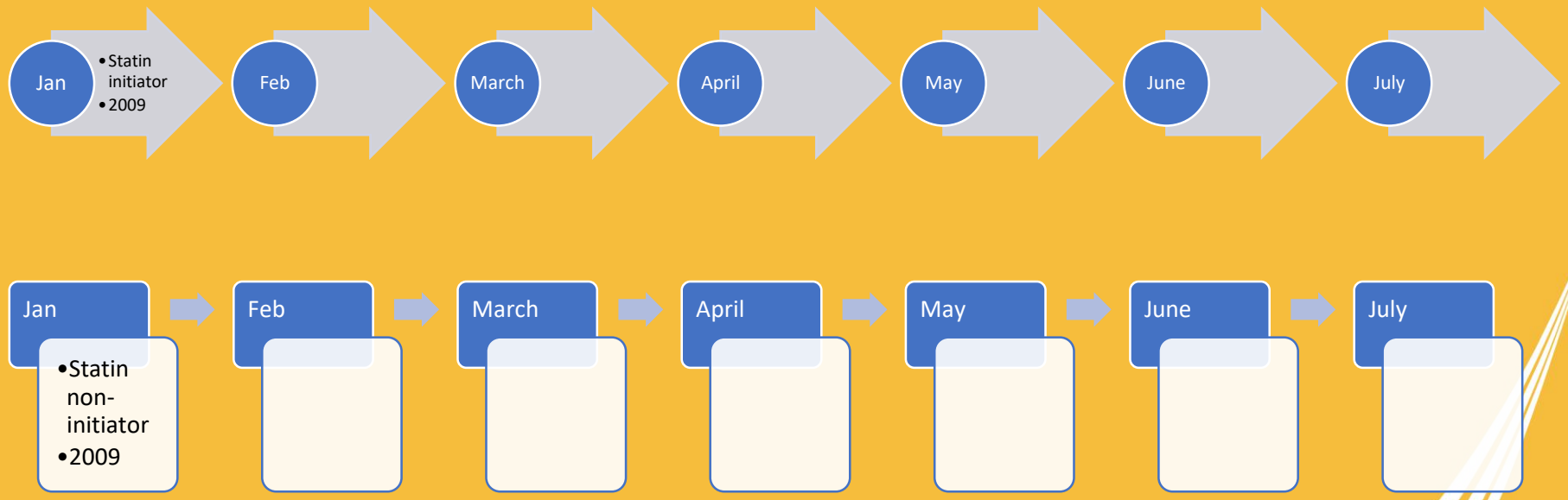
Sequential nested target trial emulation



January 2009 to December 2011

- 36 trials created
- On a rolling basis
- Each calendar month

Follow up periods

- From baseline until the
  - Occurrence of cancer
  - Death or
  - Administrative end of follow-up (31 December 2018)

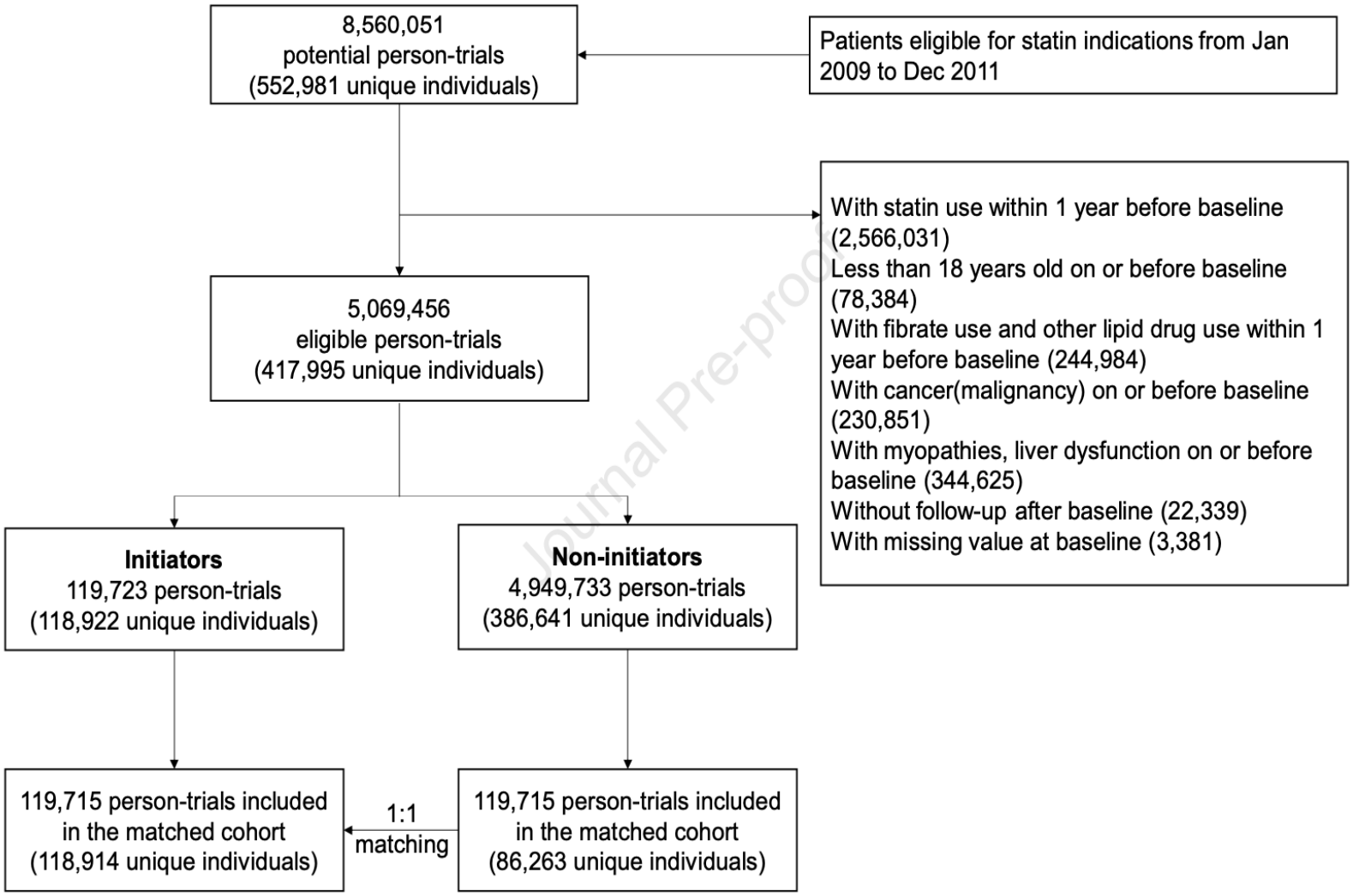
Outcomes

- Overall incidence of cancer and
- Seven common cancer types
  - Breast cancer, colorectal cancer, haematological cancer, pancreatic cancer, kidney cancer, urothelial carcinoma, and lung cancer.
- Based on criteria
  - International Classification of Primary Care, 2nd Edition (ICPC-2) a
  - International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), or
  - Relevant clinical parameters

Mimic of randomisation

- The propensity score matched at the ratio of 1:1
- Characteristics used for matching
  - Demographics
  - Comorbidities
  - Drug history one year before matching
  - Service utilisation prior to one year
  - Lifestyle behaviours (smoking)

Figure 1. Flowchart of person-trials in the analysis



Notes: The number of the individuals (in the parentheses) do not sum to the total number of unique individuals because some eligible individuals contributed to different arms in different emulated trials.

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Statistical analyis

- Intention to treat analysis
  - A time-discrete data was constructed by month for each eligible person-trial
  - Compared the cancer risks between the statin initiators and non-initiators based on their treatment strategy at baseline
  - Hazard ratio was estimated by fitting a pooled logistic model for the cancer incidence
    - Indicators of the assigned strategy (statin initiation at baseline),
    - Follow-up period (linear and quadratic terms) and
    - Baseline covariates

Statistical analysis

- Per protocol analysis
  - Compared the cancer risks between the continuous users and those who never used statins
  - The person trials were artificially censored when the patient deviated from their assigned strategy
  - Inverse probability weighting was adopted to adjust for selection bias introduced by the artificial censoring process

Statistical analysis

- Subgroup analysis
  - Sex (male/female)
  - Age (<70/ ≥ 70) years
  - Charlson Comorbidity Index (≤4/ > 4) score
  - Statin indication (Primary Vs secondary prevention or having CHD risk equivalents)

Statistical analysis

- Sensitivity analysis
  - CVD risk score (Framingham Risk Score)
  - Adjusted for competing risk (death)
  - Excluding familial hypercholesterolemia at baseline
- Non-parametric bootstrapping with 500 samples was also done to test the robustness of estimates
- Statistical significance was defined as a two-tailed p-value < 0.05
- STATA/MP 17 was used for the analysis

Results

Results

SMD after 1:1 matching between variables were far below 0.1

Table 2. Baseline characteristics of eligible person-trials

	Initiator	Non-initiator	SMD
	N=119,715	N=119,715	
Age	64.9 (11.9)	65.0 (13.1)	<0.01
Sex(male)	58,959 (49.2%)	59,362 (50%)	0.01
Smoking	5,368 (4.5%)	5,426 (5%)	<0.01
Lipid profile			
LDL-C	4.0 (0.9)	3.9 (1.0)	0.03
LDL-C Level:			
<3.4 mmol/L	32,903 (27.5%)	39,509 (33.0%)	0.07
3.4 - 4.0 mmol/L	39,919 (33.3%)	33,583 (28.1%)	
≥ 4.1 mmol/L	46,893 (39.2%)	46,623 (38.9%)	
HDL-C	1.3 (0.4)	1.3 (0.4)	<0.01
HDL-C level			
<1.3/1 mmol/L (female/male)	40,452 (33.8%)	40,801 (34.1%)	<0.01
≥1.3/1 mmol/L (female/male)	79,263 (66.2%)	78,914 (65.9%)	
Total cholesterol	6.0 (1.0)	6.0 (1.2)	0.03
Total cholesterol level:			
<5.2 mmol/L	25,481 (21.3%)	31,691 (26.5%)	0.07
5.2 - 6.1 mmol/L	49,303 (41.2%)	43,554 (36.4%)	
≥ 6.2 mmol/L	44,931 (37.5%)	44,470 (37.1%)	
Charlson comorbidity index	4.5 (2.2)	4.5 (2.6)	0.01
Comorbidities			
Hypertension	79,915 (66.8%)	80,223 (67.0%)	<0.01
Obesity	33,678 (28.1%)	34,050 (28.4%)	<0.01
Diabetes	69,838 (58.3%)	70,899 (59.2%)	0.02
Coronary heart disease	20,676 (17.3%)	20,425 (17.1%)	<0.01
Stroke	26,076 (21.8%)	26,096 (21.8%)	<0.01
Peripheral vascular disease	611 (0.5%)	623 (0.5%)	<0.01
Rheumatoid Arthritis	398 (0.3%)	433 (0.4%)	<0.01
Lupus	216 (0.2%)	216 (0.2%)	<0.01
Renal disease	16,949 (14.2%)	16,471 (13.8%)	<0.01
Dementia	1,395 (1.2%)	1,385 (1.2%)	<0.01
Drug use			
Long-term aspirin users	36,333 (30.3%)	36,953 (30.9%)	0.01
Insulin	8,180 (6.8%)	7,996 (6.7%)	<0.01
Oral antidiabetic drugs	63,534 (53.1%)	64,765 (54.1%)	0.02
AESI/ARB	56,326 (47.1%)	57,143 (47.7%)	0.01
β-blocker	46,362 (38.7%)	46,565 (38.9%)	<0.01
Calcium channel blockers	59,699 (49.9%)	60,103 (50.2%)	<0.01
Diuretic	22,587 (18.9%)	22,333 (18.7%)	<0.01
Anti-hypertension drugs	96,257 (80.4%)	94,146 (78.6%)	0.04
Service utilization			
SOPC attendance in the past 1 year	74,714 (62.4%)	74,521 (62.2%)	<0.01
Hospitalization in the past 1 year	43,617 (36.4%)	43,730 (36.5%)	<0.01

Notes: LDL-C = Low Density Lipoprotein - Cholesterol; HDL-C = High Density Lipoprotein- cholesterol; TC = Total Cholesterol; ACEI/ARB = angiotensin-converting enzyme inhibitor and angiotensin receptor blocker; SOPC = Specialist Out-patient Clinics

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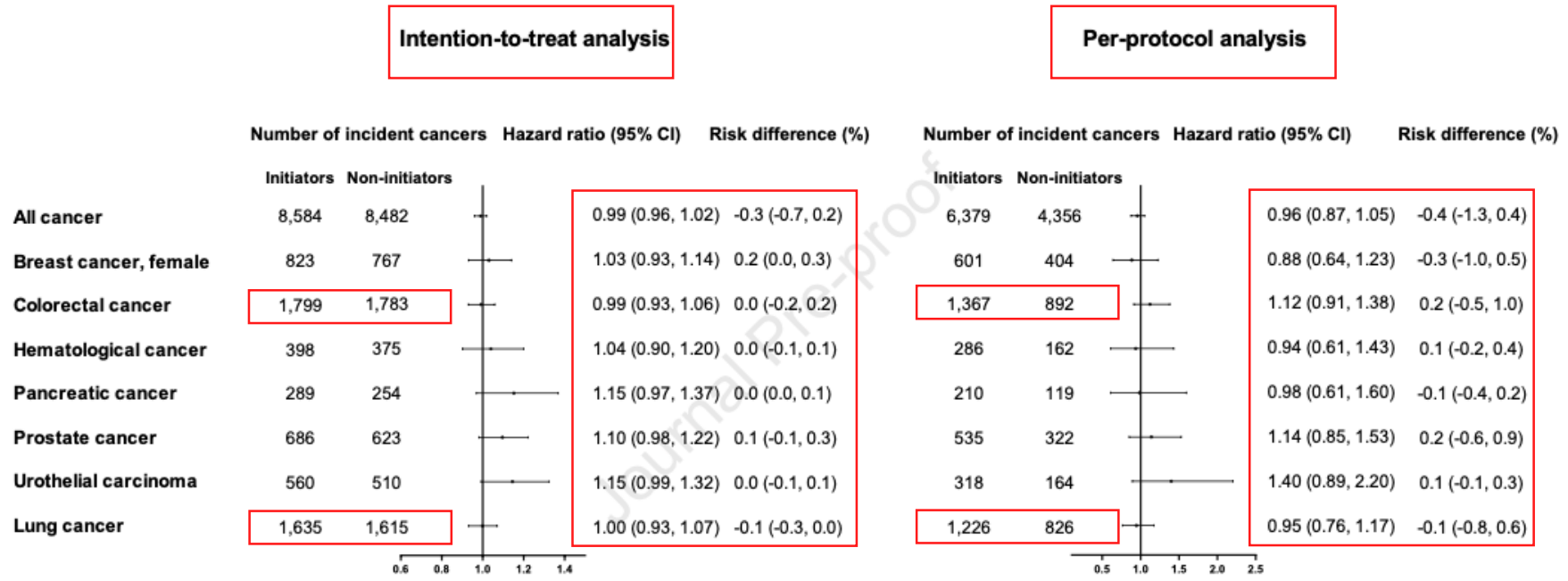
Results

Figure 2. Estimated hazard ratio and standardized 10-year risk differences for cancer



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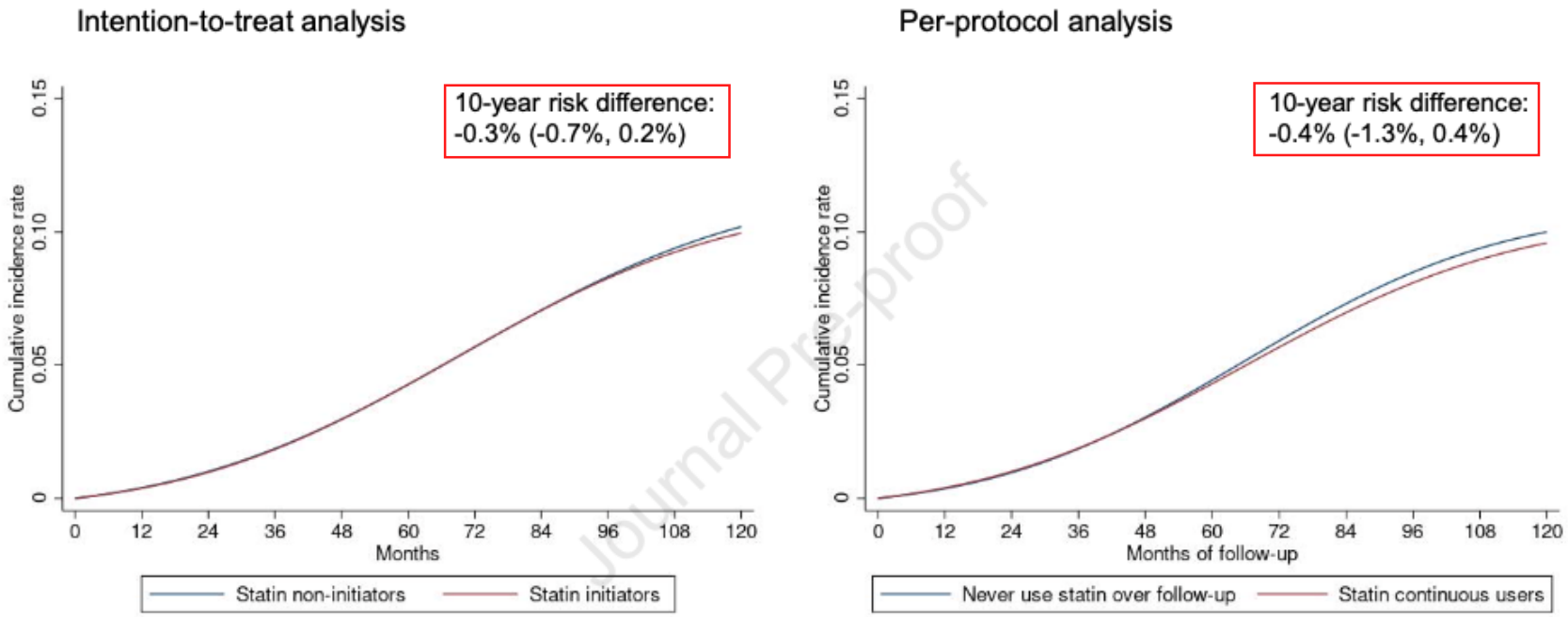
Results

Figure 3. Standardized cumulative incidence curve and risk difference of overall cancer comparing statin therapy with no statin therapy



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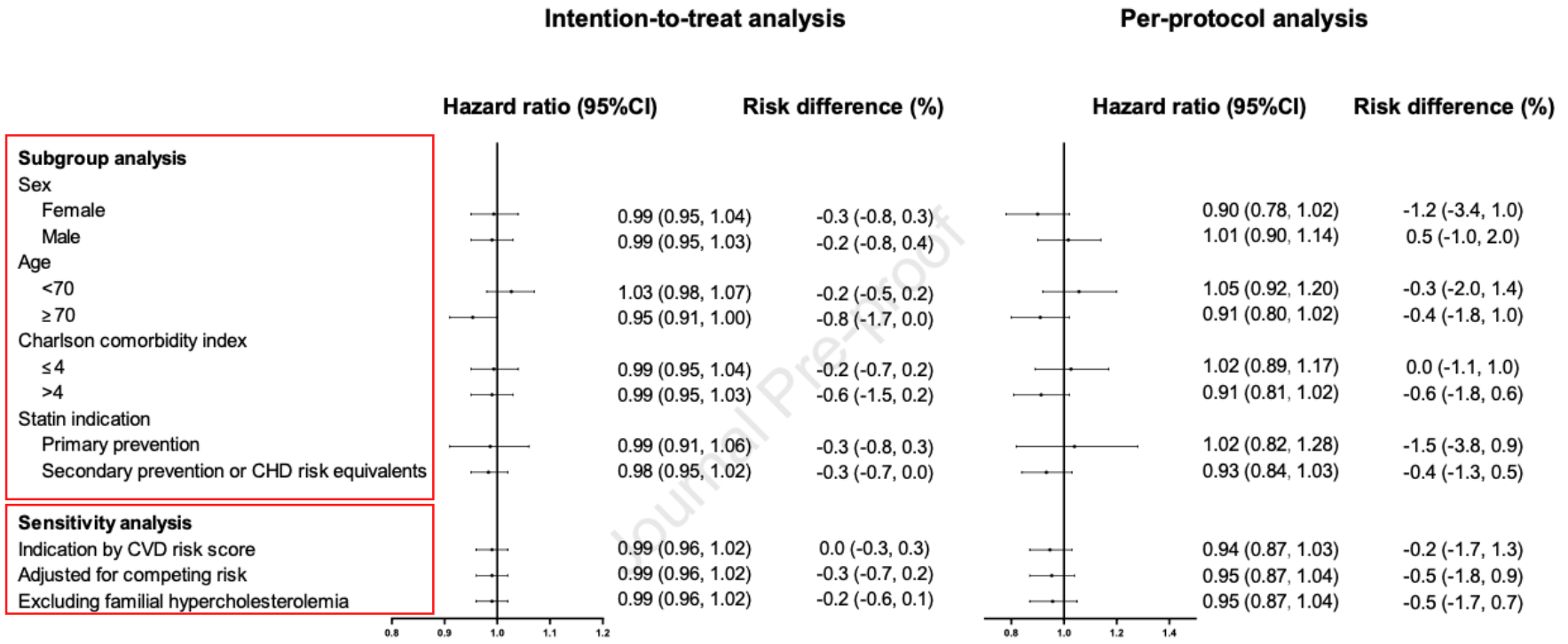
Estimated hazard ratio for overall cancer incidence in subgroup analysis and sensitivity analysis



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Discussion

Discussion

- Findings of no risks of overall cancers from long-term use of statin were consistent with meta-analysis involving 27 RCTs across all subgroups including age, sex, treatment duration and baseline LDL-C
- The median duration of follow-up included analysis was about 5 years
- Post-trial follow-up of Heart protection study investigating long-term efficacy and safety of statin had similar results
- Limit the generalizability as a result of strict eligibility criteria

Discussion

- Umbrella reviews of meta-analyses of observational studies and RCTs suggested weak evidence of the preventive effect of statin on site-specific cancers
- Substantial heterogeneity between studies and among various cancer types
- Potential selection and immortal bias as a result of including prevalent statin users in analysis
- Two TTE studies from the UK revealed similar results
- Incorporating the indication of statin therapy in both arms mirrors real-life practice in terms of cardiovascular risks and results in different ethnic population provides reassurance to patients and clinicians

Strengths

- The method employed to identify patients eligible for statin use mirrored real-life clinical practice
- The casual inference framework of the target trial emulation in this study overcomes the potential immortal time and selection biases
- Large population and long-term follow of up to 10 years that allow the capture of rare cancers

Limitations

- Unmeasured confounding such as family history or lifestyle factors (alcohol use and exercise pattern)
- Misclassification bias
- Framingham Risk Score used in the sensitivity analysis was not recalibrated in the local population

Conclusion

Conclusion

- Emulated target trial suggested that statin use has no impact on cancer incidence over a 10-year follow-up period
- No observable risk change for cancer was found in all cancer subtypes of interest and patient subgroups including sex, age, comorbidities, and statin indications
- The finding clarified the association between statin use and cancer risk in real-life clinical practice
- Additional reassurance to patients and clinical practitioners

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