Statins effective for primary cardiovascular prevention at all risk levels in type 2 diabetes

For primary prevention in people with type 2 diabetes, statin initiation is associated with reduced risk, both absolute and relative, of all-cause death and major cardiovascular events, irrespective of 10-year QRISK3® score at baseline, according to this cohort study using UK data and target trial emulation published in *Annals of Internal Medicine*. Even in the lowest-risk group, with a 10-year predicted cardiovascular risk of <10%, the risk ratio of all-cause mortality was 0.80 (0.53% absolute risk reduction) in those who initiated a statin versus those not initiating. Similarly, the risk ratio for major cardiovascular events was 0.78 (0.83% absolute risk reduction). However, in those with a 10-year risk of <10%, subgroup analyses demonstrated that these benefits were restricted to people with a baseline LDL cholesterol of ≥2.6 mmol/L or non-HDL cholesterol of ≥3.4 mmol/L. Statin initiation was associated with a small increased risk of myopathy, but only in the intermediate-risk group (10-year risk of 10–19%). No increased risk of liver enzyme abnormalities was observed. The authors hope these data on effectiveness and safety will motivate primary care teams to encourage statin initiation and persistence for primary prevention in more people living with type 2 diabetes.

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Guidelines are inconsistent about the level of cardiovascular risk that should trigger recommendation of statin therapy. The American Heart Association and American College of Cardiology recommend statins for all adults with diabetes aged 40–75 years (Arnett et al, 2019), and the European Society of Cardiology and European Atherosclerosis Society recommend reducing LDL cholesterol in people with type 2 diabetes at high or very high risk (Mach et al, 2025). In contrast, the NICE (2023) NG238 guideline recommends statin initiation in people with a 10-year predicted risk of cardiovascular disease (CVD) of 10% or more, although use in those with lower risk is not ruled out if they have made an informed choice or if risk may be underestimated.

The present study

In this population-based cohort study published in the *Annals of Internal Medicine*, Yan and colleagues used anonymised UK medical records from a large UK primary care database to evaluate the effectiveness and safety of statins for primary prevention of all-cause death and CVD in people with type 2 diabetes. The study used a target trial emulation format, designed to prevent some of the common challenges faced with observational studies, including selection bias (see *Box 1*).

People aged 25–84 years with a diagnosis of type 2 diabetes or using oral glucose-lowering drugs from January 2005 to December 2016 were studied. People with a history of statin use were excluded, as were those with pre-existing CVD (heart failure, stroke, myocardial infarction [MI]), liver disease, schizophrenia or cancer, along with those prescribed a fibrate or other lipid-lowering drugs, aspirin, digoxin or antipsychotics within 6 months of baseline. People with type 1 diabetes were also excluded.

Box 1. What is "target trial emulation"?

Target trial emulation (TTE) is an observational *"research design that aims to emulate a randomized clinical trial* [RCT] *structure within a large set of observational data"*, such as data sourced from a healthcare database or medical registry; the (hypothetical) RCT that would have ideally answered the research question is the "target trial" that is emulated.

TTE can reduce bias, improve the understanding of findings and facilitate causal inference (Andrade, 2025).

Table 1. Mortality and cardiovascular outcomes in statin initiators versus propensity score-matched non-initiators at 10 years' follow-up (intention-to-treat analysis).

QRISK3® 10-year risk	Total number of participants	Statin initiators	All-cause mortality: Risk ratio	All-cause mortality: absolute risk reduction	Major CVD events: Risk ratio	Major CVD events: Absolute risk reduction
<10%	64 589	12 933	0.80	0.53%	0.78	0.83%
10–19%	117 630	23 546	0.71	1.88%	0.72	2.14%
20–29%	101 262	20 280	0.77	2.74%	0.78	2.59%
≥30%	135 067	27 043	0.85	4.30%	0.79	4.57%

All observed risk reductions were statistically significant.
CVD=cardiovascular disease (myocardial infarction, stroke or heart failure).

Participants were stratified into four groups based on baseline QRISK3® 10-year CVD risk:

- <10%: Low risk.
- 10–19%: Intermediate risk.
- 20–29%: High risk.
- 30% or higher: Very high risk.

Those initiating a statin were propensity score-matched on baseline characteristics in a 1:4 ratio with people who had not initiated a statin. All were followed from baseline until a cardiovascular outcome or death, transfer out of the practice or the end of the study period (31 December 2021).

Primary outcomes were all-cause mortality and major CVD (MI, stroke or heart failure). Secondary outcomes included MI, stroke, heart failure, myopathy and liver dysfunction (ALT ≥200 IU/L, AST ≥80 IU/L, or a combination of ALT ≥120 IU/L and total bilirubin ≥38 µmol/L).

Intention-to-treat (everyone initiating a statin) and per-protocol (initiating and continuing a statin) analyses were presented, and absolute risk differences and risk ratios at 10 years between statin initiators and non-initiators were calculated for these outcomes.

Results

Baseline characteristics in initiators and non-initiators were well matched, apart from non-HDL and triglyceride levels, which were higher in the statin initiators, particularly in the <10% QRISK3 group. Amongst those initiating statins in the QRISK3 <10% group, all were under age 75 years and 28.3% were younger than 40 years.

Intention-to-treat results (statin initiators versus non-initiators)

Table 1 compares everyone who initiated a statin with all matched non-initiators. Statin initiation was associated with significantly reduced risk of all-cause mortality and major CVD events (including the individual CVD events separately) in all four risk groups.

Subgroup analyses (age, sex, baseline LDL and non-HDL levels, and initial statin intensity) showed consistent results, apart from in the group with baseline QRISK3 <10%, in whom significant reductions in all-cause mortality and major CVD events after statin initiation were only found in emulated trials of those with baseline LDL cholesterol ≥2.6 mmol/L or non-HDL cholesterol ≥3.4 mmol/L.

These data demonstrate that, as expected, the absolute risk reduction of all-cause mortality and major CVD events increases with greater baseline risk, and that the benefit may be larger than was previously identified.

Per-protocol results (those who initiated and continued statins versus non-initiators)

Overall, 30% of statin initiators discontinued, and around 15% of non-initiators with a QRISK3 score of <20% started statins during follow-up. Sustained use of statin therapy significantly reduced the risk of all-cause mortality and CVD events, with absolute benefits across all QRISK3 groups. As expected, there was a greater benefit associated with sustained statin treatment in the per-protocol group compared with the intention-to-treat results.

As with the intention-to-treat results, on subgroup analyses, reductions in all-cause mortality and CVD events in those with baseline QRISK3 <10% were only seen when baseline LDL was ≥2.6 mmol/L or non-HDL was ≥3.4 mmol/L.

Adverse events

In both analyses, there appeared to be a small increased risk of muscle-related adverse events in the statin initiators with baseline QRISK3 <10% versus non-initiators. If a broader definition of myopathy including muscle pain was used, those with sustained statin use (per-protocol analysis) in the QRISK3 10–19% group also had more events than non-initiators. However, these muscle adverse event risks were much lower than has previously been suggested.

Notably, a recent meta-analysis of 19 randomised controlled trials with a median duration of 4.5 years, published in *The Lancet*, identified all the adverse effects attributed to statins in the individual drug product labels and explored whether these were identified in the trials (Cholesterol Treatment Trialists' Collaboration, 2026). In addition to the well-established glucose elevations and muscle symptoms, adverse event data from the trials only supported a causative relationship between four of the 66 adverse events listed, namely liver enzyme changes, other liver test abnormalities, urinary composition changes and oedema. The majority of listed adverse events, including cognitive impairment, depression, sleep disturbances and peripheral neuropathy, which are common perceived adverse effects that influence willingness to initiate and continue statins amongst our patients, were not identified.

Discussion

The outcomes in the intention-to-treat analyses are very similar to the findings from the CARDS (Collaborative Atorvastatin Diabetes Study) randomised controlled trial in people with type 2 diabetes, in which atorvastatin 10 mg for primary prevention in people aged 40–75 years reduced the risk of a first major cardiovascular event (hazard ratio 0.63) and all-cause mortality (hazard ratio 0.68) over the 4 years of the study. The results also support the European Society of Cardiology guideline's recommendation of statin initiation for primary prevention in those with type 2 diabetes and LDL cholesterol levels above 2.6 mmol/L (Visseren et al, 2021).

Limitations include those associated with observational studies such as residual confounding or healthy user bias; however, there was careful cohort matching and negative control outcomes. Adverse effects and discontinuation of therapy may not be reported to primary care, and this study did not explore statin impact on worsening glucose control. The study was carried out in the UK, so participants were mainly white. Further exploration in those aged <40 years and >75 years is also needed.

Implications for practice

Women with type 2 diabetes are at greater risk of CVD and all-cause mortality than men (Kautzky-Willer et al, 2023) yet may be less likely to receive treatment such as statins.

Unfortunately, statin therapy has had bad media coverage for many years, and this undoubtedly influences some people when we discuss initiating statins. I hope the results of this study, using UK data for primary prevention in people with type 2 diabetes, will help to support decision-making around statin initiation going forward, particularly the very low risk of myopathy, with no increase observed amongst many groups whilst taking statins. The relative and absolute reduction in all-cause mortality and major CVD events demonstrated at all levels of QRISK3 will hopefully encourage us to be more proactive in discussing statin initiation, including in people with a 10-year risk at baseline of <10%. It is important, however, to consider the subgroup analyses, which highlighted that benefits among people with a baseline QRISK3 of <10% were only seen in those who had an LDL cholesterol of at least 2.6 mmol/L.

Although QRISK3 is not yet integrated into electronic record systems, many of us are using the standalone calculator. Unfortunately, unless our family history records are completely up to date, the risk score needs to be calculated with the person in front of us, using precious consultation time. However, the inclusion of additional risk factors ensure that this is the most accurate cardiovascular risk predictor for the UK

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population, and it has been recommended by NICE as far back as the 2014 guidelines.

This study also reminds us of the importance of encouraging people to adhere to statins over the long term in order to optimise benefits. For example, in those with <10% risk, adherence to statins for 4 years was needed before a benefit in event rates was seen compared with those not initiating therapy. We can reassure people that there is little or no increased risk of myopathy or liver abnormalities associated with statin use, although muscle pain may occur in some groups (absolute risk 1% over 10 years). It is also important to encourage people to discuss any problems with therapy so that other lipid-lowering drugs, such as ezetimibe and/or bempedoic acid when appropriate, can be considered, rather than just allowing continued, and wasted, statin prescribing.

This study adds clarity and provides "good-news" messages, and reminds us that in primary care we really can make a difference to mortality and major cardiovascular event rates by helping people with type 2 diabetes to understand the benefits of statins, and by being even more proactive in prescribing.

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