PCSK9-remming bij stroke

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Disclosures

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ODYSSEY OUTCOMES

The trial was funded by **Sanofi** and **Regeneron Pharmaceuticals**

Background

- Patients with ACS are at increased risk of subsequent stroke
- Lowering of atherogenic lipoproteins, including LDL-C, reduces the risk of ischemic stroke in chronic atherosclerotic cardiovascular disease or recent acute coronary syndrome
- The effect of lipid-lowering by PCSK9 inhibition on stroke is undetermined

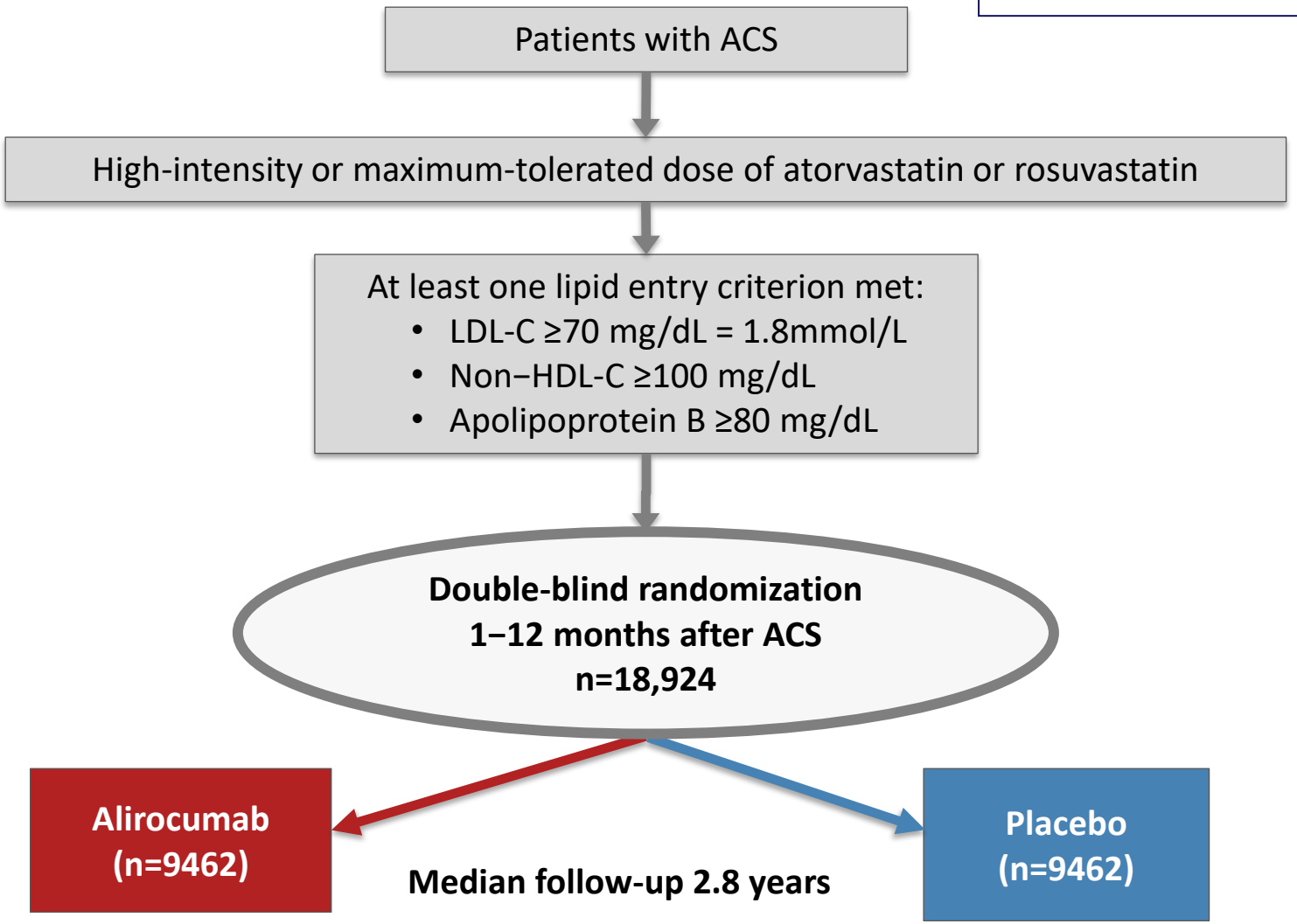
ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin–kexin type 9

Objectives

- This prespecified analysis was designed to assess the effect of alirocumab on ischemic and hemorrhagic stroke in patients with a recent ACS

- Hypothesis: for patients treated with alirocumab there would be:
  - A reduction in risk of ischemic stroke…
  - Without an increase in hemorrhagic stroke…
  - Irrespective of baseline LDL-C and history of cerebrovascular disease

Methods Odyssey Outcomes



Blinded adjustment of alirocumab dose to target achieved LDL-C 25–50 mg/dL and avoid sustained levels <15 mg/dL. CV, cardiovascular; Q2W, every 2 weeks; SC, subcutaneous.

Methods current subanalysis

Endpoints

Non-fatal or fatal ischemic or hemorrhagic stroke

Subgroups*:*

1. History of CeVD versus no history of CeVD

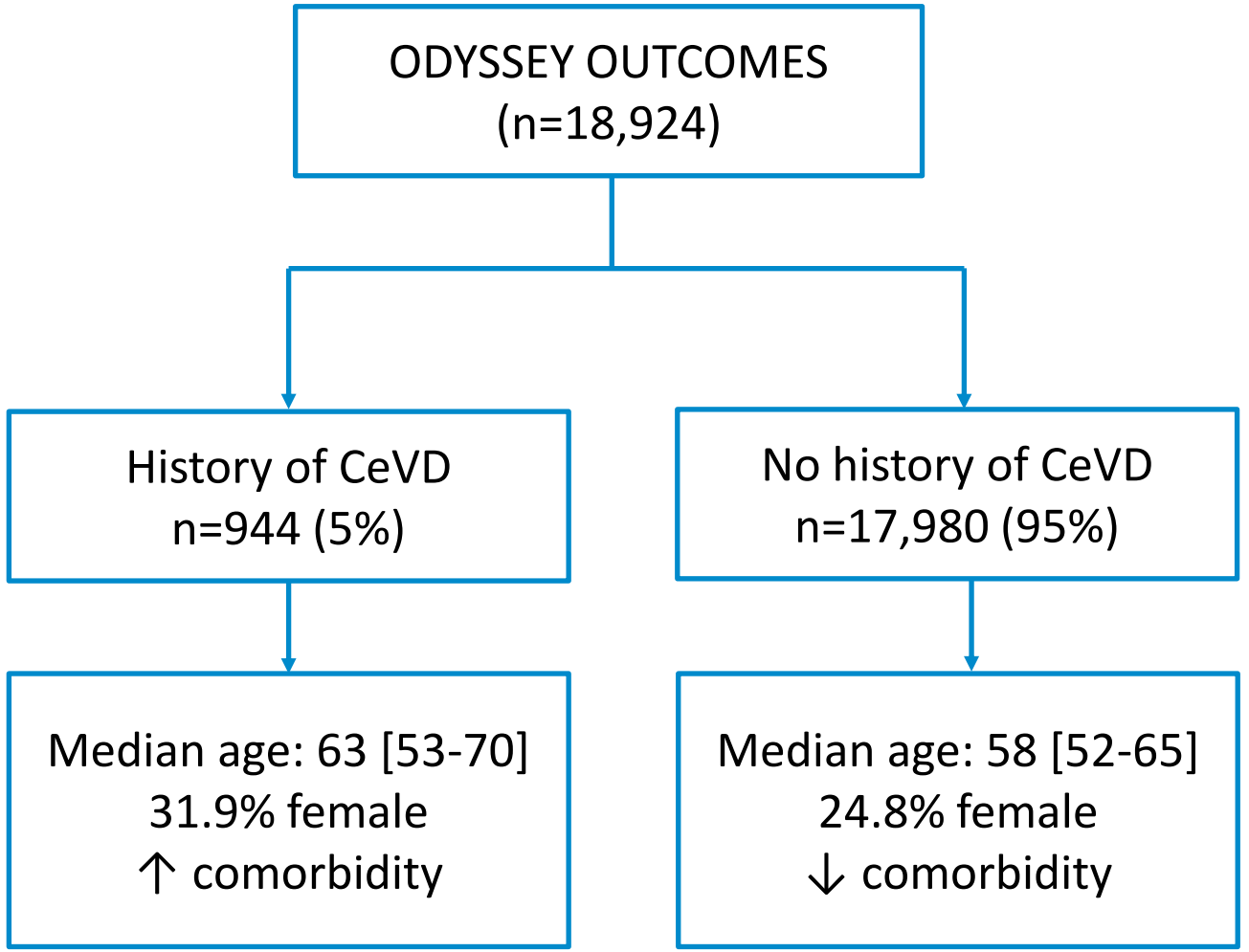
2. Baseline LDL-C

3. Safety analysis regarding achieved LDL-C

CeVD, cerebrovascular disease, defined as history of carotid endarterectomy or carotid stenting, prior stroke or transient ischemic attack.

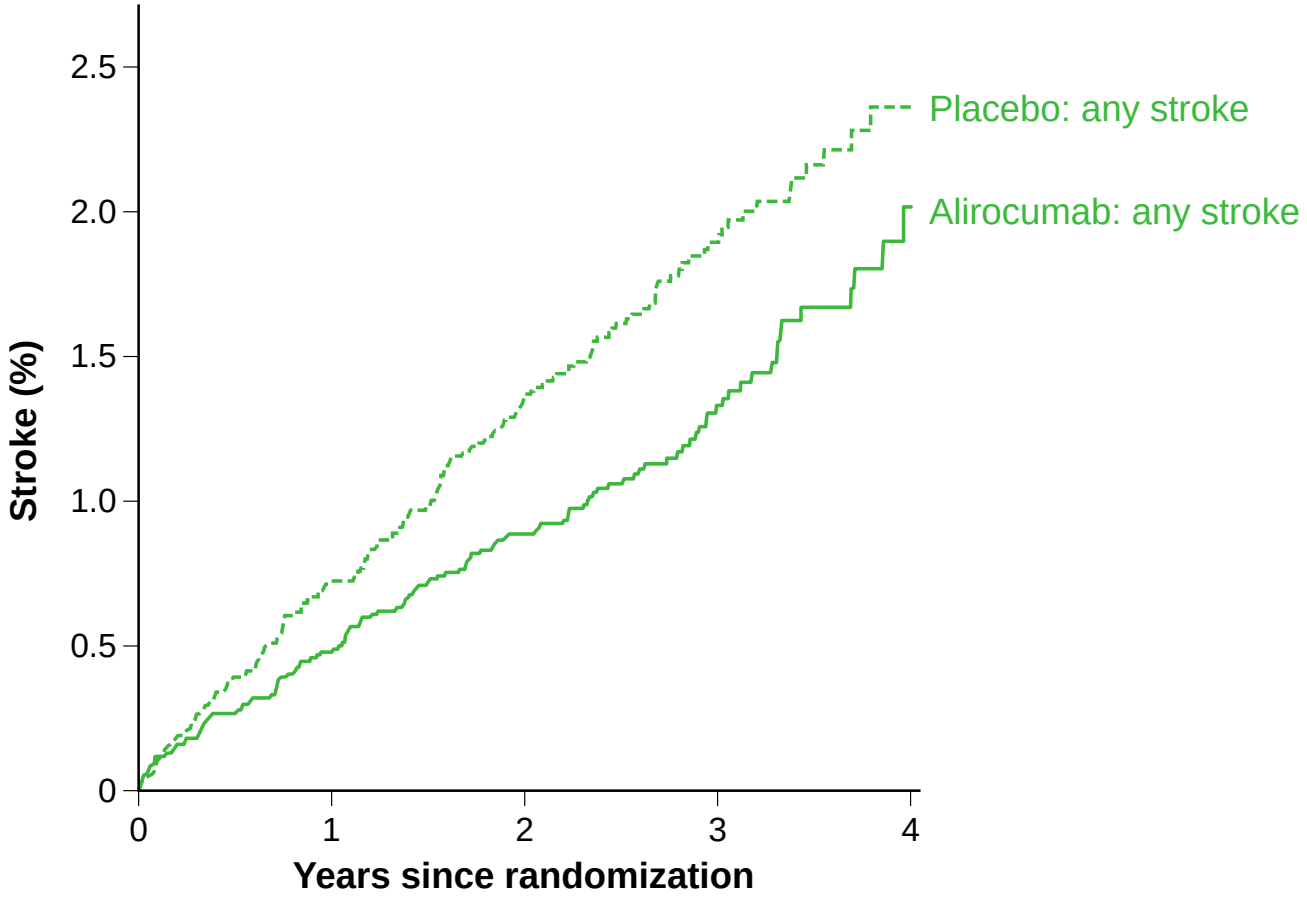
Baseline characteristics

History of cerebrovascular disease



CeVD, cerebrovascular disease, defined as history of carotid endarterectomy or carotid stenting (n=129), prior stroke (n=611) or transient ischemic attack (n=309).

Main outcome:
Any Stroke

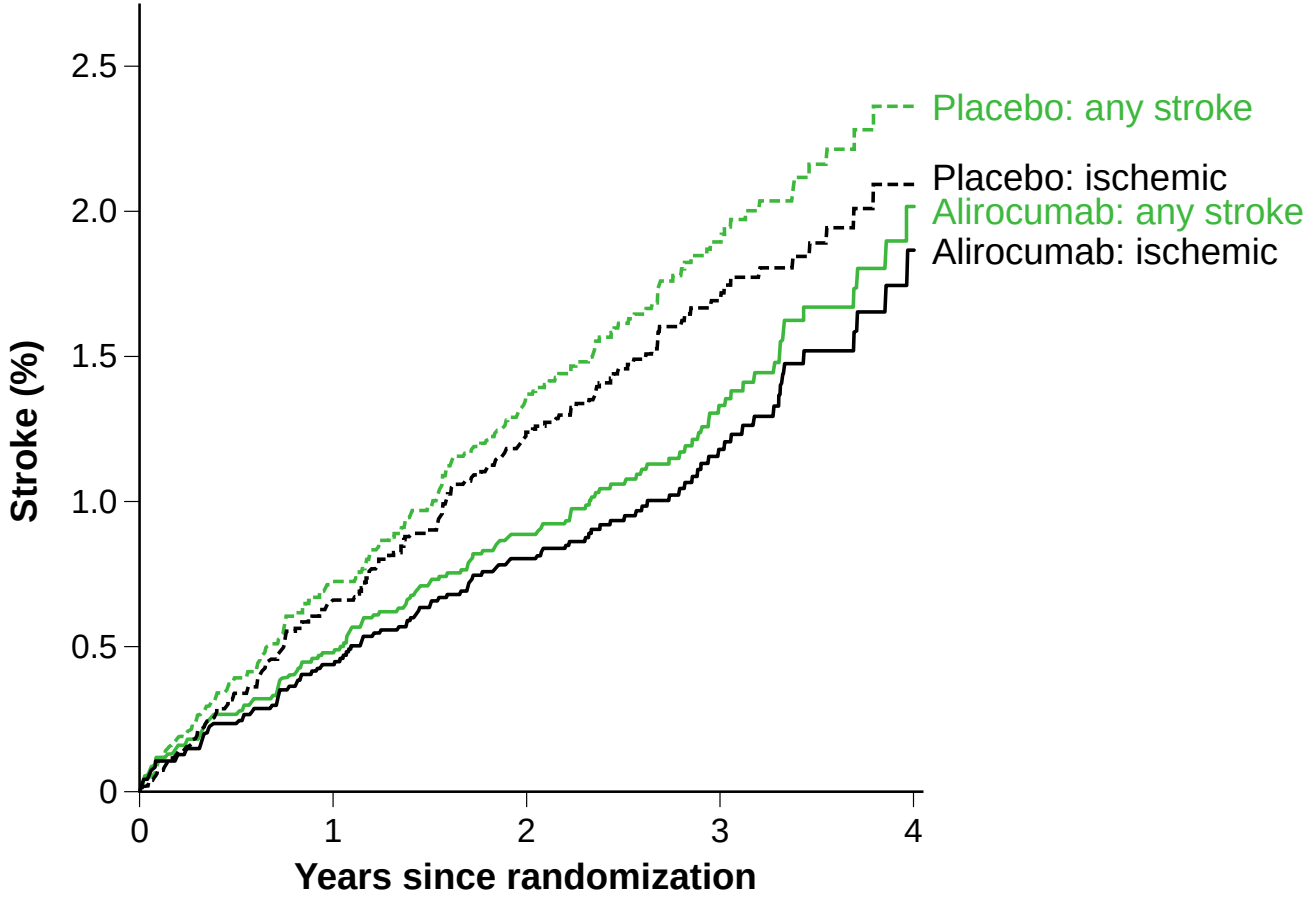


Number at risk

Placebo	9462	9162	8789	3838	724
Alirocumab	9462	9179	8856	3901	729

Any stroke: HR 0.72
(95% CI 0.57−0.91), *P*=0.005

Main outcome:
Any Stroke or Ischemic Stroke



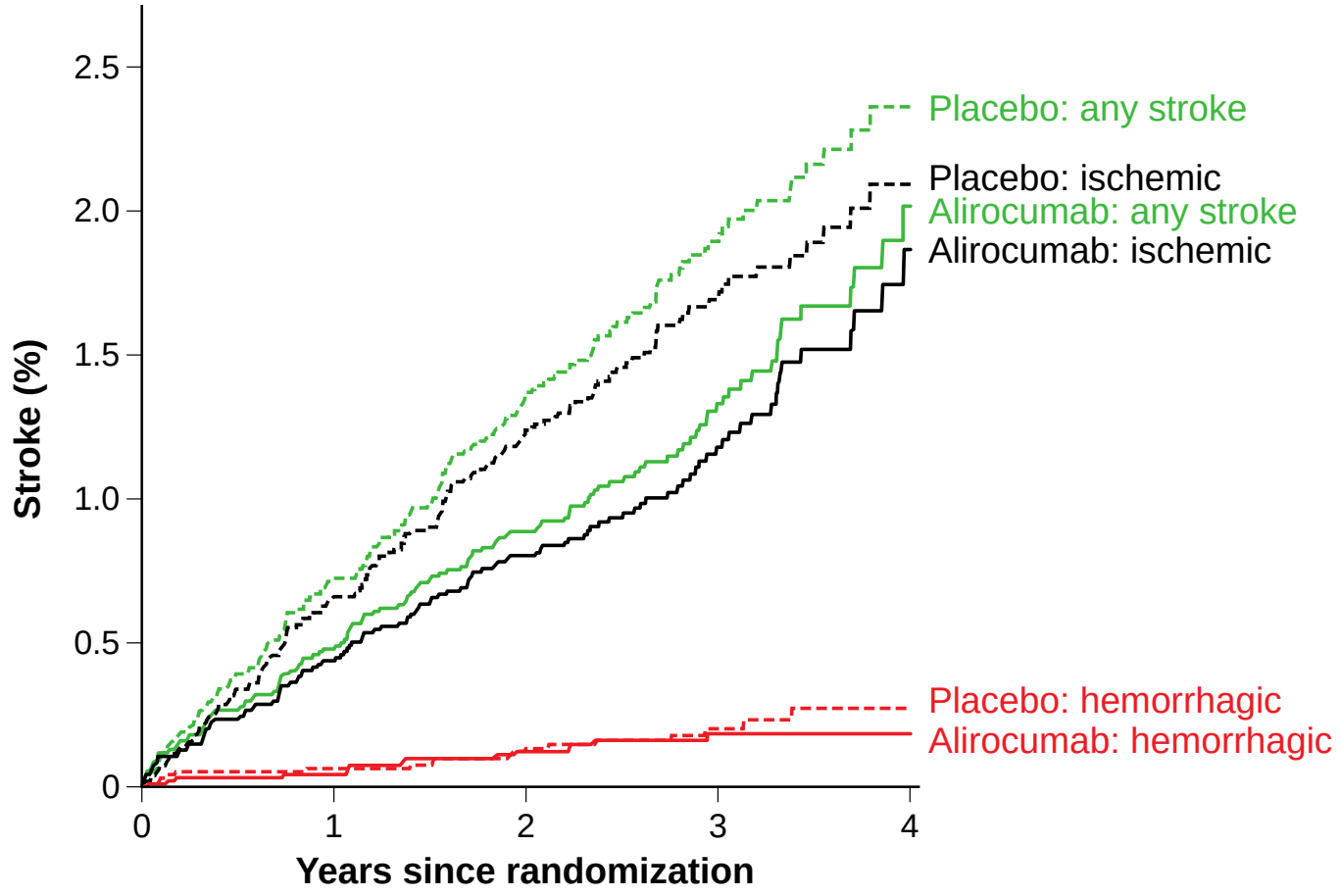
Number at risk

Placebo	9462	9162	8789	3838	724
Alirocumab	9462	9179	8856	3901	729

Any stroke: HR 0.72
(95% CI 0.57−0.91), *P*=0.005

Ischemic: HR 0.73
(95% CI 0.57−0.93), *P*=0.01

Main outcome:
Any, Ischemic, or Hemorrhagic Stroke



Number at risk

Placebo	9462	9162	8789	3838	724
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Any stroke: HR 0.72
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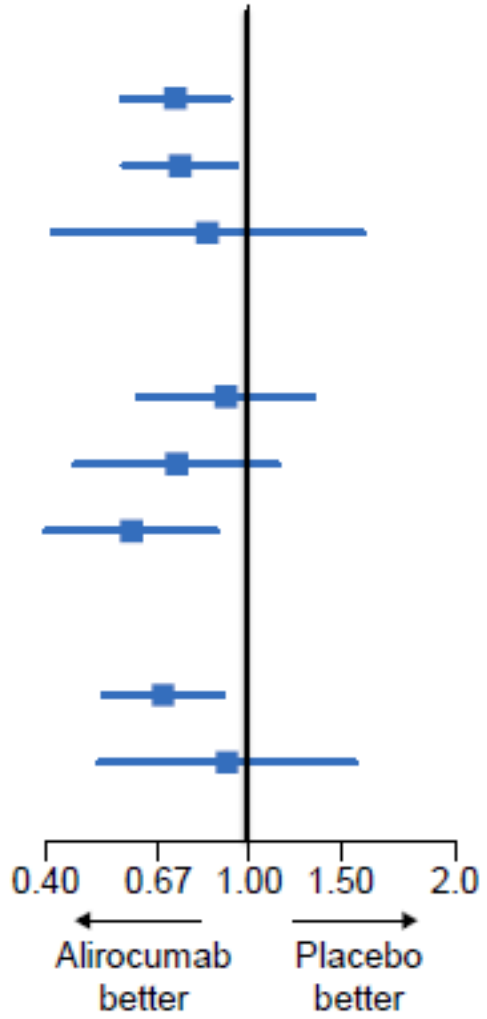
Ischemic: HR 0.73
(95% CI 0.57−0.93), *P*=0.01

Hemorrhagic: HR 0.83
(95% CI 0.42−1.65), *P*=0.59

In total, 263 ischemic and 33 hemorrhagic strokes occurred

Subgroups and Endpoints

Subgroup and endpoint	Alirocumab (%)	Placebo (%)	HR (95% CI)
All patients			
Any stroke	1.3	1.8	0.72 (0.57–0.91)
Ischemic	1.2	1.6	0.73 (0.57–0.93)
Hemorrhagic	0.2	0.2	0.83 (0.42–1.65)
Baseline LDL-C, mg/dL			
<80: any stroke	1.3	1.3	0.90 (0.61–1.34)
80–<100: any stroke	1.1	1.3	0.72 (0.46–1.12)
≥100: any stroke	1.5	2.4	0.59 (0.40–0.86)
History of CeVD			
No: any stroke	1.1	1.6	0.68 (0.53–0.88)
Yes: any stroke	5.2	5.6	0.90 (0.52–1.56)

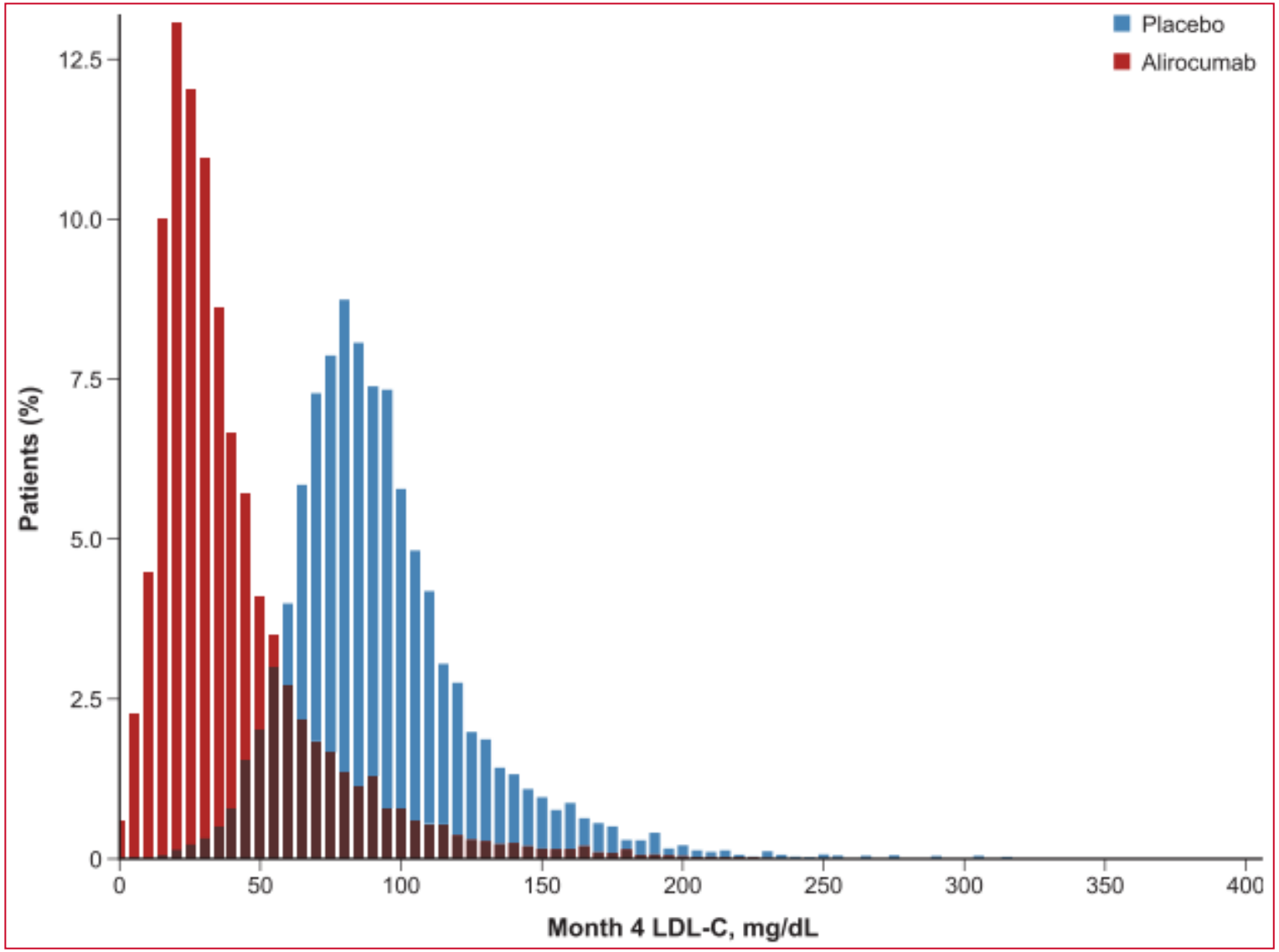


LDL-C $P_{interaction}$ = 0.31

CeVD $P_{interaction}$ = 0.37

P-values are from the interaction term in a proportional hazards model; (<100mg/dL = <2.59 mmol/L)

Safety analysis: Achieved LDL-C
hemorrhagic stroke in the alirocumab group



LDL-C in mg/dL. To convert the values for cholesterol to mmol/L, multiply by 0.02586. (<25mg/dL = <0.65 mmol/L)

Safety analysis: Achieved LDL-C
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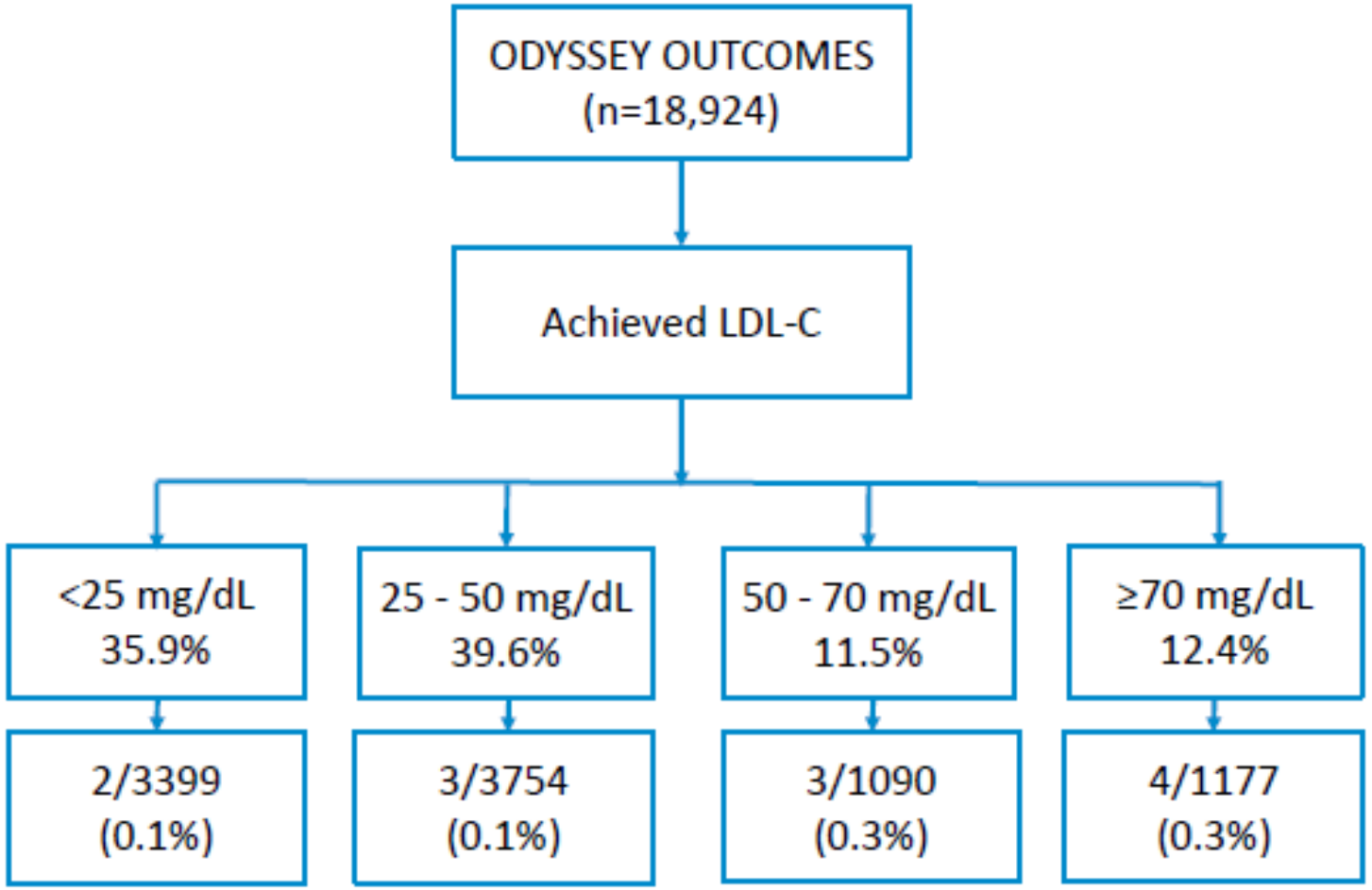

LDL-C in mg/dL. To convert the values for cholesterol to mmol/L, multiply by 0.02586. (<25mg/dL = <0.65 mmol/L)

Conclusions

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In patients with recent ACS and dyslipidemia despite intensive statin therapy:

- The PCSK9 inhibitor alirocumab decreased the risk of stroke, irrespective of baseline LDL-C and of history of cerebrovascular disease, over a median follow-up of 2.8 years
- The risk of hemorrhagic stroke did not depend on achieved LDL-C levels in the alirocumab group

Clinical Implications

- Alirocumab added to intensive statin therapy provides an opportunity to lower LDL-C to levels not previously achievable in most patients with statins and/or ezetimibe
- Lowering of LDL-C to very low levels reduces the risk of ischemic stroke without increasing the risk of hemorrhagic stroke

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for the ODYSSEY OUTCOMES Investigators

Effect of Alirocumab on Stroke in ODYSSEY OUTCOMES

Circulation. 2019; 140(25): 2054-62.

Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Alirocumab on Stroke in ODYSSEY OUTCOMES

Editorial, see p 2063

BACKGROUND: Lowering of atherogenic lipoproteins, including low-density lipoprotein cholesterol (LDL-C), reduces the risk of ischemic stroke. However, concerns have been raised about very low LDL-C levels and a potential increased risk of hemorrhagic stroke. ODYSSEY OUTCOMES compared the PCSK9 inhibitor alirocumab with placebo in 18 924 patients with recent acute coronary syndrome and elevated atherogenic lipoproteins, despite intensive statin therapy, targeting LDL-C levels of 25 to 50 mg/dL and avoiding sustained LDL-C <15 mg/dL. This prespecified analysis was designed to assess the effect of alirocumab on ischemic and hemorrhagic stroke. We hypothesized that for patients treated with alirocumab there would be a reduction in risk of ischemic stroke without increasing hemorrhagic stroke, irrespective of baseline LDL-C and of history of cerebrovascular disease.

METHODS: Patients were randomized to alirocumab or placebo 1 to 12 months after acute coronary syndrome. The risk of nonfatal or fatal ischemic or hemorrhagic stroke was evaluated, stratified by baseline LDL-C concentration and history of cerebrovascular disease. A potential association of very low achieved LDL-C with alirocumab treatment at month 4 and subsequent hemorrhagic stroke was assessed.

RESULTS: Median follow-up was 2.8 years. In total, 263 ischemic and 33 hemorrhagic strokes occurred. Alirocumab reduced the risk of any stroke (HR, 0.72 [95% CI, 0.57–0.91]) and ischemic stroke (HR, 0.73 [95% CI, 0.57–0.93]) without increasing hemorrhagic stroke (HR, 0.83 [95% CI, 0.42–1.65]). In total, 7164 (37.9%), 6128 (32.4%), and 5629 (29.7%) patients had a baseline LDL-C of <80, 80 to 100, and >100 mg/dL, respectively. The treatment effect on stroke appeared numerically greater for patients with higher baseline LDL-C, but there was no formal evidence of heterogeneity ($P_{interaction}$=0.31). The effect of alirocumab on stroke was similar among 944 patients (5.0%) with a history of previous cerebrovascular disease and among those without a history of cerebrovascular disease ($P_{interaction}$=0.37). There was no apparent adverse relation between lower achieved LDL-C and incidence of hemorrhagic stroke in the alirocumab group.

CONCLUSIONS: In patients with recent acute coronary syndrome and dyslipidemia despite intensive statin therapy, alirocumab decreased the risk of stroke, irrespective of baseline LDL-C and history of cerebrovascular disease, over a median follow-up of 2.8 years. Furthermore, risk of hemorrhagic stroke did not depend on achieved LDL-C levels within the alirocumab group.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01663402.

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Key Words: acute coronary syndrome ■ cerebrovascular disorders ■ lipoprotein, LDL ■ stroke

Sources of Funding, see page 2061

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