Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

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Summary

Background LDL cholesterol is a well established risk factor for atherosclerotic cardiovascular disease. How much one should or safely can lower this risk factor remains debated. We aimed to explore the relationship between progressively lower LDL-cholesterol concentrations achieved at 4 weeks and clinical efficacy and safety in the FOURIER trial of evolocumab, a monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9).

Methods In this prespecified secondary analysis of 25 982 patients from the randomised FOURIER trial, the relationship between achieved LDL-cholesterol concentration at 4 weeks and subsequent cardiovascular outcomes (primary endpoint was the composite of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or unstable angina; key secondary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke) and ten prespecified safety events of interest was examined over a median of 2·2 years of follow-up. We used multivariable modelling to adjust for baseline factors associated with achieved LDL cholesterol. This trial is registered with ClinicalTrials.gov, number NCT01764633.

Findings Between Feb 8, 2013, and June 5, 2015, 27 564 patients were randomly assigned a treatment in the FOURIER study. 1025 (4%) patients did not have an LDL cholesterol measured at 4 weeks and 557 (2%) had already had a primary endpoint event or one of the ten prespecified safety events before the week-4 visit. From the remaining 25 982 patients (94% of those randomly assigned) 13 013 were assigned evolocumab and 12 969 were assigned placebo. 2669 (10%) of 25 982 patients achieved LDL-cholesterol concentrations of less than 0·5 mmol/L, 8003 (31%) patients achieved concentrations between 0·5 and less than 1·3 mmol/L, 3444 (13%) patients achieved concentrations between 1·3 and less than 1·8 mmol/L, 7471 (29%) patients achieved concentrations between 1·8 to less than 2·6 mmol/L, and 4395 (17%) patients achieved concentrations of 2·6 mmol/L or higher. There was a highly significant monotonic relationship between low LDL-cholesterol concentrations and lower risk of the primary and secondary efficacy composite endpoints extending to the bottom first percentile (LDL-cholesterol concentrations of less than 0·2 mmol/L; p=0·0012 for the primary endpoint, p=0·0001 for the secondary endpoint). Conversely, no significant association was observed between achieved LDL cholesterol and safety outcomes, either for all serious adverse events or any of the other nine prespecified safety events.

Interpretation There was a monotonic relationship between achieved LDL cholesterol and major cardiovascular outcomes down to LDL-cholesterol concentrations of less than 0·2 mmol/L. Conversely, there were no safety concerns with very low LDL-cholesterol concentrations over a median of 2·2 years. These data support further LDL-cholesterol lowering in patients with cardiovascular disease to well below current recommendations.

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Introduction

LDL cholesterol has been well established as a modifiable risk factor for atherosclerotic cardiovascular disease in epidemiological studies. In a series of landmark randomised controlled trials with statins, significant reductions in cardiovascular events were shown in patients with very high LDL-cholesterol concentrations (eg, decreasing LDL cholesterol from 5 to 3 mmol/L), average LDL-cholesterol concentrations (eg, decreasing LDL cholesterol from 3·5 to 2·5 mmol/L), and below average LDL-cholesterol concentrations (eg, decreasing LDL cholesterol from 2·5 to 1·5–2 mmol/L).[1] Although the trials did not allocate patients to different LDL-cholesterol targets, the data suggested that lowering LDL cholesterol across a broad range of concentrations conferred similar cardiovascular risk reduction per unit reduction of LDL cholesterol. Based on these trials, the LDL-cholesterol target or threshold for treatment in published guidelines decreased to 2·5 mmol/L and then 1·8 mmol/L in high-risk patients.[2–5]

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Research in context

Evidence before this study

We searched MEDLINE on July 24, 2017, with the terms "cholesterol, LDL" and either "myocardial infarction" or "stroke." The search was limited to publications from 2014 onwards since that was the date of a comprehensive meta-analysis on this topic. Abstracts were reviewed by two of the authors (RPG and MSS) to find publications describing the association of on-treatment LDL cholesterol and cardiovascular outcomes in patients with atherosclerotic cardiovascular disease. Relevant publications were supplemented with additional relevant publications known by the authors. None of the trials studying patients treated with statins provided data on a cutpoint of less than 1·3 mmol/L. We have published data on ezetimibe from IMPROVE-IT, in which the lowest cutpoint was 0·8 mmol/L, but there were fewer than 1000 patients in that subgroup. There is a published pooled analysis of smaller lipid-lowering trials of another proprotein convertase subtilisin-kexin type 9 inhibitor, alirocumab, but with approximately a tenth of the number of patients with an LDL-cholesterol concentration of less than 0·5 mmol/L.

Added value of this study

We found a strong relationship between achieved LDL cholesterol down to concentrations 0·2 mmol/L and a progressive reduction in major cardiovascular outcomes, with no increase in safety events. These observations extend previous findings with statins and ezetimibe to lower concentrations of LDL cholesterol than previously reported, in a larger sample size, and with the newest and most potent lipid-lowering therapy approved to date.

Implications of all the available evidence

All evidence to date from trials of intensive lipid lowering supports reduction of LDL cholesterol in high-risk patients to concentrations below those currently recommended in cholesterol guidelines. Studies with a longer follow-up period than in this study are needed to exclude the development of late complications of persistent very-low concentrations of LDL cholesterol.

Findings from the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial[6] showed that the proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibody evolocumab, when added to background statin therapy, lowered LDL-cholesterol concentrations to a median of 0·8 mmol/L (IQR 0·5–1·2) and significantly reduced the risk of cardiovascular events in patients with stable atherosclerotic cardiovascular disease who were followed up for a median of 2·2 years. No significant differences were found in major safety events or in prospective cognitive function testing between treatment groups.[7]

Notably, the LDL-cholesterol concentrations achieved were substantially lower than those in previous clinical outcome trials with lipid-lowering therapies, and it is not known whether there is a threshold below which there is no added clinical benefit, or whether there is an increase in adverse safety events. Our aim was to explore the relationship between progressively lower LDL cholesterol achieved at 4 weeks and clinical efficacy and safety in this prespecified, secondary analysis of the FOURIER trial.

Methods

Study design and participants

FOURIER[6,8] was a randomised, double-blind, placebo-controlled trial that enrolled 27 564 patients aged 40–85 years with stable atherosclerotic cardiovascular disease (previous myocardial infarction, previous non-haemorrhagic stroke, or symptomatic peripheral arterial disease) and additional risk factors placing them at increased cardiovascular risk. Eligible patients had LDL-cholesterol concentrations of 1·8 mmol/L or higher or non-HDL concentrations of 2·6 mmol/L or higher while taking an optimised lipid-lowering regimen including a high or moderate intensity statin, with or without ezetimibe.

Key exclusion criteria were recent myocardial infarction or stroke within 4 weeks, previous haemorrhagic stroke, estimated glomerular filtration rate of less than 20 mL/min per 1·73 m², New York Heart Association class III or IV heart failure or left ventricular ejection fraction of less than 30%, malignancy in the previous 10 years, and elevation of creatine kinase more than five times above normal or hepatic aminotransferase more than three times above normal. All patients provided written informed consent. The protocol was approved by ethics committees at each centre.

Procedures

Patients were randomly assigned (1:1) either subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg once per month, per patient preference) or matching placebo injections, and were followed up for a median of 2·2 years (IQR 1·8–2·5 years).

After randomisation, follow-up visits occurred at weeks 2, 4, 12, and every 12 weeks thereafter. Blood specimens were obtained and sent to a central core laboratory for analysis at weeks 4, 12, 24, and every 24 weeks thereafter. Lipid concentrations after randomisation were not made available to patients, investigators, study personnel, or the endpoint adjudicators. LDL cholesterol was calculated based on the Friedewald equation,[11] unless the calculated value was less than 1·03 mmol/L (40 mg/dL) or the measured triglycerides were higher than 4·52 mmol/L (400 mg/dL), in which case a direct measurement using ultracentrifugation was done. Patients with an

LDL-cholesterol assessment at week 4 who did not have a primary efficacy or prespecified safety event prior to the week-4 visit were included in this analysis.

Outcomes

The primary endpoint of the FOURIER trial was the composite of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or hospital admission for unstable angina. The key secondary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke. An independent clinical endpoint committee adjudicated all efficacy endpoints as well as new-onset diabetes mellitus, without knowledge to randomisation assignment or post-randomisation lipid values.

There were ten prespecified safety endpoints: serious adverse events, adverse events leading to study drug discontinuation (excluding injection-site reactions because these were more frequent with evolocumab, as was the achievement of very low LDL cholesterol, which would confound the results), elevation in hepatic transaminase concentration of more than three times above normal, new or recurrent cancer (excluding non-melanoma skin cancer), cataract-related adverse events, elevation in creatine kinase concentration of more than five times above normal, haemorrhagic stroke, neurocognitive adverse events, new-onset diabetes mellitus, and non-cardiovascular death. Investigators reported adverse events as verbatim terms that were then mapped to the Medical Dictionary for Regulatory Activities (version 19.1) preferred terms with over reading by trained coders.

In patients who participated in the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study,[7,9] an embedded study within the FOURIER trial, we evaluated the primary endpoint of spatial working memory strategy index (executive function), the three secondary endpoints (spatial working memory between-errors score, working memory; paired associates learning score adjusted, episodic memory; and five-choice reaction time, psychomotor speed), and a global composite score (average of the four scores), as assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) tool, across the five groups of achieved LDL cholesterol. CANTAB scores were analysed in 1154 patients who had baseline cognitive testing completed before or on the first day of study drug, and who did not have an efficacy or prespecified safety event prior to the measurement of the LDL cholesterol at 4 weeks.

Patients were also asked for their self-assessment of changes in memory and executive function (including the subdomains of planning, organisation, and divided attention) at the end of the trial compared with the start using a shortened version (23 questions) of the Everyday Cognition (ECog) self-assessment scales[10] (appendix pp 2–3). Lower scores represented better function (range 1–5).

Statistical analysis

Patients were categorised into five prespecified subgroups based on the LDL cholesterol at 4 weeks, irrespective of treatment assignment: <0·5 mmol/L, 0·5 to less than 1·3 mmol/L, 1·3 to less than 1·8 mmol/L, 1·8 to less than 2·6 mmol/L, and 2·6 mmol/L or higher. We tested trends in baseline patient characteristics across achieved LDL-cholesterol groups using the Jonkheere-Terpstra trend test for continuous variables and Cochran–Armitage trend test for categorical variables. Independent predictors of achieving an LDL-cholesterol concentration of less than 0·5 mmol/L at 4 weeks (in addition to treatment assignment) were identified and served as covariates to generate multivariable adjusted hazard ratios (HRs) using Cox proportional hazard models[12,13] or odds ratios using logistic regression models[14] for outcomes of interest. These variables included the LDL-cholesterol concentration at baseline, age, sex, race, body-mass index, geographical region, and use of a P2Y12 inhibitor. We calculated adjusted p_{trend} values using Cox proportional hazard regression by testing the coefficient of the achieved LDL groups or the Cochran–Armitage trend test of proportions in achieved LDL groups, as appropriate. We compared Kaplan-Meier estimates with the log-rank test. We plotted the relationship between composite efficacy endpoints and achieved LDL cholesterol using a smoothing function applied to the averages of estimated event rates at each LDL level based on the adjusted Cox models. In a post-hoc analysis, we evaluated efficacy and safety outcomes in patients with LDL cholesterol of less than 0·4 mmol/L (15 mg/dL) and less than 0·26 mmol/L (10 mg/dL) compared with patients with LDL-cholesterol concentrations of 2·6 mmol/L (100 mg/dL) or higher.

The raw database was provided to the Thrombolysis in Myocardial Infarction (TIMI) study group, which did data analyses independently of the study sponsor. A two-sided p value of less than 0·05 was considered evidence of a significant effect; no adjustments were made for assessment of multiple endpoints.[15] Analyses were done in SAS (version 9.4). The FOURIER (NCT01764633) and EBBINGHAUS (NCT02207634) trials are registered with ClinicalTrials.gov.

For the **Cambridge Neuropsychological Test Automated Battery tool** see www.cambridgecognition.com

Role of the funding source

The funder collected and interpreted the data, and helped edit the manuscript. The executive committee (MSS, TRP, RPG, ACK, and PSS) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 27 564 patients who were randomly assigned either evolocumab or placebo in the FOURIER trial between Feb 8, 2013, and June 5, 2015, 1025 (4%) patients did not have an LDL cholesterol measured at 4 weeks and 557 (2%) had already had a primary endpoint event or one

See **Online** for appendix

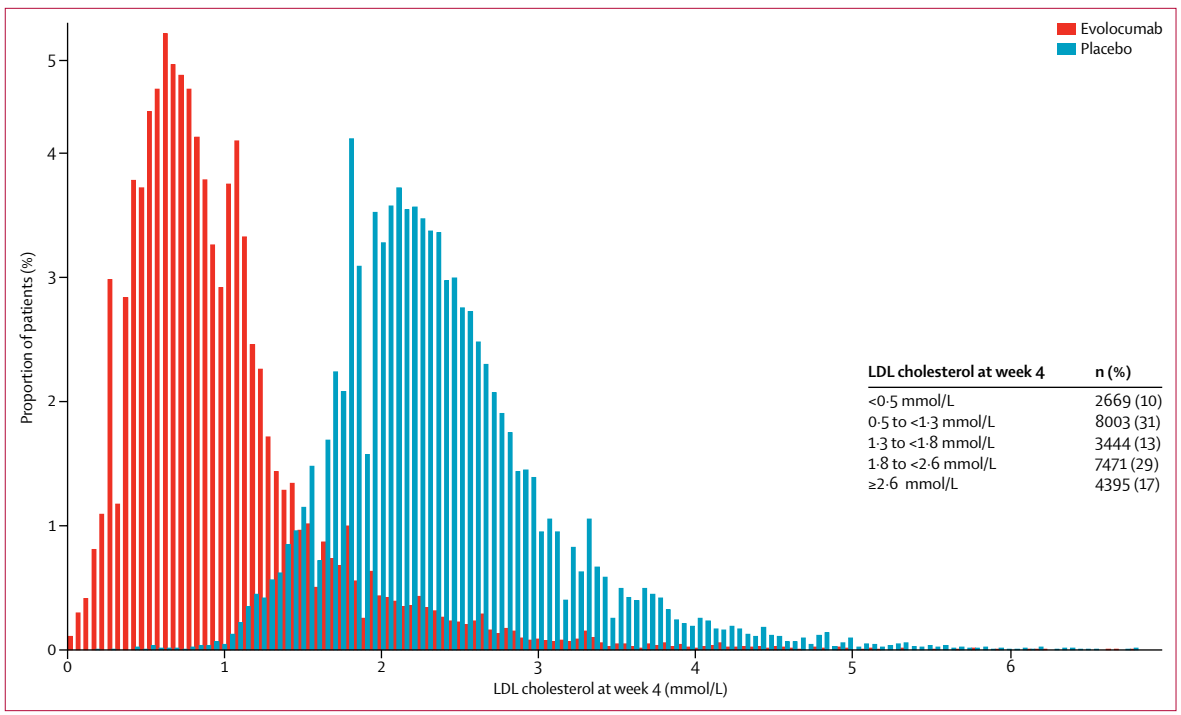
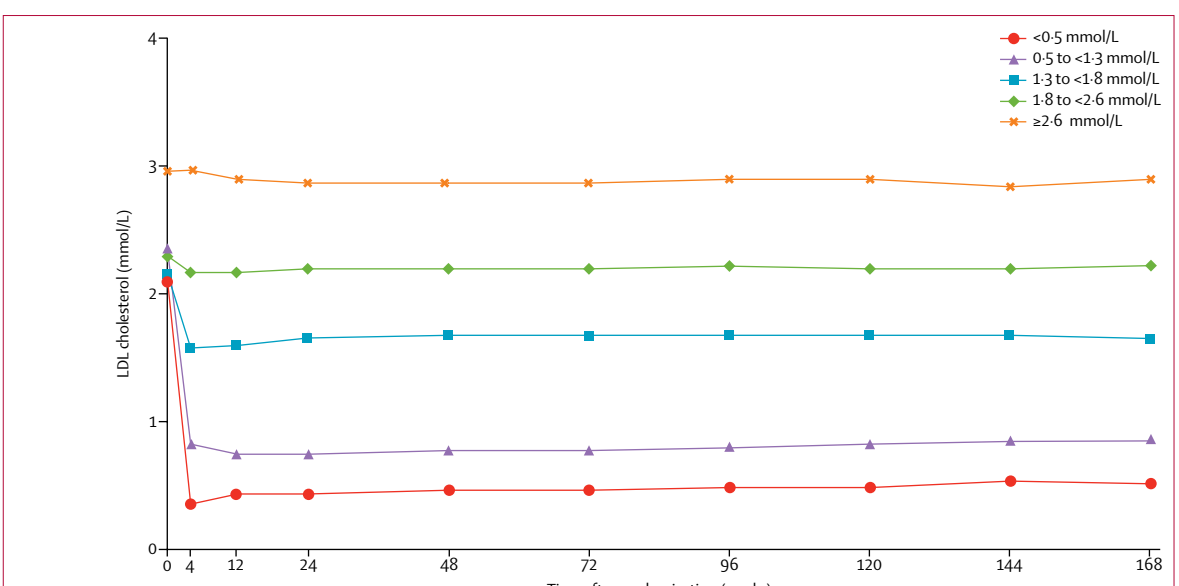


***Figure 1*: Distribution of achieved LDL-cholesterol concentrations at 4 weeks in patients who did not have a primary efficacy or prespecified safety event before the study**
Red bars are evolocumab (median 0·8 mmol/L, IQR 0·5–1·2). Blue bars are placebo (median 2·2 mmol/L, IQR 1·9–2·7).



Number of patients									
<0·5 mmol/L	2669	2610	2569	2503	2466	2123	1334	650	132
0·5 to <1·3 mmol/L	8003	7747	7646	7473	7309	6480	4223	1973	465
1·3 to <1·8 mmol/L	3444	3322	3252	3161	3094	2667	1641	741	183
1·8 to <2·6 mmol/L	7471	7235	7133	6957	6791	5992	3844	1846	428
≥2·6 mmol/L	4395	4218	4158	4028	3927	3457	2194	1087	232

***Figure 2*: Median LDL-cholesterol concentrations categorised by achieved LDL-cholesterol concentration at 4 weeks**
Time-weighted median LDL-cholesterol concentrations from week 4 onwards for the five groups categorised by LDL cholesterol at 4 weeks from lowest to highest were 0·5 mmol/L, 0·8 mmol/L, 1·7 mmol/L, 2·3 mmol/L, and 2·9 mmol/L.

	LDL-cholesterol concentration at 4 weeks					p_{trend}
	<0·5 mmol/L (n=2669)	0·5 to <1·3 mmol/L (n=8003)	1·3 to <1·8 mmol/L (n=3444)	1·8 to <2·6 mmol/L (n=7471)	≥2·6 mmol/L (n=4395)	
Demographics						
Age, years	63·6 (8·9)	62·7 (8·9)	62·0 (9·1)	62·7 (8·8)	61·4 (9·0)	<0·0001
Weight, kg	81·0 (15·0)	85·5 (17·3)	86·9 (18·6)	85·7 (17·5)	85·7 (17·3)	<0·0001
Body-mass index, kg/m²	28·1 (4·1)	29·4 (5·0)	30·1 (5·7)	29·5 (5·2)	29·5 (5·1)	<0·0001
Men	2231 (84%)	6149 (77%)	2499 (73%)	5651 (76%)	3146 (72%)	<0·0001
White	2127 (80%)	6847 (86%)	2902 (84%)	6355 (85%)	3856 (88%)	<0·0001
Medical history						
Myocardial infarction	2167 (81%)	6475 (81%)	2757 (80%)	6138 (82%)	3555 (81%)	0·09
Non-haemorrhagic stroke	534 (20%)	1541 (19%)	657 (19%)	1406 (19%)	859 (20%)	0·70
Peripheral arterial disease	320 (12%)	1081 (14%)	470 (14%)	903 (12%)	632 (14%)	0·0012
Hypertension	2081 (78%)	6393 (80%)	2808 (82%)	5974 (80%)	3561 (81%)	0·0051
Diabetes	944 (35%)	2912 (36%)	1478 (43%)	2637 (35%)	1488 (34%)	<0·0001
Current smoker	692 (26%)	2159 (27%)	999 (29%)	2093 (28%)	1410 (32%)	<0·0001
TIMI risk score for secondary prevention	3·18 (1·19)	3·25 (1·25)	3·38 (1·23)	3·26 (1·23)	3·35 (1·24)	<0·0001
Treatment at baseline						
High-intensity statin*	1685 (63%)	5548 (69%)	2406 (70%)	5225 (70%)	3149 (72%)	<0·0001
Ezetimibe	109 (4·1%)	403 (5·0%)	187 (5·4%)	347 (4·6%)	325 (7·4%)	<0·0001
Aspirin or P_2Y_{12} inhibitor	2496 (94%)	7398 (92%)	3175 (92%)	6917 (93%)	4020 (91%)	0·0290
Beta blocker	1993 (75%)	6088 (76%)	2620 (76%)	5640 (75%)	3303 (75%)	0·53
ACE-I or ARB, aldosterone antagonist, or both	2082 (78%)	6260 (78%)	2702 (78%)	5880 (79%)	3405 (77%)	0·61
Baseline laboratory measurements						
LDL cholesterol, mmol/L	2·1 (1·9–2·4)	2·4 (2·1–2·7)	2·2 (1·9–2·7)	2·3 (2·1–2·6)	3·0 (2·6–3·5)	<0·0001
Total cholesterol, mmol/L	4·0 (3·7–4·5)	4·3 (3·9–4·8)	4·2 (3·7–4·8)	4·2 (3·9–4·6)	5·0 (4·5–5·6)	<0·0001
HDL cholesterol, mmol/L	1·1 (0·9–1·3)	1·1 (1·0–1·3)	1·1 (0·9–1·3)	1·1 (1·0–1·4)	1·2 (1·0–1·4)	<0·0001
Triglycerides, mmol/L	1·5 (1·2–2·1)	1·5 (1·1–2·0)	1·6 (1·1–2·2)	1·4 (1·1–1·9)	1·6 (1·2, 2·1)	<0·0001
Lipoprotein(a), nmol/L	22 (9–53)	43 (14–176)	32 (12–153)	37 (13–163)	49 (16–188)	<0·0001

Data are mean (SD), n (%), or median (IQR). LDL-cholesterol values are rounded to the nearest 0·1 in mmol/L; the precise values converted from mg/dL are <0·52 mmol/L (<20 mg/dL), 0·52 to <1·29 mmol/L (20 to <50 mg/dL), 1·29 to <1·81 mmol/L (50 to <70 mg/dL), 1·81 to <2·59 mmol/L (70 to <100 mg/dL), and ≥2·59 mmol/L (≥100 mg/dL). TIMI=Thrombolysis in Myocardial Infarction study group. ACE-I=angiotensin-converting-enzyme inhibitor. ARB=angiotensin receptor blocker.*Defined as having an LDL-lowering potency equal to or greater than that of atorvastatin 40 mg daily.

Table 1: **Baseline characteristics by achieved LDL-cholesterol concentration at 4 weeks after randomisation**

of the ten prespecified safety events before the week-4 visit. There were no differences between treatment groups in the number of patients who did not have a week-4 LDL cholesterol measurement or in patients who had a clinical event before 4 weeks. The final analysis set consisted of 25 982 patients (94% of those included at randomisation) of whom 13 013 were randomly assigned evolocumab and 12 969 were randomly assigned placebo. 2669 (10%) patients enrolled in FOURIER achieved an LDL cholesterol of less than 0·5 mmol/L at 4 weeks (figure 1). Of these 2669 patients, the median LDL cholesterol at 4 weeks was 0·36 mmol/L (IQR 0·28–0·44). The median LDL cholesterol over time for each of the five groups categorised by the LDL-cholesterol concentration at week 4 is shown in figure 2. Across the five groups of achieved LDL cholesterol at 4 weeks ordered from lowest to highest concentration groups, 2659 (99·6%) of 2669 patients, 7721 (96%) of 8003 patients, 1427 (41%) of 3444 patients, 782 (10%) of 7471 patients, and 424 (10%) of 4395 patients were randomly assigned evolocumab. The rates of study drug persistence were high during the trial (about 90% at 2 years) and similar across the five groups categorised by achieved LDL-cholesterol concentration at 4 weeks (appendix p 4). Baseline characteristics varied across the achieved LDL-cholesterol categories at week 4 (table 1).

The risk of the primary composite efficacy endpoint after week 4 was lower with decreasing achieved LDL-cholesterol concentrations at week 4 (figure 3A). The Kaplan-Meier event rates at 3 years across the five groups of achieved LDL-cholesterol concentrations from lowest to highest groups were 10·3%, 12·4%, 13·6%, 13·7%, and 15·5% (p_{trend}<0·0001). The corresponding adjusted HRs using the group with LDL cholesterol of 2·6 mmol/L or greater as the reference group were 0·76 (95% CI 0·64–0·90), 0·85 (0·76–0·96), 0·94 (0·82–1·09), and 0·97 (0·86–1·09), for the next four groups from the lowest to the highest achieved LDL cholesterol

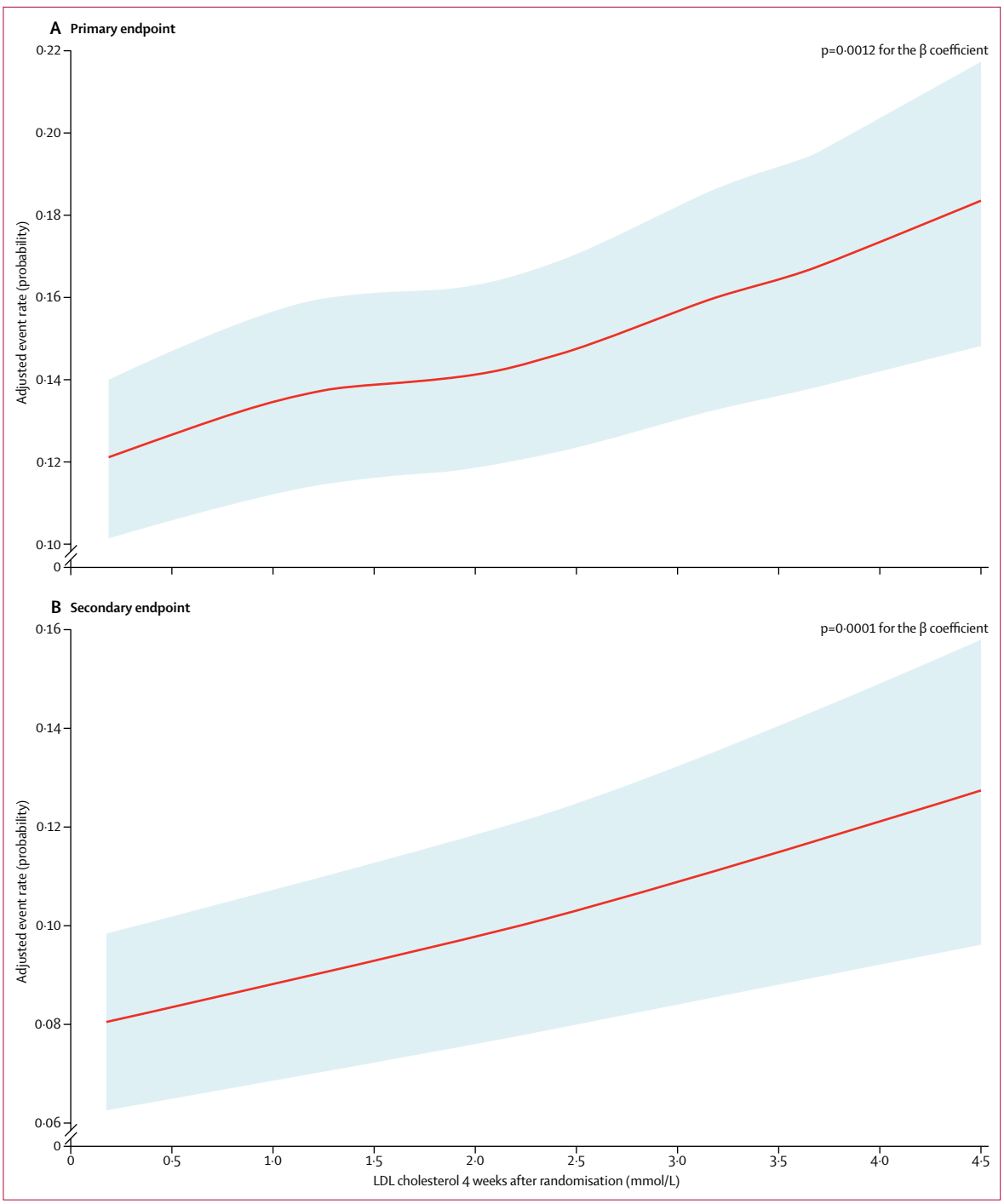


***Figure 3*: Relationship between the achieved LDL-cholesterol concentration at 4 weeks and the risk of the primary (A) and key secondary (B) efficacy composite endpoints**

The primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or hospital admission for unstable angina. The key secondary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. The red line represents the adjusted probability of an event and blue areas are the 95% CIs of the regression model estimate.

(p_{trend}<0·0001; appendix pp 5–6). Regression modelling of the relationship between achieved LDL cholesterol at 4 weeks and the subsequent risk of cardiovascular events showed a steady decline in risk as achieved LDL-cholesterol concentration decreased (p=0·0012 for the β coefficient), even down to the first percentile (LDL cholesterol <0·2 mmol/L, figure 3A). A similar monotonic reduction in the key secondary endpoint was observed (figure 3B,

	LDL-cholesterol concentration at 4 weeks					p_{trend}
	<0·5 mmol/L (n=2669)	0·5 to <1·3 mmol/L (n=8003)	1·3 to <1·8 mmol/L (n=3444)	1·8 to <2·6 mmol/L (n=7471)	≥2·6 mmol/L (n=4395)	
Serious adverse events	614 (23%)	1948 (24%)	838 (24%)	1684 (23%)	1022 (23%)	0·13
Adjusted OR (95% CI)	0·97 (0·86–1·10)	1·01 (0·92–1·11)	1·01 (0·90–1·13)	0·93 (0·84–1·02)	1 (ref)	0·30
Adverse events* leading to discontinuation of study drug	98 (4%)	295 (4%)	124 (4%)	234 (3%)	149 (3%)	0·11
Adjusted OR (95% CI)	1·08 (0·82–1·43)	1·07 (0·86–1·33)	1·07 (0·83–1·39)	0·91 (0·73–1·14)	1 (ref)	0·13
AST or ALT elevation (>3 times ULN)	41 (2%)	120 (1%)	76 (2%)	119 (2%)	83 (2%)	0·19
Adjusted OR (95% CI)	0·96 (0·64–1·43)	0·87 (0·64–1·17)	1·25 (0·90–1·74)	0·91 (0·68–1·24)	1 (ref)	0·64
Creatine kinase elevation (>5 times ULN)	18 (1%)	55 (1%)	19 (1%)	58 (1%)	26 (1%)	0·99
Adjusted OR (95% CI)	1·02 (0·53–1·96)	1·07 (0·65–1·77)	0·88 (0·47–1·65)	1·23 (0·75–2·02)	1 (ref)	0·72
Neurocognitive events	49 (2%)	122 (2%)	51 (1%)	100 (1%)	52 (1%)	0·019
Adjusted OR (95% CI)	1·28 (0·84–1·96)	1·10 (0·78–1·55)	1·10 (0·73–1·65)	0·97 (0·68–1·39)	1 (ref)	0·15
New onset diabetes mellitus†	135/1655 (8%)	389/4863 (8%)	162/1886 (9%)	356/4603 (8%)	220/2778 (8%)	0·63
Adjusted OR (95% CI)	1·06 (0·83–1·35)	1·00 (0·83–1·20)	1·03 (0·83–1·30)	0·95 (0·78–1·14)	1 (ref)	0·48
Cataract-related adverse events	56 (2%)	124 (2%)	61 (2%)	134 (2%)	55 (1%)	0·15
Adjusted OR (95% CI)	1·54 (1·03–2·31)	1·14 (0·82–1·60)	1·34 (0·91–1·98)	1·35 (0·96–1·89)	1 (ref)	0·43
New or progressive malignancy	64 (2%)	205 (3%)	87 (3%)	166 (2%)	99 (2%)	0·22
Adjusted OR (95% CI)	0·90 (64–1·27)	1·01 (0·78–1·31)	1·04 (0·77–1·42)	0·88 (0·67–1·15)	1 (ref)	0·72
Haemorrhagic stroke	3 (<1%)	19 (<1%)	7 (<1%)	17 (<1%)	7 (<1%)	0·99
Adjusted HR (95% CI)	0·71 (0·17–2·90)	1·55 (0·62–3·85)	1·39 (0·47–4·14)	1·57 (0·62–3·98)	1 (ref)	0·91
Non-cardiovascular death	25 (1%)	86 (1%)	34 (1%)	66 (1%)	45 (1%)	0·67
Adjusted HR (95% CI)	0·89 (0·53–1·50)	1·06 (0·72–1·55)	1·03 (0·65–1·64)	0·89 (0·60–1·33)	1 (ref)	0·73

Data are n (%) or n/N (%), unless otherwise specified. OR=odds ratio. ref=reference. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ULN=upper limit of normal. HR=hazard ratio. *Excludes 17 patients with injection-site reactions. †Denominator excludes patients who were diagnosed with diabetes mellitus before the week-4 visit.

***Table 2*: Safety events by achieved LDL-cholesterol concentration at 4 weeks after randomisation**

p=0·0001 for the β coefficient), with the group achieving an LDL-cholesterol concentration of less than 0·5 mmol/L at 4 weeks having the lowest risk of cardiovascular death, myocardial infarction, or stroke (3-year Kaplan-Meier rate 6·6%) with an adjusted HR of 0·69 (95% CI 0·56–0·85) compared with the group with LDL-cholesterol concentrations of 2·6 mmol/L or higher (appendix p 5). These findings were associated with reductions in myocardial infarction, ischaemic stroke, and coronary revascularisation (appendix pp 5–6, with no apparent relationship between achieved LDL cholesterol and unstable angina, cardiovascular death, or all-cause mortality in the timeframe studied.

Serious adverse events after week 4 occurred in 6106 (24%) patients. Less than 4% of all patients had an adverse event leading to drug discontinuation, and there were no differences in these events by achieved LDL-cholesterol concentration at 4 weeks (table 2). No differences in elevations in hepatic aminotransferases, creatine kinase, new-onset diabetes mellitus, cataract-related adverse events, new or progressive malignancy, haemorrhagic stroke, or non-cardiovascular death were observed. In an unadjusted analysis, more patients had neurocognitive events who had lower LDL cholesterol at 4 weeks (p_{trend}=0·019); however, after adjustment for differences in baseline characteristics, the association was no longer significant (adjusted p_{trend}=0·15; table 2).

To further explore the relationship between achieved LDL-cholesterol concentration and cognition, we also analysed 1154 patients who had formal cognitive testing as part of the EBBINGHAUS study, on or before the day of the first dose of study drug. No differences across the five groups of achieved LDL-cholesterol concentration at 4 weeks were observed in the change from baseline in the primary cognitive endpoint of spatial working memory strategy index of executive function, in any of the three secondary endpoints, or in the global composite score (appendix pp 7–8).

Patient-reported changes in memory and three subdomains of executive function from the start to the end of the trial are shown in the appendix (p 9). The total score was significantly better in patients with lower achieved LDL cholesterol (p_{trend}=0·0168), although the absolute differences in mean scores were small and the relationship across LDL-cholesterol groups was not monotonic.

In a post-hoc analysis of patients with ultra-low LDL cholesterol, 1335 (5%) patients achieved an LDL-cholesterol concentration of less than 0·4 mmol/L (15 mg/dL) and 504 (2%) patients achieved an LDL-cholesterol concentration of less than 0·26 mmol/L (10 mg/dL) at week 4 (appendix p 10). The median LDL-cholesterol concentration in the latter group was 0·18 mmol/L (7 mg/dL) with an IQR of 0·13–0·23 (5–9 mg/dL). Major

cardiovascular events progressively declined with decreasing achieved LDL-cholesterol concentrations, with adjusted HRs in the group with LDL-cholesterol concentrations of less than 0·26 mmol/L at 4 weeks of 0·69 (95% CI 0·49–0·97) for the primary and 0·59 (0·37–0·92) for the key secondary endpoints compared with the reference group (LDL cholesterol ≥2·6 mmol/L). Neither serious adverse events nor adverse events leading to drug discontinuation occurred in excess in these two groups with ultra-low LDL cholesterol compared with patients in the reference group.

Discussion

In an analysis of over 25 000 patients with atherosclerotic cardiovascular disease, we found a strong relationship between on-treatment LDL-cholesterol concentration and major cardiovascular outcomes. Conversely, we found no significant association between LDL-cholesterol concentrations and prespecified adverse events in patients followed up for a median of 2·2 years.

These data are supported by previous observations from several types of analyses. First, subgroup analyses from clinical trials have showed consistent benefit with LDL-cholesterol lowering therapy even in subgroups with the lowest baseline concentrations of LDL cholesterol. Specifically, in the Cholesterol Treatment Trialists Collaboration, the clinical benefit of LDL-cholesterol lowering with statins was consistent even in patients whose baseline LDL-cholesterol concentration was less than 2 mmol/L, in whom statin therapy lowered LDL-cholesterol concentrations to less than approximately 1·6 mmol/L.[1] Likewise, in the JUPITER trial[16] of primary prevention, there was a consistent clinical benefit with rosuvastatin even in patients starting with an LDL-cholesterol concentration of less than 1·6 mmol/L, in whom rosuvastatin lowered LDL-cholesterol concentrations to less than approximately 0·8 mmol/L. In the IMPROVE-IT trial,[17] there was consistent benefit even in patients in the lowest quartile of LDL cholesterol at randomisation (median 1·8 mmol/L) in whom the LDL cholesterol was reduced to 1·2 mmol/L. Second, in analyses of on-treatment LDL cholesterol from clinical trials of statins, a monotonic relationship was observed between LDL-cholesterol concentration and cardiovascular events.[18,19] However, the lowest subgroup in those analyses only extended down to less than 1·3 mmol/L. Using data from IMPROVE-IT,[20] we extended that relationship down to less than 0·8 mmol/L, but that subgroup consisted of fewer than 1000 patients.

We now extend these data to unprecedented low concentrations of LDL cholesterol, with the lowest prespecified group (2669 patients) with an on-treatment LDL-cholesterol concentration of less than 0·5 mmol/L, a median LDL cholesterol of 0·36 mmol/L, and a quarter of that subgroup with an LDL-cholesterol concentration of less than 0·28 mmol/L, and an exploratory subgroup of 504 patients with an on-treatment LDL cholesterol of less than 0·26 mmol/L (median 0·18 mmol/L). These clinical data are supported by mechanistic imaging data from the GLAGOV study[21] showing a similar monotonic relationship between on-treatment LDL-cholesterol concentrations and coronary atheroma volume regression down to 0·5 mmol/L. Our observations are also supported by data from a pooled analysis of smaller lipid-lowering trials of another PCKS9 inhibitor, alirocumab.[22] Establishment of which pharmacotherapies to use to achieve these concentrations of LDL cholesterol will require careful consideration in different health-care systems.

The association between LDL cholesterol and cardiovascular events was strongest for myocardial infarction, stroke, and coronary revascularisation, and not seen for cardiovascular death. It has been long-recognised, since the Cholesterol Treatment Trialist Collaboration, that the relative risk reduction per unit LDL-cholesterol lowering with statins is less for vascular death than for myocardial infarction or stroke.[1] It has also been observed in clinical trials that a mortality benefit from LDL-cholesterol lowering typically takes years to emerge,[23,24] and the median duration of follow-up in FOURIER was only 2·2 years.

With regard to safety, we found similar adjusted risk of ten prespecified safety events regardless of the achieved LDL-cholesterol concentration, even in the 2669 patients who achieved an LDL-cholesterol concentration of less than 0·5 mmol/L at 4 weeks. These findings are unique in that they represent the first analysis of a large cohort of patients to achieve such very low LDL-cholesterol concentrations, namely being less than a third of the most common treatment goal (<1·8 mmol/L) for the highest-risk patients.[25,26]

Our finding of no increase in adverse events in patients achieving very low LDL-cholesterol concentrations with the combination of evolocumab plus a statin is similar to that reported in the IMPROVE-IT trial[20] with ezetimibe plus simvastatin, in which no excess in adverse safety events were reported even in patients who achieved an LDL-cholesterol concentration of less than 0·8 mmol/L at 4 weeks and who were followed up for an average of 6 years. Both IMPROVE-IT and FOURIER were randomised trials of newer therapies on a background of a statin. In analyses from both of these trials, no significant increase risk in adverse events such as those that had been reported in earlier placebo-controlled trials of statins (eg, new-onset diabetes mellitus,[26] elevations in hepatic transaminases,[27] and muscle safety[28]) were observed. Additionally, neither the FOURIER study nor the EBBINGHAUS study reported increases in neurocognitive events, as reported in a meta-analysis[29] of phase 2 and 3 trials of PCSK9 inhibitors, or cataract-related events, as reported in 839 patients who achieved LDL-cholesterol concentrations of less than 0·6 mmol/L drawn from 14 randomised controlled trials with alirocumab.[30]

The largest evaluation of the safety of evolocumab before FOURIER showed a favourable safety profile and

good tolerability up until 4 years,[31] but this pooled analysis of four phase 2 trials was limited by a modest size (n=1324) and use of an open-label design comparing evolocumab with standard of care during the extension phase. In the FOURIER trial, because virtually all of the 2669 patients who achieved an LDL-cholesterol concentration of less than 0·5 mmol/L at 4 weeks had been randomly assigned evolocumab, the data from our current analysis now adds to the evidence supporting the safety of evolocumab, even in patients who achieve very low LDL-cholesterol concentrations.

The major limitations of this analysis were the absence of randomisation to on-treatment LDL-cholesterol concentrations (patients were classified based on post-randomisation measurement of LDL cholesterol), a median follow-up of 2·2 years, and low frequency of some safety events. We used multivariable adjustment to limit confounding due to differences in baseline characteristics across the groups of achieved LDL cholesterol, but acknowledge that this might have been incomplete and one cannot adjust for unmeasured confounders. Although most safety endpoints evaluated would be expected to manifest within the 2·2 years of follow-up based on experiences with other lipid therapies,[27,28] we acknowledge that adverse events such as cancer can take longer to manifest. However, in a smaller open-label extension study[31] of evolocumab with 4 years of follow-up, no safety concerns have emerged, and two long-term extension studies of FOURIER following approximately 6600 patients (NCT03080935 and NCT02867813) that are planned to last 5 years should provide longer-term insights. In conclusion, we observed that patients who achieved progressively lower LDL-cholesterol concentrations at 4 weeks in the FOURIER trial had progressively fewer cardiovascular events with no evidence of a plateau and with no increase in adverse events. These data support the use of intensive lipid-lowering therapies to prevent recurrent cardiovascular events in high-risk patients and suggest that a lower target LDL cholesterol than recommended in current guidelines (eg, <0·5 mmol/L) can safely be considered for the highest-risk patients.

Contributors

RPG did the literature search, designed the study, interpreted the data, wrote the first and subsequent drafts, and constructed the figures. TRP, GMDF, FM, BRO, ACK, and PSS designed the study, interpreted the data, and edited the manuscript. J-GP did data analysis, data interpretation, editing, and designed the figures. ZAG, RC, KT, IG-B, JL-M, and FS interpreted the data and edited the manuscript. EK did the data analysis, data interpretation, and editing. ALP and RS did data interpretation and editing. SMW designed the study, collected and interpreted the data, and edited the manuscript. MSS did a literature search, designed the study, interpreted the data, and edited and wrote part of the manuscript.

Declaration of interests

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