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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Summary

Background There remains a scarcity of evidence on initiating statin therapy for the primary prevention of cardiovascular diseases among older adults with chronic kidney disease due to the under-representation of this population in randomised controlled trials. This study aimed to evaluate the effectiveness and safety of using statin therapy for the primary prevention of cardiovascular diseases in older adults (aged 75–84 years) and very old adults (aged ≥85 years) with chronic kidney disease.

Methods Using territory-wide public electronic health records in Hong Kong, patients older than 60 years with chronic kidney disease and with hyperlipidaemia (defined as elevated LDL cholesterol of ≥2·6 mmol/L) were identified for inclusion in the analyses and were included on a rolling basis in each calendar month from January, 2008, to December, 2015. Patients were categorised into different age groups (ie, 60–74 years, 75–84 years, and ≥85 years) for analysis, and the 60–74 years age group was used as a benchmark group to test the validity of our emulated trial since the effect of statin therapy is well established in this age group. The framework of target trial emulation was adopted to investigate the association between statin therapy and the risk of overall cardiovascular disease incidence, specific cardiovascular disease subtypes (ie, myocardial infarction, heart failure, and stroke), and all-cause mortality, as well as major adverse events (ie, myopathies and liver dysfunction). The primary outcome was overall cardiovascular disease incidence. The hazard ratios for the outcomes were estimated by pooled logistic models in the intention-to-treat analysis and the per-protocol analysis.

Findings 711 966 person-trials from 96 trials were eligible for inclusion in the study. 19 423 unique individuals with chronic kidney disease aged 60–74 years, 22 565 unique individuals with chronic kidney disease aged 75–84 years, and 8811 unique individuals with chronic kidney disease aged 85 years and older were identified for inclusion in the analyses. In patients aged 75–84 years, a significant risk reduction was observed for overall cardiovascular disease incidence in both the intention-to-treat analysis (hazard ratio [HR] 0·94 [95% CI 0·89–0·99]) and in the per-protocol analysis (0·86 [0·80–0·92]) and for all-cause mortality (0·87 [0·82–0·91] in the intention-to-treat analysis and 0·78 [0·72–0·84] in the per-protocol analysis). This risk reduction was also observed among patients aged 85 years and older for cardiovascular diseases (HR 0·88 [0·79–0·99] in the intention-to-treat analysis and 0·81 [0·71–0·92] in the per-protocol analysis), and for all-cause mortality (0·89 [0·81–0·98] in the intention-to-treat analysis and 0·80 [0·71–0·91] in the per-protocol analysis). Substantial risk reduction for myocardial infarction, heart failure, and stroke were also observed across all age groups. No significantly increased risk of myopathies or liver dysfunction was observed in any of the age groups.

Interpretation Statin therapy is beneficial for hypercholesterolemic older patients with chronic kidney disease aged 75 years and older regarding the primary prevention against cardiovascular diseases and all-cause mortality, without posing an increased risk of major adverse events. The benefits and safety persist in those aged 85 years and older.

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Introduction

Chronic kidney disease is a prevalent condition around the world, and its prevalence is known to increase with age.[1] In the UK, chronic kidney disease affects 32·7% of individuals aged older than 75 years.[2] In the USA, chronic kidney disease is common in people aged 65 years or older (34%).[3] The prevalence of chronic kidney disease has been reported to be 29·7% in patients with type 2 diabetes in Hong Kong,[4] where the incidence rate of chronic kidney disease is around 22 per 1000 person-years among patients with hypertension.[5] Patients with chronic kidney disease have a high risk of cardiovascular disease.[6] Statins are extensively used to

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For the Chinese translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

We searched PubMed and Embase for articles published from database inception to Jan 4, 2024, using the search terms "statin", "chronic kidney disease", "primary prevention", "old adults", "very-old adults", and "cardiovascular diseases". Despite the substantial evidence on the benefits and safety of statin use in patients with chronic kidney disease, there is a noticeable scarcity of studies focusing on older patients with chronic kidney disease, particularly those older than 75 years. Although a systematic review and meta-analysis revealed that statin use reduced the risk of major cardiovascular events in patients older than 65 years, the specific effect of statins for primary prevention in individuals aged older than 75 years remains unknown. In a cohort study, subgroup analyses found that statin use was associated with a reduced risk of all-cause mortality but not cardiovascular disease in patients with chronic kidney disease who were older than 75 years. Regarding the safety profile, two systematic reviews with meta-analyses have provided evidence that the risks of liver dysfunction in patients with chronic kidney disease treated with statins are comparable to patients treated without statins. Additionally, a randomised controlled trial reported similar results regarding the occurrence of myopathy. However, these findings are limited due to small sample sizes and strict eligibility criteria in the randomised controlled trials, which often excluded patients older than 75 years or 85 years.

Add value of this study

The potential benefits and safety of using statins for primary prevention in patients with chronic kidney disease who are hypercholesterolemic with advanced age remained inconclusive in previous studies. Using population-based public electronic health records in Hong Kong, we found statin therapy to be beneficial in terms of reducing the risk of cardiovascular diseases and all-cause mortality in older patients with chronic kidney disease who are hypercholesterolemic, without posing any additional risk of major adverse events. These findings extend the existing evidence on the use of statins for primary prevention in patients with chronic kidney disease aged 75 years and older, who are generally underrepresented in randomised controlled trials.

Implications of all the available evidence

Patients with chronic kidney disease are typically at an elevated risk of developing cardiovascular disease, especially those with advanced age and with hypercholesteremia. Our study further confirms the benefits and safety of statin use for primary prevention in this population. The findings support the prescription of statin use for primary prevention in older patients with chronic kidney disease who are hypercholesterolemic. Further studies across diverse ethnic groups are essential to inform clinical practice worldwide.

mitigate the risk of cardiovascular diseases in patients with chronic kidney disease.[7] However, there is no consensus regarding the use of statin therapy for primary prevention in patients with chronic kidney disease aged 75 years and older. The 2018 American College of Cardiology and the American Heart Association guidelines recommend statin use for adults aged 40–75 years with chronic kidney disease and who have a 10-year cardiovascular disease risk of 7·5% or higher, but these guidelines do not address adults aged older than 75 years.[8] The 2023 National Institute for Health and Care Excellence guideline recommends atorvastatin 20 mg daily for the primary prevention of cardiovascular disease in people with chronic kidney disease, without age restrictions.[9] The Kidney Disease: Improving Global Outcomes clinical practice guideline also recommends statin treatment in patients with chronic kidney disease aged 50 years and older but lacks specific recommendations on old patients (aged 75–84 years) and very old patients (aged 85 years and older).[10]

The lack of consensus on statin therapy for primary prevention in older people with chronic kidney disease could be due to the inconclusive evidence in this population, who have generally been under-represented in randomised controlled trials (RCTs). Subgroup analyses from a systematic review and meta-analysis of 48 429 patients with chronic kidney disease reported that statin use reduced the risk of major cardiovascular events in patients aged older than 65 years (relative risk 0·78, 95% CI 0·61–0·99), whereas the effect for primary prevention among those aged older than 75 years remained unknown.[11] A cohort study including 14 828 individuals aged older than 65 years showed that statin initiation was significantly associated with a reduction in all-cause mortality (hazard ratio [HR] 0·91, 95% CI 0·85–0·97) but not major adverse cardiovascular events (0·96, 0·91–1·02), and a similar pattern was observed in the subgroup analysis for adults aged older than 75 years.[12] More importantly, both advanced age (ie, >75 years) and renal dysfunction have been shown to be predisposing factors for the development of the adverse event of myopathy.[13] Previous RCTs have shown non-significant differences in adverse events among statin users and non-users with chronic kidney disease,[14] but the results might be limited by small sample sizes and strict eligibility criteria. To the best of our knowledge, there remains a lack of evidence on adverse outcomes of statin therapy in patients with chronic kidney disease with advanced age. The inconclusive evidence underscores the need for additional studies to inform the guidelines regarding the use of statins in older adults with chronic kidney disease.

To address these gaps in knowledge, we used real-world electronic health records to emulate a sequence of target trials[15,16] to investigate the long-term effectiveness and safety of statin therapy for the primary prevention of cardiovascular diseases in older patients with chronic kidney disease who are hypercholesterolemic.

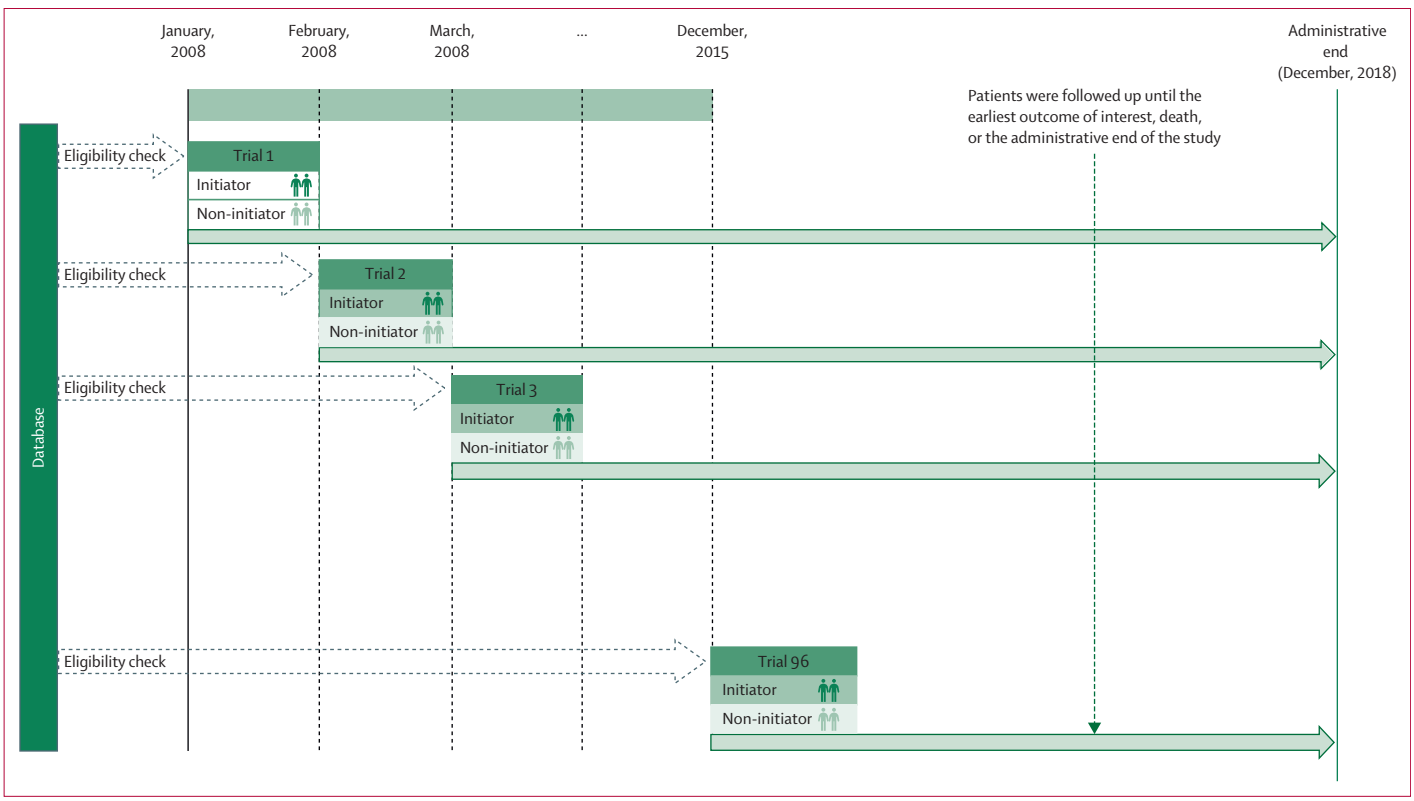

Figure 1: **Illustration of sequential trial emulation study**
In total, there were 96 target trials emulated, where the same eligibility criteria were applied in each calendar month from January, 2008 to December, 2015. The data from these 96 trials were pooled into one single model for each age group. Patients were followed up until the outcome of interest, death, or the administrative end of the study (Dec 31, 2018), whichever occurred first.

Method

Study design and participants

To examine the relationship between statin therapy and the risk of cardiovascular disease incidence, a sequence of nested target trials was emulated using electronic health records from the Hong Kong Hospital Authority (appendix 2 p 1). The Hong Kong Hospital Authority manages the majority of public clinics and hospitals in Hong Kong. According to the Hong Kong Population Census report, about 90% of the population is of Chinese ethnicity, with the non-Chinese population primarily including Filipinos, Indonesians, and South Asians.[17,18] The electronic health record database used for data retrieval has undergone validation in previous research, showing high accuracy in diagnosing myocardial infarctions and stroke, with reported positive predictive values of 85·4% (95% CI 78·8–90·6) and 91·1% (83·2–96·1), respectively.[19] The framework of target trial emulation in pharmacoepidemiology studies can help to mitigate the potential immortal time bias and prevalent user bias by aligning time zero with the point at which treatment eligibility is met and treatment strategy is assigned, and can account for time-varying confounding in estimating the causal effect.[15,20] Figure 1 shows the study design of our emulated target trials. Patients with chronic kidney disease older than 60 years with hyperlipidaemia (defined as elevated LDL cholesterol of ≥2·6 mmol/L)[21] were eligible to participate and were included on a rolling basis in each calendar month from January, 2008, to December, 2015. We included patients with a diagnosis of chronic kidney disease (ICD-9 585–86) at or before baseline or with a latest recorded estimated glomerular filtration rate of less than 60 mL per min/1·73m^2 within 3 years before baseline. Eligible patients were required to have at least one follow-up visit after baseline. For the treatment group, only new users with statin prescription records were included in the trial of each calendar month, whereas patients with previous prescription records for statins were excluded. The individuals who contributed to the treatment group were no longer eligible for a subsequent trial. However, the individuals who did not initiate statin therapy on a given calendar month could be eligible for subsequent trials. Patients were categorised into different age groups (ie, 60–74 years, 75–84 years, and ≥85 years) for analysis, and the group of adults aged 60–74 years was used as a benchmark to test the validity of our emulated trial since the effect of statin therapy is well established in this age group.[22] In total, there were 96 emulated trials in each age group.

See Online for appendix 2

Patients who had used statins before baseline or other lipid drugs at or before baseline were excluded from the analysis. Patients with a history of cardiovascular diseases

and patients with contraindications (ie, myopathies and liver dysfunction) at or before baseline were excluded. Patients with acute kidney injury were also excluded to minimise the risk of unmeasured confounding.[23]

The study was approved by the Institutional Review Board of The University of Hong Kong—the HA Hong Kong West Cluster (reference number UW 19-362) and conforms to the principles outlined in the Declaration of Helsinki. Since all data used in this study were anonymised and obtained from the electronic health records from the Hong Kong Hospital Authority, patients' consent to participate was not required.

Definition of exposure, outcomes, and follow-up period

Statin therapy was defined as treatment with simvastatin, atorvastatin, fluvastatin, rosuvastatin, lovastatin, pitavastatin, or pravastatin. The date of dispensing in the prescription record was used to define the start of statin treatment. The outcomes of interest included the overall incidence of cardiovascular diseases, specific cardiovascular disease subtypes (ie, myocardial infarction, heart failure, and stroke), all-cause mortality, and major adverse events (ie, myopathies and liver dysfunction). Case definitions were based on the International Classification of Primary Care, 2nd edition (ICPC-2) and the ICD 9th revision, Clinical Modification (ICD-9-CM) or on relevant clinical parameters (appendix 2 p 2). Patients were followed up until the outcome of interest, death, or the administrative end of the study (Dec 31, 2018), whichever occurred first.

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, total cholesterol, and estimated glomerular filtration rate); the Charlson Comorbidity Index; the presence of comorbidities (yes or no; hypertension, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, atrial fibrillation, dementia, and obesity); medication use within 1 year before baseline (yes or no) including aspirin, insulin, oral antidiabetic drugs, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker, β-blocker, calcium channel blockers, and diuretics; service use within 1 year before baseline (yes or no) including specialist outpatient clinic attendance and hospitalisation admission date; and smoking status (yes or no).

The per-protocol analysis compared risks for outcomes of interest between continuous statin users and those who never used statins during the follow-up period; the person-trials were artificially censored when the patient deviated from their assigned strategy unless the patient developed an indication or contraindication for statin therapy (appendix 2 pp 3–4). To ascertain continuous statin use, a 3-month period was used to confirm statin discontinuation, whereby patients were censored 3 months after the end of their statin prescription if it was not followed by another refill prescription. To adjust for selection bias resulting from the artificial censoring process, each person-trial was weighted at each timepoint by the inverse probability of receiving their assigned treatment strategy, conditional on baseline and time-varying covariates. A pooled logistic model was fitted to predict the probability of receiving statin therapy at each timepoint. The time-varying covariates used in this model included lifestyle behaviours, clinical parameters, comorbidities, drug use, and service use, as detailed above. The last observation carried forward (LOCF) method was used to handle the missing values of the time-varying clinical parameters during the follow-up period.[16,25] To adjust for potential bias arising from the competing event (ie, death in the present study), competing risk adjustment was performed in the per-protocol analysis, in which each person-trial additionally received a time-varying inverse probability weight of not dying. The estimated weights were truncated at the 5th and 95th percentile to avoid the influence of outliers. Finally, a pooled logistic model was fitted to estimate the HR for the outcomes between the continuous statin therapy and never using statins during the follow-up period, which includes the indicators of the assigned treatment strategy, month of follow-up (linear and quadratic term), and baseline covariates, with adjustment of stabilised weights. Additional details regarding the per-protocol analysis can be found in appendix 2 (pp 3–4). We estimated the absolute risk of outcome incidence by fitting the aforementioned pooled logistic model for the causal effect estimation, incorporating the added product terms between treatment indicator and time (linear and quadratic terms). The number needed to treat to prevent one additional cardiovascular disease event was calculated based on the estimated 5-year risk difference and 10-year risk difference of overall cardiovascular disease. The number needed to treat is calculated as the reciprocal of the estimated absolute risk reduction.

A complete case analysis was conducted for the emulated trials, for which patients with incomplete data for the study variables were excluded. Subgroup analyses were conducted based on sex, Charlson Comorbidity Index (≤8 or >8), and the chronic kidney disease stage at baseline (stage 1–3, stage 4, and stage 5). An interaction term between the treatment indicator and the subgroup identifier was fitted to test the difference in outcomes across patient subgroups. Several sensitivity analyses were conducted to test the robustness of the results, including: (1) shortening the gap for the ascertainment of statin discontinuation from 3 months to 1 month in the per-protocol analysis; (2) truncating the

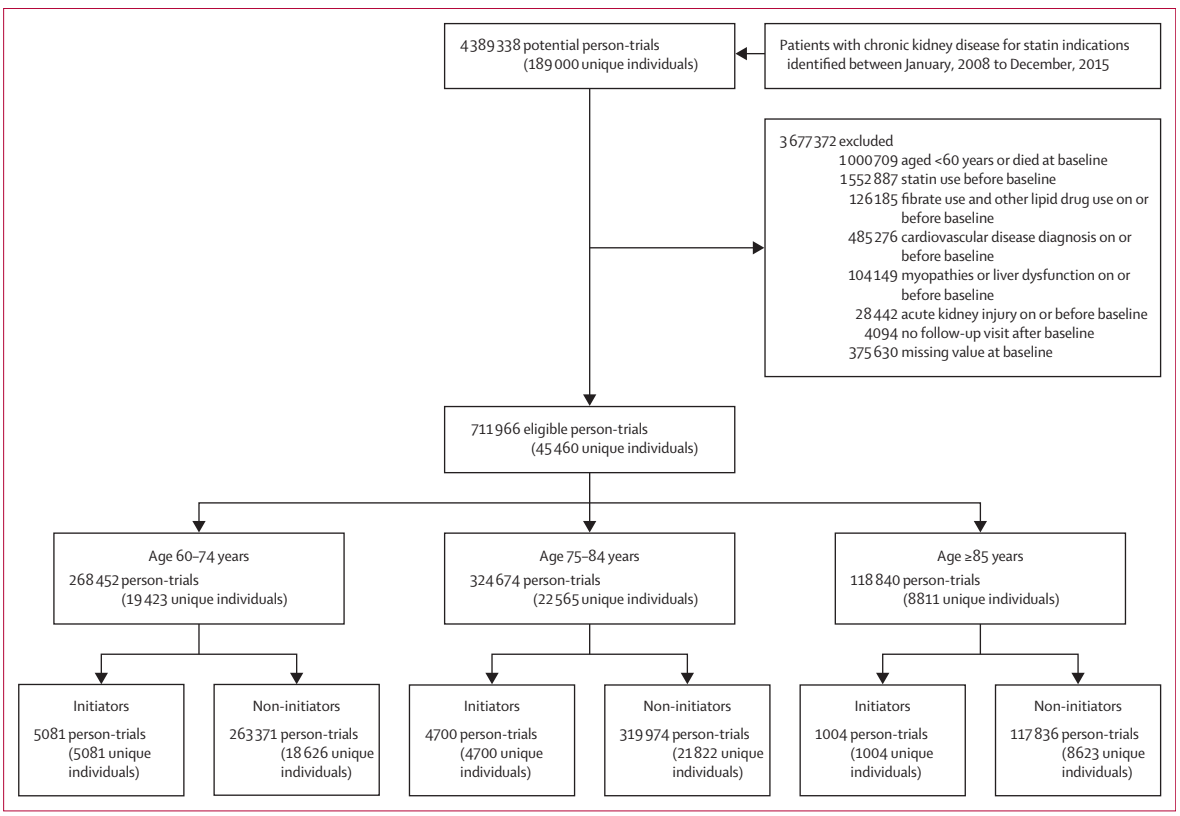

Figure 2: **Flowchart of person-trials in the analysis**
The number of the individuals in the parentheses do not sum to the total number of unique individuals because some eligible individuals contributed to different groups in different emulated trials.

weight at the 1st and 99th percentile in the per-protocol analysis; (3) adopting propensity score matching for baseline covariates, for which the initiators and non-initiators were matched in a 1:1 ratio within each age group (nearest neighbour propensity score matching without replacement, caliper value 0·2 times the standard deviation of the propensity score); (4) using the predicted 10-year cardiovascular disease risk score (>7·5%) by the Framingham Risk Score when identifying the patients eligible for statin therapy, instead of using the LDL-cholesterol threshold;[26] (5) excluding participants who had the outcome within the first year of follow-up to minimise the potential unmeasured confounding by undiagnosed diseases; (6) removing the exclusion criteria requiring at least one follow-up visit during the follow-up period, and instead censoring patients 2 years after their last visits to the local health system and additionally applying the weights for censoring due to the loss of follow-up; (7) conducting competing risk adjustment in the intention-to-treat analysis; and (8) performing multiple imputation using chained equation[27] to handle missing data on the covariates at baseline; estimates were then pooled using Rubin's rule across the five sets of imputations.[28]

All analyses were performed in Stata/MP 17.0. Statistical significance was defined as a two-tailed p-value of <0·05. A post-hoc power analysis was performed in Power Analysis & Sample Size software to test whether the sample size was sufficient for the emulated target trial in each age group, with a significance level set at 0·05 (appendix 2 p 4).[29]

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
711 966 person-trials from 96 trials were eligible for the study, with 268 452 person-trials (19 423 unique individuals) aged 60–74 years, 324 674 person-trials (22 565 unique individuals) aged 75–84 years and 118 840 person-trials (8811 unique individuals) 85 years or older (figure 2). 34·5% of person-trials were excluded from the analysis due to the incomplete information on the baseline covariates. The number of eligible person-trials and statin initiators in each trial is shown in appendix 2 (pp 5–7). The mean Charlson Comorbidity Index (initiators *vs* non-initiators) was 6·3 (SD 1·9) versus 5·4 (2·1) in the patients aged 60–74 years, 7·3 (2·0) versus 6·5 (2·0) in those aged 75–84 years, and 7·7 (1·9) versus 6·8 (1·9) in those aged 85 years and older (table).

	Aged 60–74 years (N=268 452)		Aged 75–84 years (N=324 674)		Aged ≥85 years (N=118 840)	
	Initiator (n=5081)	Non-initiator (n=263 371)	Initiator (n=4700)	Non-initiator (n=319 974)	Initiator (n=1004)	Non-initiator (n=117 836)
Age, years	68·6 (4·3)	68·9 (4·3)	79·6 (2·8)	79·9 (2·8)	88·1 (2·5)	88·7 (3·0)
Sex						
Male	2491 (49·0%)	119 728 (45·5%)	1872 (39·8%)	121 910 (38·1%)	307 (30·6%)	33 970 (28·8%)
Female	2590 (51·0%)	143 643 (54·5%)	2828 (60·2%)	198 064 (61·9%)	697 (69·4%)	83 866 (71·2%)
Smoking	258 (5·1%)	11 353 (4·3%)	158 (3·4%)	9877 (3·1%)	21 (2·1%)	2174 (1·8%)
Blood pressure						
Systolic	151·2 (18·8)	149·7 (18·2)	153·0 (17·9)	152·1 (17·6)	154·5 (18·9)	152·9 (17·9)
Diastolic	81·2 (10·7)	80·6 (10·4)	77·3 (10·0)	77·1 (10·0)	75·6 (10·0)	75·0 (10·0)
Fasting glucose	7·3 (2·6)	6·5 (2·1)	6·8 (2·2)	6·2 (1·9)	6·5 (1·8)	5·9 (1·6)
Low density lipoprotein-cholesterol	3·9 (0·9)	3·5 (0·7)	3·9 (0·9)	3·4 (0·7)	3·9 (0·9)	3·4 (0·6)
Low density lipoprotein-cholesterol concentration						
<3·4 mmol/L	1611 (31·7%)	138 899 (52·7%)	1546 (32·9%)	176 029 (55·0%)	317 (31·6%)	66 634 (56·5%)
3·4–4·0 mmol/L	1692 (33·3%)	79 587 (30·2%)	1647 (35·0%)	95 619 (29·9%)	327 (32·6%)	34 710 (29·5%)
≥4·1 mmol/L	1778 (35·0%)	44 885 (17·0%)	1507 (32·1%)	48 326 (15·1%)	360 (35·9%)	16 492 (14·0%)
High density lipoprotein-cholesterol	1·3 (0·3)	1·3 (0·4)	1·3 (0·4)	1·4 (0·4)	1·4 (0·4)	1·4 (0·4)
High density lipoprotein-cholesterol concentration						
<1·3 mmol/L for females and <1 mmol/L for males	1834 (36·1%)	95 784 (36·4%)	1611 (34·3%)	110 893 (34·7%)	340 (33·9%)	37 092 (31·5%)
≥1·3 mmol/L for females and ≥1 mmol/L for males	3247 (63·9%)	167 587 (63·6%)	3089 (65·7%)	209 081 (65·3%)	664 (66·1%)	80 744 (68·5%)
Total cholesterol	6·0 (1·1)	5·5 (0·8)	5·9 (1·0)	5·5 (0·8)	6·0 (1·0)	5·5 (0·8)
Total cholesterol concentration						
<5·2 mmol/L	1096 (21·6%)	102 690 (39·0%)	1089 (23·2%)	129 813 (40·6%)	212 (21·1%)	47 784 (40·6%)
5·2–6·1 mmol/L	2134 (42·0%)	110 700 (42·0%)	2013 (42·8%)	135 241 (42·3%)	430 (42·8%)	50 552 (42·9%)
≥6·2 mmol/L	1851 (36·4%)	49 981 (19·0%)	1598 (34·0%)	54 920 (17·2%)	362 (36·1%)	19 500 (16·5%)
Estimated glomerular filtration rate	51·6 (15·0)	53·2 (15·1)	50·5 (13·3)	51·9 (14·7)	49·7 (13·3)	51·0 (12·9)
Chronic kidney disease stage						
Stages 1–3	4715 (92·8%)	247 095 (93·8%)	4382 (93·2%)	301 497 (94·2%)	931 (92·7%)	111 304 (94·5%)
Stage 4	287 (5·6%)	11 847 (4·5%)	271 (5·8%)	15 160 (4·7%)	64 (6·4%)	5708 (4·8%)
Stage 5	79 (1·6%)	4429 (1·7%)	47 (1·0%)	3317 (1·0%)	9 (0·9%)	824 (0·7%)
Comorbidities						
Charlson Comorbidity Index	6·3 (1·9)	5·4 (2·1)	7·3 (2·0)	6·5 (2·0)	7·7 (1·9)	6·8 (1·9)
Hypertension	4551 (89·6%)	236 920 (90·0%)	4412 (93·9%)	301 807 (94·3%)	945 (94·1%)	112 783 (95·7%)
Diabetes	3256 (64·1%)	105 185 (39·9%)	2853 (60·7%)	118 066 (36·9%)	552 (55·0%)	34 694 (29·4%)
Peripheral vascular disease	41 (0·8%)	1402 (0·5%)	57 (1·2%)	2205 (0·7%)	16 (1·6%)	995 (0·8%)
Chronic obstructive pulmonary disease	143 (2·8%)	9276 (3·5%)	244 (5·2%)	18 524 (5·8%)	69 (6·9%)	8315 (7·1%)
Atrial fibrillation	119 (2·3%)	6155 (2·3%)	200 (4·3%)	12 131 (3·8%)	54 (5·4%)	5990 (5·1%)
Dementia	29 (0·6%)	1240 (0·5%)	89 (1·9%)	7537 (2·4%)	41 (4·1%)	6340 (5·4%)
Obesity	2311 (45·5%)	103 071 (39·1%)	1831 (39·0%)	104 456 (32·6%)	310 (30·9%)	27 139 (23·0%)
Drug use						
Long-term aspirin use	622 (12·2%)	18 515 (7·0%)	811 (17·3%)	31 030 (9·7%)	190 (18·9%)	13 225 (11·2%)
Insulin	684 (13·5%)	21 470 (8·2%)	413 (8·8%)	16 590 (5·2%)	54 (5·4%)	3351 (2·8%)
Oral antidiabetic drugs	3076 (60·5%)	100 199 (38·0%)	2539 (54·0%)	105 420 (32·9%)	460 (45·8%)	28 076 (23·8%)
Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker	3210 (63·2%)	130 184 (49·4%)	2770 (58·9%)	139 482 (43·6%)	517 (51·5%)	45 251 (38·4%)
β-blocker	2457 (48·4%)	124 821 (47·4%)	2128 (45·3%)	136 699 (42·7%)	406 (40·4%)	43 119 (36·6%)
Calcium channel blockers	4001 (78·7%)	190 223 (72·2%)	3803 (80·9%)	245 515 (76·7%)	861 (85·8%)	93 456 (79·3%)
Diuretic	1418 (27·9%)	71 618 (27·2%)	1345 (28·6%)	93 471 (29·2%)	270 (26·9%)	35 017 (29·7%)
Service use within 1 year before baseline						
Specialist outpatient clinics attendance	3590 (70·7%)	179 526 (68·2%)	3234 (68·8%)	213 211 (66·6%)	675 (67·2%)	72 606 (61·6%)
Hospital admissions	1372 (27·0%)	58 440 (22·2%)	1418 (30·2%)	83 165 (26·0%)	375 (37·4%)	37 079 (31·5%)

Data are n (%) or mean (SD). The initiators and non-initiators refer to the person-trials in the sequential target trial emulation.

Table: **Baseline characteristics**

	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	1106	55274	0·92 (0·86–0·97)	929	39629	0·86 (0·78–0·93)
75–84 years	1475	97878	0·94 (0·89–0·99)	1242	79508	0·86 (0·80–0·92)
≥85 years	333	40662	0·88 (0·79–0·99)	284	37638	0·81 (0·71–0·92)
Myocardial infarction						
60–74 years	416	18067	0·97 (0·88–1·07)	342	11885	0·90 (0·77–1·04)
75–84 years	449	28998	0·86 (0·78–0·94)	376	22848	0·87 (0·76–1·00)
≥85 years	109	12057	0·88 (0·73–1·07)	84	10886	0·73 (0·57–0·93)
Heart failure						
60–74 years	471	21058	0·99 (0·90–1·09)	389	13815	0·85 (0·74–0·98)
75–84 years	691	45451	0·94 (0·87–1·01)	579	34432	0·80 (0·72–0·89)
≥85 years	173	20353	0·94 (0·80–1·09)	152	18405	0·86 (0·72–1·04)
Stroke						
60–74 years	526	29756	0·82 (0·75–0·89)	445	21809	0·80 (0·71–0·91)
75–84 years	737	48961	0·97 (0·90–1·05)	607	39742	0·89 (0·81–0·99)
≥85 years	151	18693	0·87 (0·74–1·02)	124	17246	0·75 (0·61–0·93)
All-cause mortality						
60–74 years	1050	55394	0·89 (0·83–0·94)	803	35988	0·75 (0·68–0·83)
75–84 years	1487	111161	0·87 (0·82–0·91)	1115	84496	0·78 (0·72–0·84)
≥85 years	460	58818	0·89 (0·81–0·98)	345	52538	0·80 (0·71–0·91)
Myopathies						
60–74 years	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	648	31920	0·96 (0·89–1·04)	535	21300	0·91 (0·81–1·02)
75–84 years	618	42034	0·92 (0·85–1·00)	508	31942	0·97 (0·87–1·09)
≥85 years	117	14546	0·92 (0·76–1·10)	96	12879	0·89 (0·70–1·12)

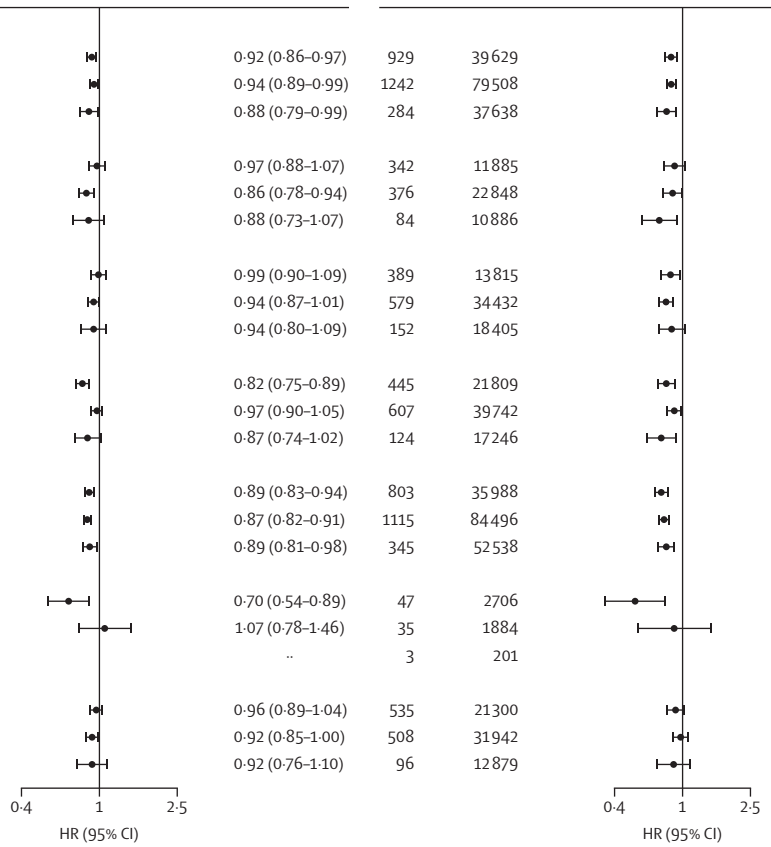

Figure 3: **Estimated HR (95% CI) for outcomes of interest between statin initiators and non-initiators in the three age groups (ie, aged 60–74 years, 75–84 years, and ≥85 years)**
The initiators and non-initiators refer to the person-trials in the sequential target trial emulation. The outcome incidence refers to the number of events during the follow-up period in the intention-to-treat analysis and per-protocol analysis, respectively. The analysis was adjusted for sex, age, smoking status, fasting glucose, systolic blood pressure, diastolic blood pressure, LDL cholesterol, HDL cholesterol, total cholesterol, estimated glomerular filtration rate, comorbidities (ie, Charlson Comorbidity Index, hypertension, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, atrial fibrillation, dementia, and obesity), drug use (ie, aspirin, insulin, oral antidiabetic drugs, angiotensin converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics), month of follow-up and its square term, specialist outpatient clinics attendance (ie, within 1 year before baseline), and hospital admission (ie, within 1 year before baseline). HR=hazard ratio. *Estimates cannot be obtained due to small number of events in treatment group (n=3).

The crude incidence rates of each outcome of interest over the 11-year study period (median 5·3 years, IQR 3·8 to 7·1) for the statin initiators and non-initiators are shown in appendix 2 (p 8). In the intention-to-treat analysis (figure 3), the estimated HR for overall cardiovascular disease incidence associated with statin initiation was 0·92 (95% CI 0·86 to 0·97) in those aged 60–74 years (the benchmark age group), 0·94 (0·89 to 0·99) in those aged 75–84 years, and 0·88 (0·79 to 0·99) in those 85 years and older. The estimated HR for the all-cause mortality was 0·89 (0·83 to 0·94), 0·87 (0·82 to 0·91), and 0·89 (0·81 to 0·98) in the three age groups respectively. The estimated HR for the specific cardiovascular disease subtype is shown in figure 3. No significantly increased risks of myopathies and liver dysfunction were observed in any of the age groups, with only three cases of myopathies being reported in adults aged 85 years and older who initiated statins (appendix 2 p 8). The estimated 5-year absolute risk difference for overall cardiovascular disease incidence in the intention-to-treat analysis was –1·3% (95% CI –2·1 to –0·4, statistical power 0·827) in those aged 60–74 years, –1·5% (–2·7 to –0·4, 0·802) in those aged 75–84 years, and –4·0% (–7·0 to –1·0, 0·846) in those aged 85 years and older (figure 4). The number needed to treat to prevent one cardiovascular disease incidence in the intention-to-treat analysis was 77 (95% CI 46 to 224) in those aged 60–74 years, 67 (38 to 295) in those aged 75–84 years, and 25 (14 to 101) in those aged 85 years and older. The estimated 5-year and 10-year standardised risk differences for other outcomes of interest are presented in appendix 2 (p 9).

In the per-protocol analysis, the estimated HR for overall cardiovascular disease was 0·86 (95% CI 0·78 to 0·93) in patients aged 60–74 years, 0·86 (0·80 to 0·92) in those aged 75–84 years, and 0·81 (0·71 to 0·92) in those 85 years and

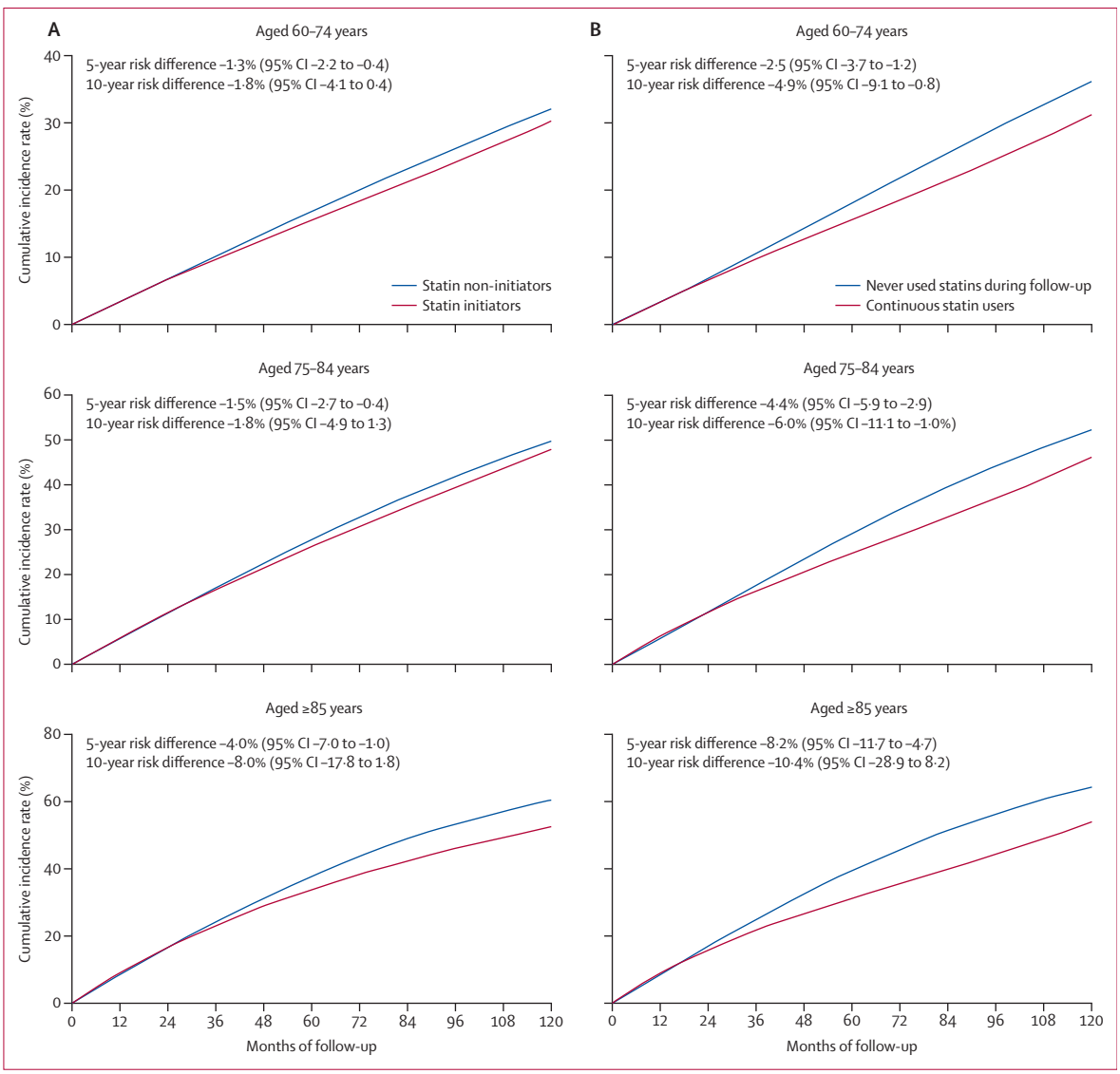

Figure 4: **Standardised cumulative incidence curve and 5-year and 10-year risk difference for cardiovascular diseases over the follow-up period between statin users and non-users**

(A) Intention-to-treat analysis. (B) Per-protocol analysis. Analyses were adjusted for sex, age, smoking status, fasting glucose, systolic blood pressure, diastolic blood pressure, LDL cholesterol, HDL cholesterol, total cholesterol, estimated glomerular filtration rate, comorbidities (ie, Charlson Comorbidity Index, hypertension, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, atrial fibrillation, dementia, and obesity), drug use (ie, aspirin, insulin, oral antidiabetic drugs, angiotensin converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics), month of follow-up and its square term, specialist outpatient clinics attendance (ie, within 1 year before baseline) and hospital admission (ie, within 1 year before baseline), with the added product terms between treatment and time (linear and quadratic term).

older, and the HR for all-cause mortality was 0·75 (0·68 to 0·83), 0·78 (0·72 to 0·84), and 0·80 (0·71 to 0·91), respectively for the three age groups. Substantial risk reduction was also observed for all cardiovascular subtypes, including myocardial infarction (HR in the three age groups 0·90 [95% CI 0·77 to 1.04], 0·87 [0·76 to 1·00], and 0·73 [0·57 to 0·93]), heart failure (0·85 [0·74 to 0·98], 0·80 [0·72 to 0·89], and 0·86 [0·72 to 1·04]), and stroke (0·80 [0·71 to 0·91], 0·89 [0·81 to 0·99], and 0·75 [0·61 to 0·93]). No significant risk increase in the myopathies or liver dysfunction was found (figure 3). The estimated 5-year absolute risk difference in the per-protocol analysis was –2·5% (–3·7 to –1·2), –4·4% (–5·9 to –2·9), and –8·2% (–11·7 to –4·7) respectively in each age group, and the corresponding number needed to treat to prevent one cardiovascular disease event in 5 years was 41 (95% CI 27 to 84) among those aged 60–74 years, 23 (17 to 35) in those aged 75–84 years, and 12 (9 to 21) in those aged 85 years and older; the estimated 10-year absolute risk difference for overall cardiovascular disease incidence was –4·9% (–9·1 to –0·8), –6·0% (–11·1 to –1·0),

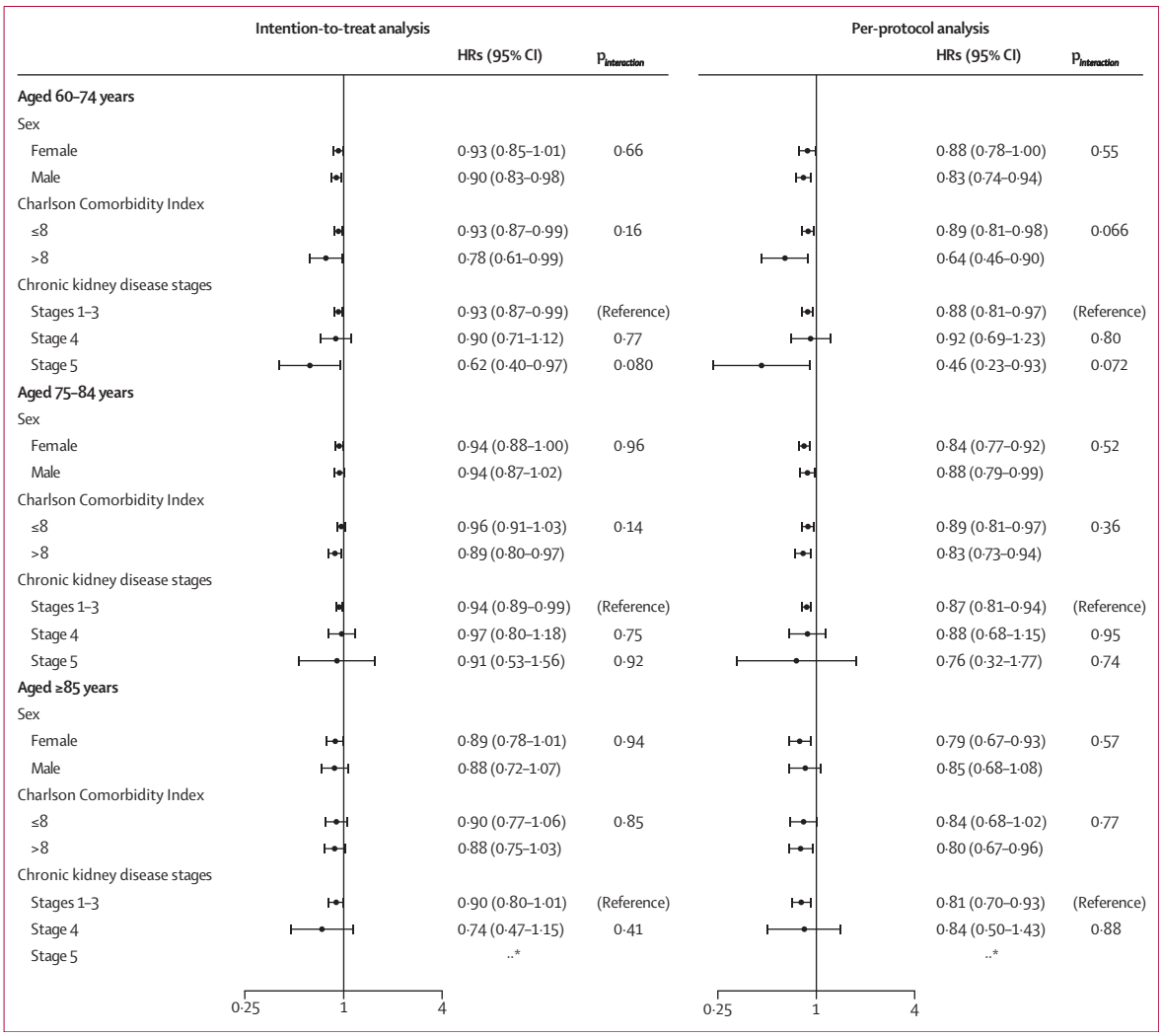

***Figure 5*: Estimated HRs (95% CIs) for overall incidence of cardiovascular diseases between statin initiators in subgroup analyses**
Analyses were adjusted for sex, age, smoking status, fasting glucose, systolic blood pressure, diastolic blood pressure, LDL cholesterol, HDL cholesterol, total cholesterol, estimated glomerular filtration rate, comorbidities (ie, Charlson Comorbidity Index, hypertension, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, atrial fibrillation, dementia, and obesity), drug use (ie, aspirin, insulin, oral antidiabetic drugs, angiotensin converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics), month of follow-up and its square term, specialist outpatient clinics attendance (ie, within 1 year before baseline), and hospital admission (ie, within 1 year before baseline). An interaction term between the treatment indicator and the subgroup was fitted to test the difference in outcomes across patient subgroups. For the chronic kidney disease stages, stages 1–3 were considered the reference group in the interaction test. *Robust estimates could not be obtained due to a small number of events.

and –10·4% (–28·9 to 8·2) respectively in each age group in the per-protocol analysis.

The HR estimates in the subgroup analyses are presented in figure 5 and appendix 2 (pp 10–11). Cardiovascular disease risk reduction associated with statin initiation was consistently found in all patient subgroups by sex and by Charlson Comorbidity Index scores (≤8 or >8) in each age group. Risk reduction of overall cardiovascular disease associated with statin use was found in patients with stage 1–3 chronic kidney disease across all age groups; a directional but insignificant association between statin treatment and cardiovascular disease risk reduction was observed in the patients with stage 4 and stage 5 (HR <1). The test of interaction term indicated no significant differences in the estimated effect of statins between patients in stages 4 and 5 and those in stages 1–3 ($p_{interaction}$ >0·05). Similar estimates for outcomes were consistently observed in all sensitivity analyses (appendix 2 pp 12–20).

Discussion

Our study suggests that statin therapy is effective in the primary prevention of cardiovascular diseases and all-cause mortality in older adults (ie, those aged ≥75) with chronic kidney disease who are hypercholesterolemic. Moreover, our findings also indicate that there is no significantly

increased risk of major adverse events associated with statin therapy in this population.

Our results in the reference age group (aged 60–74 years) were similar to results from the JUPITER trial, which showed risk reductions for cardiovascular disease (0·55 [95% CI 0·38–0·82]) and all-cause mortality (0·56 [0·37–0·85]) in older patients (median age of 70 years) with estimated glomerular filtration rates of <60 ml per min/1·73 m^2. The similarity in findings shows the validity of our analysis and the reliability of the results. To the best of our knowledge, our study is the first to investigate the effectiveness of statin therapy for primary prevention in two distinct age groups (ie, 75–84 years and ≥85 years) of older patients with chronic kidney disease. In a previous cohort study done in the USA that used a target trial emulation, subgroup analyses of patients with chronic kidney disease aged older than 75 years showed potential association between statin use and incidence of major cardiovascular diseases (HR 0·93, 0·86–1·01), and a significant risk reduction in all-cause mortality (0·89, 0·82 –0·97).[12] The lack of a significant risk reduction for major cardiovascular events might be partly due to the small sample size for this age subgroup. With a larger sample size, our study was able to verify the effectiveness of statin use for primary prevention with enhanced statistical power. Moreover, our study also provided evidence on the effectiveness of statin therapy in very old patients (≥85 years) with chronic kidney disease.

Notably, the estimated number needed to treat over 5 years to prevent one additional cardiovascular disease event in older adults aged 75–84 years and in those aged 85 years and older in the per-protocol analysis in our study was lower than the number needed to treat in the benchmark age group and lower than the estimated number needed to treat shown in a meta-analysis, which showed that the number needed to treat to prevent one additional cardiovascular event was 32 (95% CI 23–50) in older patients (mean or median age ranged from 50 to 70 years) with chronic kidney disease (restricted to stages 1–3);[30] taken together, these findings show the beneficial effects of statin use in older people with chronic kidney disease. Older adults inherently have a higher baseline risk of cardiovascular diseases due to age-related physiological changes,[31] and thus the absolute benefits from statin treatment also increase, resulting in a lower number needed to treat. In addition to improving the lipid profile, statins exert an anti-inflammatory and anti-oxidative effect, which is clinically important in slowing the progression of chronic kidney disease and preventing complications.[32,33] Increased oxidative stress and inflammation are important factors contributing to premature vascular ageing and progressive vascular disease in patients with chronic kidney disease.[34] The development and progression of chronic kidney disease is associated with inflammation, and increased inflammatory markers could be one of the contributors to various complications of chronic kidney disease, including major cardiovascular diseases and mortality.[33,35] Therefore, as patients with chronic kidney disease reach advanced age, they are more susceptible to vascular ageing. In light of this, the anti-inflammatory property of statins could have a more substantial effect for this particular population.

In a previous meta-analysis on patients with chronic kidney disease with mean ages ranging between 42 years to 73 years, a significant risk reduction of cardiovascular events was consistently observed across each stage of chronic kidney disease (ie, stages 2–3, stage 4, and stage 5).[11] Another cohort study in the USA found that the association between elevated LDL cholesterol concentrations and a higher risk of cardiovascular mortality attenuated as chronic kidney disease progressed.[36] As the numbers of patients with stage 4 and stage 5 chronic kidney disease who initiated statins are relatively small, the effectiveness of statins in these patients could not be verified in our study due to inadequate statistical power in the subgroup analysis. Further studies with larger sample sizes are needed to investigate whether risk reduction associated with statin use persists in older patients with stage 4 or stage 5 chronic kidney disease.

Our study also confirmed the safety of statin therapy for older adults and very old adults with regard to major adverse events. The association between statin use and the adverse events of myopathy and liver dysfunction has been observed in previous studies.[37,38] Two systematic reviews with meta-analyses have shown that the risks of liver dysfunction in patients with chronic kidney disease treated with statins were comparable to patients treated without statins.[11,14] Regarding myopathy, one large RCT assessing the effectiveness of statins in patients with chronic kidney disease showed no significant difference of reported cases of myopathy in statin users and non-users.[39] Nevertheless, the evidence from these studies might be limited by small sample sizes and strict eligibility criteria. Using population-based data from real-world practice, we verified the absence of an increased risk of myopathy and liver dysfunction in patients with chronic kidney disease who initiated statins, and we expanded the existing body of evidence regarding the safety of statin therapy in old adults and very old adults.

One of the key strengths of our study is the use of population-based data covering a span of more than 10 years, which allowed us to assess the long-term effectiveness and safety of initiating statin therapy among older patients with chronic kidney diseases in real-world settings. Moreover, our per-protocol analysis of the emulated trials carefully accounted for drug adherence by adjusting for time-varying confounders when estimating the effect of continuous statin use.

Our study has some limitations. First, our results could be subject to unmeasured confounders, including lifestyle factors such as diet and physical activity. Additionally, the time since the first diagnosis of chronic kidney disease, as well as age at diagnosis, could not be identified for each individual and adjusted for in our study. However, in the sequential target trial emulation, the eligibility criteria for

statin therapy were assessed for each patient with chronic kidney disease at each calendar month during the participant inclusion period on a rolling basis, and our analysis in the reference age group yielded consistent results with randomised trials in younger patients with chronic kidney disease, which suggests that any influence of potential unmeasured confounding is limited. Second, the identification of outcome events in our study was based on the diagnostic coding of the ICPC-2 and the ICD-9-CM in the electronic health records, which could cause misclassification bias. However, a high coding accuracy has been reported for diagnosing myocardial infarctions and stroke in the clinical management database used for data extraction,[19] and it is highly unlikely that any measurement error in the outcome would be differential with respect to statin initiation. Third, data regarding statin dosage were not available for analyses. Previous studies in Hong Kong have found a notably low prescription prevalence of high-intensity statins,[40] with only 6·2% of patients admitted to hospital with acute coronary syndrome receiving high-intensity statin therapy.[41] Thus, our findings primarily pertain to the use of low-intensity and moderate-intensity statin therapies. Further studies are needed to explore the potential differences across various doses of statins. Additionally, some important endpoints, such as percutaneous coronary intervention and coronary artery bypass grafting,[42] could not be included in the analysis, as the procedure codes were not included in the initial research protocol for data extraction. This exclusion could result in potential bias as patients with a history of percutaneous coronary intervention or coronary artery bypass grafting would not be identified at baseline and during the follow-up period. Further research with additional data extraction for these two procedure codes is warranted to enhance the comprehensiveness of the understanding of our research question. Fourth, we adopted a complete case analysis to address missing values for baseline covariates, for which about 34·5% of person-trials were excluded from the analysis (see appendix 2 p 21 for the data completion rate of each covariate). This exclusion of person-trials might introduce potential selection bias at baseline. Nevertheless, our sensitivity analysis adopting multiple imputations to handle missing data at baseline yielded consistent findings, suggesting a small likelihood of substantial selection bias in the complete case analysis. Additionally, LOCF was adopted to handle missing values for the time-varying covariates in the weighting models.[16,25] This approach might affect the performance of the weighting models, as it cannot account for any changes in the confounders that occur between observations and thus might influence the adjustment for the time-varying confounders in the causal estimates. Fifth, due to the granularity of our available data (ie, monthly data), we are unable to account for intermittent statin use in the present study. Future research that uses data with greater granularity and a tailored design is warranted to explore this important topic. Sixth, our study results might not be generalisable to all populations. Further studies in different ethnicities and health systems can better inform the benefits of statins in older patients with chronic kidney disease.

Our results provided real-world evidence supporting the effectiveness of statin therapy for the primary prevention of cardiovascular diseases and all-cause mortality in older adults and very old adults with chronic kidney disease. Our study also provides reassurance regarding the safety of statin therapy in this population, specifically in terms of the risk of myopathies and liver dysfunction.

Contributors

EYFW and WX: conceptualisation and methodology. EYFW: data curation. WX, YP, and EYFW: formal data analysis. WX and YKY: writing the original draft. CLKL, ETYT, and EYFW: reviewing and editing subsequent drafts. EYFW: funding acquisition. EYFW: supervision. WX and EYFW have directly accessed and verified the underlying data reported in the manuscript. All authors had access to the underlying data and accept responsibility for the submission.

Declaration of interests

EYFW has received research grants from the Health Bureau, the Hong Kong Research Grants Council, the Narcotics Division, the Security Bureau, the Social Welfare Department, and the Labour and Welfare Bureau, which are all part of the Hong Kong Government, and the National Natural Science Foundation of China, all outside the submitted work. CLKL has received research grants from the Health Bureau of the Government of Hong Kong, the Hong Kong Research Grant Council, the Hong Kong College of Family Physicians, and the Kerry Group Kuok Foundation; payments from the Malaysian College of Family Physicians, and the International Association of Chinese Nephrologists (Hong Kong); and support from the Malaysian College of Family Physicians, all outside the submitted work. ETYT has received research grants from the Health Bureau of the Government of Hong Kong and the Kerry Group Kuok Foundation, all outside the submitted work. All other authors declare no competing interests.

Data sharing

The data underlying this Article were provided by the Hospital Authority of Hong Kong. The data can be accessed upon request to the Hospital Authority of Hong Kong.

For the **Hospital Authority of Hong Kong** see https://www3.ha.org.hk/data/Provision/ApplicationProcedure

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References

1 Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* 2011; **12:** 7–11.

2 Barron E. Chronic kidney disease prevalence model. October, 2014. https://assets.publishing.service.gov.uk/media/5a82c379e5274a2e8ab593af/ChronickidneydiseaseCKDprevalencemodelbriefing.pdf (accessed Dec 28, 2024).

3 Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2023*. US Department of Health and Human Services, Centers for Disease Control and Prevention, 2023.

4 Yang L, Chu TK, Lian J, et al. Risk factors of chronic kidney diseases in Chinese adults with type 2 diabetes. *Sci Rep* 2018; **8:** 14686.

5 Wan EY, Fung CS, Yu EY, Fong DY, Chen JY, Lam CL. Association of visit-to-visit variability of systolic blood pressure with cardiovascular disease and mortality in primary care Chinese patients with type 2 diabetes—a retrospective population-based cohort study. *Diabetes Care* 2017; **40:** 270–79.

6 Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015; **3:** 514–25.

7 Mefford MT, Rosenson RS, Deng L, et al. Trends in statin use among US adults with chronic kidney disease, 1999–2014. *J Am Heart Assoc* 2019; **8:** e010640.

8 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; **139:** e1082–143.

9 National Institue for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. 2023. https://www.nice.org.uk/guidance/ng238 (accessed Dec 28, 2024).

10 Wanner C, Tonelli M, Cass A, et al. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int* 2014; **85:** 1303–09.

11 Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J* 2013; **34:** 1807–17.

12 Barayev O, Hawley CE, Wellman H, et al. Statins, mortality, and major adverse cardiovascular events among US veterans with chronic kidney disease. *JAMA Netw Open* 2023; **6:** e2346373.

13 Toth PP, Patti AM, Giglio RV, et al. Management of statin intolerance in 2018: still more questions than answers. *Am J Cardiovasc Drugs* 2018; **18:** 157–73.

14 Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157:** 263–75.

15 Keogh RH, Gran JM, Seaman SR, Davies G, Vansteelandt S. Causal inference in survival analysis using longitudinal observational data: sequential trials and marginal structural models. *Stat Med* 2023; **42:** 2191–225.

16 Danaei G, Rodríguez LA, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. *Stat Methods Med Res* 2013; **22:** 70–96.

17 The Government of Hong Kong Special Administrative Region, Census and Statistics Department. 2021 Population census. 2022. https://www.censtatd.gov.hk/en/scode600.html (accessed Dec 28, 2024).

18 The Government of Hong Kong Special Administrative Region, Census and Statistics Department. Hong Kong 2016 population by-census—thematic report: ethnic minorities. 2017. https://www.censtatd.gov.hk/en/EIndexbySubject.html?pcode=B1120100&scode=459#section2 (accessed Dec 28, 2024).

19 Wong AYS, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ* 2016; **352:** h6926.

20 Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016; **183:** 758–64.

21 Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; **41:** 111–88.

22 Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention—an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol* 2010; **55:** 1266–73.

23 Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders H-J. Acute kidney injury. *Nat Rev Dis Primers* 2021; **7:** 52.

24 Ngwa JS, Cabral HJ, Cheng DM, et al. A comparison of time dependent Cox regression, pooled logistic regression and cross sectional pooling with simulations and an application to the Framingham Heart Study. *BMC Med Res Methodol* 2016; **16:** 148.

25 Leyrat C, Carpenter JR, Bailly S, Williamson EJ. Common methods for handling missing data in marginal structural models: what works and why. *Am J Epidemiol* 2021; **190:** 663–72.

26 D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation* 2008; **117:** 743–53.

27 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011; **30:** 377–99.

28 Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons, 2004.

29 NCSS Statistical Software. PASS 2021 power analysis and sample size software. 2021. https://www.ncss.com/software/pass (accessed Dec 16, 2024).

30 Major RW, Cheung CK, Gray LJ, Brunskill NJ. Statins and cardiovascular primary prevention in CKD: a meta-analysis. *Clin J Am Soc Nephrol* 2015; **10:** 732–39.

31 Fajemiroye JO, da Cunha LC, Saavedra-Rodríguez R, et al. Aging-induced biological changes and cardiovascular diseases. *BioMed Res Int* 2018; **2018:** 7156435.

32 Babelova A, Sedding DG, Brandes RP. Anti-atherosclerotic mechanisms of statin therapy. *Curr Opin Pharmacol* 2013; **13:** 260–64.

33 Wang J, Chen Z, Qiu Y, et al. Statins have an anti-inflammation in CKD patients: a meta-analysis of randomized trials. *BioMed Res Int* 2022; **2022:** 4842699.

34 Tanriover C, Copur S, Mutlu A, et al. Early aging and premature vascular aging in chronic kidney disease. *Clin Kidney J* 2023; **16:** 1751–65.

35 Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. *Blood Purif* 2015; **39:** 84–92.

36 Hashemi L, Hsiung J-T, Arif Y, et al. Serum low-density lipoprotein cholesterol and cardiovascular disease risk across chronic kidney disease stages (data from 1·9 million United States veterans). *Am J Cardiol* 2022; **170:** 47–55.

37 Ramos R, Comas-Cufí M, Martí-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ* 2018; **362:** k3359.

38 Talbert RL. Safety issues with statin therapy. *J Am Pharm Assoc (2003)* 2006; **46:** 479–88.

39 Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9438 patients with chronic kidney disease. *Am Heart J* 2010; **160:** 785–94.e10.

40 Blais JE, Chan EW, Law SWY, et al. Trends in statin prescription prevalence, initiation, and dosing: Hong Kong, 2004–2015. *Atherosclerosis* 2019; **280:** 174–82.

41 Yan B, Chan C, Wong M, To O, Lee V. Long-term efficacy of lower intensity statin therapy in Chinese acute coronary syndrome patients. *Value Health* 2018; **21:** S26.

42 Orkaby AR, Driver JA, Ho YL, et al. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. *JAMA* 2020; **324:** 68–78.