Stroke Prevention With the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Evolocumab Added to Statin in High-Risk Patients With Stable Atherosclerosis

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Background and Purpose—The PCSK9 (proprotein convertase subtilisin-kexin type 9) monoclonal antibody evolocumab lowered LDL (low-density lipoprotein) cholesterol by 59% to 0.8 (0.5–1.2) mmol/L and significantly reduced major vascular events in the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk). Herein, we report the results of a prespecified analysis of cerebrovascular events in the overall trial population and in patients stratified by prior stroke.

Methods—FOURIER was a randomized, double-blind trial comparing evolocumab versus placebo in patients with established atherosclerosis, additional risk factors, and LDL cholesterol levels ≥1.8 (or non-HDL [high-density lipoprotein] ≥2.6 mmol/L) on statin therapy. The median follow-up was 2.2 years. We analyzed the efficacy of evolocumab to reduce overall stroke and stroke subtypes, as well as the primary cardiovascular composite end point by subgroups according to a history of stroke.

Results—Among the 27 564 patients, 469 (1.7%) experienced a total of 503 strokes of which 421 (84%) were ischemic. Prior ischemic stroke, diabetes mellitus, elevated CRP (C-reactive protein), history of heart failure, older age, nonwhite race, peripheral arterial disease, and renal insufficiency were independent predictors of stroke. Evolocumab significantly reduced all stroke (1.5% versus 1.9%; hazard ratio, 0.79 [95% CI, 0.66–0.95]; *P*=0.01) and ischemic stroke (1.2% versus 1.6%; hazard ratio, 0.75 [95% CI, 0.62–0.92]; *P*=0.005), with no difference in hemorrhagic stroke (0.21% versus 0.18%; hazard ratio, 1.16 [95% CI, 0.68–1.98]; *P*=0.59). These findings were consistent across subgroups, including among the 5337 patients (19%) with prior ischemic stroke in whom the hazard ratios (95% CIs) were 0.85 (0.72–1.00) for the cardiovascular composite, 0.90 (0.68–1.19) for all stroke, and 0.92 (0.68–1.25) for ischemic stroke (*P* interactions, 0.91, 0.22, and 0.09, respectively, compared with patients without a prior ischemic stroke).

Conclusions—Inhibition of PCSK9 with evolocumab added to statin in patients with established atherosclerosis reduced ischemic stroke and cardiovascular events in the total population and in key subgroups, including those with prior ischemic stroke.

Registration—URL: https://www.clinicaltrials.gov; Unique identifier: NCT01764633.

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See related article, p 1361

The American Heart Association estimates that ≈795 000 Americans experience new or recurrent stroke annually of which 87% are ischemic.[1] In a large international registry of outpatients with atherothrombosis, patients with symptomatic atherosclerotic arterial disease had a 1.9% rate of nonfatal stroke in the first year (compared with 0.8% in patients without symptomatic disease but with multiple cardiovascular risk factors), and the rate was doubled (3.7%) among patients with prior stroke.[2] Lipid lowering with statins reduced the relative risk of ischemic stroke by 21% per 1 mmol/L reduction in LDL (low-density lipoprotein) cholesterol (LDL-C)

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over 5 years of follow-up in a meta-analysis of 21 randomized trials.[3] More recently in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the cholesterol absorption inhibitor ezetimibe, when added to background statin therapy in patients hospitalized for acute coronary syndrome, significantly reduced the risk of ischemic stroke compared with placebo over an average follow-up of 6 years.[4,5] Robust reductions in LDL-C can be achieved with the addition of monoclonal antibodies that inhibit PCSK9 (proprotein convertase subtilisin-kexin type 9).[6,7] In the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) conducted in 27 564 patients with stable atherosclerosis, the PCSK9 inhibitor evolocumab reduced LDL-C by 59% (absolute reduction of 1.45 mmol/L) on a background of moderate- or high-intensity statin and significantly reduced cardiovascular events over a median follow-up of 2.2 years.[8] In this analysis, we assess the benefit of evolocumab on prevention of stroke and stroke subtypes in the overall population and in selected patient subgroups (including those with prior ischemic stroke) in the FOURIER trial.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure; however, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Study Population and Procedures

The FOURIER trial was a multinational double-blind, placebo-controlled trial of 27 564 patients 40 to 85 years of age with a history of myocardial infarction (MI), ischemic stroke, or symptomatic peripheral arterial disease and additional high-risk features.[9] Eligible patients had an LDL-C of ≥1.8 mmol/L or non-HDL (high-density lipoprotein) cholesterol ≥2.6 mmol/L after at least 2 weeks' stabilization on a moderate- or high-intensity statin, with or without ezetimibe. Key exclusion criteria included a qualifying event within 4 weeks, previous hemorrhagic stroke, severe heart failure, severe renal failure, malignancy within the past 10 years, and severe concomitant noncardiovascular disease.

Patients were randomly assigned (1:1) subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg every 4 weeks per patients' preference) or matching placebo. The protocol was approved by the relevant ethics committees at all participating sites. Written informed consent was obtained from all the patients.

End Points

The primary prespecified study end point was the time to the first of any of the following events: cardiovascular death, MI, stroke (ischemic or hemorrhagic), hospitalization for unstable angina, or coronary revascularization. Ischemic stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of infarction, while similar events without acute infarction and lasting <24 hours were classified as transient ischemic attack (TIA).[8] Hemorrhagic strokes included hemorrhages that were intraparenchymal, intraventricular, or in the subarachnoid space. Hemorrhages into the subdural or epidural space were not classified as hemorrhagic strokes (but were considered intracranial hemorrhages). All events were adjudicated by an independent end point committee unaware of the treatment allocation and lipid levels during the trial. The modified Rankin Scale (mRS) global disability score was determined ≥30 days after the event in patients experiencing a stroke. In the statistical analysis plan, all stroke (combined ischemic, hemorrhagic, and strokes of unknown type) and the composite of ischemic stroke or TIA were prespecified secondary end points, while the subgroup of patients with prior ischemic stroke was prespecified.[8] A small number of strokes of unknown type (n=27 without imaging or pathology data) were included in analyses of all strokes but excluded from analyses of ischemic and hemorrhagic stroke subtypes.

Statistical Analysis

Time-to-first-event efficacy analyses were performed in the intention-to-treat population using Cox proportional hazards modeling with randomized treatment (evolocumab versus placebo) and stratification by randomization stratification factors (final screening LDL-C above versus below 2.2 mmol/L and region). The FOURIER trial was powered for the primary and key secondary composite end points but not for individual components of these end points or any one subgroup. All event rates are frequency rates (n/N), except where otherwise specified. The subgroup of patients with a history of ischemic stroke was defined by a prior clinical diagnosis, as assessed by the investigator. We evaluated for heterogeneity of the treatment effect of evolocumab versus placebo using Cox proportional-hazards regression modeling, including a treatment-by-subgroup interaction term.

Negative binomial regression analysis—a type of modified Poisson model—was performed to compare the total number of strokes (first and subsequent strokes) in patients treated with evolocumab and placebo, as described previously.[10] For the total events analysis, the first event refers to the first individual end point event after randomization. A subsequent or recurrent event is an additional event that occurred after the first postrandomization event. The negative binomial model included an exposure variable for duration of follow-up because this could vary by subject. Incidence risk ratio (RR) and corresponding 95% CIs are reported from the negative binomial regression model.

Independent predictors of stroke were identified by consistency of forward, backward, and stepwise model selection using 15 candidate baseline variables selected based on a significance level of $P<0.05$ on univariate analysis: randomized treatment, age group, sex, white race, diabetes mellitus, hypertension, congestive heart failure, peripheral artery disease, prior MI, prior stroke, prior TIA, history of atrial fibrillation, aspirin use, eGFR <60, and elevated high-sensitivity CRP (C-reactive protein; hs-CRP). Except for estimated glomerular filtration rate and hs-CRP (measured), all other candidate variables (eg, hypertension and diabetes mellitus) were defined by a prior clinical diagnosis as assessed by the investigator. All reported P values are 2 sided. $P<0.05$ signified nominal statistical significance with no adjustment for multiple comparisons. All analyses were conducted using Stata 14.2 (College Station, TX) or SAS 9.4 (Cary, NC).

Results

Total Population

Of the 27 564 patients randomized, 469 (1.7%) patients experienced a total of 503 strokes (including 9 who experienced 2 different types of stroke) during a median follow-up of 2.2 years. Among total strokes, most were ischemic (421, 84%), whereas 55 (11%) were hemorrhagic, and only 27 (5%) were of unknown type. Investigators reported the mRS in 434 (93%) first strokes of which 270 (62%) were judged to have functional independent outcome (mRS, 0–2), 72 (17%) had a dependent outcome (mRS, 3–5), and 92 (21%) were fatal (mRS, 6). Of the 92 fatal strokes, the Clinical Event Committee adjudicated stroke as the primary cause of death in 64 patients (14% of all strokes); the remaining 28 patients with fatal stroke died within 30 days of stroke onset from another primary cause. There were an additional 127 patients who experienced a TIA without an ischemic stroke during trial follow-up, yielding a

total of 524 patients with cerebral ischemic events (10 patients had both TIA and an ischemic stroke).

The baseline characteristics of patients who did and did not experience a stroke during follow-up are shown in Table 1; these characteristics were similar by randomized treatment group (Table I in the Data Supplement). The most potent predictor of any stroke was a history of stroke (hazard ratio [HR], 2.85 [2.36–3.43]), followed by history of heart failure, elevated hs-CRP, history of diabetes mellitus, nonwhite race, age, elevated systolic blood pressure, randomization to placebo, history of peripheral arterial disease, and renal insufficiency (Figure I in the Data Supplement). Independent predictors of ischemic stroke generally were similar and also included prior TIA but not systolic blood pressure or renal insufficiency. The strongest predictors of hemorrhagic stroke were nonwhite race, prior stroke, elevated hs-CRP, age, and also included the use of an anticoagulant.

Evolocumab Versus Placebo

Compared with placebo, evolocumab significantly reduced the incidence of any type of stroke (1.5% versus 1.9%; HR, 0.79 [0.66–0.95]; *P*=0.01), ischemic stroke (1.2% versus 1.6%; HR, 0.75 [0.62–0.92]; *P*=0.005), and ischemic stroke or TIA (1.7% versus 2.1%; HR, 0.77 [0.65–0.92]; *P*=0.003; Table 2; Kaplan-Meier estimates are shown in Figure 1). Hemorrhagic strokes were infrequent (n=54), and rates were similar between treatment groups (0.21% versus 0.18%; HR, 1.16 [0.68–1.98]; *P*=0.59). Among the 434 first strokes with an mRS assessment, evolocumab reduced both strokes with an independent outcome (mRS 0–2: odds ratio, 0.75 [95% CI, 0.59–0.96]) and strokes causing dependency (mRS 3–5: odds ratio, 0.56 [95% CI, 0.35–0.91]).

In addition to the 469 first strokes, there were an additional 34 recurrent strokes in 32 patients that occurred after a first stroke. There were an additional 10 fewer recurrent strokes with evolocumab compared with placebo, yielding a total of 65 fewer total strokes observed in the evolocumab group (RR, 0.77 [0.64–0.93]; *P*=0.007). The total number of ischemic strokes were lower with evolocumab compared with placebo (177 versus 244; RR, 0.72 [0.59–0.89]; *P*=0.002), while there were no differences between treatment group in total hemorrhagic strokes (29 versus 26; RR, 1.12 [0.64–1.93]; *P*=0.70).

Patients With Prior Ischemic Stroke

There were 5337 (19%) patients with a history of an ischemic stroke before randomization (patients with prior hemorrhagic stroke were not eligible for FOURIER). The median time between prior stroke and randomization was 3.3 years (interquartile range, 1.1–7.2 years), and 23% of these patients were randomized <1 year after the stroke. Patients with a history of stroke before randomization had a higher risk profile (Table II in the Data Supplement) than patients without a prior stroke. Baseline characteristics between treatment groups, stratified by history of stroke, were similar (Table III in the Data Supplement). Among patients with prior stroke, median follow-up was 2.1 (1.8–2.5) years in each treatment group.

Among patients with prior stroke, the median LDL-C at randomization was 2.4 mmol/L (interquartile range, 2.1–2.8). After 4 weeks, the least-squares mean percentage reduction in LDL-C levels with evolocumab as compared with placebo was 55.6% ([95% CI, 54.4–56.9] *P*<0.001) to a median concentration of 0.8 mmol/L (interquartile range, 0.5–1.2) in the evolocumab arm (Figure 2). The difference between treatment groups persisted throughout the trial follow-up (56.3% [95% CI, 54.5–58.2]; *P*<0.001) with a median LDL-C at 48 weeks of 0.8 (0.5–1.2) mmol/L in the evolocumab group.

Among the patients enrolled with prior stroke, significantly fewer patients randomized to evolocumab experienced a primary end point event (259 versus 300; HR, 0.85 [0.72–1.00]; *P*=0.047), with a similar reduction seen in those without a prior stroke (HR, 0.85 [0.79–0.93]; *P*<0.001) with no evidence of heterogeneity (*P* interaction, 0.91; Figure 3). In patients with a more recent prior stroke (within 1 year before randomization, n=1235), the HR for the primary end point was 0.72 (0.51–1.02), whereas for those more distant from their prior stroke (n=4082), it was 0.87 ([0.72–1.05] *P* interaction, 0.35).

Evolocumab reduced postrandomization cerebrovascular events, including all stroke, ischemic stroke, and the composite of ischemic stroke or TIA to a similar degree, regardless of whether patients had a prior stroke or not (Table 3). There was no difference between treatment groups in the small number of hemorrhagic strokes observed in patients with a prior stroke.

Total stroke events among patients with prior stroke were nominally reduced with evolocumab versus placebo (102 versus 116; RR, 0.87 [0.65–1.16]) to a similar degree (*P* interaction, 0.29) as was observed in those without a prior stroke (117 versus 168; RR, 0.70 [0.54–0.90]). Similar findings were present with regards the total numbers of ischemic strokes, ischemic strokes or TIAs, and hemorrhagic strokes.

As was seen in the overall population, evolocumab was well tolerated among patients enrolled with prior stroke, and there were no differences for any specific adverse events between the treatment groups, except for minor injection site reactions (Table IV in the Data Supplement). Specifically, there was no increase in neurocognitive adverse events in the group with a history of stroke randomized to evolocumab versus placebo (2.0% versus 2.0%; *P*=0.94). Only 2 of the 544 (0.4%) patients with prior stroke who achieved a very low LDL-C (<0.5 mmol/L) at 4 weeks treated with evolocumab experienced a hemorrhagic stroke compared with 0.6% of those with a prior stroke who had an LDL ≥0.5 mmol/L at 4 weeks in the evolocumab group.

Stroke Outcomes in Other Key Subgroups

The relative benefit of evolocumab in the prevention of first stroke was consistent (*P* interactions, all >0.05) across major subgroups stratified by baseline LDL-C, statin intensity, age, sex, race, history of stroke, qualifying vascular disease, diabetes mellitus, heart failure, renal function, history of atrial fibrillation, and hs-CRP at baseline (Figure II in the Data Supplement). Similar consistency in the prevention of ischemic stroke or TIA was observed across subgroups (Figure III in the Data Supplement).

Discussion

Intensive further lowering of LDL-C levels by adding the PCSK9 inhibitor evolocumab to moderate–to-intensive

Table 1. Baseline Characteristics in Patients With Stroke of Any Etiology Versus No Stroke During Follow-Up

Variable	No Stroke (N=27 095)	Any Stroke (N=469)	*P* Value
Demographics			
Age, y; median (IQR)	63 (56–69)	65 (59–72)	<0.001
Age ≥75 y	9.1	15.4	<0.001
Women	24.5	26.2	0.40
Nonwhite*	14.8	20.5	<0.001
Body mass index, kg/m^2; median (IQR)	28.8 (25.9–32.1)	28.8 (25.7–32.4)	0.88
Region			0.15
North America	16.5	20.3	
Europe	63.0	58.8	
Latin America	6.6	7.0	
Asia Pacific and South Africa	13.9	13.9	
Qualifying type of atherosclerosis†			<0.001
Ischemic stroke alone	12.0	27.1	
Myocardial infarction alone	69.8	43.7	
Peripheral artery disease alone	5.5	4.5	
Polyvascular disease	12.7	24.7	
Coexisting conditions			
Congestive heart failure	23.0	31.8	<0.001
Hypertension	80.0	86.1	<0.001
Diabetes mellitus	36.3	50.5	<0.001
Current smoking	28.3	26.2	0.33
Atrial fibrillation	8.4	13.0	<0.001
CHA_2DS_2-VASc score, mean (SD)	3.6 (1.5)	4.5 (1.5)	<0.001
Lipid-lowering therapy			
High-intensity‡ statin	69.4	64.6	0.080
Moderate-intensity statin	30.4	35.2	
Low intensity, unknown intensity, or no statin data	0.3	0.2	
Ezetimibe	5.2	5.8	0.60
Other cardiovascular medications			
Aspirin, $P2Y_{12}$ inhibitor, or both	92.4	88.7	0.003
β-Blocker	75.6	72.2	0.088
Renin-angiotensin-aldosterone inhibitor	78.2	79.5	0.49
Median laboratory measures at baseline (IQR)			
LDL cholesterol, mmol/L	2.4 (2.1–2.8)	2.4 (2.1–2.8)	0.28
Non-HDL total cholesterol, mmol/L	3.1 (2.7–3.7)	3.2 (2.7–3.7)	0.55
Total cholesterol, mmol/L	4.3 (3.9–4.9)	4.4 (3.9–4.9)	0.62
HDL cholesterol, mmol/L	1.1 (1.0–1.4)	1.1 (0.9–1.4)	0.49
Triglycerides, mmol/L	1.5 (1.1–2.1)	1.5 (1.1–2.1)	0.59
Lipoprotein (a), nmol/L	37 (13–165)	40 (14–156)	0.54
hs-CRP, mg/L	1.7 (0.9–3.5)	2.5 (1.1–5.0)	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	75 (64–88)	71 (57–83)	<0.001

Data represent proportion (%) unless otherwise specified. To convert the values for cholesterol to milligrams per deciliter, multiply by 38.67. To convert the values for triglycerides to milligrams per deciliter, multiply by 88.57. HDL indicates high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; and LDL, low-density lipoprotein.

*Race was reported by the patients.

†Patients could have >1 type of atherosclerosis.

‡Statin intensity was categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.[7]

Table 2. First Stroke Events by Randomized Treatment

End point	Placebo, n (%) N=13 780	Evolocumab, n (%) N=13 784	95% CI Hazard ratio	*P* Value
All stroke	262 (1.9)	207 (1.5)	0.79 (0.66–0.95)	0.01
Ischemic	226 (1.6)	171 (1.2)	0.75 (0.62–0.92)	0.005
Hemorrhagic	25 (0.18)	29 (0.21)	1.16 (0.68–1.98)	0.59
Unknown	14 (0.10)	13 (0.09)	0.93 (0.44–1.97)	0.84
Ischemic stroke or TIA	295 (2.1)	229 (1.7)	0.77 (0.65–0.92)	0.003
TIA	76 (0.55)	61 (0.44)	0.80 (0.57–1.12)	0.20
mRS outcome in patients with stroke*	n=247	n=187	Odds ratio	
0–2 (functionally independent)	154 (1.2)	116 (0.84)	0.75 (0.59–0.96)	0.020
3–5 (dependent)	46 (0.33)	26 (0.19)	0.56 (0.35–0.91)	0.018
6 (fatal)	47 (0.33)	45 (0.34)	0.96 (0.64–1.44)	0.84

Rates shown are n/N. Nine patients experienced both ischemic and hemorrhagic strokes. mRS indicates modified Rankin Scale; and TIA, transient ischemic attack.

*Modified Rankin Scale score was missing in 15 and 20 patients randomized to placebo and evolocumab, respectively.

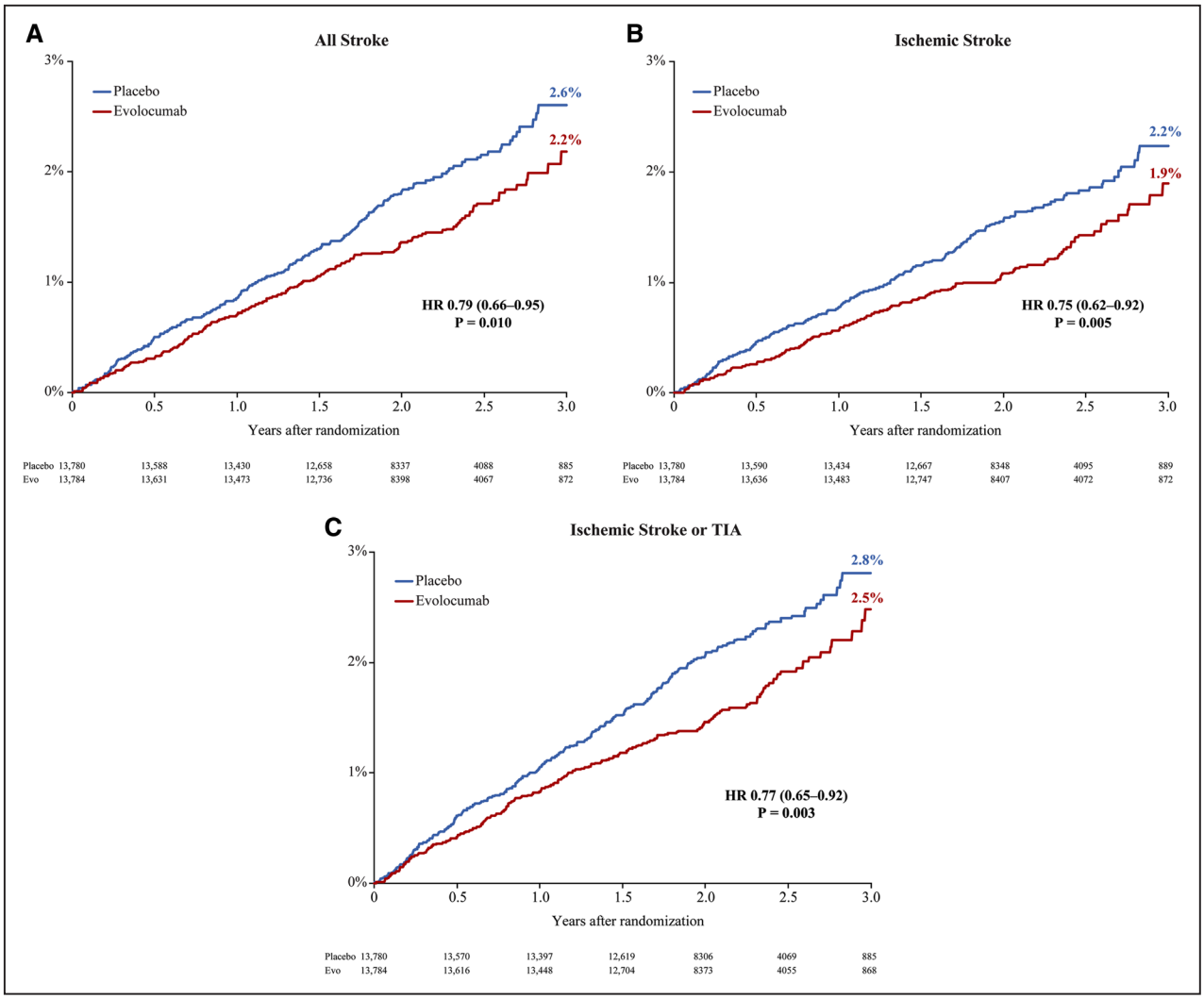

Figure 1. Cumulative incidence of cerebrovascular events by randomized treatment. **A**, Cumulative event rates for the end point of first stroke (of any kind). **B**, Rates for first ischemic stroke. **C**, Rates for first ischemic stroke or transient ischemic attack (TIA). HR indicates hazard ratio. Evo indicates evolocumab.

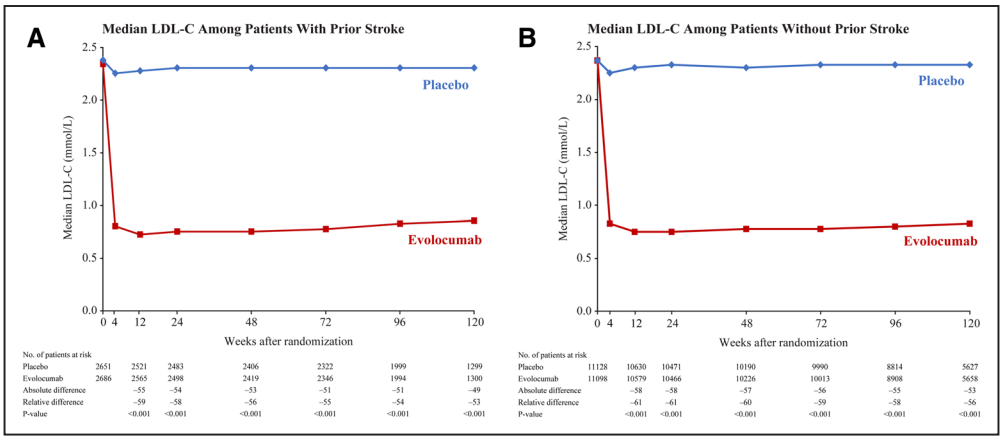

Figure 2. LDL (low-density lipoprotein) cholesterol (LDL-C) levels over time stratified by prior stroke and randomized treatment. Shown are the median values of the 2 randomized treatment groups, stratified by history of ischemic stroke. Below the graph, the absolute and percentage reduction in LDL-C levels in the evolocumab group are compared with those in the placebo group, stratified by prior ischemic stroke, and are presented as least-squares means. To convert cholesterol to milligrams per deciliter, multiply by 38.67.

statin therapy has been shown to significantly reduce the composite of cardiovascular death, MI, stroke, unstable angina requiring hospitalization, and coronary revascularization by 15% and the triple end point of cardiovascular death, MI, or stroke by 20% over a median of 2.2 years in patients with established atherosclerosis.[8] In this in-depth analysis of stroke in patients receiving a PCSK9 inhibitor, we demonstrated significant reductions with evolocumab in both first and total (including recurrent) strokes of any type, ischemic stroke, the composite of ischemic stroke or TIA, and the degree of dependency poststroke. The event rates begin to diverge within months after randomization, sooner than was seen for other cardiovascular events in the FOURIER trial,[8] including MI.[11] This observation coupled with the robust relative reduction in stroke suggests that patients at high risk for stroke may benefit from earlier and more aggressive LDL-C reduction.

Moreover, among patients with a history of ischemic stroke, evolocumab, when added to statin therapy, significantly reduced the risk of cardiovascular events, with a 15% reduction in the primary composite end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. These effects and those for all secondary end points were consistent with the findings among the entire study population, indicating that patients with a prior ischemic stroke benefitted to a similar degree from evolocumab as patients with prior MI[11] or peripheral arterial disease.[12]

Despite achieving unprecedented low levels of LDL-C (median, 0.7 mmol/L at 48 weeks), with more than a quarter of patients achieving an LDL-C ≤0.5 mmol/L, patients with prior ischemic stroke allocated to evolocumab did not experience an increase in adverse clinical events (other than local injection site reactions) or laboratory abnormalities, as was also seen in the overall trial population.[13] In particular, there was

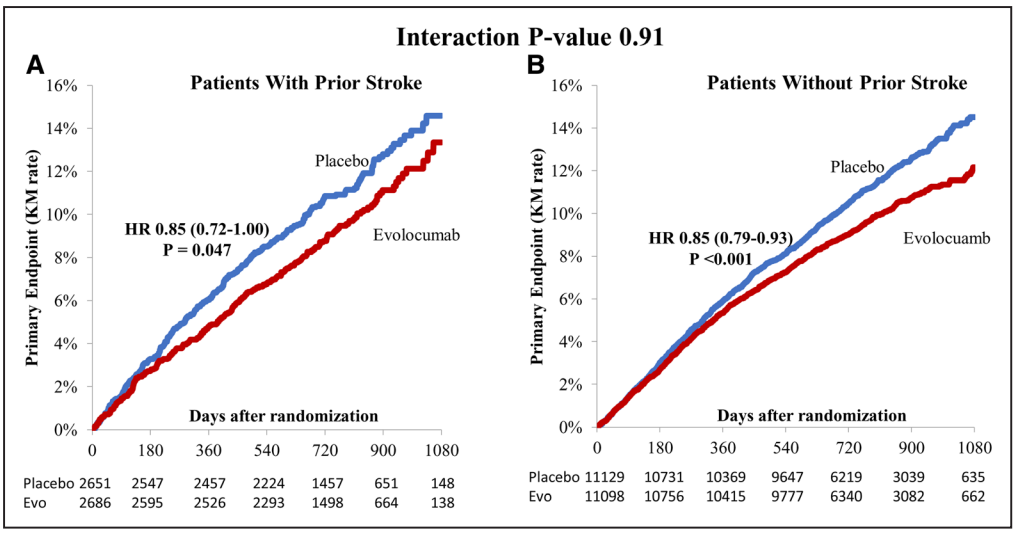

Figure 3. First occurrence of a primary outcome event in patients stratified by prior stroke and randomized treatment. Kaplan-Meier (KM) curves for the first occurrence of a cardiovascular death, myocardial infarction, any stroke, unstable angina requiring hospitalization, or coronary revascularization by evolocumab (Evo) and placebo randomized treatment groups. Hazard ratio (HR) and 95% CIs are shown. The numbers below the *x* axis indicate the number of patients at risk for the patients randomized to placebo and Evo.

Table 3. Outcomes by Treatment Stratified by History of Stroke Before Randomization

End Point	Prior Stroke			No Prior Stroke			*P* Interaction
	Placebo (N=2651), n (%)	Evolocumab (N=2686), n (%)	Hazard Ratio (95% CI)	Placebo (N=11 129), n (%)	Evolocumab (N=11 098), n (%)	Hazard Ratio (95% CI)	
Primary composite	300 (11.3)	259 (9.6)	0.85 (0.72–1.00)	1263 (11.3)	1085 (9.8)	0.85 (0.79–0.93)	0.91
Key secondary composite	224 (8.4)	202 (7.5)	0.89 (0.74–1.08)	789 (7.1)	614 (5.5)	0.77 (0.70–0.86)	0.20
Any stroke	105 (4.0)	95 (3.5)	0.90 (0.68–1.19)	157 (1.4)	112 (1.0)	0.71 (0.56–0.91)	0.22
Ischemic stroke	86 (3.2)	80 (3.0)	0.92 (0.68–1.25)	140 (1.3)	91 (0.8)	0.65 (0.50–0.84)	0.087
Hemorrhagic stroke	14 (0.63)	14 (0.61)	0.99 (0.47–2.07)	11 (0.14)	15 (0.16)	1.37 (0.63–2.98)	0.55
Myocardial infarction	100 (3.8)	75 (2.8)	0.74 (0.55–1.00)	539 (4.8)	393 (3.5)	0.73 (0.64–0.83)	0.89
Coronary revascularization	128 (4.8)	89 (3.3)	0.68 (0.52–0.90)	837 (7.5)	670 (6.0)	0.80 (0.72–0.88)	0.29
Unstable angina	33 (1.2)	29 (1.1)	0.86 (0.52–1.42)	206 (1.9)	207 (1.9)	1.01 (0.83–1.22)	0.59
Cardiovascular death	65 (2.5)	73 (2.7)	1.11 (0.80–1.56)	175 (1.6)	178 (1.6)	1.02 (0.83–1.25)	0.64
Ischemic stroke or TIA	113 (4.3)	102 (3.8)	0.89 (0.68–1.17)	182 (1.6)	127 (1.1)	0.70 (0.56–0.87)	0.17

Event rate (%) represents n/N rate. Stratified Cox modeling was performed within each subgroup to generate hazards by treatment for each end point. *P* interaction values were calculated in a Cox model including all patients with a term for subgroup treatment for each end point. The primary trial end point was a composite of death from cardiovascular disease, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. TIA indicates transient ischemic attack.

no excess in hemorrhagic stroke associated with extremely low levels of LDL-C, despite prior brain injury (by definition) from a prior stroke. These findings are reassuring given prior signals from observational studies[14] and randomized trials of earlier lipid-lowering agents that had raised the concern that low LDL-C levels might be associated with a mild increased risk of hemorrhagic stroke. In meta-analyses, statin therapy was associated with a nominally increased risk of hemorrhagic stroke across 21 primary and secondary prevention trials (RR, 1.15 [95% CI, 0.87–1.51]),[3] statistically increased risk across 7 randomized controlled trials of high-dose statin therapy (RR, 1.53 [95% CI, 1.16–2.01]),[15] and statistically increased risk across 2 trials of secondary prevention specifically in patients with prior symptomatic cerebrovascular disease (RR, 1.71 [1.19–2.50]).[16,17] Similarly, in a large trial of the cholesterol absorption inhibitor ezetimibe, there was a nonsignificant trend for increased risk of hemorrhagic stroke (HR, 1.38 [0.89–2.04]).[5] The lack of association with hemorrhagic stroke despite more extreme lowering of LDL-C in the current trial and with 2 other PCSK9 monoclonal antibodies[18,19] suggests that cholesterol lowering per se may not increase hemorrhagic stroke risk, and any hemorrhagic tendencies of statins and, to a lesser degree with ezetimibe, may be mediated by other mechanisms such as those agents' known pleiotropic, off-target, antiplatelet, and antithrombotic effects,[20,21] which may differ quantitatively and qualitatively from the profile of PCSK9 inhibitors.

Our findings extend insights from previous trials regarding the benefit of moderate and intensive reductions of LDL-C level among patients with an ischemic stroke and atherosclerotic risk factors. In 4 trials comparing statin therapy with no cholesterol-lowering therapy, statins lowered LDL-C levels from 3.3 to 3.9 mmol/L to 2.0 to 2.8 mmol/L and reduced by 18% the risk of subsequent nonfatal and fatal stroke.[22–25] In a more recent trial,[4] the addition of ezetimibe to statin therapy lowered LDL-C levels from 1.8 to 1.4 mmol/L and, in a subgroup of patients with prior stroke, nonsignificantly further reduced the hazard of major cardiovascular events (HR, 0.84 [95% CI, 0.66–1.07]).[5] In extending this concept in FOURIER, we found additional reductions in cardiovascular event rates among patients with ischemic stroke when LDL-C levels were further lowered to a median of 0.7 mmol/L. These observations with PCSK9 monoclonal antibodies align well with observational studies demonstrating an association of PCSK9 gene polymorphisms and plasma levels of LDL-C with development and progression of carotid artery intima-media thickness and atherosclerosis.[26–28]

Prior stroke was the strongest predictor of subsequent stroke in FOURIER with a HR of ≈3; several other elements of the $CHADS_2$-VASc score also were independent predictors. In addition, we identified an elevated hs-CRP at baseline, nonwhite race, and renal insufficiency as independent contributors to the FOURIER stroke model. Not unexpectedly, an additional independent predictor of hemorrhagic stroke included a history of atrial fibrillation (likely due to concomitant use of oral antithrombotic therapy), while prior TIA predicted ischemic stroke.

We acknowledge several limitations. Although this was a prespecified subgroup analysis, the FOURIER trial was powered based on all eligible patients for a composite cardiovascular end point, and thus the power to explore individual secondary end points and subgroup effects among patients enrolled with prior ischemic stroke was moderate. The duration of follow-up in the FOURIER trial was relatively short, and since differences in outcomes may be delayed, we cannot comment on results beyond 3 years. Data were not collected regarding mechanistic subtypes of stroke such as ischemic stroke due to large versus small artery atherosclerosis or cardioembolism, and hemorrhagic stroke due to hypertension versus cerebral amyloid angiopathy versus vascular malformations, but the requirement for the presence of atherosclerotic

risk factors and the exclusion of patients with prior hemorrhagic stroke would select for patients with ischemic stroke of atherosclerotic origin. Since patients enrolled must have met specific entry criteria, our results may not apply to all patients in general clinical practice.

Conclusions

In conclusion, among patients with established atherosclerosis and an LDL-C ≥1.8 mmol/L (or non-HDL cholesterol ≥2.6 mmol/L) on moderate- to high-intensity statin, the PCSK9 inhibitor evolocumab significantly reduced ischemic cerebrovascular events with no increase in hemorrhage stroke. Among the subgroup with prior ischemic stroke, evolocumab safely lowered LDL-C to a median of 0.7 mmol/L and reduced the risk of future cardiovascular events, including ischemic stroke and TIA. These findings indicate that patients with ischemic stroke and additional atherosclerotic risk factors benefit from lowering LDL-C levels below current targets.

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References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
2. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–1206. doi: 10.1001/jama.297.11.1197
3. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681. doi: 10.1016/S0140-6736(10)61350-5
4. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489
5. Bohula EA, Wiviott SD, Giugliano RP, Blazing MA, Park JG, Murphy SA, et al. Prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2017;136:2440–2450. doi: 10.1161/CIRCULATIONAHA.117.029095
6. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol*. 2015;65:2638–2651. doi: 10.1016/j.jacc.2015.05.001
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S1–45. doi: 10.1161/01.cir.0000437738.63853.7a
8. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664
9. Sabatine MS, Giugliano RP, Keech A, Honarpour N, Wang H, Liu T, et al. Rationale and design of the further cardiovascular outcomes research with PCSK9 Inhibition in subjects with elevated risk trial. *Am Heart J*. 2016;173:94–101. doi: 10.1016/j.ahj.2015.11.015
10. Murphy SA, Cannon CP, Blazing MA, Giugliano RP, White JA, Lokhnygina Y, et al. Reduction in total cardiovascular events with Ezetimibe/Simvastatin post-acute coronary syndrome: the IMPROVE-IT trial. *J Am Coll Cardiol*. 2016;67:353–361. doi: 10.1016/j.jacc.2015.10.077
11. Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, et al. Clinical benefit of evolocumab by severity and extent of coronary artery disease: analysis from FOURIER. *Circulation*. 2018;138:756–766. doi: 10.1161/CIRCULATIONAHA.118.034309
12. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk). *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.117.032235
13. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al; FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390:1962–1971. doi: 10.1016/S0140-6736(17)32290-0

14. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke*. 2013;44:1833–1839. doi: 10.1161/STROKEAHA.113.001326
15. Pandit AK, Kumar P, Kumar A, Chakravarty K, Misra S, Prasad K. High-dose statin therapy and risk of intracerebral hemorrhage: a meta-analysis. *Acta Neurol Scand*. 2016;134:22–28. doi: 10.1111/ane.12540
16. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol*. 2009;8:453–463. doi: 10.1016/S1474-4422(09)70058-4
17. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024
18. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al; SPIRE Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017;376:1527–1539. doi: 10.1056/NEJMoa1701488
19. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174
20. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circ Res*. 2017;120:229–243. doi: 10.1161/CIRCRESAHA.116.308537
21. Pesaro AE, Serrano CV Jr, Fernandes JL, Cavalcanti AB, Campos AH, Martins HS, et al. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. *Int J Cardiol*. 2012;158:400–404. doi: 10.1016/j.ijcard.2011.01.062
22. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559. doi: 10.1056/NEJMoa061894
23. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757–767. doi: 10.1016/S0140-6736(04)15690-0
24. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–1357. doi: 10.1056/NEJM199811053391902
25. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996;335:1001–1009. doi: 10.1056/NEJM199610033351401
26. Chan DC, Pang J, McQuillan BM, Hung J, Beilby JP, Barrett PH, et al. Plasma proprotein convertase subtilisin kexin type 9 as a predictor of carotid atherosclerosis in asymptomatic adults. *Heart Lung Circ*. 2016;25:520–525. doi: 10.1016/j.hlc.2015.10.017
27. Norata GD, Garlaschelli K, Grigore L, Raselli S, Tramontana S, Meneghetti F, et al. Effects of PCSK9 variants on common carotid artery intima media thickness and relation to ApoE alleles. *Atherosclerosis*. 2010;208:177–182. doi: 10.1016/j.atherosclerosis.2009.06.023
28. Xie W, Liu J, Wang W, Wang M, Qi Y, Zhao F, et al. Association between plasma PCSK9 levels and 10-year progression of carotid atherosclerosis beyond LDL-C: a cohort study. *Int J Cardiol*. 2016;215:293–298. doi: 10.1016/j.ijcard.2016.04.103