Initiation of statin therapy in patients with diabetes mellitus: a target trial emulation study (abridged secondary publication)

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KEY MESSAGES

1. Initiation of statins in diabetic patients with baseline low-density lipoprotein cholesterol levels of 1.8 to 2.5 mmol/L was associated with reduced risks of incident cardiovascular diseases and all-cause mortality, without significant increases in the risks of myopathy or liver dysfunction.
2. Compared with initiation of statin therapy at a threshold of 2.6 mmol/L, initiation at a threshold of 1.8 mmol/L may provide additional benefits in preventing cardiovascular diseases and all-cause mortality among patients with diabetes.

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Introduction

The treatment of hyperlipidaemia can prevent cardiovascular diseases (CVDs) in patients with type 2 diabetes mellitus (T2DM). Statins are the most commonly used lipid-lowering agents for reduction of low-density lipoprotein cholesterol (LDL-C) levels. The optimal timing for statin initiation is important in clinical practice, depending on the balance among potential benefits, adverse events, and medical costs. The American College of Cardiology and the American Heart Association recommend initiating statins at LDL-C levels ≥1.8 mmol/L in patients aged 40 to 75 years with diabetes mellitus.[1] However, there are no definitive recommendations concerning the timing of statin initiation in non-Caucasian populations. In mainland China and Hong Kong, a less stringent treatment target of LDL-C <2.6 mmol/L is recommended for patients with T2DM; lipid-lowering treatment is initiated when the therapeutic target is not achieved. This study aimed to investigate the long-term effects of statin therapy in Chinese patients with T2DM using target trial emulation and population-based observational data.

Methods

Electronic medical records of patients aged ≥18 years with T2DM and LDL-C levels ≥1.8 mmol/L in each calendar month between January 2008 and December 2014 were included in the emulated randomised controlled trials. To enhance statistical power, a sequence of trials was conducted every calendar month to increase the number of initiators and cases.

Statin initiation was defined as any treatment with simvastatin, atorvastatin, fluvastatin, rosuvastatin, lovastatin, pitavastatin, pravastatin, or any combination at baseline. Patients were categorised into two groups according to baseline LDL-C levels (1.8-2.5 vs ≥2.6 mmol/L). Within each group, those who initiated statin therapy were compared with those who did not.

Outcome measures included the overall incidence of CVDs (including myocardial infarction, heart failure, and stroke), five subcategories of CVD (myocardial infarction, heart failure, stroke, ischaemic stroke, and haemorrhagic stroke), two major adverse events related to statin therapy (myopathies and liver dysfunction), and all-cause mortality. All patients were followed up until death, the occurrence of any outcome measure, or the end of the study, whichever happened first. To minimise potential confounding by undiagnosed disease at baseline, patients who experienced an outcome within the first year of follow-up were excluded from analysis.

The intention-to-treat effect and per-protocol effect of statin therapy were estimated and expressed as hazard ratios (HRs). Baseline covariates were selected based on a priori knowledge and included sex, age, smoking status, clinical parameters (systolic and diastolic blood pressure, haemoglobin A1c, triglyceride level, high-density lipoprotein

cholesterol, and estimated glomerular filtration rate), comorbidities (hypertension, peripheral vascular disease, atrial fibrillation, dyslipidaemia, asthma, chronic obstructive pulmonary disease, and dementia), drug history within the past year (aspirin, insulin, oral antidiabetic drugs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics), and service utilisation.

The per-protocol analysis was conducted by artificially censoring participants who deviated from their assigned strategy unless a medical justification was present. For instance, among statin initiators at baseline, those who discontinued statins were censored unless cessation was related to the occurrence of myopathies or liver dysfunction. Among non-statin initiators at baseline, those who commenced statin therapy were censored unless there was an indication of dyslipidaemia. To adjust for selection bias introduced by the censoring process, each patient was weighted at each time point by the inverse probability of receiving their assigned treatment strategy, conditional on baseline and time-varying covariates.

Subgroup analyses were conducted at baseline according to sex, age, and 10-year CVD risk. Sensitivity analysis was conducted by extending the statin discontinuation gap from 1 month to 3 months. Additionally, to evaluate residual confounding by indication, sensitivity analysis was performed by excluding patients with high cholesterol levels (total cholesterol >6.2 mmol/L) at baseline.

Results

In the intention-to-treat analysis, over a mean follow-up duration of 6.7 years, the estimated HRs for CVD incidence associated with statin initiation were 0.78 (95% confidence interval [CI]=0.72-0.84) in patients with baseline LDL-C of 1.8-2.5 mmol/L and 0.90 (95% CI=0.88-0.92) in patients with baseline LDL-C of ≥2.6 mmol/L. In the per-protocol analysis, the respective HRs were 0.59 (95% CI=0.51-0.68) and 0.77 (95% CI=0.74-0.81) [Fig 1]. This risk reduction was consistently observed for CVD subtypes and all-cause mortality in both LDL-C groups; there was no significant increase in major adverse event risk (Fig 2). In the per-protocol analysis, the absolute 10-year risk difference for overall CVD was -7.1% (95% CI= -10.7% to -3.6%) in patients with baseline LDL-C of 1.8-2.5 mmol/L and -3.9% (95% CI= -5.1% to -2.7%) in patients with baseline LDL-C of ≥2.6 mmol/L. The benefits of statin use including reductions in overall CVD risk and all-cause mortality were also observed among patients aged ≥75 years at different LDL-C thresholds for statin initiation.

Discussion

Our findings align with current evidence that statins reduce CVD risk irrespective of baseline LDL-C; benefits were observed in all patients with pre-treatment LDL-C of ≥1.8 mmol/L. A meta-analysis found that the reduction in major adverse cardiovascular event risk per unit change in LDL-C was significant among patients who initiated LDL-C lowering at a threshold of 1.6 mmol/L; there was no increase in serious adverse event risk.[2] Early initiation of statins during disease progression may further reduce inflammation and improve endothelial function,[3] contributing to early prevention of CVDs.

Significant reductions in CVD and all-cause mortality risks were observed among patients aged ≥75 years who initiated statin treatment at different

	Intention-to-treat analysis		Per-protocol analysis	
	10-year risk difference (%)	Hazard ratio (95% confidence interval)	10-year risk difference (%)	Hazard ratio (95% confidence interval)
Baseline low-density lipoprotein cholesterol: 1.8-2.5 mmol/L				
Overall cardiovascular diseases	-3.5 (-4.7, -2.3)	0.78 (0.72, 0.84)	-7.1 (-10.7, -3.6)	0.59 (0.51, 0.68)
Myocardial infarction	-0.9 (-1.7, -0.2)	0.84 (0.74, 0.96)	-2.8 (-3.6, -2.0)	0.61 (0.39, 0.95)
Heart failure	-0.3 (-1.3, 0.7)	0.87 (0.77, 0.98)	-3.9 (-7.2, -0.6)	0.39 (0.23, 0.65)
Stroke	-3.1 (-3.8, -2.4)	0.72 (0.65, 0.80)	-8.1 (-9.7, -6.4)	0.41 (0.31, 0.55)
Ischaemic stroke	-1.5 (-2.1, -0.9)	0.65 (0.55, 0.76)	-2.9 (-4.3, -1.5)	0.41 (0.22, 0.76)
Haemorrhage	-0.5 (-0.7, -0.3)	0.73 (0.55, 0.98)	-1.6 (-1.9, -1.2)	0.24 (0.05, 1.12)
Myopathies	0.0 (-0.3, 0.3)	1.03 (0.74, 1.42)	0.3 (-0.8, 1.4)	0.45 (0.13, 1.50)
Liver dysfunction	-2.0 (-3.0, -1.1)	0.86 (0.79, 0.93)	-1.7 (-5.6, 2.1)	0.96 (0.71, 1.30)
Mortality	-2.5 (-3.7, -1.4)	0.80 (0.74, 0.86)	-4.3 (-8.5, -0.1)	0.70 (0.52, 0.94)
Baseline low-density lipoprotein cholesterol ≥2.6 mmol/L				
Overall cardiovascular diseases	-2.2 (-2.6, -1.8)	0.90 (0.88, 0.92)	-3.9 (-5.1, -2.7)	0.77 (0.74, 0.81)
Myocardial infarction	-1.0 (-1.2, -0.7)	0.86 (0.82, 0.89)	-1.9 (-2.6, -1.2)	0.68 (0.62, 0.75)
Heart failure	-0.8 (-1.1, -0.5)	0.91 (0.88, 0.95)	-2.4 (-3.1, -1.7)	0.69 (0.63, 0.75)
Stroke	-1.2 (-1.6, -0.9)	0.89 (0.87, 0.92)	-2.2 (-3.1, -1.3)	0.78 (0.73, 0.83)
Ischaemic stroke	-0.7 (-0.9, -0.5)	0.82 (0.78, 0.86)	-1.5 (-2.1, -0.9)	0.65 (0.58, 0.72)
Haemorrhage	-0.1 (-0.2, 0.0)	0.92 (0.85, 1.01)	-0.2 (-0.5, 0.1)	0.85 (0.69, 1.04)
Myopathies	0.0 (-0.2, 0.2)	1.02 (0.92, 1.13)	-0.2 (-0.4, 0.1)	0.87 (0.67, 1.14)
Liver dysfunction	-1.6 (-2.0, -1.3)	0.92 (0.89, 0.94)	-2.8 (-3.5, -2.2)	0.85 (0.80, 0.90)
Mortality	-1.5 (-1.9, -1.1)	0.92 (0.90, 0.94)	-3.4 (-4.1, -2.7)	0.81 (0.76, 0.86)

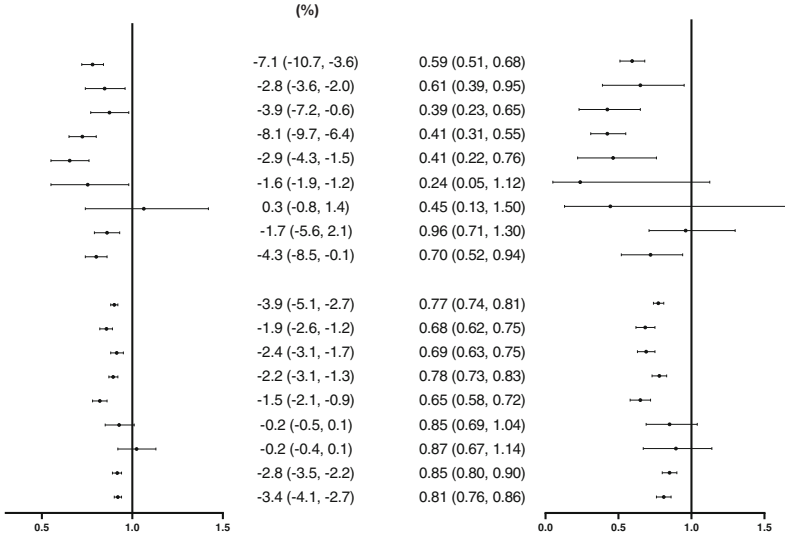

FIG 1. Hazard ratios and 10-year risk differences in the incidences of myocardial infarction, heart failure, stroke, major adverse events, and mortality between statin initiators and non-initiators.

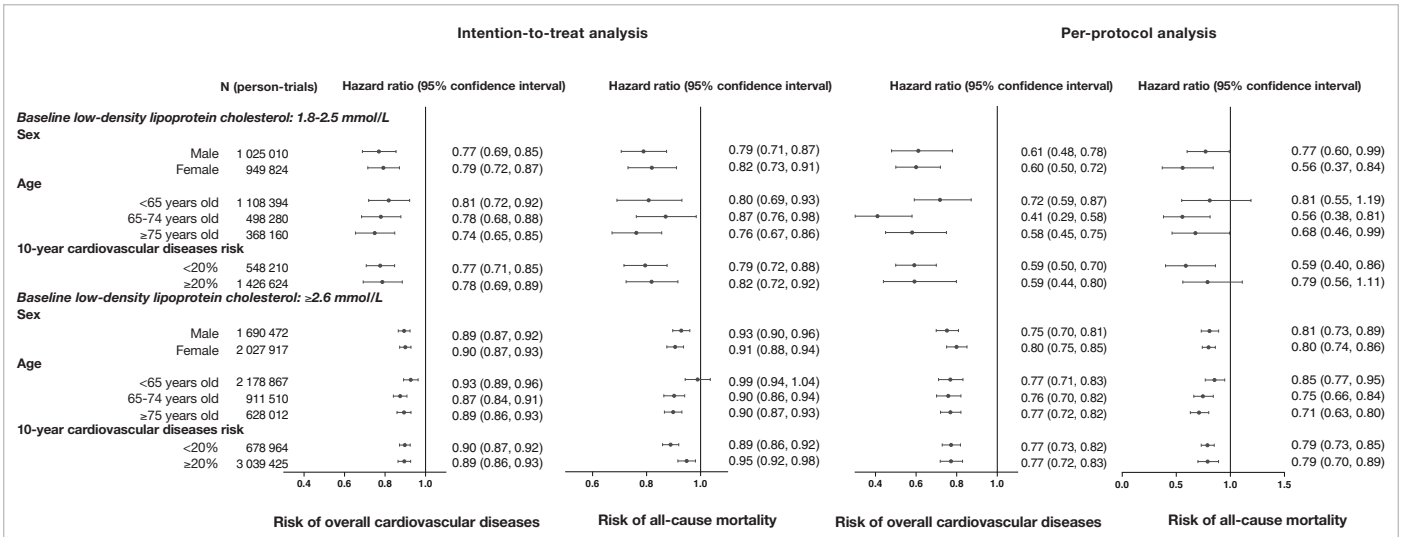

FIG 2. Hazard ratios for the effect of statin therapy on the incidences of myocardial infarction, heart failure, stroke, and mortality in subgroup analyses.

LDL-C levels. A meta-analysis showed that lipid-lowering treatment was similarly effective among patients aged >75 or <75 years in terms of reducing cardiovascular events (risk ratio=0.82, 95% CI=0.73-0.91).[4] Our findings indicate that statins are safe and effective for older adults aged ≥75 years with T2DM, although current guidelines provide no specific recommendations for this age group.

The anticipated adverse effects of statins may have limited their widespread use in real-world settings. However, statin use is not associated with increased risks of myopathy or liver dysfunction in Chinese patients.[5] Given the potential benefits of statins and the minimal adverse effects, statin therapy should be encouraged for CVD prevention in Chinese patients with T2DM.

Conclusion

Initiation of statin therapy in Chinese patients with T2DM and LDL-C levels of 1.8-2.5 mmol/L was associated with reduced risks of incident CVD and all-cause mortality, without significant increases in the risks of myopathy or liver dysfunction. Compared with initiation of statin therapy at an LDL-C level of 2.6 mmol/L, initiation at a threshold of 1.8 mmol/L may provide additional benefits in preventing CVDs and all-cause mortality.

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Disclosure

The results of this research have been previously published in:

1. Wan EYF, Xu W, Mok AHY, et al. Evaluating different low-density lipoprotein cholesterol thresholds to initiate statin for prevention of cardiovascular diseases in patients with type 2 diabetes mellitus: a target trial emulation study. Diabetes Obes Metab 2024;26:1877-87.

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