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Efficacy and Safety of Long-Term Evolocumab Use Among Asian Subjects

— A Subgroup Analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) Trial —

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Background: There are concerns that Asian patients respond differently to some medications. This study evaluated the efficacy and safety of evolocumab among Asian vs. other subjects in the FOURIER trial, which randomized stable atherosclerosis patients to receive either evolocumab or placebo.

Methods and Results: Effects of adding evolocumab vs. placebo to background statin therapy on low-density lipoprotein cholesterol (LDL-C) reductions, cardiovascular outcomes, and adverse events were compared among 27,564 participants with atherosclerotic disease, according to self-reported Asian (n=2,723) vs. other (n=24,841) races followed for a median of 2.2 years in the FOURIER trial. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. At randomization, Asians had slightly lower LDL-C (median 89 [IQR 78–104] mg/dL vs. 92 [80–109] mg/dL; P<0.001) and were much less likely to be on a high-intensity statin (33.3% vs. 73.3%; P<0.001). Evolocumab lowered LDL-C more in Asians than in others (66% vs. 58%; P<0.001). The effect of evolocumab on the primary endpoint was similar in Asians (HR, 0.79; 95% CI, 0.61–1.03) and others (HR, 0.86; 95% CI, 0.79–0.93; P interaction=0.55). There was no excess of serious adverse events with evolocumab among Asians over others.

Conclusions: Use of evolocumab robustly lowers LDL-C and is equally efficacious in lowering the risk of cardiovascular events and safe in Asians as it is in others.

Key Words: Asians; Evolocumab; LDL cholesterol; PCSK9 inhibitor

Asian patients are commonly treated with lower doses of pharmacological agents than are Western patients. The importance has been well documented for use of certain β-blockers and anesthetic agents, where genetic traits influence drug metabolism and significantly slow drug clearance in Asian populations, hence modifying the dose-effect relationship.[1–3] However, a pattern of prescribing reduced doses has also occurred for other agents where there is less evidence of altered drug pharmacokinetics, including for the use of lipid-lowering agents. The efficacy of statins on low-density lipoprotein cholesterol (LDL-C) reduction at any given dose appears broadly similar among individuals of Asian vs. other backgrounds,[3] although a

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(Footnote continued the next page.)

higher rate of statin-induced myopathy has been associated with a genetic mutation thought to occur more commonly in Asian individuals.[4]

However, LDL-C is a major modifiable risk factor for cardiovascular disease (CVD), with a large body of evidence demonstrating the benefits of lowering LDL-C.[5] Statins are currently the mainstay in the management of hypercholesterolemia and the prevention of CVD.[6–8] Recent studies have shown that adding a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor can further reduce the risk of cardiovascular events.[9,10] Guidelines subsequently have been modified globally to include recommendation for adding PCSK9 inhibitors.[11–13]

Any concerns about efficacy and safety of PCSK9 inhibition specifically in Asian patients could lead to failure to initiate such therapy or underdosing, which might prevent patients from achieving optimal LDL-C control and hence optimal cardiovascular risk reduction. For these reasons, we were interested to examine the effects of evolocumab in the FOURIER (Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial to determine whether treatment responses or safety were different in individuals of Asian vs. other races.

Methods

Study Design

The FOURIER trial has been described in detail previously.[9,14] In brief, 27,564 individuals with established vascular disease (prior myocardial infarction, stroke or symptomatic peripheral vascular disease, combined with additional risk factors placing them at higher cardiovascular risk) and an LDL-C ≥70 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL were randomized, after optimization of their background lipid-lowering regimen according to physician satisfaction and local regulations, between evolocumab (140 mg by subcutaneous injection every 2 weeks, or 420 mg every 4 weeks) and matching placebo for the duration of follow up, with clinical review every 4 months. Subjects were required to be receiving an effective stable statin dose at study entry, defined as a minimum of 20 mg daily atorvastatin or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, was recommended. Follow up occurred for an average of 2.2 years, at which time the study was closed upon reaching its stopping rule. Analyses of all efficacy outcomes and safety events were performed according to a pre-specified protocol and statistical analysis plan. All patients provided written informed consent. The protocol was approved by the ethics committees at each center.

Participants

For this analysis, the FOURIER population was divided into those who self-reported as being of Asian ethnic background and all others, mainly Caucasian.

Main Outcome Measures

The primary outcome measure was major adverse cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary outcome measure was the composite of cardiovascular death, myocardial infarction, or stroke. Other secondary outcomes included the individual components aforementioned. Exploratory outcomes were percentage changes in LDL-C and other lipid measures.

Safety was assessed through collection of data on adverse events and central laboratory testing. A central clinical events committee led by the TIMI Study Group, whose members were unaware of study-group assignments and lipid levels, adjudicated all potential efficacy end-point events and cases of new-onset diabetes.

In this analysis, we assessed cognition in 2 ways: (1) investigator-reported cognitive adverse events; and (2) cognitive decline defined as Everyday Cognition (ECog) score ≥2 at the end of the study.[15–17]

Statistical Analyses

For changes in lipid, the least-squares mean was used based on a repeated measures ANCOVA model including treatment, randomization strata (LDL ≥85 mg/dL and region), visit and the interaction of treatment-by-visit interaction with the baseline value. For lipoprotein(a), the estimated treatment effect was provided in terms of ratios of geometric means, which was calculated by exponentially back transforming the least-squares means based on the ANCOVA model above. Time to first event efficacy analyses were performed using intention-to-treat methods according to randomized treatment and Cox proportional hazards modeling, based on the time from assignment to randomized treatment to the first occurrence of any element of the composite primary or secondary endpoint. Hazard ratios and 95% confidence intervals were determined by using the Cox proportional hazard model stratified by screening LDL-C and region. We evaluated the interaction by Asian or other races by using treatment by a subgroup interaction term in the model. Categorization according to racial background, Asian or other, was determined by self-reported race as recorded within the FOURIER database. All reported P values are 2-sided. $P<0.05$ signified nominal statistical significance with no adjustment made for multiple comparisons. All analyses were conducted using Stata 14.2 (College Station, TX, USA) or SAS 9.4 (Cary, NC, USA).

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Table 1. Baseline Characteristics for Asians and Others

Characteristics	Asians (N=2,723)	Others (N=24,841)	P value
Age, median (IQR), years	62 (55–68)	63 (56–69)	<0.001
Male, n (%)	2,164 (79.5)	18,631 (75.0)	<0.001
Body weight, median (IQR), kg	70 (62–79)	85 (75–97)	<0.001
Region of enrolment, n (%)			n/a
Asia	2,481 (91.2)	0 (0.0)	
North America	70 (2.6)	4,501(18.1)	
Europe	51 (1.9)	17,284 (69.6)	
Latin America	1 (0.0)	1,822 (7.3)	
South Africa	115 (4.2)	822 (3.3)	
Pacific	5 (0.2)	412 (1.7)	
BMI, median (IQR), kg/m^2	26 (23–28)	29 (26–32)	<0.001
Type of atherosclerosis, n (%)			
Myocardial infarction	2,085 (76.6)	20,266 (81.6)	<0.001
Non-hemorrhagic stroke	786 (28.9)	4,551 (18.3)	<0.001
Peripheral artery disease	137 (5.0)	3,505 (14.1)	<0.001
Polyvascular disease	272 (10.0)	3,291 (13.2)	<0.001
Coexisting conditions, n (%)			
Hypertension	1,955 (71.8)	20,129 (81.0)	<0.001
Diabetes mellitus	1,371 (50.3)	8,710 (35.1)	<0.001
Current cigarette use	739 (27.1)	7,038 (28.3)	0.19
Lipid measures, median (IQR)			
LDL cholesterol, mg/dL	89 (78–104)	92 (80–109)	<0.001
Total cholesterol, mg/dL	161 (147–181)	168 (152–189)	<0.001
HDL cholesterol, mg/dL	43 (36–51)	44 (37–53)	<0.001
Triglycerides, mg/dL	126 (94–172)	134 (101–183)	<0.001
Lipoprotein(a), nmol/L	39 (16–124)	37 (12–168)	0.47
eGFR <60 mL/min/1.73 m^2	439 (16.1)	4,763 (19.2)	<0.001
Lipid lowering therapy, n (%)			
Statin			<0.001
High intensity	906 (33.3)	18,197 (73.3)	
Moderate intensity	1,816 (66.7)	6,576 (26.5)	
Low, unknown or no data	1 (0.0)	68 (0.3)	
Ezetimibe	101 (3.7)	1,339 (5.4)	<0.001
Other cardiovascular medications, n (%)			
Aspirin, P2Y12 inhibitor or both	2,571 (94.5)	22,861 (92.1)	<0.001
β-blocker	1,637 (60.2)	19,178 (77.3)	<0.001
Renin-angiotensin-aldosterone inhibitor	1,685 (61.9)	19,848 (80.0)	<0.001

Data are expressed as n (%), mean±SD, or median (interquartile range). BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

Results

Baseline Characteristics of Study Participants

Of the 27,564 participants in the FOURIER trial, 2,723 participants (9.9%) self-reported to be Asian, of whom 2,481 were recruited at study sites within Asian countries (China 1,021, Japan 429, Philippines 294, India 266, South Korea 181, Taiwan 144, other countries 146), and 242 were recruited elsewhere (**Table 1**). The remaining 24,841 participants reported to be of other racial backgrounds, mainly Caucasian. Racial groups were well balanced in terms of treatment allocation.

History of non-hemorrhagic stroke was more common in Asian patients (28.9% vs. 18.3%), whereas prior myocardial infarction (76.6% vs. 81.6%) and peripheral artery disease (5.0% vs. 14.1%) were less frequent in Asians than in others. History of hypertension was less commonly present in Asian patients compared to other patients (71.8% vs. 81.0%), whereas history of diabetes was more frequent (50.3% vs. 35.1%). On average, Asian subjects weighted 15 kg less than others (median 70 kg, interquartile range [IQR] 62–79 kg vs. 85 kg, IQR 75–97 kg). High-intensity statin use was far less frequent in Asian participants compared with others (33.3% vs. 73.3%) (**Table 1**).

Lipid Levels and Changes With Evolocumab

Baseline LDL-C levels were slightly lower among Asian than among other trial participants (median 89 mg/dL, IQR 78–104 mg/dL vs. 92 mg/dL, IQR 80–109 mg/dL; P<0.001) (**Table 1**). Other lipid levels were also lower, including HDL-C, total cholesterol, and triglyceride levels, whereas lipoprotein(a) levels were similar (**Table 1**). Evolocumab

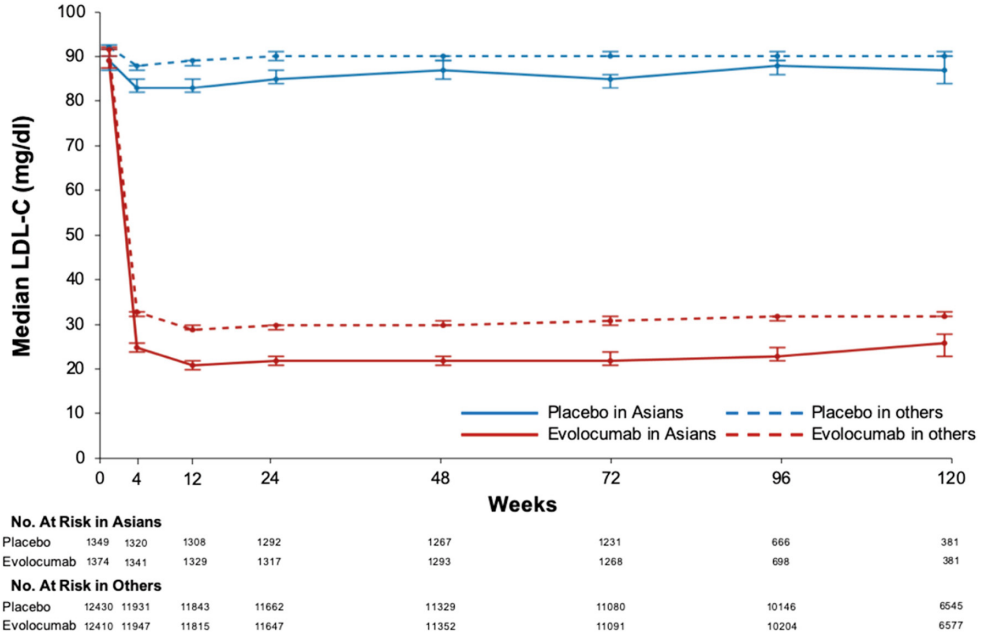

Figure 1. Low-density lipoprotein cholesterol (LDL-C) levels over time stratified according to treatment allocation for Asians vs. others. Median LDL-C levels over time by treatment allocation and racial groups. Red indicates the evolocumab arm; blue indicates the placebo arm; solid line indicates Asians; dashed line indicates others; I bars indicate 95% confidence intervals.

lowered LDL-C levels (baseline to 48 weeks) more in Asian patients than in others, from a median of 89 to 22 (IQR 14–36) mg/dL, compared with from 92 to 30 (IQR 19–48) mg/dL respectively (**Figure 1**). At 48 weeks, the least-squares mean absolute and percentage reductions in LDL-C levels with evolocumab, as compared with placebo, were greater in Asians than in others (61 mg/dL vs. 55 mg/dL for absolute reduction; 66% vs. 58% for percentage reduction; P<0.001 for comparison of differences for both) (**Figure 1**). After patients were stratified to those on high-intensity or non-high-intensity statin therapy, the least-squares percentage reductions in LDL-C levels with evolocumab in both groups, as compared with placebo, were larger in Asians than in others (62% vs. 57%; P=0.02 in patients on high-intensity statin; 68% vs. 61%; P<0.001 in patients on non-high-intensity statin). Percent LDL-C reduction with evolocumab compared with placebo differed between Asians and others despite adjustment for both baseline body weight and high-intensity statin use (P interaction<0.001). Percentage reductions in other lipid parameters between Asians and others are shown in the **Supplementary Table**.

Effects of Allocation to Evolocumab on Clinical Efficacy, Adherence and Safety Outcomes

Compared with placebo, the reduction in risk of the primary endpoint with evolocumab was similar among Asian patients (2.5-year Kaplan-Meier event rate 10.0% vs. 13.0%; HR, 0.79; 95% CI, 0.61–1.03), and among others (11.0% vs. 12.8%; HR, 0.86; 95% CI, 0.79–0.93; P interaction=0.55) (**Figures 2**,**3**). Likewise, the reduction in the risk of the key secondary endpoint with evolocumab was similar among Asian patients (6.3% vs. 9.0%; HR 0.73; 95% CI 0.53–1.01), and others (6.7% vs. 8.3%; HR 0.81; 95% CI 0.73–0.89; P interaction=0.58 (**Figures 2**,**3**). The effects of evolocumab on the individual component endpoints of the composite primary endpoint according to racial background are shown in **Figure 3** and were similar for Asians and others.

Adherence to study medication was also similar among Asian and other study participants, with discontinuations from active study drug use due to adverse events being very low in both Asian and other subjects (0.9% vs. 1.0%; P=0.80 in Asians; 1.7% vs. 1.5%; P=0.19 in others; P interaction=0.57) (**Table 2**). Serious adverse event rates were similar between evolocumab and placebo groups both in participants of Asian and other race (19.4% vs. 20.8%; P=0.35 in Asians; 25.4% vs. 25.2%; P=0.73 in others; P interaction=0.32), and hemorrhagic stroke events were rare in both racial groups, and were not increased by evolocumab (0.5% vs. 0.3%; P=0.55 in Asians; 0.2% vs. 0.2%; P=0.87 in others; P interaction=0.48). New-onset diabetes was similar between evolocumab and placebo groups both in participants of Asian and other race (13.6% vs. 13.6%; P=0.99 in Asians; 7.7% vs. 7.2%; P=0.33 in others; P interaction=0.72). Injection-site reactions were based on subjective patient assessment and rare, but they were more frequent with evolocumab among both racial study groups, and they were more likely to occur among Asian participants than among other participants (2.2% vs. 0.6%; P<0.001 in Asians; 2.1% vs. 1.7%; P=0.01 in others; P interaction=0.01). Subject incidences of investigator-reported cognitive adverse events were not higher with evolocumab vs. placebo in Asians than in others (1.5% vs. 2.3% in Asians; 1.6% vs. 1.4% in others; P interaction=0.047), and patient-reported cognitive decline (ECog score ≥2) at the end of the study was similar with evolocumab vs. pla-

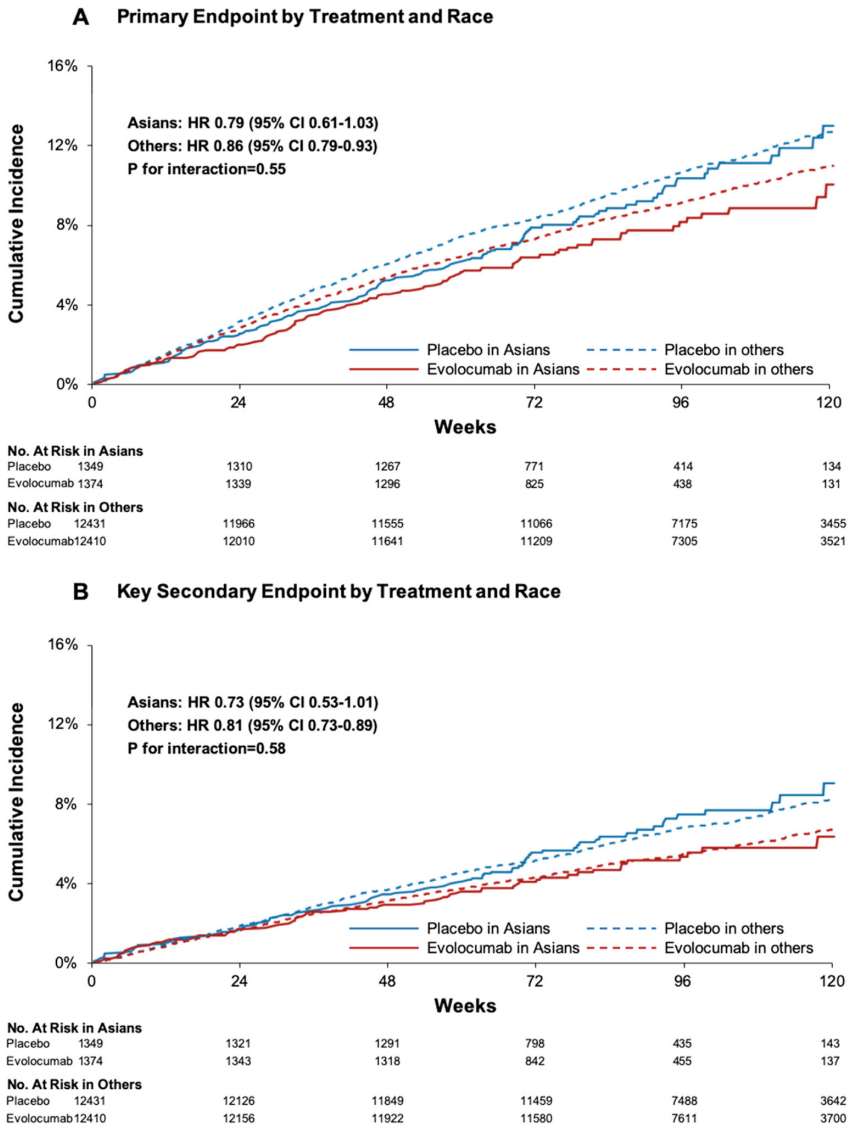

Figure 2. Kaplan-Meier curves for the primary and key secondary endpoints according to treatment allocation for Asians vs. others. Kaplan-Meier curves for the primary (**A**) and key secondary (**B**) efficacy endpoints according to treatment allocation for Asians vs. others. HR, hazard ratio. Red, evolocumab arm; blue, placebo arm; solid line, Asians; dashed line, others.

cebo both in Asians and others (2.6% vs. 1.8% in Asians; 3.8% vs. 3.8% in others; P interaction=0.22).

Discussion

A known sensitivity to some drugs has resulted in widespread prescribing of lower doses of many medications to Asian individuals over decades of clinical care.[18] The more recent recognition that statin-related myopathy, although still rare, can occur more frequently among Asian populations associated with a higher prevalence of a SLCO1B1 gene T521C polymorphism, has reinforced the caution with drug dosing that has been widely practiced before by clinicians in Asia.[4] The more conservative approach generally in Asia to drug dosing has raised questions about whether giving similar doses of the PCSK9 inhibitor, evolocumab, which has been used in largely non-Asian populations, will be necessary to achieve similar clinical benefits among Asian individuals, and whether such treatment will be less safe among Asians compared with other populations. Moreover, due to a higher proportion of hemorrhagic stroke in Asians than among Caucasian populations, combined with the possibility from analyses reported by the Cholesterol Trialists' Treatment Collaboration that statins may increase the risk of hemorrhagic stroke, the ability of evolocumab to lower LDL-C to very low levels raised legitimate concerns about whether such profound lowering of LDL-C would be safe in Asian individuals.[19] These concerns led us to examine the clinical efficacy and safety of evolocumab in the FOURIER trial among those of Asian race compared with others.

Asian patients were taking lower doses of background statin therapy than the other subjects at baseline, but had 3 mg/dL lower baseline LDL-C level on average. Despite that, the LDL-C reductions seen with evolocumab treatment, compared with placebo, were indeed nominally statistically larger among Asian subjects. This effect was seen regardless of statin dose and weight. The cause of this difference is unknown. It may be related to differences in drug metabolism, PCSK9 levels, response to background statin ther-

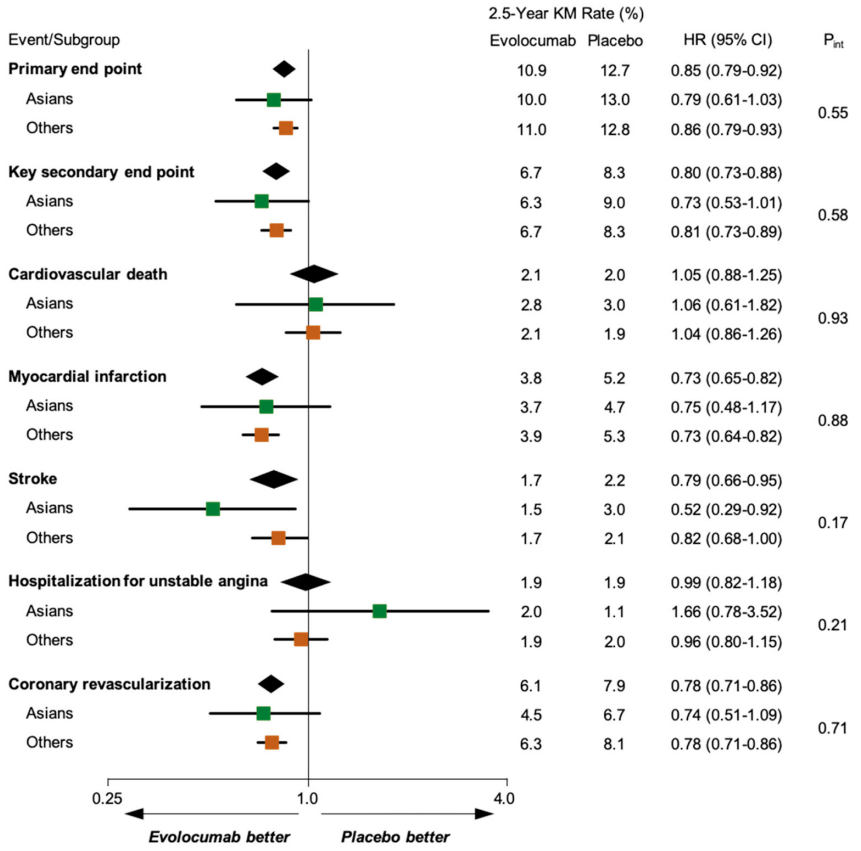

Figure 3. Efficacy of evolocumab on key clinical outcomes for Asians vs. others. Clinical effects of evolocumab vs. placebo on key outcomes according to Asians and others. Primary endpoint indicates a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; key secondary endpoint indicates a composite of cardiovascular death, myocardial infarction, or stroke. CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; P_{int}, P value for treatment-race interaction. Green, Asians; orange, others.

Table 2. Adherence and Safety by Treatment Allocation and Race

Event	Asians			Others			P value for interaction
	Evolocumab	Placebo	P value	Evolocumab	Placebo	P value	
Adherence							
Treatment discontinuation, n (%)	120 (8.7)	123 (9.1)	0.71	1,562 (12.6)	1,623 (13.1)	0.26	0.96
Treatment discontinuation thought to be related to the study agent, n (%)	13 (0.9)	14 (1.0)	0.80	213 (1.7)	187 (1.5)	0.19	0.57
Adverse events							
Serious, n (%)	266 (19.4)	280 (20.8)	0.35	3,144 (25.4)	3,124 (25.2)	0.73	0.32
Allergic reaction, n (%)	46 (3.4)	45 (3.3)	0.99	374 (3.0)	348 (2.8)	0.32	0.74
Injection site reaction, n (%)	30 (2.2)	8 (0.6)	<0.001	266 (2.1)	211 (1.7)	0.01	0.01
Muscle-related event, n (%)	36 (2.6)	32 (2.4)	0.69	646 (5.2)	624 (5.0)	0.51	0.81
Rhabdomyolysis, n (%)	1 (0.1)	0 (0.0)	0.49	10 (0.1)	8 (0.1)	0.64	0.98
Cataract, n (%)	23 (1.7)	26 (1.9)	0.61	205 (1.7)	216 (1.7)	0.60	0.76
New-onset diabetes, n (%)	88 (13.6)	85 (13.6)	0.99	589 (7.7)	559 (7.2)	0.33	0.72
Hemorrhagic stroke, n (%)	7 (0.5)	4 (0.3)	0.55	22 (0.2)	21 (0.2)	0.87	0.48
Investigator-reported neurocognitive event, n (%)	20 (1.5)	31 (2.3)	0.10	197 (1.6)	171 (1.4)	0.17	0.047
Cognitive decline (ECog score ≥2), n (%)	30 (2.6)	20 (1.8)	0.18	388 (3.8)	381 (3.8)	0.85	0.22
Laboratory							
Aminotransferase level >3-fold the upper limit of the normal range	12 (0.9)	24 (1.8)	0.04	228 (1.9)	218 (1.8)	0.63	0.04
Binding anti-body,* %	0.90	0	–	0.26	0	–	–

Data are expressed as n (%) or mean (SD). ECog score, Everyday Cognition score. *Antibodies were transient and none were neutralizing.

apy, or some combination of these in Asian populations. The trends to somewhat larger proportional event reductions in cardiovascular events with evolocumab allocation seen in Asians compared with the other populations might partly involve such an advantage, or may simply be the play of chance. In any event, the relative risk reductions in Asians are at least comparable to those seen in others without any safety concerns.

Importantly, there was no excess of serious adverse events with evolocumab vs. placebo arms in Asians compared to others, including hemorrhagic stroke, myopathy, transaminitis, new-onset diabetes or cognitive effects, despite a very low median-achieved LDL-C of 22 mg/dL in Asians (with a lower quartile of 14 mg/dL). Discontinuation rates from study agent for emergent adverse events were also similar between the evolocumab and placebo groups both in Asians and other subjects when administering identical doses of evolocumab over several years. Such findings provide strong reassurance that, at least for this drug, no modification of dose is required when treating individuals of Asian background, and expected benefits can be similar. Longer-term data up to 5 years further informing such conclusions will become available over time from the open-label extension studies in which some of the FOURIER subjects are continuing to receive active treatment post-trial, and other on-going follow up of other FOURIER trial subjects, including formal cognitive testing (ClinicalTrials.gov number, NCT02867813).

The ODYSSEY Outcomes trial of another PCSK9 inhibitor, alirocumab, in patients after an acute coronary syndrome, reported a 15% reduction in the primary outcome with treatment. However, the signal for benefit among the Asian subgroup in the ODYSSEY Outcomes trial was less clear.[10] Although there was no statistical heterogeneity between the effects in the Asian subjects compared with others in the ODYSSEY Outcomes trial, the estimated effect in Asian patients was of no benefit.[10]

We recognize our analysis has limitations. Because patients who participate in a randomized clinical trial are selected based on strict entry criteria, the results described may not apply to all patients in clinical practice. The FOURIER trial was not powered for subgroup analyses and the number of patients of Asian race was modest. We were not able to assess the impact of the country on randomization among patients of Asian race, which may have influenced outcomes.

We conclude that evolocumab is safe and effective in both Asian and other individuals, with no important concerns, or need to modify the dose used according to racial background. Guidelines for product use in clinical practice should reflect these reassuring findings and minimize reasons for any geographical differences in recommendations based on race.

Acknowledgments

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Disclosures

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IRB Information

The protocol and amendments were locally, centrally, or nationally approved by the relevant ethics committees.

Data Availability

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions. URL: https://www.clinicaltrials.gov. Unique identifier: NCT01764633.

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Supplementary Files

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