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FULL RESEARCH PAPER

LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial

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Aims

Some trials have reported diminished efficacy for statins in the elderly, and in women compared with men. We examined the efficacy and safety of evolocumab by patient age and sex in the FOURIER trial, the first major cardiovascular outcome trial of a PCSK9 inhibitor.

Methods and results

FOURIER was a randomised, double blind trial, comparing evolocumab with placebo in 27,564 patients with atherosclerotic cardiovascular disease receiving statin therapy (median follow-up 2.2 years). The primary endpoint was cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation. Cox proportional hazards models were used to assess the efficacy of evolocumab versus placebo stratified by quartiles of patient age and by sex. There were small variations in the cardiovascular event rate across the age range (for the primary endpoint, Kaplan–Meier at 3 years 15.6%, >69 years, vs. 15.1%, ≤56 years, $P = 0.45$); however, the relative efficacy of evolocumab was consistent regardless of patient age (for the primary endpoint (Q1 hazard ratio, 95% confidence interval) 0.83, 0.72–0.96, Q2 0.88, 0.76–1.01, Q3 0.82, 0.71–0.95, Q4 0.86, 0.74–1.00; $P_{interaction} = 0.91$), and the key secondary endpoint (cardiovascular death, myocardial infarction, stroke) (Q1 0.74 (0.61–0.89), Q2 0.83 (0.69–1.00), Q3 0.78 (0.65–0.94), Q4 0.82 (0.69–0.98)); $P_{interaction} = 0.81$). Women had a lower primary endpoint rate than men (Kaplan–Meier at 3 years 12.5 vs. 15.3%, respectively, $P < 0.001$). Relative risk reductions in the primary endpoint and key secondary endpoint were similar in women (0.81 (0.69–0.95) and 0.74 (0.61–0.90), respectively) compared with men (0.86 (0.80–0.94) and 0.81 (0.73–0.90), respectively), $P_{interaction} = 0.48$ and 0.44, respectively. Adverse events were more common in women and with increasing age but, with the exception of injection site reactions, there were no important significant differences reported by those assigned evolocumab versus placebo.

Conclusions

The efficacy and safety of evolocumab are similar throughout a broad range of ages and in both men and women.

Keywords

LDL-cholesterol • evolocumab • age • gender • cardiovascular outcomes

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Introduction

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) was a large cardiovascular outcomes trial of the PCSK9 inhibitor evolocumab, which recruited patients with a history of atherosclerotic disease, including prior myocardial infarction (MI), ischaemic stroke and symptomatic peripheral artery disease.[1] Evolocumab reduced low-density lipoprotein (LDL) cholesterol by a median of 59% resulting in a significant benefit on major cardiovascular endpoints over a median follow-up of 2.2 years.[2]

Although the elderly are at high risk of complications from cardiovascular disease, they have traditionally been underrepresented in clinical trials of statin therapy. Although the data are mixed, a more recent analysis of statin trials has suggested that there may be attenuation of the cardiovascular benefits in the elderly population (>75 years) compared with those in younger age groups.[3,4] In addition, some trials of statins have shown less compelling benefits in women compared with men;[5,6] however, an updated pooled analysis of trials focusing on outcomes in women suggests that the clinical benefits of statin treatment are comparable between men and women.[7]

In view of the conflicting data regarding the clinical benefit of LDL-cholesterol lowering in women and the elderly, we examined the efficacy and safety of evolocumab in the large FOURIER trial that had robust effects on LDL-cholesterol lowering and robust representation from these patient subgroups.

Methods

Patients

The study design, organisation and main results of the study have previously been published.[1,2] The patients eligible for FOURIER were men and women aged between 40 and 85 years, with stable atherosclerotic cardiovascular disease (MI, non-haemorrhagic stroke, or symptomatic peripheral artery disease) and additional risk factors placing them at increased cardiovascular risk. Patients were potentially eligible for inclusion if they had a LDL-cholesterol of 70 mg/dL or greater (1.8 mmol/L) or non-high-density lipoproteion (HDL) cholesterol of 100 mg/dL or greater (2.6 mmol/L), while taking an optimised lipid-lowering regimen including a high or moderate intensity statin, with or without ezetimibe. Patients were randomly assigned, in a 1:1 ratio, to evolocumab or placebo and were followed for a median of 2.2 years. The primary efficacy endpoint was major cardiovascular events, defined as the composite of cardiovascular death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation. The key secondary endpoint (SEP) was the composite of cardiovascular death, MI or stroke. Other SEPs included the components of the primary endpoint (PEP). Key exclusions were recent MI or stroke within 4 weeks, prior haemorrhagic stroke, estimated glomerular infiltration rate of less than 20 mL/min/1.73 m^2, New York Heart Association class 3 or 4 heart failure or left ventricular ejection fraction less than 30%, malignancy in the prior 10 years, and elevation of creatinine kinase five-fold or greater or hepatic aminotransferases greater than three-fold above normal.[2] Cardiovascular events were adjudicated by an independent blinded committee.

Patients in FOURIER were recruited from 49 countries. The study conformed to Good Clinical Practice guidelines and was undertaken following the guidelines of the Declaration of Helsinki. The protocol and all subsequent amendments were reviewed and ratified by ethical review boards.

Statistical methods

Age groups were stratified by quartiles (≤56, 56–63, 63–69 and >69 years). Baseline characteristics were compared by subgroup of interest, using the Wilcoxon rank sum for continuous variables and chi squared test for categorical variable. Efficacy analyses were conducted in the intention-to-treat population based on time from randomisation to the first occurrence of any element of the composite endpoint. Safety evaluations included all the patients who underwent random assignment and received at least one dose of study drug. Chi squared tests were used for treatment comparisons of subject incidences of adverse events by subgroups of interest. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated with the use of a stratified Cox proportional hazards model using randomisation strata for cardiovascular endpoints; *P* values for time to event analyses were calculated with the use of log rank tests. For the current analysis, analyses were restricted to subgroups of interest including age by quartile and patient sex. A sensitivity analysis was also conducted using prespecified age cut-offs (<65, 65–74, >75 years). Tests for subgroup heterogeneity were conducted by including a treatment by subgroup interaction term in the Cox proportional hazards model. Given the exploratory nature of the analysis, a *P* value less than 0.05 was considered significant. Absolute risk reduction of cardiovascular endpoints between treatment groups at month 36, by subgroups of interest, were calculated based on Kalpan–Meier estimates at month 36 between treatment groups.

Results

Baseline demographics and characteristics

The baseline demographics by age and sex are shown in Tables 1 and 2, respectively.

Older patients and female patients were more likely to have a background history of non-haemorrhagic stroke and peripheral artery disease and less likely to have a history of MI. They were more likely to be hypertensive and less likely to be current smokers.

Lipid responses

Baseline values

Baseline LDL-cholesterol tended to be slightly higher in younger than older patients (Q1 median LDL-cholesterol 94 mg/dL, Q2 93 mg/dL, Q3 91 mg/dL, Q4 90 mg/dL; *Table 1*, *Figure 1*). HDL-cholesterol levels were higher in older patients (Q1, 41 mg/dL vs. Q4, 48 mg/dL) and triglyceride levels were lower (Q1, 145 mg/dL vs. Q4, 121 mg/dL). Lipoprotein (a) levels were similar regardless of age.

There were small differences in median LDL-cholesterol at baseline between men (91 mg/dL) and women (95 mg/dL); (*Table 2*, *Figure 2*). Median HDL-cholesterol levels were lower in men (42 mg/dL) compared with women (49 mg/dL). Triglyceride levels were similar in the two sexes. In women lipoprotein (a) levels were higher than in men (median 51.0 vs. 34.0 nmol/L, $P < 0.0001$) but there was marked variation in levels in both sexes (*Table 2*).

Table 1 Characteristics of patients at baseline by age quartile.

Characteristics	Q1 Age <56 (*N* = 7122)	Q2 56< age ≤ 63 (*N* = 7154)	Q3 63< age ≤ 69 (*N* = 7055)	Q4 Age >69 (*N* = 6233)	*P* value
Age (years) mean (SD)	50.8 (4.2)	60.0 (2.0)	66.4 (1.6)	74.2 (3.5)	
Male sex, no. (%)	5729 (80.4)	5512 (77.0)	5276 (74.8)	4278 (68.6)	<0.0001
White race, no. (%)	5827 (81.8)	6104 (85.3)	6104 (86.5)	5423 (87.0)	<0.0001
Weight, kg mean (SD)	89.4 (18.7)	86.5 (17.4)	84.4 (16.2)	80.1 (15.6)	<0.0001
Type of atherosclerosis					
Myocardial infarction, no.(%)	6095 (85.6)	5773 (80.7)	5667 (80.3)	4816 (77.3)	<0.0001
Median time from most recent previous myocardial infarction (IQR), years	2.0 (0.5–4.6)	3.3 (0.9–7.1)	4.2 (1.4–9.5)	4.7 (1.7–10.8)	<0.0001
Nonhemorrhagic stroke	1055 (14.8)	1401 (19.6)	1392 (19.7)	1489 (23.9)	<0.0001
Median time from most recent previous stroke (IQR), years	2.4 (0.8–5.1)	3.4 (1.1–7.2)	3.5 (1.2–8.1)	3.7 (1.3–8.3)	<0.0001
Peripheral artery disease, no. (%)	672 (9.4)	1074 (15.0)	1005 (14.2)	891 (14.3)	<0.0001
Cardiovascular risk factors					
Hypertension, no./total no. (%)	5250/7121 (73.7)	5869/7154 (82.0)	5727/7055 (81.2)	5238/6233 (84.0)	<0.0001
Diabetes mellitus, no. (%)	2456 (34.5)	2943 (41.1)	2515 (35.6)	2167 (34.8)	<0.0001
Current cigarette use, no./total no. (%)	3179/7121 (44.6)	2753/7154 (38.5)	1279/7055 (18.1)	566/6232 (9.1)	<0.0001
Statin use, no. (%)					
High intensity	5304 (74.5)	5196 (72.6)	4711 (66.8)	3892 (62.4)	<0.0001
Moderate intensity	1806 (25.4)	1946 (27.2)	2324 (32.9)	2316 (37.2)	
Low intensity, unknown intensity, or no data	12 (0.2)	12 (0.2)	20 (0.3)	25 (0.4)	
Ezetimibe, no. (%)	442 (6.2)	352 (4.9)	371 (5.3)	275 (4.4)	<0.0001
Other cardiovascular medications, no./total no. (%)					
Aspirin, $P2Y_{12}$ inhibitor, or both	6780/7117 (95.3)	6697/7146 (93.7)	6464/7050 (91.7)	5491/6226 (88.2)	<0.0001
Beta-blocker	5559/7117 (78.1)	5471/7146 (76.6)	5225/7050 (74.1)	4560/6226 (73.2)	<0.0001
ACE inhibitor or ARB, aldosterone antagonist, or both	5400/7117 (75.9)	5634/7146 (78.8)	5556/7050 (78.8)	4943/6226 (79.4)	<0.0001
Median lipid measures (IQR)					
LDL-cholesterol, mg/dl	94.0 (80.5–113.5)	92.5 (80.0–110.5)	90.5 (79.0–105.0)	90.0 (79.0–105.0)	<0.0001
Total cholesterol, mg/dl	168.5 (151.0–192.5)	168.5 (151.0–190.0)	166.5 (151.0–185.5)	166.0 (151.0–185.5)	<0.0001
HDL-cholesterol, mg/dl	40.5 (34.5–48.0)	43.0 (36.5–51.0)	45.5 (38.0–54.5)	47.5 (40.0–56.5)	<0.0001
Triglycerides, mg/dl	145.0 (106.0–200.5)	138.5 (104.0–188.0)	129.0 (97.5–176.5)	121.0 (93.0–161.0)	<0.0001
Lipoprotein (a), nmol/litre	38.0 (13.0–163.0)	36.0 (12.0–165.0)	37.0 (13.0–167.0)	37.0 (13.0–161.0)	0.5739

P values test of association between age quartiles and baseline characteristics based on chi-square or rank sum test. To convert the values for cholesterol to millimoles per litre, multiply by 0.02586. To convert the values for triglycerides to millimoles per litre, multiply by 0.01129.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; SD: standard deviation.
*Race was reported by the patients.
†Patients could have more than one type of atherosclerosis.
‡Statin intensity was categorised in accordance with the guidelines of the American College of Cardiology and American Heart Association.[14]

Effect of treatment

Evolocumab significantly reduced LDL-cholesterol in all age groups, with clinically similar reductions at 4 weeks (54–59%; *Figure 1*), although there was statistical heterogeneity owing largely to the very large sample size ($P_{interaction} < 0.001$). Likewise, evolocumab reduced LDL-cholesterol in both men and women at 4 weeks, with a nominally greater reduction in men (58% vs. 52%; $P < 0.001$; *Figure 2*).

Clinical efficacy of evolocumab

There were small variations in the cardiovascular event rate across the age range (for the PEP, Kaplan–Meier (KM) at 3 years 15.6%, >69 years, vs. 15.1%, ≤56 years, $P = 0.45$. For PEP: cardiovascular death, MI, stroke, hospitalisation for unstable angina, coronary revascularisation), there were no significant differences in the clinical effects of evolocumab by quartile of age (Q1 HR 0.83, 95% CI 0.72–0.96, Q2

Table 2 Characteristics of patients at baseline by sex.

Characteristics	Male (*N* = 20,795)	Female (*N* = 6769)	*P* value
Age, years mean (SD)	62.0 (9.0)	64.1 (8.8)	<0.0001
White race, no. (%)	17,783 (85.5)	5675 (83.8)	0.0008
Weight, kg mean (SD)	88.1 (16.6)	76.7 (16.9)	<0.0001
Type of atherosclerosis			
Myocardial infarction, no. (%)	17,544 (84.4)	4807 (71.0)	<0.0001
Median time from most recent previous myocardial infarction	3.4 (1.0–7.8)	3.0 (0.9–6.6)	<0.0001
Non-haemorrhagic stroke	3505 (16.9)	1832 (27.1)	<0.0001
Median time from most recent previous stroke (IQR)	3.2 (1.1–7.1)	3.4 (1.1–7.3)	0.1477
Peripheral artery disease, no. (%)	2616 (12.6)	1026 (15.2)	<0.0001
Cardiovascular risk factors			
Hypertension, no./total no. (%)	16,314/20,794 (78.5)	5770/6769 (85.2)	<0.0001
Diabetes mellitus, no. (%)	7345 (35.3)	2736 (40.4)	<0.0001
Current cigarette use, no./total no. (%)	6097/20,793 (29.3)	1680/6769 (24.8)	<0.0001
Statin use, no. (%)			
High intensity	14,404 (69.3)	4699 (69.4)	0.9431
Low intensity, unknown intensity, or no data	53 (0.3)	16 (0.2)	
Moderate intensity	6338 (30.5)	2054 (30.3)	
Ezetimibe, no. (%)	1077 (5.2)	363 (5.4)	0.5555
Other cardiovascular medications, no./total no. (%)			
Aspirin, $P2Y_{12}$ inhibitor, or both	19,325/20,777 (93.0)	6107/6762 (90.3)	<0.0001
Beta-blocker	15,948/20,777 (76.8)	4867/6762 (72.0)	<0.0001
ACE inhibitor or ARB, aldosterone antagonist, or both	16,330/20,777 (78.6)	5203/6762 (76.9)	0.0043
Median lipid measures (IQR)			
LDL-cholesterol, mg/dl	91.0 (79.0–107.0)	95.0 (81.5–113.5)	<0.0001
Total cholesterol, mg/dl	164.5 (148.5–184.5)	176.0 (159.5–198.0)	<0.0001
HDL-cholesterol, mg/dl	42.0 (36.0–50.0)	49.0 (41.5–59.0)	<0.0001
Triglycerides, mg/dl	133.0 (99.0–182.5)	133.5 (102.0–179.5)	0.1626
Lipoprotein (a), nmol/litre	34.0 (12.0–154.0)	51.0 (16.0–192.0)	<0.0001

P values test of association between sex and baseline characteristics based on chi-square or rank sum test. To convert the values for cholesterol to millimoles per litre, multiply by 0.02586. To convert the values for triglycerides to millimoles per litre, multiply by 0.01129.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; SD: standard deviation.

HR 0.88, 95% CI 0.76–1.01, Q3 HR 0.82, 95% CI 0.71–0.95, Q4 HR 0.86, 95% CI 0.74–0.99); $P_{interaction} = 0.91$; *Table 3*, Supplementary *Figure 1*), or for the key SEP (cardiovascular death, MI, stroke; Q1 HR 0.74, 95% CI 0.61–0.89, Q2 HR 0.83, 95% CI 0.69–1.00, Q3 HR 0.78, 95% CI 0.65–0.94, Q4 HR 0.82, 95% CI 0.69–0.98; $P_{interaction} = 0.81$; *Table 3*, Supplementary *Figure 2*). The absolute risk reduction with evolocumab was largely consistent across quartiles of age (Q1, 3.0% vs. Q4, 2.0% and for the SEP, Q1, 2.6% vs. Q4, 2.5% (*Table 3*)). Similar results were observed for the individual components (Supplementary *Table 1*).

A sensitivity analysis was conducted using prespecified age cut-offs (<65, 65–75, >75 years) and yielded consistent results; specifically, the clinical efficacy of evolocumab was similar in those aged over 75 years (HR 0.78; 95% CI 0.60–1.02), 65–75 years (HR 0.86; 95% CI 0.76–0.97) and less than 65 years (HR 0.86; 95% CI 0.78–0.94); $P_{interaction}$ for the three age groups = 0.84). Likewise, for the key SEP, absolute risk reductions at month 36 were similar (HR 0.78 (95% CI 0.58–1.04), HR 0.82 (95% CI 0.70–0.95) and HR 0.79 (95% CI 0.69–0.90) for the three age groups, respectively; $P_{interaction}$ for the three age groups = 0.94).

Women had a lower PEP rate than men (KM at 3 years 12.5% vs. 15.3%, respectively, $P < 0.001$). For women, compared with men, there were no differences in the relative risk reduction for the PEP (HR 0.81 (95% CI 0.69–0.95) vs. HR 0.86 (95% CI 0.80–0.94),

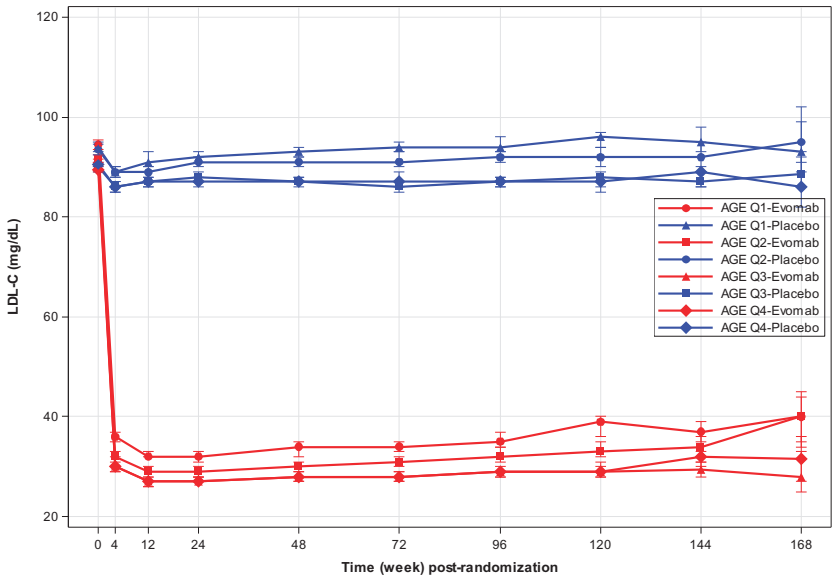

Figure 1 LDL-cholesterol reduction with evolocumab and placebo stratified by age quartile. The median and 95% confidence interval LDL-cholesterol in mg/dL during the trial is shown for evolocumab and placebo, stratified by age quartiles (Q1–4) of less than 56 years, 56 to less than 63 years, 63 to less than 69 years, greater than 69 years, respectively (symbols and colour codes on figure). The treatment difference in LDL-cholesterol ranged from 57 and 60 mg/dL across the four age quartiles. To convert the values for LDL-cholesterol to millimoles per litre, multiply by 0.02586. Evomab: evolocumab; LDL-C: low-density lipoprotein cholesterol.

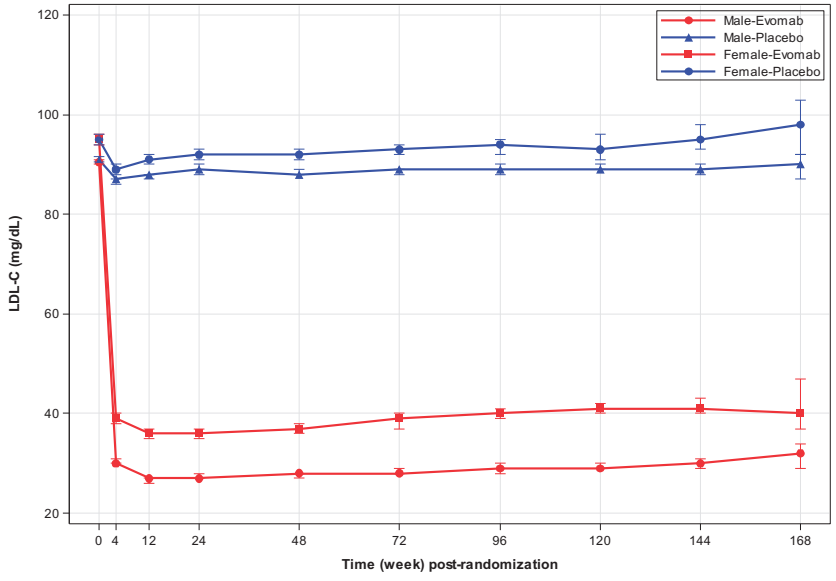

Figure 2 LDL-cholesterol reduction with evolocumab and placebo stratified by sex. The median and 95% confidence interval LDL-cholesterol in mg/dL during the trial is shown for evolocumab and placebo, stratified by sex (symbols and colour codes on figure). The treatment difference in LDL-cholesterol was, on average, 59 to 60 mg/dL in men and from 50 to 52 mg/dL in women after randomisation. To convert the values for LDL-cholesterol to millimoles per litre, multiply by 0.02586. Evomab: evolocumab; LDL-C: low-density lipoprotein cholesterol.

Table 3 Efficacy endpoint subgroup analysis by age quartile.

Endpoints	Subgroup	Evolocumab			placebo					
		Total *N*	Events *N*	36-month KM (%)	Total *N*	Events *N*	36-month KM (%)	HR (95% CI)	Log-rank *P* value	$P_{interaction}$
Primary: endpoint	Age ≤56	3601	354	12.16	3521	407	15.14	0.83 (0.72–0.96)	0.010	0.908
	Age >56–63	3493	344	12.84	3661	409	13.56	0.88 (0.76–1.01)	0.077	
	Age >63–69	3512	315	11.81	3543	381	14.32	0.82 (0.71–0.95)	0.009	
	Age >69	3178	331	13.58	3055	366	15.62	0.86 (0.74–0.99)	0.049	
Secondary: endpoint	Age ≤56	3601	188	6.69	3521	243	9.33	0.74 (0.61–0.89)	0.002	0.813
	Age >56–63	3493	197	7.71	3661	249	8.84	0.83 (0.69–0.99)	0.047	
	Age >63–69	3512	191	7.57	3543	244	9.50	0.78 (0.65–0.94)	0.010	
	Age >69	3178	240	9.93	3055	277	12.42	0.82 (0.69–0.98)	0.029	

Evolocumab significantly and consistently reduced the primary endpoint of cardiovascular death, myocardial infarction, stroke, unstable angina requiring rehospitalisation, and coronary revascularisation, and the key secondary endpoint of cardiovascular death, myocardial infarction and stroke across the age quartiles (Q1–4) of <56 years, 56– < 63 years, 63– < 69 years, ≥69 years, respectively. No statistical evidence of treatment effect modification by age was observed ($P_{interaction}$=0.91 and 0.81 for the primary and secondary endpoint, respectively).
KM: Kaplan–Meier; CI: confidence interval; HR: hazard ratio.

Table 4 Efficacy endpoint subgroup analysis by sex.

Subgroup	Evolocumab			placebo					
	Total *N*	Events *N*	36-month KM (%)	Total, *N*	Events, *N*	36-month KM (%)	HR (95% CI)	Log rank *P* value	$P_{interaction}$
Primary endpoint									
Male	10,397	1068	13.50	10398	1229	15.32	0.86 (0.80–0.94)	<0.001	0.477
Female	3387	276	9.88	3382	334	12.54	0.81 (0.69–0.95)	0.008	
Secondary endpoint									
Male	10,397	643	8.39	10,398	785	10.17	0.81 (0.73–0.90)	<0.001	0.436
Female	3387	173	6.48	3382	228	9.17	0.74 (0.61–0.90)	0.003	

Evolocumab significantly and consistently reduced the primary endpoint of cardiovascular death, myocardial infarction, stroke, unstable angina requiring rehospitalisation, and coronary revascularisation, and the key secondary endpoint of cardiovascular death, myocardial infarction and stroke and in men and women. No statistical evidence of treatment effect modification by sex was observed ($P_{interaction}$ = 0.48 and 0.44 for the primary and key secondary endpoint, respectively).
KM: Kaplan–Meier; CI: confidence interval; HR: hazard ratio.

$P_{interaction}$ for sex = 0.48 (*Table 4*, Supplementary *Figure 3*)), or SEP (HR 0.74 (95% CI 0.61–0.90), vs. HR 0.81 (95% CI 0.73–0.90) *P* = 0.44 (*Table 4*, Supplementary *Figure 4*)). For the individual components, there were no significant differences between men and women (Supplementary *Table 2*).

The absolute risk reduction of events at month 36, in women and men were similar for both the PEPs and SEPs (2.66% vs. 1.82 %, *Table 4*).

Adverse events

In aggregate, adverse events, serious adverse events and discontinuations of the study drug (evolocumab or placebo) were slightly more common in older than younger patients and in women versus men. There was a small and significant increase in injection site reactions associated with the use of evolocumab compared with placebo. This difference was numerically greater in the youngest age quartile and in men versus women. Overall, there were no clinically important differences between evolocumab and placebo and no excess of new-onset diabetes in any subgroup of patients studied.

Discussion

Despite the overwhelming evidence of cardiovascular benefits from trials of lipid lowering with statins, there is a reluctance to prescribe statins in elderly patients, often based on misconceptions about the balance of benefits and harms.[8] There is also evidence that in clinical practice women are often undertreated,[9] despite the fact that trial data confirm benefits in both sexes.[7] It was important, therefore, to establish whether treatment with a PCSK9 monoclonal antibody, which produced substantial reductions in LDL-cholesterol, would

confer consistent cardiovascular benefits across all age groups and in both sexes.

The results of the FOURIER trial demonstrated that, when added to statin therapy, the PCSK9 inhibitor evolocumab, lowered LDL-cholesterol by 59% compared with placebo, reduced the risk of the primary composite endpoint of cardiovascular death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation by 15%, and reduced the main SEP of cardiovascular death, MI or stroke by 20%, during a median follow-up period of 2.2 years.[2]

In a recent Bayesian network meta-analysis, compared with statins, PCSK9 inhibitors were ranked as better treatment for the prevention of major adverse cardiovascular events, most likely explained by their greater effect on lowering LDL-cholesterol.[10]

The present analyses extend our observations on the main cardiovascular outcomes from FOURIER, and demonstrate beyond reasonable doubt, that the proportional reductions in these cardiovascular endpoints are consistent throughout the age range and are similar in men and women.

Overall in FOURIER there was no excess of either serious adverse events or adverse events (other than minor injection site reactions – approximately 2.1% vs. 1.6% with evolocumab and placebo, respectively) reported in association with evolocumab, and these findings are borne out in the current analyses. We found some minor differences in the rates of adverse events in men versus women, and across the age range, but there are no differences in those reported by those assigned evolocumab or placebo, with the exception of minor injection site reactions as previously described.

These results are very reassuring in comparison with the statin trials, in which in some studies it appears that the cardiovascular benefits of lipid lowering with statins may be attenuated in the elderly, and in women.[3,5,6] A recent report based on data from the Cholesterol Treatment Trialists Collaboration (CTTC) showed that the proportional reduction in the risk of major vascular events per mmol/l LDL-cholesterol reduction appears to be smaller among individuals older than 75 years (13% risk reduction) compared with those younger than 65 years (22% risk reduction) ($P_{trend} = 0.06$).[3] The authors offered as a potential explanation the fact that these patients had a higher prevalence of severe heart failure and end-stage renal disease. Interestingly, in the same analysis of the CTTC data, women profited less than men (16% vs. 22% risk reduction, respectively, $P_{heterogeneity} = 0.02$).

A recent analysis of the IMPROVE-IT trial also showed that the beneficial effects of adding ezetimibe to statins is present in both men and women,[11] with women having a 12% risk reduction compared with 5% in men, for the composite PEP ($P_{interaction} = 0.26$). In the same trial the reduction in the PEP was significantly greater in subjects older than 75 years of age ($P_{interaction} = 0.005$).[12]

The preliminary results of the ODYSSEY OUTCOMES trial with the PCSK9 inhibitor alirocumab showed that the relative risk reductions for the primary composite endpoint were broadly similar in women and men (9% vs. 17%, respectively, $P_{interaction} = 0.35$) and also when stratified by age 65 or greater versus less than 65 years (21% vs. 11%, respectively, $P_{interaction} = 0.19$).[13]

There are some limitations of the current analyses. The comparisons by age quartile and by sex are influenced by the different patient demographics as age increases, and in women compared with men. Older patients and female patients were more likely to have a background history of non-haemorrhagic stroke and peripheral artery disease, and less likely to have a history of MI. They were more likely to be hypertensive and less likely to be current smokers. These differences will affect the absolute risk of event rates in the various subgroups, but we have no *a priori* reason why they should influence proportional risk reductions in events associated with evolocumab treatment.

Although the current analyses have been based on quartiles of age, a subsidiary analysis using specific age breakdowns confirms that with evolocumab there is no diminution in the cardiovascular benefits in the older age groups. The large size of the FOURIER trial population provides a robust way in which to look at the cardiovascular benefits of evolocumab, subdivided by age and sex, and the results are reassuring.

In conclusion, the benefits of evolocumab are similar throughout a broad range of ages and in both men and women. No important safety issues were observed with evolocumab across age groups or in either sex.

Supplemental material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Author contribution

PS, AK, RG, TRP, BK, MSS and MLO'D contributed to the conception or design. PS, IG-B, AK, RG, TRP, KI, HW, BK, MSS and MLO'D contributed to the acquisition, analysis or interpretation. PS drafted the manuscript. PS, IG-B, AK, RG, TRP, KI, HW, BK, MSS and MLO'D critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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