Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

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Summary

Background The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab reduced LDL cholesterol and cardiovascular events in the FOURIER trial. In this prespecified analysis of FOURIER, we investigated the efficacy and safety of evolocumab by diabetes status and the effect of evolocumab on glycaemia and risk of developing diabetes.

Methods FOURIER was a randomised trial of evolocumab (140 mg every 2 weeks or 420 mg once per month) versus placebo in 27 564 patients with atherosclerotic disease who were on statin therapy, followed up for a median of 2·2 years. In this prespecified analysis, we investigated the effect of evolocumab on cardiovascular events by diabetes status at baseline, defined on the basis of patient history, clinical events committee review of medical records, or baseline HbA_{1c} of 6·5% (48 mmol/mol) or greater or fasting plasma glucose (FPG) of 7·0 mmol/L or greater. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation. The key secondary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. We also assessed the effect of evolocumab on glycaemia, and on the risk of new-onset diabetes among patients without diabetes at baseline. HbA_{1c} was measured at baseline then every 24 weeks and FPG was measured at baseline, week 12, week 24, and every 24 weeks thereafter, and potential cases of new-onset diabetes were adjudicated centrally. In a post-hoc analysis, we also investigated the effects on glycaemia and diabetes risk in patients with prediabetes (HbA_{1c} 5·7–6·4% [39–46 mmol/mol] or FPG 5·6–6·9 mmol/L) at baseline. FOURIER is registered with ClinicalTrials.gov, number NCT01764633.

Findings At study baseline, 11 031 patients (40%) had diabetes and 16 533 (60%) did not have diabetes (of whom 10 344 had prediabetes and 6189 had normoglycaemia). Evolocumab significantly reduced cardiovascular outcomes consistently in patients with and without diabetes at baseline. For the primary composite endpoint, the hazard ratios (HRs) were 0·83 (95% CI 0·75–0·93; p=0·0008) for patients with diabetes and 0·87 (0·79–0·96; p=0·0052) for patients without diabetes ($p_{interaction}$=0·60). For the key secondary endpoint, the HRs were 0·82 (0·72–0·93; p=0·0021) for those with diabetes and 0·78 (0·69–0·89; p=0·0002) for those without diabetes ($p_{interaction}$=0·65). Evolocumab did not increase the risk of new-onset diabetes in patients without diabetes at baseline (HR 1·05, 0·94–1·17), including in those with prediabetes (HR 1·00, 0·89–1·13). Levels of HbA_{1c} and FPG were similar between the evolocumab and placebo groups over time in patients with diabetes, prediabetes, or normoglycaemia. Among patients with diabetes at baseline, the proportions of patients with adverse events were 78·5% (4327 of 5513 patients) in the evolocumab group and 78·3% (4307 of 5502 patients) in the placebo group; among patients without diabetes at baseline, the proportions with adverse events were 76·8% (6337 of 8256 patients) in the evolocumab group and 76·8% (6337 of 8254 patients) in the placebo group.

Interpretation PCSK9 inhibition with evolocumab significantly reduced cardiovascular risk in patients with and without diabetes. Evolocumab did not increase the risk of new-onset diabetes, nor did it worsen glycaemia. These data suggest evolocumab use in patients with atherosclerotic disease is efficacious and safe in patients with and without diabetes.

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Introduction

In 2015, about 415 million adults aged 20–79 worldwide were estimated to have diabetes, and the prevalence is projected to grow to more than 640 million by 2040.[1] Not only does diabetes increase the risk of developing atherosclerotic cardiovascular disease,[2] but in patients with atherosclerotic cardiovascular disease concomitant diabetes is associated with worse outcomes.[3] Not surprisingly, cardiovascular disease is the greatest cause of morbidity and mortality in patients with diabetes.[4]

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Research in context

Evidence before this study

We searched MEDLINE using the terms "PCSK9," "proprotein convertase 9," "evolocumab," "alirocumab," or "bococizumab" combined with "diabetes mellitus", for articles published up to Aug 22, 2017, with no language restrictions. Abstracts were reviewed to identify original research publications describing the effect of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on cardiovascular outcomes stratified by baseline diabetes, or the effects of PCSK9 inhibitors on glycaemia or incident diabetes. This search was supplemented with additional relevant publications known by the authors. In terms of reduction in major cardiovascular events with a PCSK9 inhibitor in patients with and without diabetes, a dedicated cardiovascular outcomes trial with alirocumab is ongoing. A pooled analysis of the phase 3 trials to date only had a total of 104 major cardiovascular events, a number too small for subgroup analysis. For bococizumab, the dedicated cardiovascular outcomes trial was terminated early due to development of neutralising antibodies and there were only 749 major cardiovascular events. There was a statement of comparable relative risk reduction in patients with and without diabetes, but no data were presented and no comment on differences in event rates or absolute risk reduction. For new-onset diabetes, a significant risk with the use of PCSK9 inhibitors has not been reported previously, but there were only 174 cases with alirocumab in a pooled analysis of the phase 3 trials and 492 in the aborted trial with bococizumab.

Added value of this study

The findings of our analysis of the largest study to date suggest that PCSK9 inhibition with evolocumab lowered LDL cholesterol and significantly reduced cardiovascular risk with similar efficacy in patients with and without diabetes, but greater absolute risk reduction in patients with diabetes. PCSK9 inhibition did not increase the risk of new-onset diabetes, even in patients with prediabetes, nor did it worsen glycaemia over several years. The number of cardiovascular and new-onset diabetes events in this study are approximately three-times greater than in the studies reported to date.

Implications of all the available evidence

Recent guidelines have recommended identifying patients with diabetes and established atherosclerotic cardiovascular disease as having an extreme risk and requiring more intensive treatment to achieve lower LDL cholesterol goals. With similar relative and greater absolute risk reduction in patients with diabetes, and no discernible effect on glycaemia, PCSK9 inhibition might be a particularly attractive therapy in this population.

As a result, patients with diabetes need intensive management of their cardiovascular risk factors. Lowering of LDL cholesterol with a high-intensity statin is recommended for patients with diabetes, both in those with and without atherosclerotic cardiovascular disease.[5–7] Yet despite such therapy, patients with diabetes remain at high risk of recurrent cardiovascular events. Conversely, for patients without diabetes, there is concern regarding the initiation of a statin because of data that statins increase the risk of developing diabetes, either due to the drug itself or through its effect on transmembrane cholesterol transport.[8–11]

See Online for appendix

In the FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial,[12] the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab was shown to significantly reduce the risk of cardiovascular events in patients with atherosclerotic cardiovascular disease. In this prespecified analysis of the FOURIER trial, we report the efficacy of evolocumab in patients with and without diabetes, as well as data for the safety profile of evolocumab, particularly with respect to glycaemia and the development of new-onset diabetes.

Methods

Study design and population

FOURIER was a randomised, double-blind, placebo-controlled trial done at 1242 sites in 49 countries.[12,13] The trial included 27 564 patients aged 40–85 years with clinically evident atherosclerotic cardiovascular disease (previous myocardial infarction, previous non-haemorrhagic stroke, or symptomatic peripheral arterial disease) and additional risk factors (including diabetes), placing them at increased cardiovascular risk.[13] Patients were required to have an LDL cholesterol concentration of 1·8 mmol/L or higher, or a non-HDL cholesterol concentration of 2·6 mmol/L or higher, while taking an optimised lipid-lowering regimen including a high-intensity or moderate-intensity statin. Full inclusion and exclusion criteria are listed in the appendix (pp 1–3). All patients provided written informed consent and the study protocol and amendments were approved by ethics committees at each participating centre. The full study population was included in the present analyses.

Procedures

Patients were randomly assigned (1:1) to receive subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg once per month, per patient preference) or matching placebo injection. Randomisation was done with the use of a central computerised system, with stratification by final screening LDL cholesterol concentration (<85 or ≥85 mg/dL [<2·2 or ≥2·2 mmol/L]) and region.[12] The trial had a double-blind design, with patients and investigators masked to assigned treatment group.

Follow-up visits occurred at weeks 2, 4, 12, and every 12 weeks thereafter, and patients were followed up for a

median of 2·2 years (IQR 1·8–2·5). Blood specimens were obtained and sent to a central core laboratory for analysis at baseline and at weeks 4, 12, 24, and every 24 weeks thereafter, including for measurement of HbA_{1c} (NGSP-certified assay) every 24 weeks and fasting (≥9 h) plasma glucose (FPG) at weeks 12 and 24, and every 24 weeks thereafter. LDL cholesterol was calculated based on the Friedewald equation, unless the calculated value was below 1·03 mmol/L (40 mg/dL) or the measured triglycerides were greater than 4·52 mmol/L (400 mg/dL), in which case ultracentrifugation was done.

Outcomes

In this prespecified analysis, we examined the cardiovascular efficacy and safety of evolocumab by baseline diabetes status. As in the overall FOURIER trial, the primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or hospital admission for unstable angina. The key secondary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke.[12,13] Other secondary clinical endpoints were the individual components of the primary efficacy endpoint. LDL cholesterol and other reported lipid measures were prespecified exploratory outcomes, and HbA_{1c} and FPG were prespecified safety outcomes. Safety was assessed through collection of adverse events and central laboratory testing (aminotransferases and creatine kinase).

We also investigated the risk of new-onset diabetes among patients who did not have diabetes at baseline. New-onset diabetes was defined in accordance with the American Diabetes Association and National Diabetes Information Clearinghouse definitions (appendix p 4).[14,15] The definition of new-onset diabetes used did not differentiate between diabetes type.

A central clinical events committee led by the TIMI Study Group, the members of which were unaware of treatment assignment and post-randomisation lipid concentrations, adjudicated all efficacy endpoints and cases of new-onset diabetes.

Statistical analyses

As part of a prespecified analysis, patients were stratified into those with diabetes or not on the basis of patient history (per local investigator), clinical events committee review of baseline medical records, or baseline HbA_{1c} of 6·5% (48 mmol/mol) or greater or FPG of 7·0 mmol/L or greater. Only patients with diabetes identified on the basis of patient history had data available for diabetes type. In a post-hoc analysis, patients without diabetes were subdivided into those with prediabetes (baseline HbA_{1c} 5·7–6·4% [39–46 mmol/mol] or FPG 5·6–6·9 mmol/L) or normoglycaemia. Baseline characteristics of the subgroups were compared using Kruskal-Wallis tests for continuous data and χ^2 tests for categorical data.

All efficacy analyses of evolocumab versus placebo were done on an intention-to-treat basis (ie, all patients who were randomly assigned were analysed, irrespective of study drug compliance). Safety analyses included all randomly assigned patients who received at least one dose of study treatment and for whom post-dose data were available. Kaplan-Meier event rates were calculated up to 3 years and p values for time-to-event analyses are from log-rank tests. Hazard ratios (HRs) and 95% CIs for the effect of evolocumab versus placebo were generated by use of a Cox proportional hazards model, without adjustment (because of the randomised design). We tested effect modification by diabetes subgroup on the efficacy of evolocumab by incorporating interaction terms into Cox models. We also did landmark analyses, in which patients who were alive and in follow-up after 1 year formed the group at risk. For the analysis of risk of cardiovascular outcomes in patients with and without diabetes in the placebo group, a multivariable-adjusted HR was obtained from a Cox model that included the following baseline covariates: age, sex, BMI, self-reported ethnic origin, region, history of myocardial infarction, history of stroke, history of peripheral artery disease, hypertension, current smoking, history of heart failure, estimated glomerular filtration rate (eGFR), LDL cholesterol concentration, HDL cholesterol concentration, triglycerides concentration, and use of a high-intensity statin. Schoenfeld residuals were assessed in the Cox models and the proportional hazards assumptions were not violated. p values below 0·05 were regarded as significant. We used SAS (version 9.4) for the statistical analyses.

For more on **NGSP** see http://www.ngsp.org/

Role of the funding source

FOURIER was designed in collaboration between the trial executive committee (MSS, RPG, ACK, PSS, and TRP) and the study funder. The funder was responsible for data collection. The raw database was provided to the TIMI Study Group, which analysed the data independently of the funder. The funder helped to interpret the data and provided commentary on the manuscript. The corresponding author had full access to all the data in the study. The trial executive committee had final responsibility for the decision to submit for publication and assumes responsibility for the accuracy and completeness of the data and analyses.

Results

At baseline, using all of the data available, 11031 (40%) of the 27564 FOURIER trial participants had diabetes (10081 prevalent cases defined on the basis of patient history, 784 additional cases defined on the basis of clinical events committee review of baseline medical records, and 166 additional cases defined on the basis of HbA_{1c} or FPG measurement). There were significant differences in the baseline characteristics of patients with and without diabetes (table), notably including that

	Diabetes (n=11 031)	No diabetes (n=16 533)
Age (years)	62·6 (8·7)	62·5 (9·2)
Sex		
Men	8091 (73%)	12 704 (77%)
Women	2940 (27%)	3829 (23%)
Ethnic origin*		
White	8834 (80%)	14 624 (88%)
Non-white	2197 (20%)	1909 (12%)
Bodyweight (kg)	88·4 (18·6)	83·1 (16·2)
BMI (kg/m²)	30·7 (5·5)	28·5 (4·7)
Region		
North America	2033 (18%)	2538 (15%)
Europe	6312 (57%)	11 023 (67%)
Latin America	885 (8%)	938 (6%)
Asia Pacific and South Africa	1801 (16%)	2034 (12%)
Type of atherosclerosis†		
Myocardial infarction	8686 (79%)	13 665 (83%)
Non-haemorrhagic stroke	2391 (22%)	2946 (18%)
Peripheral artery disease	1696 (15%)	1946 (12%)
Cardiovascular risk factors		
Hypertension	9639 (87%)	12 445 (75%)
Current cigarette use	2434 (22%)	5343 (32%)
History of heart failure	2819 (26%)	3575 (22%)
eGFR (mL/min per 1·73m²)	74·8 (20·8)	76·4 (17·3)
Statin use‡		
High intensity	7379 (67%)	11 724 (71%)
Moderate intensity	3628 (33%)	4764 (29%)
Low intensity, unknown intensity, or no data	24 (<1%)	45 (<1%)
Ezetimibe use	485 (4%)	955 (6%)
Median lipid measures		
LDL cholesterol (mmol/L)	2·3 (2·0–2·8)	2·4 (2·1–2·8)
Total cholesterol (mmol/L)	4·3 (3·9–4·8)	4·4 (3·9–4·9)
HDL cholesterol (mmol/L)	1·1 (0·9–1·3)	1·2 (1·0–1·4)
Triglycerides (mmol/L)	1·7 (1·3–2·3)	1·4 (1·1–1·9)

Data are mean (SD), n (%), or median (IQR). All baseline characteristics differed significantly between patients with and without diabetes at baseline (p<0·0001), apart from age (p=0·55). *Ethnic origin was self-reported. †Patients could have more than one type of atherosclerosis. ‡Statin intensity was categorised as per the American College of Cardiology and American Heart Association guidelines.[5]

Table: **Baseline characteristics, by diabetes status**

patients with diabetes were more likely to be female; have higher BMIs and levels of triglycerides; have a history of hypertension, stroke, and peripheral artery disease; and have lower eGFR. Of the 10 081 patients who had data available for diabetes type (from patient medical history), 9795 (97%) had type 2 diabetes; the remainder all had type 1 diabetes. The median duration of diabetes was 5·7 years (IQR 1·9–11·9). At baseline, 7884 (72%) of the 11 022 patients with diabetes who had available data were taking an antihyperglycaemic drug, including 2721 (25%) who were taking insulin. In a post-hoc analysis of the 16 533 patients without diabetes at baseline, 10 344 (38% of total trial population) had prediabetes and 6189 patients (22%) were normoglycaemic. The baseline characteristics of the patients with prediabetes were in between those with diabetes and those with normoglycaemia (appendix p 5). As expected in a large randomised trial, there were no important imbalances in baseline characteristics by treatment group within these subgroups (appendix pp 6–7).

In the placebo group, the primary composite endpoint occurred in 739 of 5516 patients (3-year Kaplan-Meier rate 17·1%) with diabetes at baseline and in 824 of 8264 patients (3-year Kaplan-Meier rate 13·0%) without diabetes at baseline (p<0·0001). Likewise, again in the placebo group, the 3-year Kaplan-Meier rates of the key secondary composite endpoint were 12·2% (508 events in 5516 patients) in those with diabetes at baseline versus 8·4% (505 events in 8264 patients) in those without diabetes (p<0·0001). Compared with patients without diabetes, and after adjustment for baseline characteristics, in the placebo group patients with diabetes were at significantly greater risk for the primary endpoint (HR 1·26, 95% CI 1·13–1·40, p<0·0001) and key secondary endpoint (1·40, 1·23–1·60, p<0·0001). Patients with prediabetes at baseline had slightly higher rates of the primary and key secondary endpoints compared with patients with normoglycaemia (13·6% [546 events in 5191 patients] *vs* 12·1% [278 in 3073 patients] and 8·7% [332 events in 5191 patients] *vs* 8·0% [173 events in 3073 patients], respectively). However, after multivariable adjustment, the risk of primary and key secondary endpoint events was not significantly higher in patients with prediabetes than in those with normoglycaemia (primary endpoint: HR 1·14, 95% CI 0·98–1·32, p=0·08; key secondary endpoint: 1·09, 0·90–1·31, p=0·38).

Median baseline LDL cholesterol concentrations were 2·3 mmol/L in patients with diabetes and 2·4 mmol/L in those without diabetes at baseline (table). Compared with placebo, evolocumab lowered LDL cholesterol by 57% (95% CI 56–58; p<0·0001) in the diabetes subgroup and 60% (60–61; p<0·0001) in the non-diabetes subgroup at 48 weeks, down to 0·8 mmol/L in both subgroups (figure 1). Evolocumab similarly lowered related atherogenic lipid measures. Compared with placebo, at 48 weeks evolocumab reduced non-HDL cholesterol by 50% (95% CI 49–51) and 53% (52–54), apolipoprotein B by 48% (46–49) and 50% (49–50), and triglycerides by 16% (14–18) and 17% (14–17) in patients with and without diabetes at baseline, respectively (p<0·0001 for evolocumab *vs* placebo for all lipid measures in both subgroups; data for these and other lipid measures are shown in the appendix, pp 15–17).

Evolocumab significantly reduced cardiovascular outcomes to a consistent degree irrespective of baseline

diabetes status, with HRs of 0·83 (95% CI 0·75–0·93; p=0·0008) and 0·87 (0·79–0·96; p=0·0052) for the primary endpoint ($p_{interaction}$=0·60) and 0·82 (0·72–0·93; p=0·0021) and 0·78 (0·69–0·89; p=0·0002) for the key secondary endpoint ($p_{interaction}$=0·65) in patients with and without diabetes at baseline, respectively (figures 2 and 3, appendix pp 8–9). However, because of the higher baseline risk, the absolute risk reductions in the primary endpoint with evolocumab tended to be greater in patients with diabetes (2·7% [95% CI 0·7–4·8] over 3 years; number needed to treat 37 [95% CI 21–137]) than in patients without diabetes (1·6% [0·1–3·2] over 3 years; number needed to treat 62 [32–1226]), driven largely by a greater absolute risk reduction in coronary revascularisation (2·7% [1·1–4·2] *vs* 1·8% [0·6–3·1]). Event rates for the outcomes included in the primary and secondary endpoints in each treatment group for patients with and without diabetes are listed in the appendix (pp 8–9). The absolute risk reductions in the key secondary endpoint were 2·0% (95% CI 0·2–3·9) in patients with diabetes and 2·0% (0·7–3·3) in patients without diabetes, leading to number needed to treat over 3 years of 50 (95% CI 26–600) and 50 (30–139), respectively.

As was seen in the overall trial,[12] the magnitude of the risk reduction in the primary endpoint with evolocumab treatment tended to increase over time, from an HR of 0·90 (95% CI 0·77–1·04) in the first year to an HR of 0·77 (0·67–0·89) beyond the first year in patients with diabetes, and from a HR of 0·87 (0·76–0·99) in the first year to a HR of 0·84 (0·73–0·97) beyond the first year in patients without diabetes. Likewise, for the key secondary endpoint the risk reduction increased from an HR of 0·87 (0·73–1·04) in the first year to an HR of 0·75 (0·63–0·89) beyond the first year in patients with diabetes, and from an HR of 0·81 (0·67–0·97) in the first year to an HR of 0·75 (0·63–0·90) beyond the first year in patients without diabetes (appendix pp 18–19).

The overall rates of adverse events and serious adverse events were similar between evolocumab and placebo in patients with and without diabetes (appendix pp 10–11). Likewise, the rates of specific adverse events of interest were similar between treatment groups, with the only exception being injection-site reactions, which tended to occur more frequently in patients treated with evolocumab in both diabetes and non-diabetes subgroups. Anti-evolocumab-binding antibodies developed in 11 (<1%) of 5311 patients with diabetes and 32 (<1%) of 8032 patients without diabetes in the evolocumab group. Among patients with diabetes who were on insulin at baseline and who were in the evolocumab treatment group (n=1270), binding antibodies developed in three patients (<1%). No patients developed neutralising antibodies.

Evolocumab did not increase the risk of new-onset diabetes in participants without diabetes at baseline (8·0% [663 of 8256] *vs* 7·6% [631 of 8254]; HR 1·05, 95% CI 0·94–1·17; figure 4). In post-hoc analyses, a total of 90% (1163 of 1294) of the conversions occurred in patients with prediabetes at baseline, with no imbalance by treatment group (11·3% [582 of 5150] in the evolocumab group *vs* 11·2% [581 of 5188] in the placebo group; HR 1·00, 0·89–1·13]). The remaining 10% (131 of 1294) of events occurred in patients with normoglycaemia at baseline, with a nominal imbalance between the evolocumab and placebo groups (2·6% [81 of 3106] *vs* 1·6% [50 of 3066]; HR 1·60, 1·13–2·28).

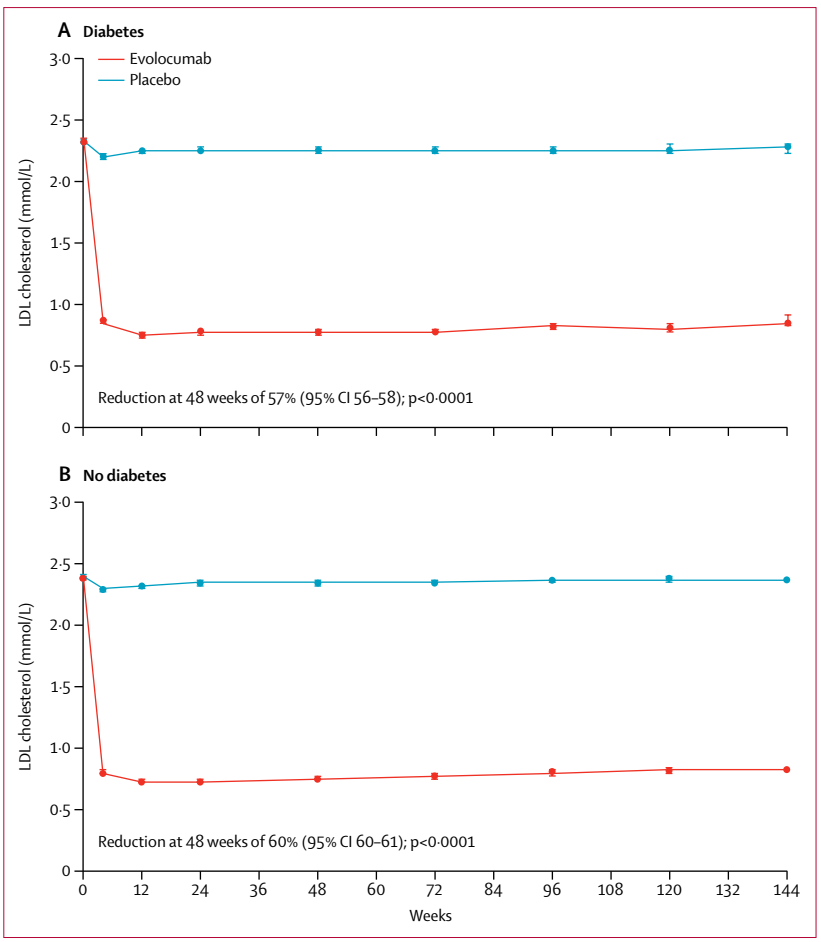

Figure 1: **LDL cholesterol concentrations over time**
Data are median values in the evolocumab and placebo treatment groups, for patients with and without diabetes at baseline. Error bars are 95% CIs.

No heterogeneity in risk of new-onset diabetes was seen in patients concomitantly on or not on a high-intensity statin: in the patients concomitantly on a high-intensity statin, 8·0% (474 of 5899) in the evolocumab group had new-onset diabetes compared with 7·6% (441 of 5810) in the placebo group (HR 1·06, 95% CI 0·93–1·20); the corresponding numbers in patients not on a high-intensity statin were 8·0% (189 of 2357) versus 7·8% (190 of 2444; HR 1·03, 0·84–1·26).

Levels of HbA_{1c} and FPG were similar between the two treatment groups over time in patients with or without diabetes (figure 5, appendix p 20), as well as in patients with prediabetes (appendix p 21). Likewise, changes in

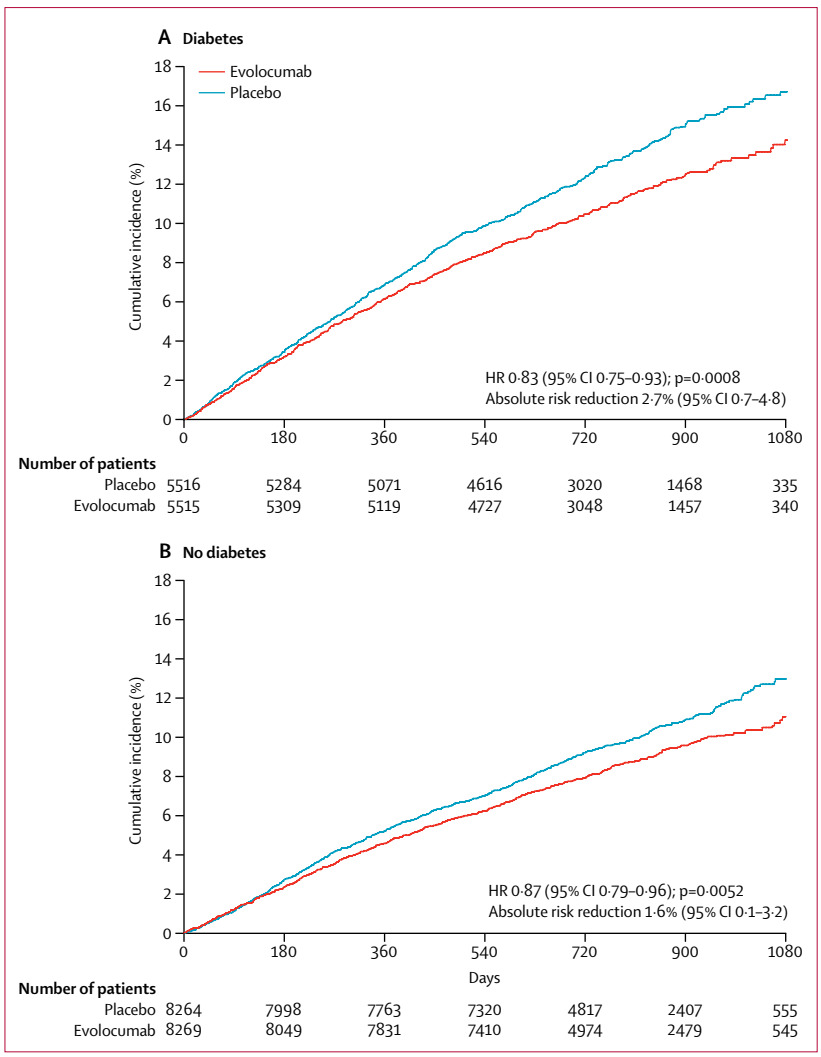

Figure 2: **Primary endpoint**
Data are the cumulative event rates for the primary efficacy endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation) in the evolocumab and placebo treatment groups, for patients with and without diabetes at baseline. p values were calculated with log-rank tests. Hazard ratios (HRs) and 95% CI are from a Cox model. The $p_{interaction}$ value between baseline diabetes status and efficacy of evolocumab was 0·60.

HbA_{1c} and FPG from baseline were similar between the evolocumab and placebo groups in patients with diabetes, prediabetes, and normoglycaemia (appendix pp 12–13). In patients with diabetes at baseline, the proportion with an HbA_{1c} of 7·0% or higher in the evolocumab and placebo groups were 46·1% (2329 of 5049) and 45·3% (2271 of 5015), respectively, at 48 weeks and 43·6% (539 of 1236) and 43·4% (561 of 1292), respectively, at 144 weeks (totals are those with available data for these timepoints). The proportion of patients with diabetes who initiated insulin therapy was only nominally lower (considering the post-hoc nature of the analysis and no correction for multiplicity) in the evolocumab group than in the placebo group (5·3% [221 of 4164] *vs* 6·4% [262 of 4103], p=0·037). There was no difference in the change in bodyweight over time with evolocumab versus placebo in patients with or without diabetes at baseline (appendix p 14).

Discussion

This analysis of the FOURIER trial yielded three main findings. First, among patients with atherosclerotic cardiovascular disease, the presence of diabetes, but not prediabetes, was independently associated with a substantially increased risk of cardiovascular morbidity and mortality. Second, evolocumab lowered LDL cholesterol and significantly reduced cardiovascular risk with similar efficacy in patients with and without diabetes. However, because of their heightened baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with evolocumab treatment. Third, evolocumab did not increase the risk of new-onset diabetes, nor did it worsen glycaemia, over a median of 2·2 years of follow-up.

The similar relative risk reductions in cardiovascular outcomes seen with LDL cholesterol lowering with evolocumab in patients with and without diabetes is supported by analogous evidence for LDL cholesterol lowering with statin therapy.[16] However, the rate of cardiovascular events was about 50% higher in patients with diabetes than in those without. This observation, coupled with the equivalent LDL cholesterol lowering and relative risk reduction in cardiovascular events with evolocumab, resulted in greater absolute benefit with respect to the primary composite outcome, which might have implications for therapeutic decision making. Specifically, some professional societies have focused on the absolute risk reduction as a means by which to determine which patients should be treated with a PCSK9 inhibitor.[17] Likewise, recent guidelines have recommended identifying people with diabetes and established atherosclerotic cardiovascular disease as having an extreme risk requiring more intensive treatment to achieve lower LDL goals (eg, <1·4 mmol/L).[18] The roughly 50% higher baseline risk in patients with diabetes in the present analysis was modifiable and translated into a roughly 50% greater absolute cardiovascular risk reduction with more intensive LDL cholesterol lowering with evolocumab. Practically, these findings mean that the number needed to treat with evolocumab over 3 years to prevent one primary endpoint event was 62 in patients without diabetes, but only 37 in patients with diabetes, suggesting that use of evolocumab in patients with atherosclerotic cardiovascular disease and diabetes might be particularly attractive from a cost-effectiveness standpoint.

The European Society of Cardiology and European Atherosclerosis Society guidelines for dyslipidaemia use the same LDL cholesterol target (<1·8 mmol/L) for patients with diabetes without atherosclerotic cardiovascular disease (but older than 40 years and with cardiovascular risk factors or markers of target organ

damage) as they do for patients with atherosclerotic cardiovascular disease because of their high risk for cardiovascular events.[7] In view of the FOURIER inclusion criteria, our data do not inform on the potential benefits of PCSK9 inhibition in patients with diabetes without atherosclerotic cardiovascular disease. However, these data suggest this population might be a high-yield primary prevention population to investigate in future studies.

Equally important is the safety profile of evolocumab. In addition to providing reassurance that the overall safety profile was similar in patients with and without diabetes, our data suggest that the risk of new-onset diabetes (which was adjudicated by a centralised clinical events committee) were similar in the evolocumab and placebo groups. We also did not identify any appreciable effect of evolocumab on glycaemia in patients with or without diabetes. Lastly, evolocumab did not affect bodyweight. Our findings are generally supported by evidence from much smaller datasets with the PCSK9 inhibitors alirocumab and bococizumab, neither of which was associated with an increased risk of new-onset diabetes, although bococizumab was associated with a very small increase (0·1 mmol/L) in blood glucose concentrations at 52 weeks compared with placebo.[19,20] These data also complement the findings of another recent analysis from the FOURIER trial,[21] in which we identified no association between low levels of achieved LDL cholesterol and the risk of developing diabetes.

Our findings stand in contradistinction to evidence for statins, which have been shown to increase HbA_{1c} levels by 0·12% in patients with diabetes,[22] increase bodyweight,[11] and cause a 9% increase in the risk of new-onset diabetes.[8] High-intensity statins have been shown to cause a further 12% increase in the odds of new-onset diabetes compared with moderate-intensity statins.[8,9,11] In the JUPITER trial, researchers compared a high-intensity statin with placebo over a median follow-up of 1·9 years. The mean difference in LDL cholesterol between the two groups was 1·2 mmol/L, and the HR for new-onset diabetes with the statin was 1·25 (95% CI 1·05–1·49).[23] By way of comparison, FOURIER had a greater mean LDL cholesterol difference between the two groups (1·38 mmol/L) and longer follow-up (median 2·2 years).[12] Based on the number of cases of new-onset diabetes in FOURIER, there was greater than 90% power to detect the HR of 1·25 seen in JUPITER.

Results of genetic analyses have shown that variants in *HMGCR* (mimicking the effect of statins) are associated with an increased risk of diabetes and glucose concentration, as well as increased bodyweight.[11] Findings from recent mendelian randomisation studies suggest that genetic variants in *PCSK9* were also associated with an increased risk of diabetes, and of a similar magnitude as genetic variants in *HMGCR*.[24,25] Indeed, some data suggest an association between the risk of diabetes and variants in several genes that affect LDL cholesterol.[26,27] Investigators have extrapolated from the small effects on LDL cholesterol seen with individual variants (several of which were non-significant on their own) to estimate the odds ratio for new-onset diabetes per 1 mmol/L lower LDL cholesterol mediated through PCSK9 to be 1·19 to 1·29.[25,26] Using the effect estimates from the genetic studies and the LDL cholesterol-lowering effect of evolocumab seen in FOURIER, odds ratios of 1·27–1·42 for new-onset diabetes would be expected; on this basis, the present analysis had greater than 90% statistical power to detect such an increased risk.

In both statin trials and genetic studies, the risk of diabetes seemed to be largely confined to patients at clinically high risk for developing diabetes, such as those with prediabetes.[23,24,28] In post-hoc analyses, we did not identify an increased risk of diabetes in patients with prediabetes at baseline, nor did evolocumab adversely

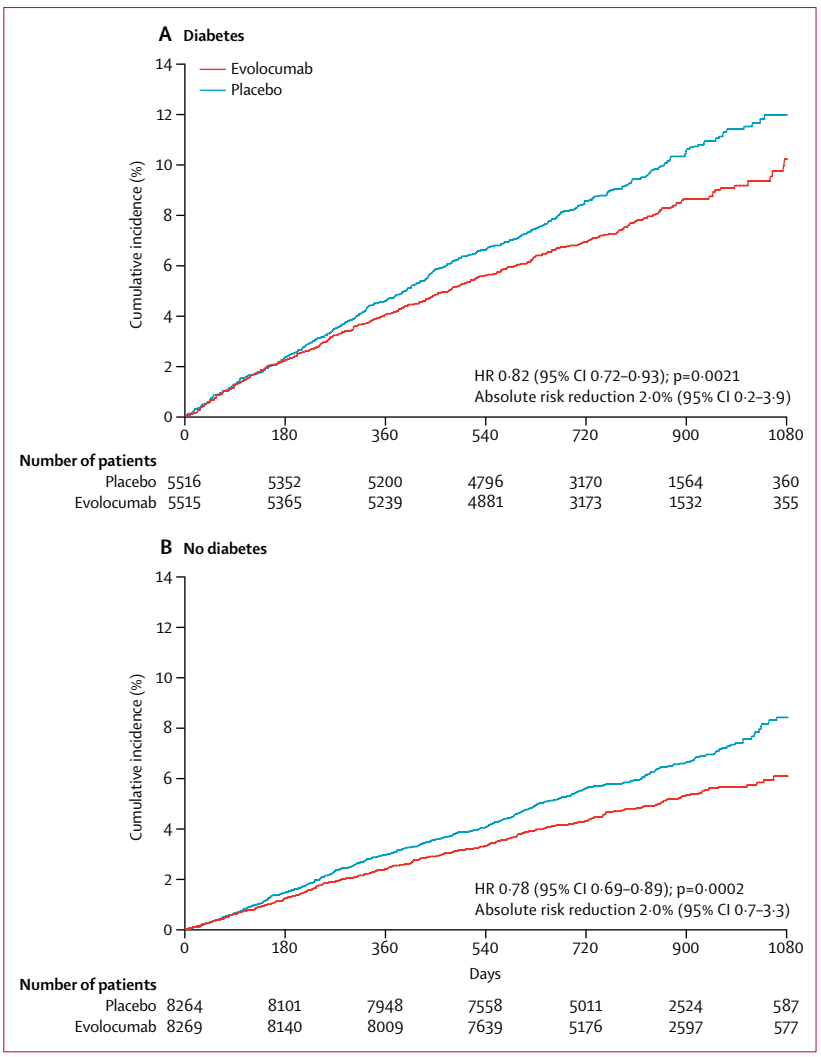

Figure 3: **Key secondary endpoint**
Data are the cumulative event rates for the key secondary efficacy endpoint (composite of cardiovascular death, myocardial infarction, or stroke) in the evolocumab and placebo treatment groups, for patients with and without diabetes at baseline. p values were calculated with log-rank tests. Hazard ratios (HRs) and 95% CI are from a Cox model. The $p_{interaction}$ value between baseline diabetes status and efficacy of evolocumab was 0·65.

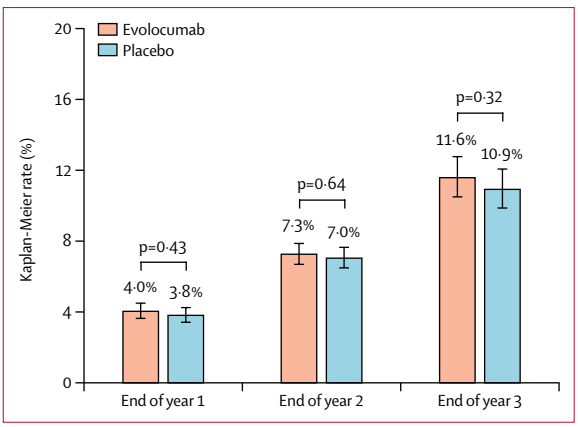

Figure 4: **New-onset diabetes**
Data are the cumulative incidence of new-onset diabetes at the end of 1, 2, and 3 years of follow-up in the evolocumab and placebo treatment groups, among patients without diabetes at baseline. Error bars are 95% CIs.

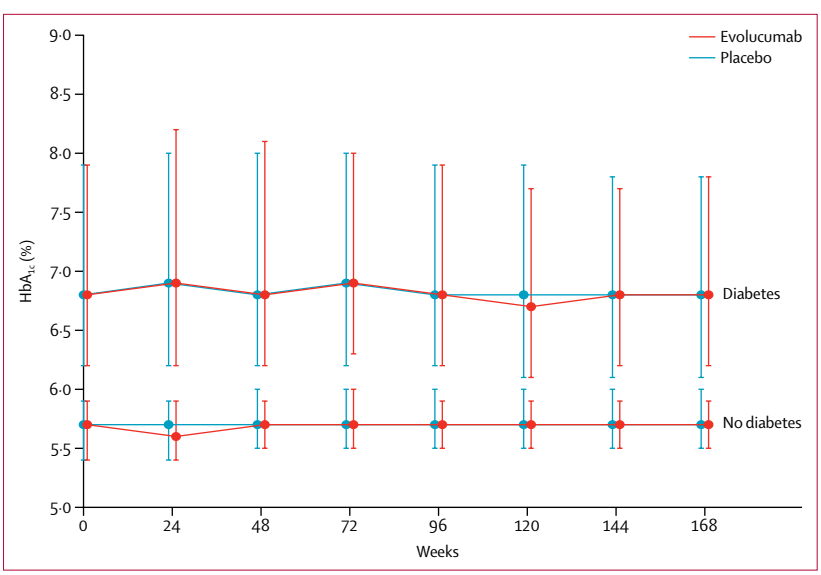

Figure 5: **HbA_{1c} over time**
Data are median values in the evolocumab and placebo treatment groups, for patients with and without diabetes. Error bars are IQRs.

affect glycaemia in patients with prediabetes. Considering the post-hoc nature of the analyses and the absence of correction for multiplicity, there was only a nominal excess of new-onset diabetes in patients with normoglycaemia at baseline. However, there was no effect on glycaemia in patients with normoglycaemia at baseline, and in view of the absence of excess of new-onset diabetes with evolocumab in the patient subset in whom statins show the greatest risk (those with prediabetes), we believe that the imbalance in new-onset diabetes in patients with normoglycaemia at baseline (in whom only 10% of the cases occurred) in the present analysis is likely to be a chance finding.

An important point to note is that the statin trials were typically of longer duration (about 5 years) and mendelian randomisation studies reflect lifelong differences, whereas in FOURIER the median follow-up was only 2·2 years. Thus, we cannot rule out that long-term exposure to a PCSK9 inhibitor might lead to an increased risk of diabetes. However, in smaller, open-label extension studies of evolocumab done for up to 4 years, an excess of new-onset diabetes was not seen.[29] Moreover, the event curves for diabetes tended to diverge early in the statin trials and significant risk was seen in a statin trial with a median follow-up of only 1·9 years.[23] Another point is that genetic variants would be expected to affect both intracellular and extracellular PCSK9 concentrations, whereas evolocumab is a monoclonal antibody that binds only to extracellular PCSK9. The biological relevance of this difference is unknown.

Although the FOURIER trial is the largest study of clinical and glycaemic outcomes with a PCSK9 inhibitor and had central adjudication of new-onset diabetes, some potential limitations should be acknowledged. As noted, the median duration of follow-up was only 2·2 years. Longer follow-up data (which is being gathered for about 6600 patients for roughly 5 years [NCT03080935 and NCT02867813]) should add important information. Additionally, patients in FOURIER were on background statin therapy, with close to 70% being on high-intensity statin therapy; thus, we cannot assess the effect of evolocumab on diabetes in patients not on statin therapy. However, no effect of evolocumab on glycaemia was seen in patients not on a statin in a previous 52-week study.[30] Finally, the case record form for FOURIER did not capture data on antihyperglycaemic drugs other than insulin, and the protocol did not require routine glucose tolerance testing, which would have detected post-challenge glucose abnormalities.

In conclusion, evolocumab lowered LDL cholesterol and significantly reduced cardiovascular risk with similar relative efficacy in patients with and without diabetes. Due to their heightened baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with evolocumab therapy. Evolocumab did not increase the risk of new-onset diabetes, including in patients with prediabetes, nor did it worsen glycaemia. These data suggest that use of evolocumab in patients with atherosclerotic cardiovascular disease and diabetes is particularly efficacious and that evolocumab treatment is equally safe in patients with and without diabetes.

Contributors
MSS contributed to the design of the study, searched the scientific literature, contributed to data interpretation, wrote the first draft of the report, wrote subsequent drafts of the report (with input from all coauthors), and constructed figures. LAL, SDW, RPG, ACK, PSS, and TRP contributed to the design of the study, contributed to data interpretation, and contributed to revision of the draft report. PD, GMDF, IG-B, BSL, and YH contributed to data interpretation and revision of the draft report. SAM and JFK did the data analysis, contributed to data interpretation, contributed to revision of the draft report, and designed the figures. ALP and NH collected data, contributed to data interpretation, and contributed to revision of the draft report.

Declaration of interests
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