Effectiveness and safety of using statin therapy for the primary prevention of cardiovascular diseases in older patients with chronic kidney disease who are hypercholesterolemic: a target trial emulation study

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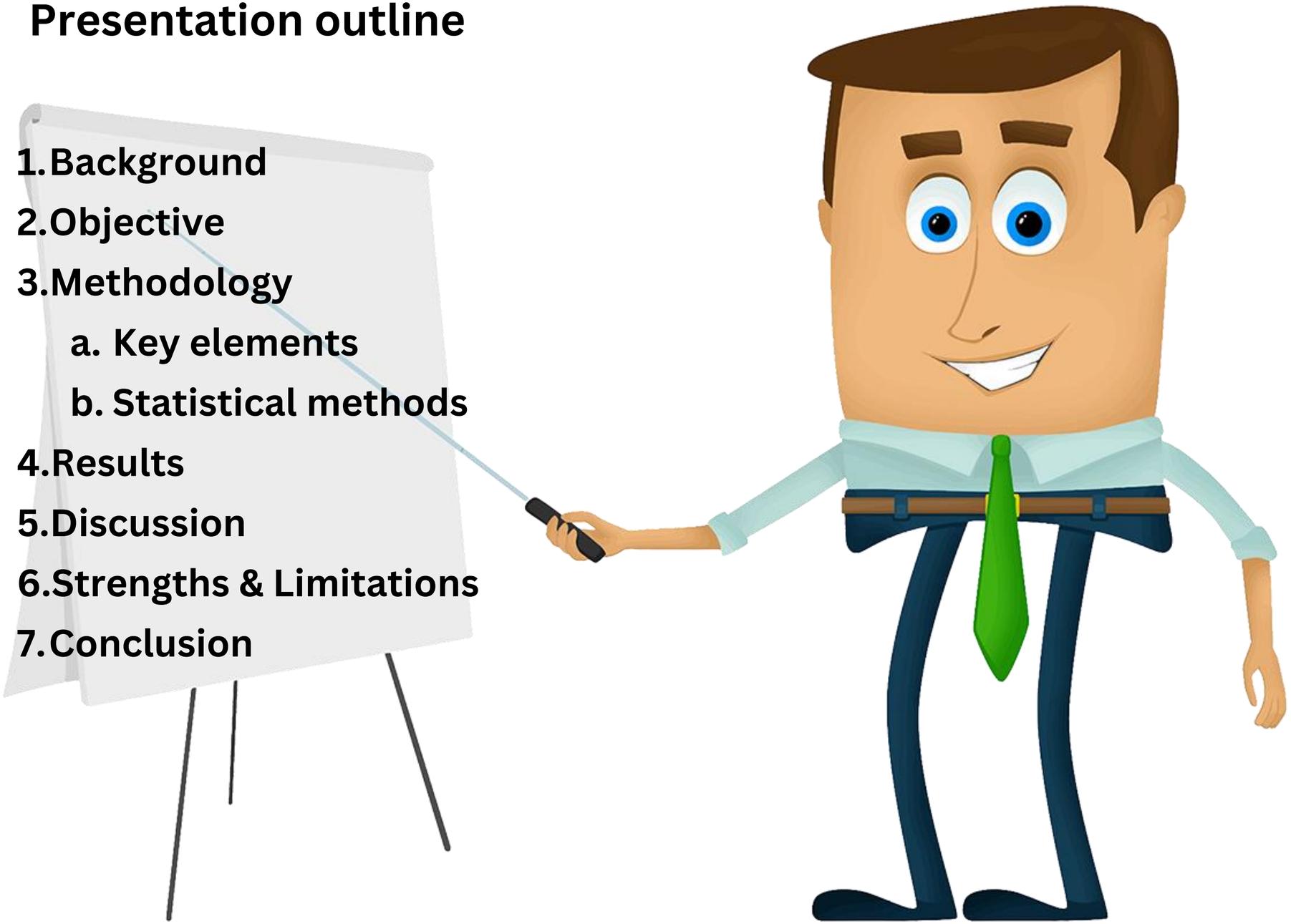
Presentation outline

1. Background
2. Objective
3. Methodology
    a. Key elements
    b. Statistical methods
4. Results
5. Discussion
6. Strengths & Limitations
7. Conclusion



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1. Background ⟶ Research Question

There remains a scarcity of evidence on initiating statin therapy for the primary prevention of cardiovascular diseases among older adults with chronic kidney disease.

Should statins be used for the primary prevention of CVD in older adults with CKD and high cholesterol?

- Older adults (≥ 75) with CKD are at high risk for CVD events.
- Yet, they are often underrepresented in clinical trials.
- Current guidelines are unclear about starting statins in this population, especially for those without established cardiovascular disease.

Prevalence of CKD

- 32.7% in UK (those > 75 years)
- 34.0% in the USA (those ≥ 65 years)
- 29.7 % in Hong Kong (those with type 2 DM)

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1. Background ⟶ Rationale

Limited RCT evidence

- **Older adults with CKD are often excluded or underrepresented in major randomised controlled trials evaluating statins.**

Uncertain benefit-risk balance

- While statins reduce CVD risk in many populations, their benefits for primary prevention in CKD patients—especially the elderly—remain unclear.
- Concerns include potential adverse effects such as myopathy, liver injury, and new-onset diabetes.

Clinical uncertainty persists

- Due to this evidence gap, guidelines offer limited or cautious recommendations, leaving many clinicians uncertain about initiating statins in this subgroup.

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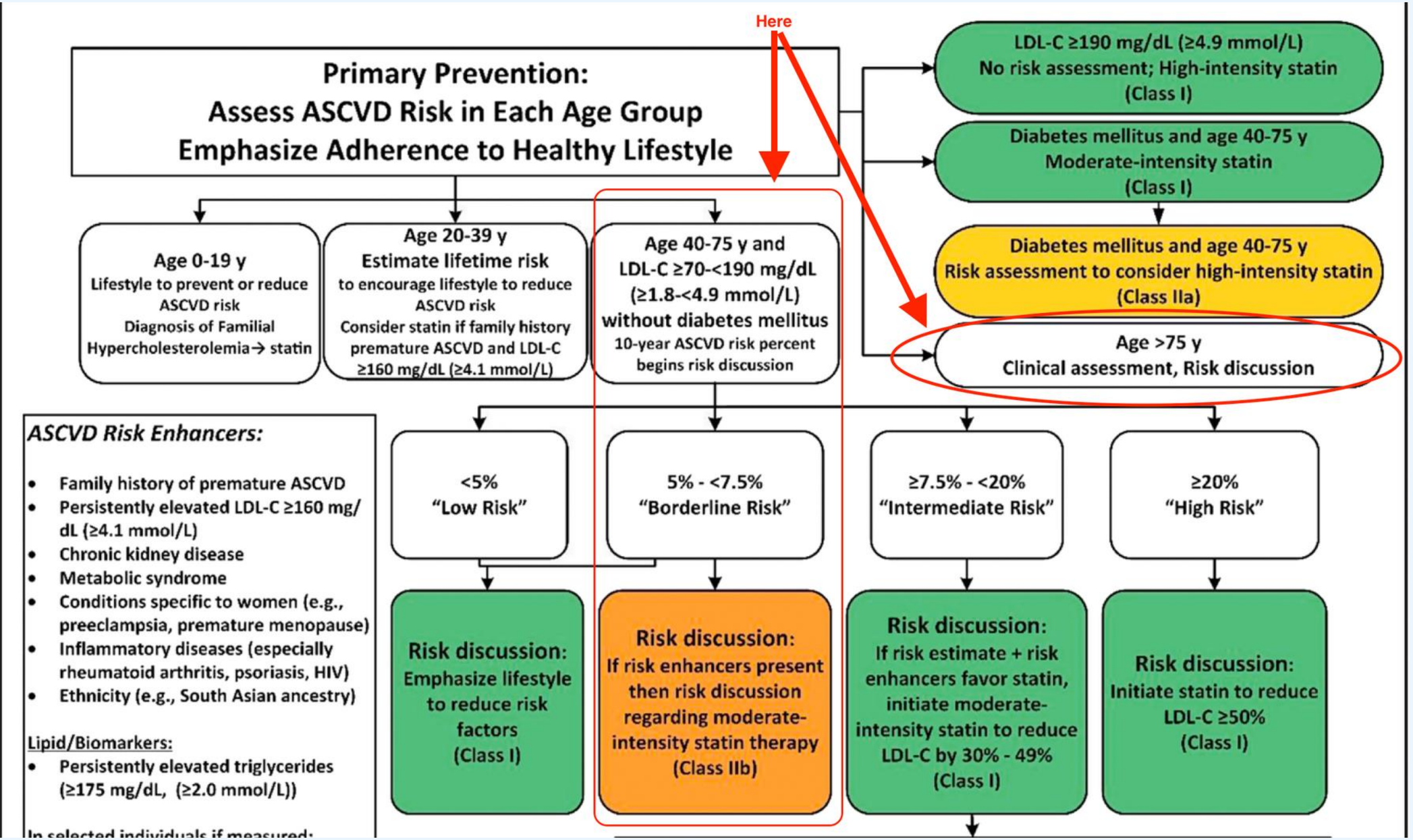
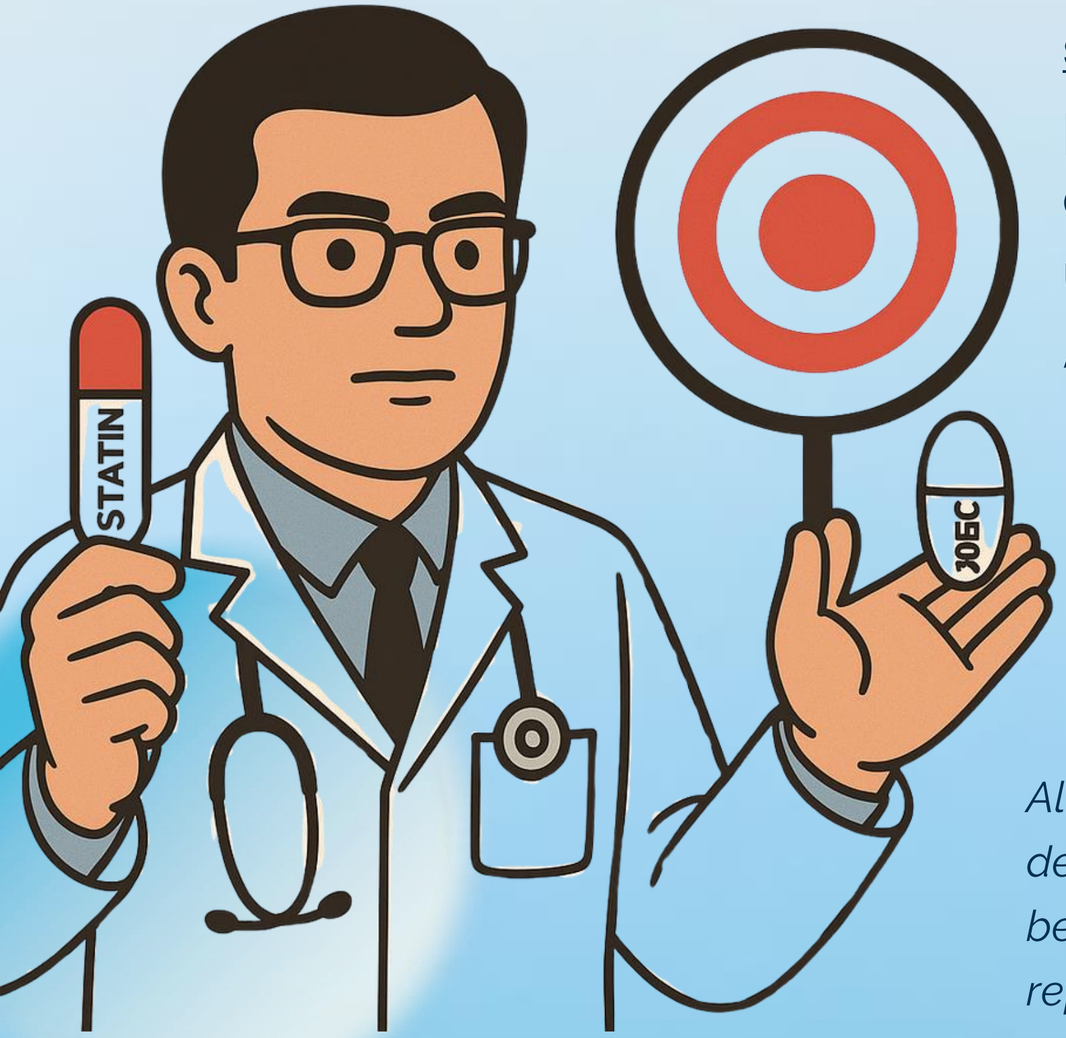
2018 ACC/AHA Guideline on the Management of Blood Cholesterol



2. Objective



To emulate a target trial evaluating the effectiveness and safety of statin therapy versus no statin therapy for the primary prevention of cardiovascular disease in older adults (≥75 years) with CKD and hypercholesterolemia, using real-world data of EHR from the Hong Kong Hospital Authority.

Although the stated objective centres on individuals ≥75 years, the study design included patients ≥60 years to allow for stratified age analyses and better covariate balance through matching. The age group 60–74 served as a reference to contrast outcomes across age categories.

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3. Methodology → Key elements (1)

A sequence of nested target trails was emulated using EHR from HK Hospital Authority

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- *Data from public clinics and hospitals in HK*
- *90% Chinese and 10% others (Filipinos, Indonesians & South Asians*
- *EHR database has undergone validation in previous research, showing high accuracy in MI (PPV: 85.4%, 95%CI: 78.8-90.6) & stroke diagnosis (PPV: 91.1%, 95%CI: 83.2-96.1)*

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3. Methodology ⟶ Key elements (2)

Defining target trial: Hypothetical RCT features

- ***Population: Older adults (≥65) with CKD and LDL ≥160 mg/dL, no prior CVD***
- ***Intervention: Start statins***
- ***Comparator: No statins***
- ***Follow-up: From the treatment decision***
- ***Outcomes: CVD events, death, safety***

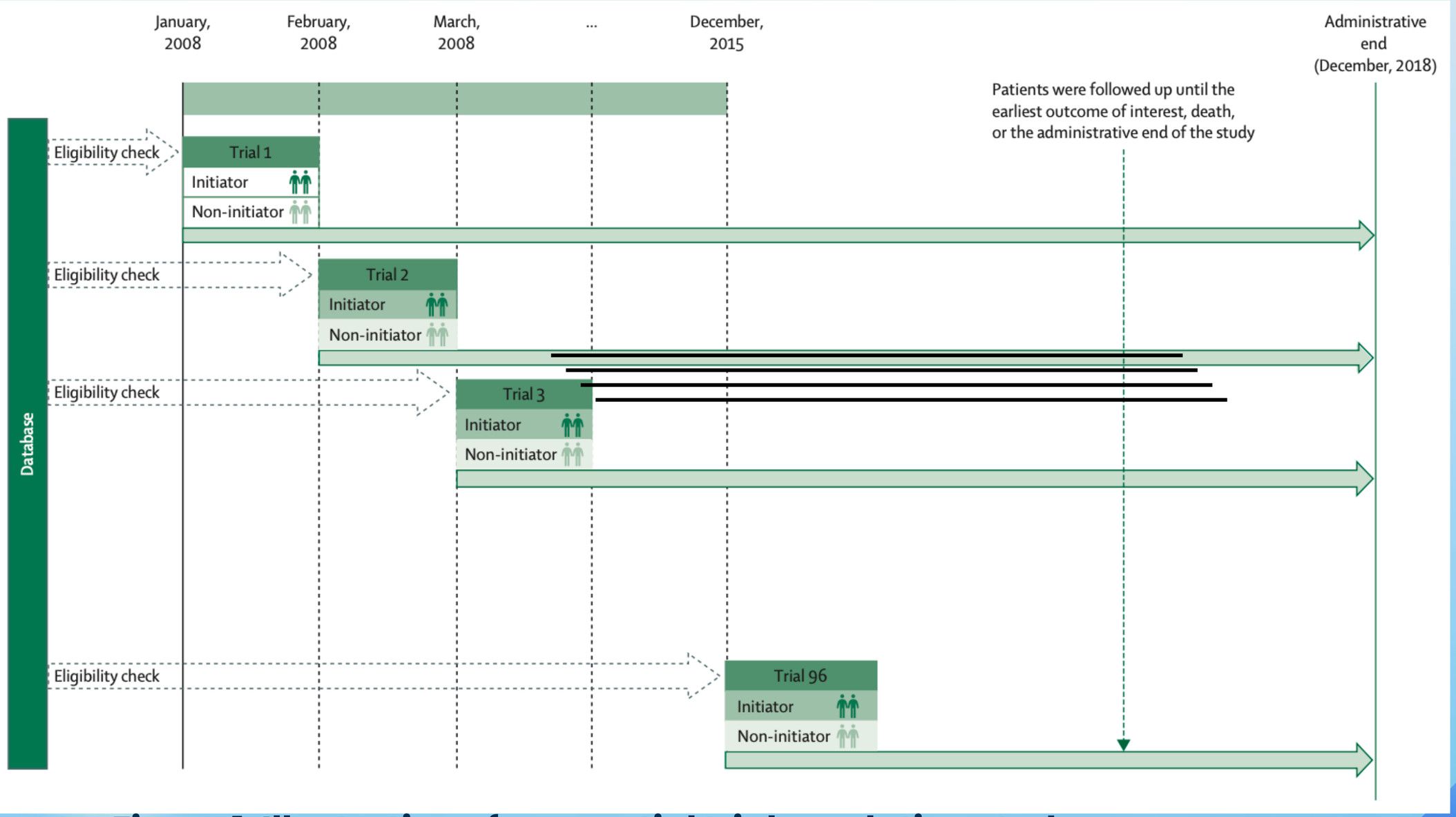
Inclusion

- Age ≥65
- CKD: eGFR <60
- LDL-C ≥160 mg/dL
- No history of CVD

Exclusion

- Previous CVD
- Acute kidney disease
- Cancer, liver disease, and recent statin use
- Missing lab or claim data

3. Methodology → Key elements (3)



96 target trials (12* 8 years) during Jan 2008 and Dec 2015

Figure 1. Illustration of sequential trial emulation study

3. Methodology ⟶ Key elements (4)

Treatment Strategy

- *Treatment group - Only new statin users with prescription records*
- *Control group - Never initiated statins*

Follow-up

- *Statin users - date of statin prescription*
- *Non-users - matched index date*

Treatment group

- Those with previous prescription records were excluded
- No longer eligible for subsequent trial

Control group

- Eligible for subsequent trial

3. Methodology → Key elements (5)

Exposure

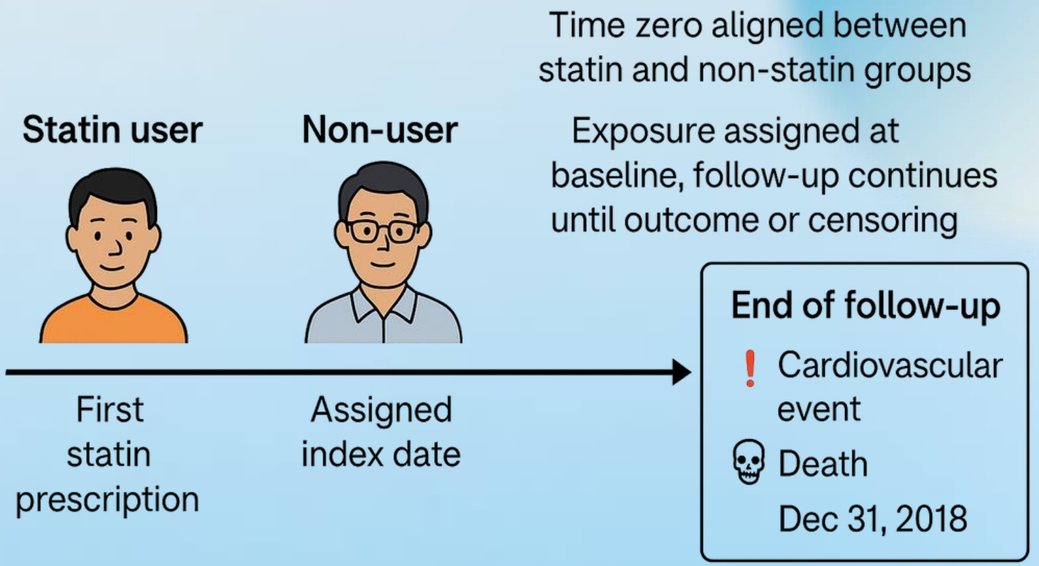
- *Statin therapy was defined as treatment with simvastatin, atorvastatin, fluvastatin, rosuvastatin, lovastatin, pitavastatin, or pravastatin.*

Index date and end of the study

- *Statin users - date of dispensing in the prescription record*
- *Non-users - likely same index date as their matched statin user*
- *Follow-up until the outcome of interest, death, or the end of the study (Dec 31, 2018), whichever occurred first.*

Outcomes

- *Overall incidence of CVD, specific subtypes (i.e, MI, HF, and stroke), and all-cause mortality*
- *Major adverse events - myopathies and liver dysfunction*



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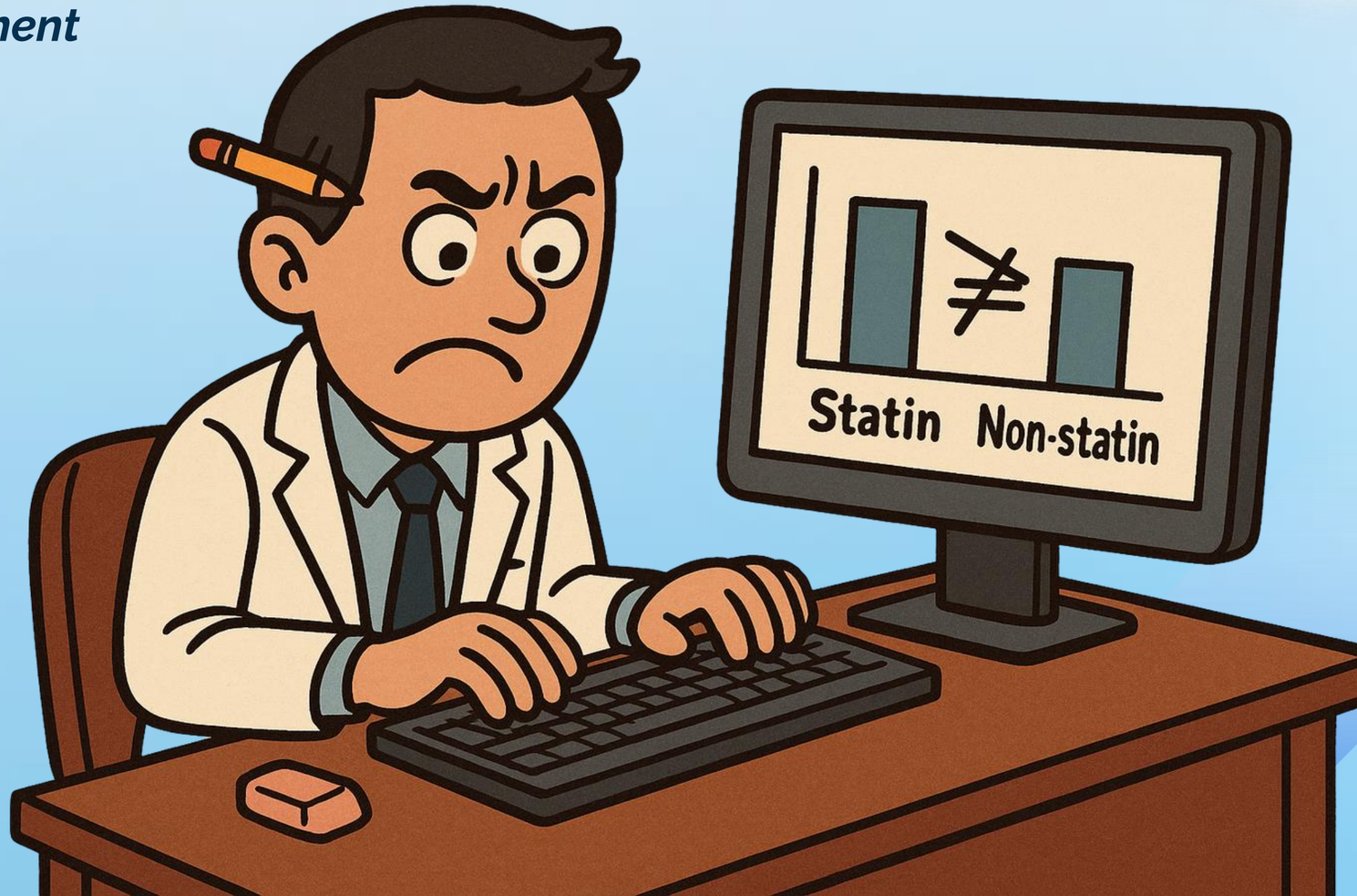
3. Methodology → Statistical analysis

Overall treament effect estimation

1. *Intention-to-treat (ITT): Based on treatment assignment at baseline*
2. *Per-protocol: Based on actual treatment adherence during follow-up*



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3. Method/Statistical/ITT (1)

Intention-to-treat

- *All individuals in the groups to which they were assigned at baseline, regardless of treatment adherence or subsequent changes*
- *Mimics the principle of randomisation in RCTs*
- *Preserves baseline comparability and reduces bias due to post-assignment behaviours*
- *Pooled logistic regression - to model outcome incidence over discrete time intervals.*
  - *Estimated odds ratios (ORs) interpreted as hazard ratios (HRs) due to the rare-event assumption*
- *Model included:*
  - *Treatment indicator (statin initiation at baseline - yes/no)*
  - *Follow-up time (linear & quadratic terms)*
  - *Baseline covariates*

3. Method/Statistical/ ITT (2)

Rare event assumption

Statistical analysis

The intention-to-treat and per-protocol effects on the prevention of cardiovascular diseases and all-cause mortality were estimated in the emulated target trials in the three age groups. The intention-to-treat HR was estimated by fitting a pooled logistic model for the outcome incidence, including the indicators of the assigned strategy (statin initiation at baseline), follow-up period (linear and quadratic terms), and the covariates at baseline. As the outcome of the models is rare, the odds ratio from the pooled logistic model approximates the HR.[24] Included covariates were demographic characteristics (sex and age); clinical parameters (fasting glucose, systolic blood pressure, diastolic blood pressure, LDL cholesterol, HDL cholesterol,

Supplementary Table 3 (continued)

Trial	Baseline	60-74 years old					75-84 years old					
		Participants	Initiators		Non-initiators		Participants	Initiators		Non-initiators		Pa
			Num	CVD cases	Num	CVD cases		Num	CVD cases	Num	CVD cases	
87	201503	2,542	55	1	2,487	276	3,410	66	14	3,344	659	
88	201504	2,499	45	5	2,454	265	3,371	52	6	3,319	635	
89	201505	2,488	52	6	2,436	265	3,325	46	9	3,279	606	
90	201506	2,491	66	8	2,425	255	3,265	53	6	3,212	575	
91	201507	2,440	64	8	2,376	246	3,268	63	8	3,205	577	
92	201508	2,429	54	4	2,375	240	3,242	51	5	3,191	548	
93	201509	2,413	48	5	2,365	242	3,191	39	6	3,152	530	
94	201510	2,389	50	5	2,339	229	3,199	62	14	3,137	526	
95	201511	2,358	58	6	2,300	211	3,164	62	15	3,102	520	
96	201512	2,360	56	7	2,304	203	3,144	59	12	3,085	507	
		90,146					324,674	4,700	1475	319,974	39,742	

Cumulative risk over the entire follow-up
Statin user, 1475/4700 = 31.4%
Non-user, 39742/319974 = 12.4%

However, monthly risk,
median follw-up = 5.3 years (63.6 months)
Statin users, 0.314/63.6 = 0.0049 (0.49%)
Non-users, 0.124/63.6 = 0.0019 (0.2%)

3. Method/Statistical/ITT (2)

Baseline covariates

- *Demographics: Age, Sex*
- *Clinical parameters: Glucose, SBP, DBP, LDL-C, HDL-C, eGFR, etc.*
- *Charlson Comorbidity Index and comorbidities:*
- *Hypertension, Diabetes, COPD, PVD, AF, Dementia, Obesity*
- *Medication use (past year): e.g., ACEI/ARBs, β-blockers, statins*
- *Healthcare use: Clinic visits, hospital admissions*
- *Smoking status*

3. Method/Statistical/per-protocol (1)

Per-protocol analysis

Estimates the effect of actually continuing statin therapy, better representing the effect among compliers.

Exposure Groups:

- *Continuous statin users: who remained on statin during follow-up for 3 months.*
- *Never users: who never initiated statins throughout follow-up.*

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Censoring rules:

- *Patients were censored 3 months after discontinuing statins, defined as:*
  - *No refill prescription within 3 months after the last dose.*
- *Patients were also censored if they deviated from their assigned strategy, unless they developed a new clinical indication or contraindication for statins.*

3. Method/Statistical/per-protocol (2)

Adjusting for Censoring Bias

Problem:

Censoring due to treatment discontinuation may introduce selection bias, especially if those who stop treatment differ systematically from those who remain.

Solution:

- ***Applied Inverse Probability of Treatment Weighting (IPTW) at each timepoint.***
- ***Weights reflect the probability of remaining adherent, based on:***
  - ***Baseline and time-varying covariates (e.g., labs, comorbidities, drug use, healthcare use)***
  - ***Estimated using pooled logistic models***
  - ***Handled missing time-varying data via LOCF***
- ***Weights truncated at 5th and 95th percentiles to reduce the impact of outliers.***

3. Method/Statistical/per-protocol (3)

Competing Risk Adjustment

Why?

- *Death may occur before CVD events and must be treated as a competing risk.*
- *Otherwise, censoring due to death would bias the effect estimates.*

How?

- *Used time-varying inverse probability of survival weighting, similar to IPCW.*
- *Final weights = IPTW × IP of not dying*

3. Method/Statistical/Final Model

Pooled logistic regression, adjusted with stabilized weights

Included:

- *Assigned treatment indicator*
- *Time terms (linear, quadratic)*
- *Baseline covariates*

Estimates generated:

- *Hazard Ratios (HRs) for outcomes*
- *Absolute risks over 5 and 10 years (differences)*
- *Number Needed to Treat (NNT) from absolute risk difference (=1/absolute risk difference)*

Complete case analysis as well, by removing those who are lost to follow-up.

3. Method/Statistical/Subgroup Analysis

To explore whether treatment effects vary across patient subgroups

Subgroups analysed:

- *Sex: Male vs. Female*
- *Charlson Comorbidity Index: ≤8 vs. >8*
- *CKD Stage at baseline:*
  - *Stage 1–3*
  - *Stage 4*
  - *Stage 5*

Method:

- *Added interaction terms between treatment and subgroup indicator in the regression model.*

Interpretation: Tests for effect modification (e.g., whether statins work differently across CKD stages or comorbidity levels).

3. Method/Statistical/Sensitivity Analysis (1)

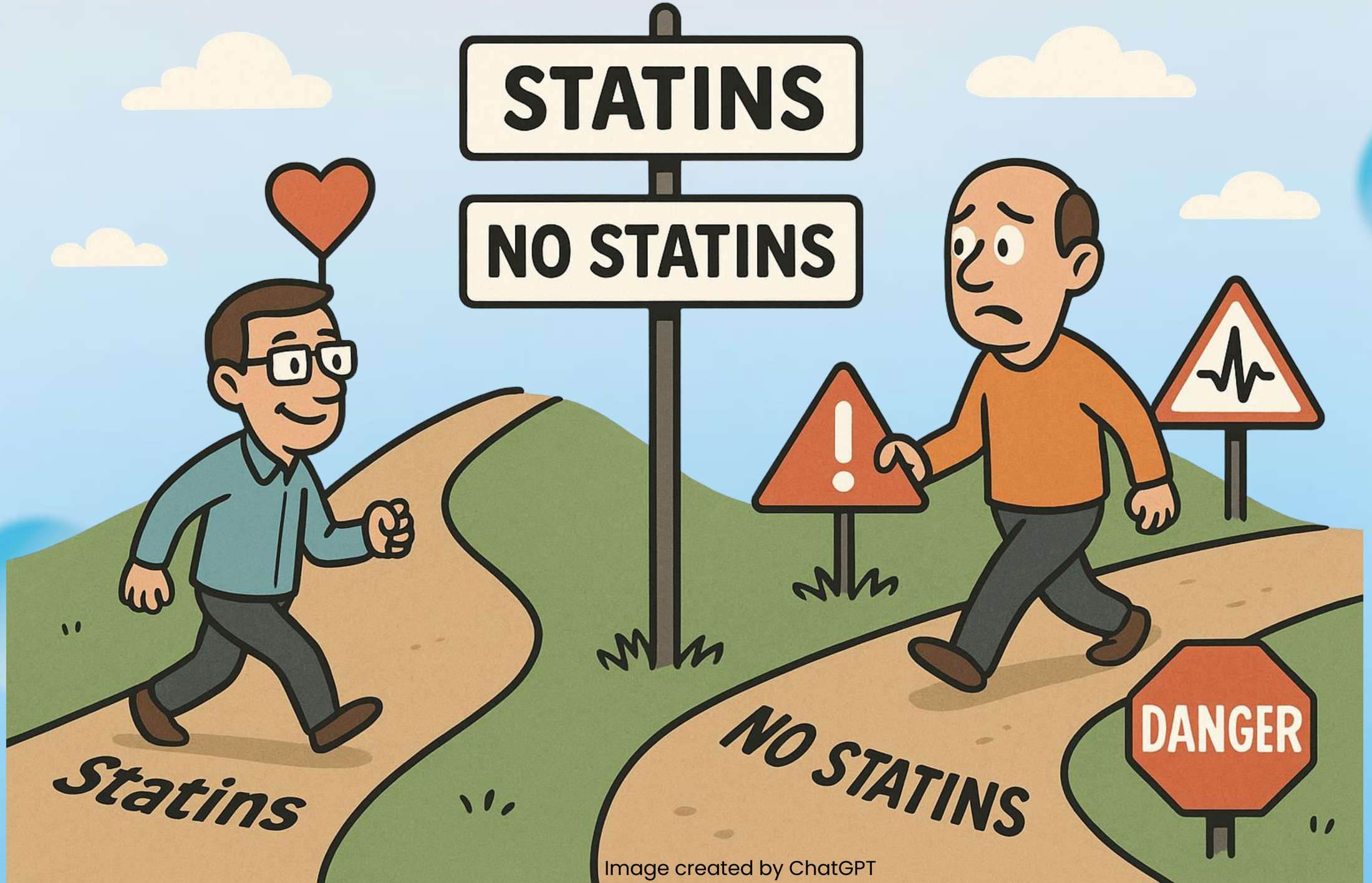
To assess the robustness of findings under different assumptions and methods

1. *Stricter adherence definition:*
    a. *Changed statin discontinuation gap from 3 months to 1 month in per-protocol analysis.*
2. *Different weight truncation:*
    a. *Truncated IP weights at the 1st and 99th percentiles instead of 5th/95th.*
3. *Propensity score matching (PSM):*
    a. *1:1 nearest-neighbour matching within each age group.*
    b. *Calliper = 0.2 × SD of the PS.*
4. *Alternative eligibility criterion:*
    - *Used Framingham 10-year CVD risk >7.5% instead of LDL threshold.*

3. Method/Statistical/Sensitivity Analysis (2)

To assess the robustness of findings under different assumptions and methods

1. *Lag-time analysis:*
    a. *Excluded patients who experienced outcomes in the first year to reduce bias from undiagnosed diseases.*
2. *Follow-up visit exclusion removed:*
    a. *Instead of excluding those with <1 follow-up, censored at 2 years after last visit and applied censoring weights.*
3. *Competing risk adjustment (in ITT):*
    a. *Addressed death as a competing risk in the intention-to-treat analysis, not just per-protocol.*
4. *Multiple imputation:*
    a. *Used chained equations to impute missing baseline covariates.*
    b. *Estimates combined using Rubin's rule from 5 imputed datasets.*



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4. Results (1)

Study Population & Person-Trials

- *Total person-trials: 711,966 from 96 trials*
- *Age groups:*
  - *60–74 years: 268,452 trials (19,423 individuals)*
  - *75–84 years: 324,674 trials (22,565 individuals)*
  - *≥85 years: 118,840 trials (8,811 individuals)*
- *Exclusion: 34.5% excluded due to incomplete baseline data*
- *Median follow-up: 5.3 years (IQR 3.8–7.1)*

4. Results (2)

Intention-to-Treat (ITT) Results

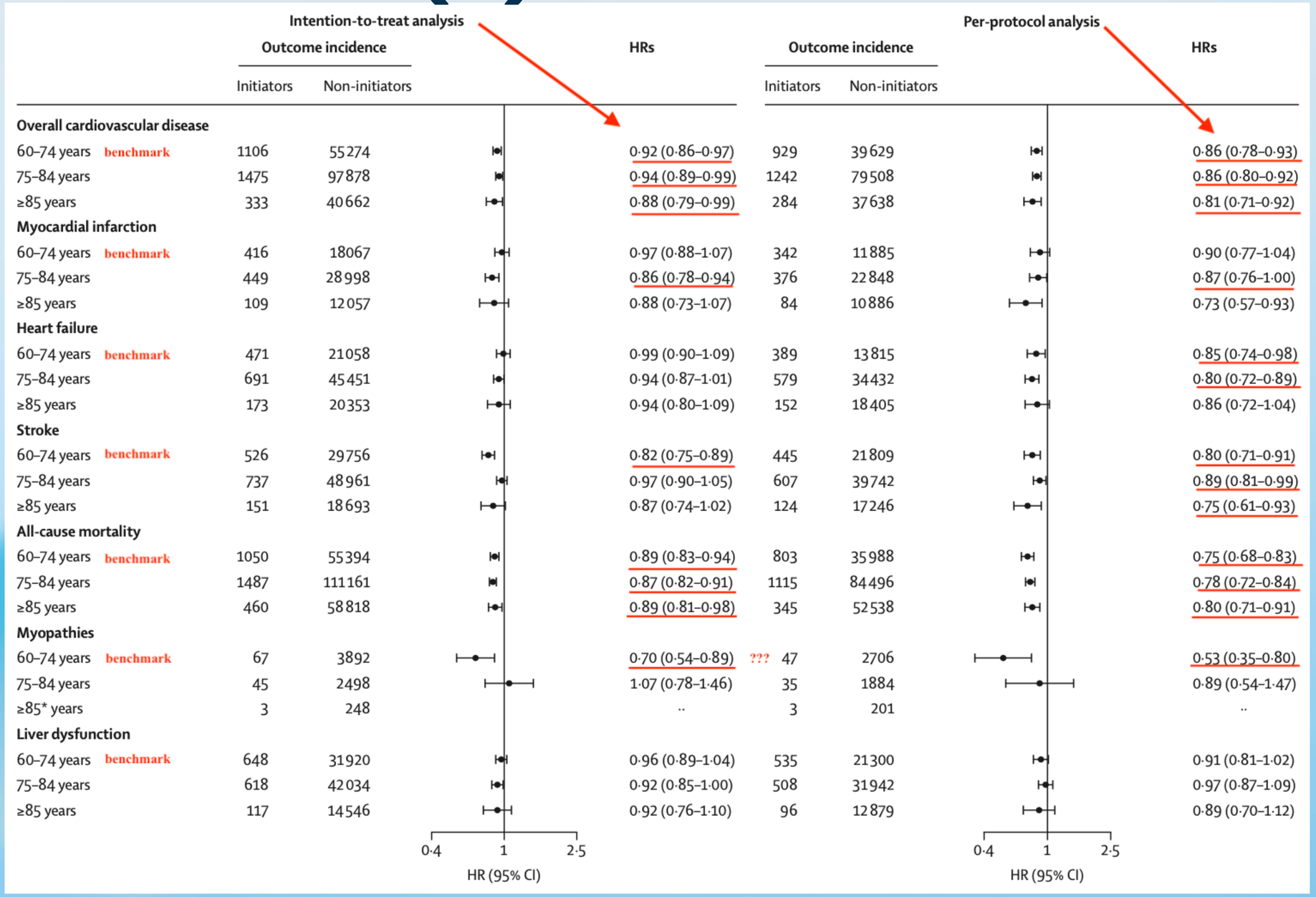
- *HR for CVD incidence (statin vs non-statin):*
  - *60–74 years: 0.92 (95% CI: 0.86–0.97)*
  - *75–84 years: 0.94 (0.89–0.99)*
  - *≥85 years: 0.88 (0.79–0.99)*
- *HR for all-cause mortality:*
  - *60–74 years: 0.89 (0.83–0.94)*
  - *75–84 years: 0.87 (0.82–0.91)*
  - *≥85 years: 0.89 (0.81–0.98)*
- *Number Needed to Treat (NNT, 5-year):*
  - *77, 67, and 25 for the three age groups, respectively*

4. Results (3)

Per-Protocol Results

- *HR for CVD incidence*
  - *60–74 years: 0.86 (0.78–0.93)*
  - *75–84 years: 0.86 (0.80–0.92)*
  - *≥85 years: 0.81 (0.71–0.92)*
- *HR for all-cause mortality:*
  - *60–74 years: 0.75 (0.68–0.83)*
  - *75–84 years: 0.78 (0.72–0.84)*
  - *≥85 years: 0.80 (0.71–0.91)*

4. Results (4)



	Intention-to-treat analysis			Per-protocol analysis		
	Outcome incidence		HRs	Outcome incidence		HRs
	Initiators	Non-initiators		Initiators	Non-initiators	
Overall cardiovascular disease						
60–74 years benchmark	1106	55 274	0·92 (0·86–0·97)	929	39 629	0·86 (0·78–0·93)
75–84 years	1475	97 878	0·94 (0·89–0·99)	1242	79 508	0·86 (0·80–0·92)
≥85 years	333	40 662	0·88 (0·79–0·99)	284	37 638	0·81 (0·71–0·92)
Myocardial infarction						
60–74 years benchmark	416	18 067	0·97 (0·88–1·07)	342	11 885	0·90 (0·77–1·04)
75–84 years	449	28 998	0·86 (0·78–0·94)	376	22 848	0·87 (0·76–1·00)
≥85 years	109	12 057	0·88 (0·73–1·07)	84	10 886	0·73 (0·57–0·93)
Heart failure						
60–74 years benchmark	471	21 058	0·99 (0·90–1·09)	389	13 815	0·85 (0·74–0·98)
75–84 years	691	45 451	0·94 (0·87–1·01)	579	34 432	0·80 (0·72–0·89)
≥85 years	173	20 353	0·94 (0·80–1·09)	152	18 405	0·86 (0·72–1·04)
Stroke						
60–74 years benchmark	526	29 756	0·82 (0·75–0·89)	445	21 809	0·80 (0·71–0·91)
75–84 years	737	48 961	0·97 (0·90–1·05)	607	39 742	0·89 (0·81–0·99)
≥85 years	151	18 693	0·87 (0·74–1·02)	124	17 246	0·75 (0·61–0·93)
All-cause mortality						
60–74 years benchmark	1050	55 394	0·89 (0·83–0·94)	803	35 988	0·75 (0·68–0·83)
75–84 years	1487	111 161	0·87 (0·82–0·91)	1115	84 496	0·78 (0·72–0·84)
≥85 years	460	58 818	0·89 (0·81–0·98)	345	52 538	0·80 (0·71–0·91)
Myopathies						
60–74 years benchmark	67	3892	0·70 (0·54–0·89)	??? 47	2706	0·53 (0·35–0·80)
75–84 years	45	2498	1·07 (0·78–1·46)	35	1884	0·89 (0·54–1·47)
≥85* years	3	248	..	3	201	..
Liver dysfunction						
60–74 years benchmark	648	31 920	0·96 (0·89–1·04)	535	21 300	0·91 (0·81–1·02)
75–84 years	618	42 034	0·92 (0·85–1·00)	508	31 942	0·97 (0·87–1·09)
≥85 years	117	14 546	0·92 (0·76–1·10)	96	12 879	0·89 (0·70–1·12)

HRs for main and individual outcomes

4. Results (5)

5-year Absolute Risk Difference for overall CVD incidence

5-year Absolute Risk Difference for overall CVD incidence

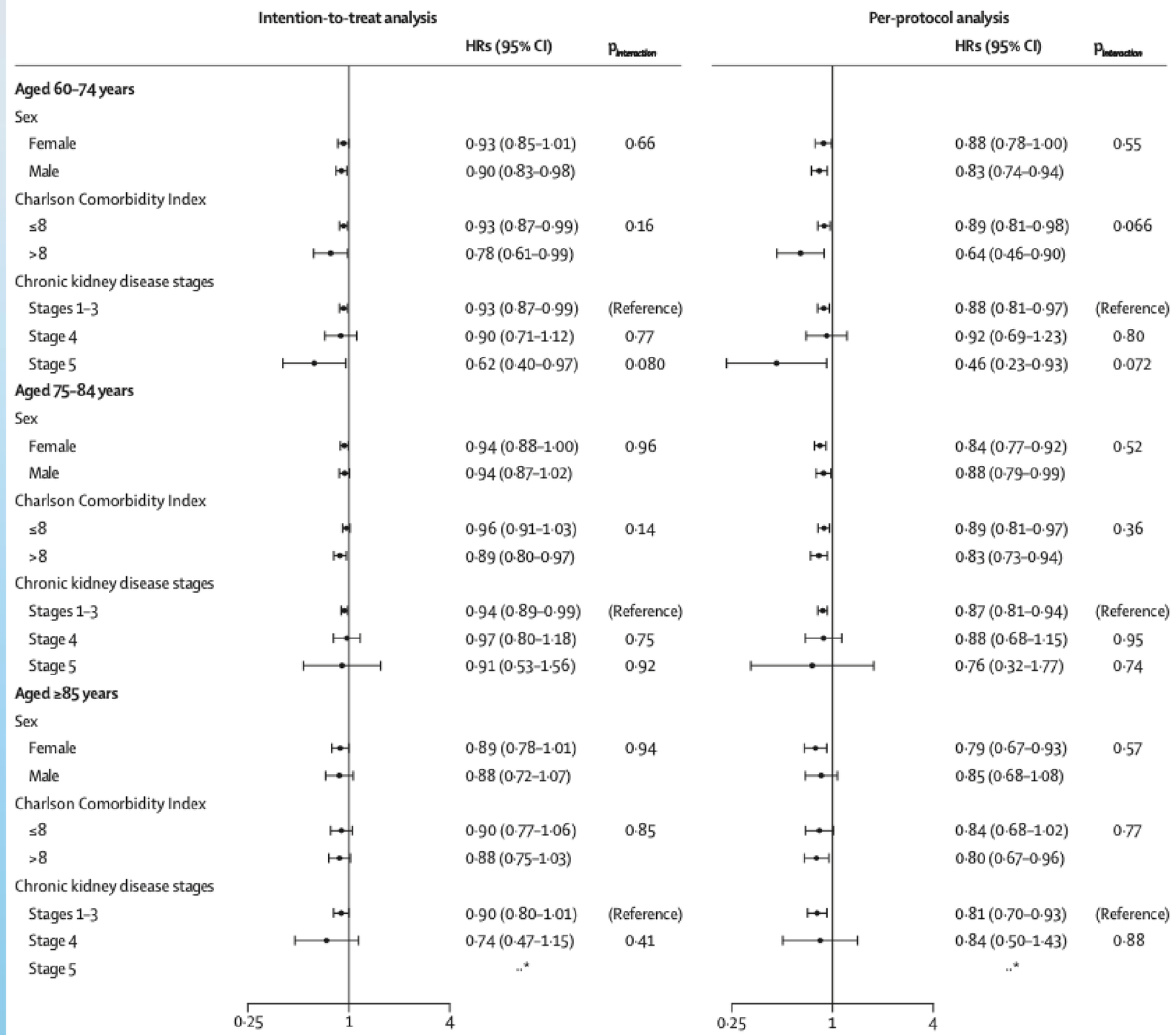
Age groups	ITT		Per-protocol	
	ARD (%, 95%CI)	NNT (n, 95%CI)	ARD (%, 95%CI)	NNT (n, 95%CI)
60-74 years	-1.3% (-2.1 to -0.4)	77 (46 to 224)	-2.6 (-3.7 to -1.2)	41 (27 to 84)
75-84 years	-1.5% (-2.7 to -0.4)	67 (38 to 295)	-4.4 (-5.9 to -2.9)	23 (17 to 35)
≥ 85 years	-4.0% (-7.0 to -1.0)	25 (14 to 101)	-8.2 (-11.7 to -4.7)	12 (9 to 21)

ITT: intention-to-treat, ARD: absolute risk difference, NNT: number needed to treat

4. Results (6)

Subgroup Analysis (Effect modification)

Interaction term → not significant (Pinteraction > 0.05)



4. Results (7)

Sensitivity Analysis (1): statin discontinuation gap from 3 months to 1 month

Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.92	(0.86, 0.97)	0.84	(0.76, 0.92)
Myocardial infarction	0.97	(0.88, 1.07)	0.86	(0.74, 1.01)
Heart failure	0.99	(0.90, 1.09)	0.82	(0.71, 0.95)
Stroke	0.82	(0.75, 0.89)	0.80	(0.70, 0.91)
Death	0.89	(0.83, 0.94)	0.72	(0.65, 0.80)
Myopathies	0.70	(0.54, 0.89)	0.57	(0.37, 0.87)
Liver dysfunction	0.96	(0.89, 1.04)	0.95	(0.84, 1.07)
75-84 years old				
Overall CVD	0.94	(0.89, 0.99)	0.86	(0.80, 0.93)
Myocardial infarction	0.86	(0.78, 0.94)	0.87	(0.75, 1.00)
Heart failure	0.94	(0.87, 1.01)	0.81	(0.72, 0.90)
Stroke	0.97	(0.90, 1.05)	0.91	(0.82, 1.01)
Death	0.87	(0.82, 0.91)	0.76	(0.70, 0.82)
Myopathies	1.07	(0.78, 1.46)	0.80	(0.46, 1.40)
Liver dysfunction	0.92	(0.85, 1.00)	0.93	(0.82, 1.05)
≥85 years old				
Overall CVD	0.88	(0.79, 0.99)	0.85	(0.74, 0.97)
Myocardial infarction	0.88	(0.73, 1.07)	0.77	(0.60, 0.99)
Heart failure	0.94	(0.80, 1.09)	0.89	(0.74, 1.08)
Stroke	0.87	(0.74, 1.02)	0.79	(0.64, 0.98)
Death	0.89	(0.81, 0.98)	0.79	(0.70, 0.89)
Myopathies*	/	/	/	/
Liver dysfunction	0.92	(0.76, 1.10)	0.87	(0.68, 1.11)

4. Results (8)

Sensitivity Analysis (2): truncating the weights at 1st/99th percentile (not 5th/95th)

Same results as in the main analysis

	ITT Analysis		Per-protocol Analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.92	(0.86, 0.97)	0.65	(0.52, 0.82)
Myocardial infarction	0.97	(0.88, 1.07)	0.59	(0.38, 0.90)
Heart failure	0.99	(0.90, 1.09)	0.60	(0.41, 0.89)
Stroke	0.82	(0.75, 0.89)	0.70	(0.48, 1.01)
Death	0.89	(0.83, 0.94)	0.62	(0.47, 0.81)
Myopathies	0.70	(0.54, 0.89)	0.74	(0.26, 2.05)
Liver dysfunction	0.96	(0.89, 1.04)	0.72	(0.52, 1.01)
75-84 years old				
Overall CVD	0.94	(0.89, 0.99)	0.67	(0.57, 0.79)
Myocardial infarction	0.86	(0.78, 0.94)	1.15	(0.87, 1.53)
Heart failure	0.94	(0.87, 1.01)	0.53	(0.39, 0.72)
Stroke	0.97	(0.90, 1.05)	0.54	(0.41, 0.70)
Death	0.87	(0.82, 0.91)	0.76	(0.65, 0.90)
Myopathies	1.07	(0.78, 1.46)	0.56	(0.15, 2.05)
Liver dysfunction	0.92	(0.85, 1.00)	1.27	(0.99, 1.63)
≥85 years old				
Overall CVD	0.88	(0.79, 0.99)	0.57	(0.44, 0.72)
Myocardial infarction	0.88	(0.73, 1.07)	0.47	(0.30, 0.72)
Heart failure	0.94	(0.80, 1.09)	0.61	(0.42, 0.89)
Stroke	0.87	(0.74, 1.02)	0.52	(0.33, 0.82)
Death	0.89	(0.81, 0.98)	0.79	(0.64, 0.98)
Myopathies*	/	/	/	/
Liver dysfunction	0.92	(0.76, 1.10)	0.73	(0.45, 1.18)

4. Results (9)

Sensitivity Analysis (3): propensity score matching

Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
60-74 years old				
Overall CVD	0.90	(0.83, 0.98)	0.88	(0.76, 1.03)
Myocardial infarction	0.95	(0.83, 1.08)	0.90	(0.68, 1.18)
Heart failure	0.91	(0.80, 1.03)	0.81	(0.63, 1.04)
Stroke	0.88	(0.78, 0.99)	0.88	(0.70, 1.10)
Death	0.86	(0.79, 0.93)	0.80	(0.67, 0.95)
Myopathies	0.89	(0.63, 1.23)	0.78	(0.40, 1.50)
Liver dysfunction	0.89	(0.81, 0.99)	0.82	(0.66, 1.01)
75-84 years old				
Overall CVD	0.93	(0.87, 1.00)	0.85	(0.75, 0.97)
Myocardial infarction	0.85	(0.75, 0.97)	0.99	(0.78, 1.27)
Heart failure	0.95	(0.85, 1.05)	0.79	(0.64, 0.97)
Stroke	0.96	(0.87, 1.06)	0.85	(0.71, 1.03)
Death	0.85	(0.80, 0.92)	0.79	(0.68, 0.91)
Myopathies	1.24	(0.80, 1.93)	0.41	(0.17, 0.99)*
Liver dysfunction	0.90	(0.81, 1.00)	1.15	(0.92, 1.43)
≥85 years old				
Overall CVD	0.81	(0.69, 0.93)	0.68	(0.54, 0.85)
Myocardial infarction	0.87	(0.67, 1.13)	0.70	(0.47, 1.06)
Heart failure	0.94	(0.76, 1.16)	0.81	(0.57, 1.14)
Stroke	0.72	(0.58, 0.89)	0.51	(0.36, 0.71)
Death	0.86	(0.76, 0.97)	0.83	(0.66, 1.04)
Myopathies*	/	/	/	/
Liver dysfunction	0.84	(0.65, 1.08)	0.65	(0.42, 1.00)

4. Results (10)

Sensitivity Analysis (4): predicted 10-year CVD risk score (>7·5%) by the Framingham Risk Score when identifying the patients eligible for statin therapy, instead of using the LDL-cholesterol threshold

Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.92	(0.86, 0.97)	0.86	(0.79, 0.94)
Myocardial infarction	0.96	(0.88, 1.06)	0.89	(0.76, 1.03)
Heart failure	1.00	(0.91, 1.10)	0.86	(0.75, 0.99)
Stroke	0.82	(0.75, 0.89)	0.82	(0.72, 0.93)
Death	0.90	(0.85, 0.96)	0.78	(0.71, 0.87)
Myopathies	0.70	(0.55, 0.89)	0.62	(0.40, 0.95)
Liver dysfunction	0.98	(0.91, 1.06)	0.95	(0.84, 1.07)
75-84 years old				
Overall CVD	0.95	(0.90, 1.00)	0.87	(0.81, 0.93)
Myocardial infarction	0.88	(0.80, 0.96)	0.91	(0.80, 1.05)
Heart failure	0.94	(0.88, 1.02)	0.81	(0.73, 0.91)
Stroke	0.97	(0.90, 1.04)	0.89	(0.81, 0.99)
Death	0.88	(0.84, 0.93)	0.79	(0.73, 0.86)
Myopathies	1.12	(0.83, 1.50)	0.83	(0.49, 1.43)
Liver dysfunction	0.94	(0.87, 1.02)	0.98	(0.87, 1.10)
≥85 years old				
Overall CVD	0.94	(0.84, 1.04)	0.87	(0.76, 0.99)
Myocardial infarction	0.91	(0.75, 1.09)	0.74	(0.58, 0.95)
Heart failure	1.01	(0.87, 1.16)	0.91	(0.76, 1.09)
Stroke	0.93	(0.80, 1.08)	0.79	(0.65, 0.97)
Death	0.91	(0.84, 1.00)	0.83	(0.74, 0.93)
Myopathies*	/	/	/	/
Liver dysfunction	0.95	(0.80, 1.14)	0.91	(0.72, 1.15)

4. Results (11)

Sensitivity Analysis (5): excluding participants who experienced the outcome incidence within the first year of follow-up

Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.89	(0.83, 0.96)	0.79	(0.71, 0.87)
Myocardial infarction	0.95	(0.85, 1.06)	0.83	(0.70, 0.99)
Heart failure	1.00	(0.90, 1.10)	0.81	(0.69, 0.96)
Stroke	0.79	(0.71, 0.87)	0.73	(0.62, 0.85)
Death	0.90	(0.84, 0.96)	0.73	(0.65, 0.81)
Myopathies	0.77	(0.60, 0.99)	0.55	(0.36, 0.86)
Liver dysfunction	0.94	(0.86, 1.03)	0.84	(0.73, 0.97)
75-84 years old				
Overall CVD	0.89	(0.84, 0.95)	0.74	(0.67, 0.80)
Myocardial infarction	0.83	(0.75, 0.92)	0.83	(0.71, 0.97)
Heart failure	0.94	(0.86, 1.02)	0.74	(0.65, 0.84)
Stroke	0.88	(0.81, 0.96)	0.71	(0.62, 0.81)
Death	0.85	(0.80, 0.90)	0.74	(0.68, 0.81)
Myopathies	1.10	(0.79, 1.53)	0.90	(0.52, 1.55)
Liver dysfunction	0.91	(0.83, 0.99)	0.95	(0.83, 1.09)
≥85 years old				
Overall CVD	0.84	(0.74, 0.96)	0.70	(0.59, 0.83)
Myocardial infarction	0.88	(0.71, 1.09)	0.66	(0.49, 0.89)
Heart failure	0.88	(0.74, 1.06)	0.75	(0.59, 0.95)
Stroke	0.85	(0.70, 1.02)	0.68	(0.52, 0.88)
Death	0.90	(0.81, 1.00)	0.79	(0.69, 0.91)
Myopathies*	/	/	/	/
Liver dysfunction	0.94	(0.76, 1.15)	0.89	(0.67, 1.19)

4. Results (12)

Sensitivity Analysis (6): censoring the patients 2 years after their last visits

Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.92	(0.86, 0.97)	0.85	(0.78, 0.93)
Myocardial infarction	0.98	(0.89, 1.08)	0.90	(0.78, 1.04)
Heart failure	0.99	(0.90, 1.09)	0.85	(0.75, 0.98)
Stroke	0.82	(0.75, 0.89)	0.80	(0.70, 0.90)
Death	0.89	(0.83, 0.94)	0.75	(0.68, 0.82)
Myopathies	0.70	(0.54, 0.89)	0.55	(0.37, 0.82)
Liver dysfunction	0.96	(0.89, 1.04)	0.91	(0.81, 1.02)
75-84 years old				
Overall CVD	0.94	(0.89, 0.99)	0.86	(0.80, 0.92)
Myocardial infarction	0.86	(0.78, 0.94)	0.87	(0.76, 0.99)
Heart failure	0.93	(0.87, 1.01)	0.81	(0.72, 0.90)
Stroke	0.97	(0.90, 1.05)	0.89	(0.81, 0.98)
Death	0.87	(0.82, 0.91)	0.78	(0.72, 0.84)
Myopathies	1.06	(0.77, 1.45)	0.92	(0.57, 1.51)
Liver dysfunction	0.92	(0.85, 1.00)	0.97	(0.87, 1.08)
≥85 years old				
Overall CVD	0.89	(0.79, 0.99)	0.81	(0.71, 0.93)
Myocardial infarction	0.89	(0.73, 1.07)	0.73	(0.57, 0.94)
Heart failure	0.94	(0.81, 1.09)	0.88	(0.73, 1.06)
Stroke	0.87	(0.74, 1.02)	0.74	(0.60, 0.91)
Death	0.89	(0.81, 0.98)	0.80	(0.71, 0.90)
Myopathies*	/	/	/	/
Liver dysfunction	0.92	(0.76, 1.10)	0.89	(0.71, 1.13)

4. Results (13)

Sensitivity Analysis (7): additionally adjusting for competing risk in the ITT analysis, not just per-protocol

Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.91	(0.86, 0.97)	0.86	(0.78, 0.93)
Myocardial infarction	0.96	(0.87, 1.06)	0.90	(0.77, 1.04)
Heart failure	0.99	(0.90, 1.09)	0.85	(0.74, 0.98)
Stroke	0.81	(0.74, 0.89)	0.80	(0.71, 0.91)
Death	0.89	(0.83, 0.94)	0.75	(0.68, 0.83)
Myopathies	0.68	(0.53, 0.88)	0.53	(0.35, 0.80)
Liver dysfunction	0.98	(0.90, 1.06)	0.91	(0.81, 1.02)
75-84 years old				
Overall CVD	0.94	(0.89, 0.99)	0.86	(0.80, 0.92)
Myocardial infarction	0.86	(0.78, 0.95)	0.87	(0.76, 1.00)
Heart failure	0.93	(0.86, 1.00)	0.80	(0.72, 0.89)
Stroke	0.97	(0.90, 1.04)	0.89	(0.81, 0.99)
Death	0.87	(0.82, 0.91)	0.78	(0.72, 0.84)
Myopathies	1.04	(0.74, 1.46)	0.89	(0.54, 1.47)
Liver dysfunction	0.92	(0.84, 1.00)	0.97	(0.87, 1.09)
≥85 years old				
Overall CVD	0.90	(0.81, 1.01)	0.81	(0.71, 0.92)
Myocardial infarction	0.93	(0.75, 1.15)	0.73	(0.57, 0.93)
Heart failure	0.97	(0.83, 1.14)	0.86	(0.72, 1.04)
Stroke	0.88	(0.74, 1.05)	0.75	(0.61, 0.93)
Death	0.89	(0.81, 0.98)	0.80	(0.71, 0.91)
Myopathies*	/	/	/	/
Liver dysfunction	0.83	(0.68, 1.01)	0.89	(0.70, 1.12)

4. Results (14)

Sensitivity Analysis (8): adopting multiple imputation for handling the missing value of the covariates at baseline

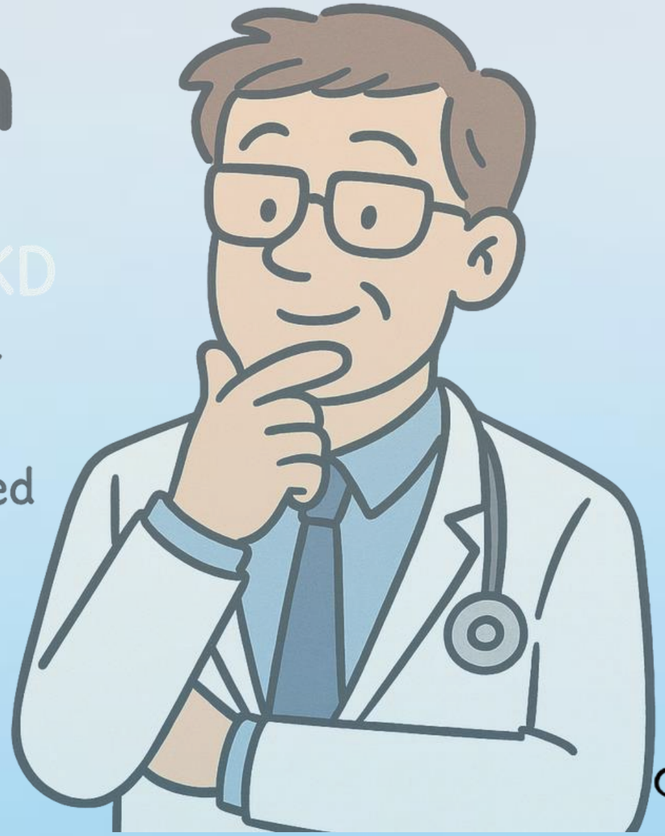
Same results as in the main analysis

	ITT analysis		Per-protocol analysis	
	Hazard ratio	95% CI	Hazard ratio	95% CI
60-74 years old				
Overall CVD	0.93	(0.88, 0.97)	0.88	(0.82, 0.94)
Myocardial infarction	0.98	(0.91, 1.05)	0.95	(0.84, 1.07)
Heart failure	0.97	(0.90, 1.04)	0.83	(0.74, 0.93)
Stroke	0.86	(0.80, 0.92)	0.84	(0.76, 0.93)
Death	0.89	(0.85, 0.93)	0.74	(0.69, 0.81)
Myopathies	0.84	(0.70, 1.00)	0.74	(0.54, 1.01)
Liver dysfunction	0.97	(0.91, 1.03)	0.93	(0.85, 1.03)
75-84 years old				
Overall CVD	0.92	(0.88, 0.96)	0.87	(0.82, 0.93)
Myocardial infarction	0.85	(0.79, 0.92)	0.90	(0.81, 1.01)
Heart failure	0.91	(0.86, 0.97)	0.79	(0.72, 0.87)
Stroke	0.93	(0.88, 0.99)	0.89	(0.81, 0.97)
Death	0.86	(0.83, 0.90)	0.76	(0.71, 0.81)
Myopathies	0.90	(0.70, 1.16)	0.70	(0.45, 1.07)
Liver dysfunction	0.92	(0.87, 0.98)	0.91	(0.82, 1.00)
≥85 years old				
Overall CVD	0.92	(0.84, 1.01)	0.89	(0.80, 0.99)
Myocardial infarction	0.90	(0.78, 1.05)	0.83	(0.68, 1.02)
Heart failure	0.89	(0.79, 1.01)	0.84	(0.71, 0.98)
Stroke	0.93	(0.82, 1.06)	0.87	(0.74, 1.03)
Death	0.87	(0.81, 0.94)	0.76	(0.69, 0.84)
Myopathies*	/	/	/	/
Liver dysfunction	0.98	(0.86, 1.13)	0.95	(0.78, 1.14)

Discussion

Statin therapy in older adults with CKD

- Reduced cardiovascular events and mortality
- Greater benefit observed with increasing age
- No increased risk of adverse effects



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5. Discussion (1)

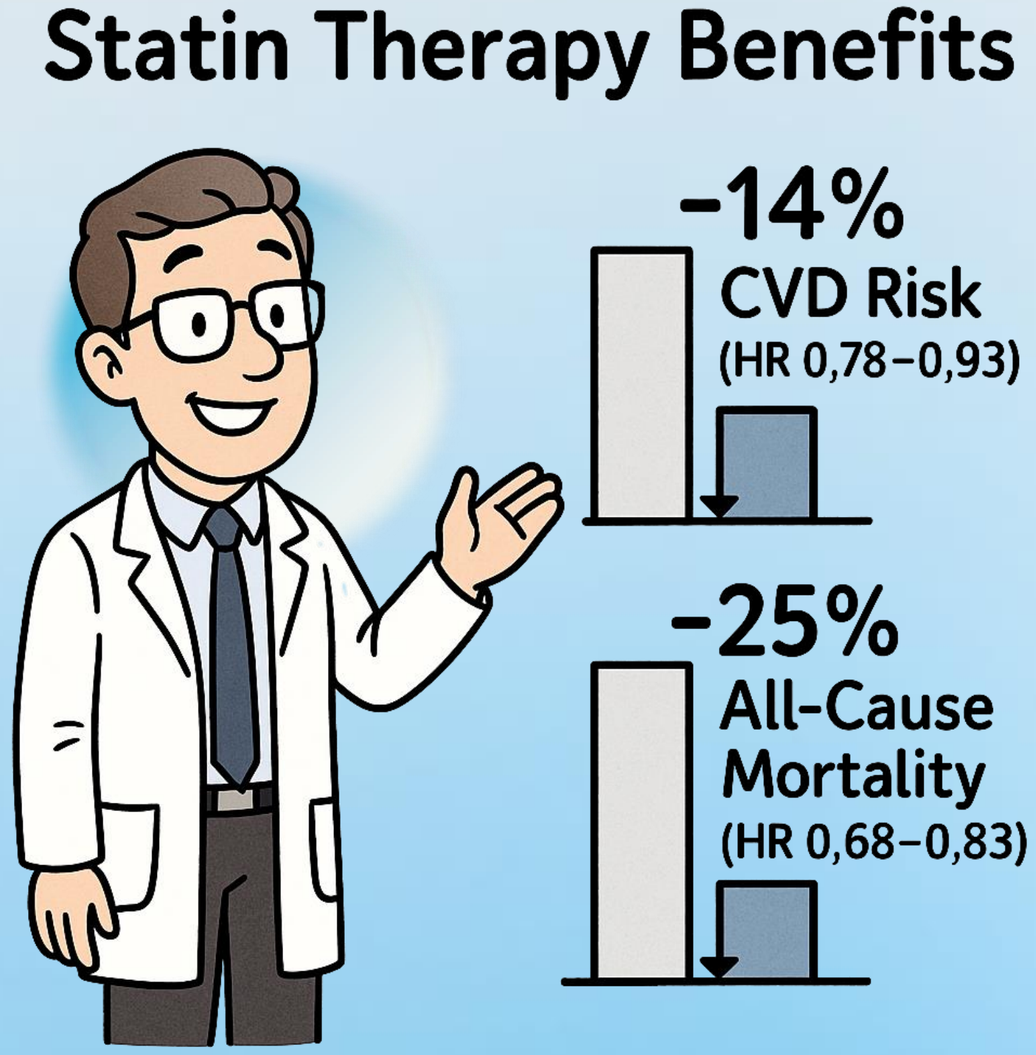
Effectiveness of statins

- Statin therapy significantly reduced:
  - Cardiovascular events (HR ~0.88–0.94 across age groups)
  - All-cause mortality (HR ~0.75–0.89)
- Per-protocol NNT over 5 years:
  - Age 60–74: NNT = 41
  - Age 75–84: NNT = 23
  - Age ≥85: NNT = 12

(Greater benefit in older age due to higher baseline risk)

Comparison with Prior Evidence

- Findings aligned with the JUPITER trial in older patients (eGFR <60)
- Builds upon a previous US target trial emulation, which had:
  - Weaker evidence for CVD reduction in ≥75 years (possibly underpowered)
- First study to assess statins for primary prevention in ≥85-year-old CKD population



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5. Discussion (2)

Mechanistic Insights

- Statins benefit older CKD patients via:
  - Lipid-lowering
  - Anti-inflammatory and antioxidant effects
- CKD is associated with:
  - Inflammation
  - Oxidative stress
  - Accelerated vascular ageing
- ➤ Statins may help delay progression and reduce complications

Safety Profile

- No increased risk of:
  - Myopathies (few cases, even in the ≥85 group)
  - Liver dysfunction
- Results supported by prior RCTs and meta-analyses
- Confirms statin safety in real-world, older CKD patients

6. Strengths and Limitations (1)

Strengths

- **Real-World, Long-Term Data**
  - Population-based data covering >10 years
  - Large sample size (N= 711,966) enhances external validity
- **Accurate Target Trial Emulation**
  - Per-protocol analysis incorporated time-varying confounders
  - Accounted for adherence to statin therapy
- **Consistency with RCTs**
  - Findings align with the JUPITER trial and other major studies
  - Supports the validity of the emulated trial design

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6. Strengths and Limitations (2)

Limitations

1. **Unmeasured Confounders**
   a. Diet, physical activity, and CKD duration were not captured
2. **Misclassification Bias**
   a. Based on ICD-9/ International Classification of Primary Care 2nd revision (ICPC-2 codes)
3. **Lack of Statin Dose Info**
   a. Study reflects mostly low/moderate intensity statins
   b. No data on dose-response effects
4. **Missing Revascularisation Data**
   a. PCI/CABG not included in outcomes
5. **Missing Data & Selection Bias**
   a. 34.5% person-trials excluded (complete case analysis)
   b. Sensitivity analysis with multiple imputation showed consistent results
6. **LOCF for Time-varying Covariates**
   a. May not fully reflect changing patient status
7. **Monthly Data Limit**
   a. Unable to detect intermittent statin use
8. **Generalizability**
   - Based on data from the Hong Kong Hospital Authority

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7. Conclusion

- Statins therapy is effective and safe for the primary prevention of cardiovascular disease and all-cause mortality in older adults (≥74 years) with chronic kidney disease.
- These findings support the use of statins in real-world settings, including very old patients (≥85 years), without increasing the risk of major adverse events such as myopathy or liver dysfunction.

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Thank you so much!