Πρόγραμμα Μεταπτυχιακών Σπουδών ΕΚΠΑ
Καρδιομεταβολική Ιατρική
2023-2024

Πανεπιστημιακό Γενικό Νοσοκομείο Λάρισας

Δυσλιπιδαιμία στο ισχαιμικό εγκεφαλικό επεισόδιο…
απο την οξεία φάση στη δευτερογενή πρόληψη

Δημήτριος Σαγρής

Παθολόγος, Επιμελητής Β’

Πανεπιστημιακή Παθολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Λάρισας

Patient with ischemic stroke

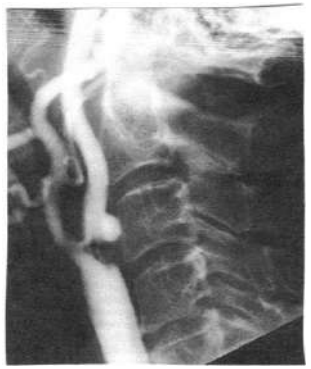
- Arterial hypertension 58%
- Diabetes 21%
- Coronary artery disease 19%
- Atrial fibrillation 18%
- Heart failure 7%

59% of stroke survivors in the UK are also living with **3 or more of any comorbidity.**

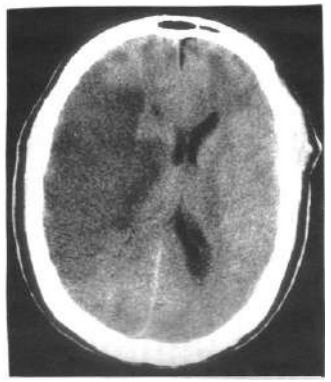
Source
IQVIA Medical Research Data (IMRD) 2018
Dataset includes all patients with a diagnosis of stroke on or before the 1st January 2018

Ischemic Stroke Classification based on etiology (TOAST criteria)

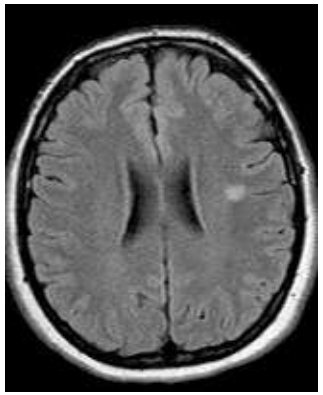
Atherosclerotic
15-25%



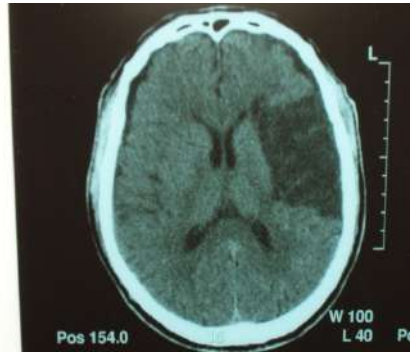
Cardioembolic
18-33%



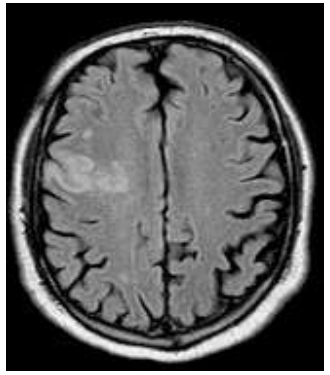
Lacunar
17-25%



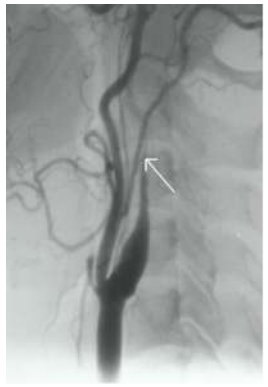
Cryptogenic
12-37%



E S U S



Other causes (e.g. dissection)
5-10%



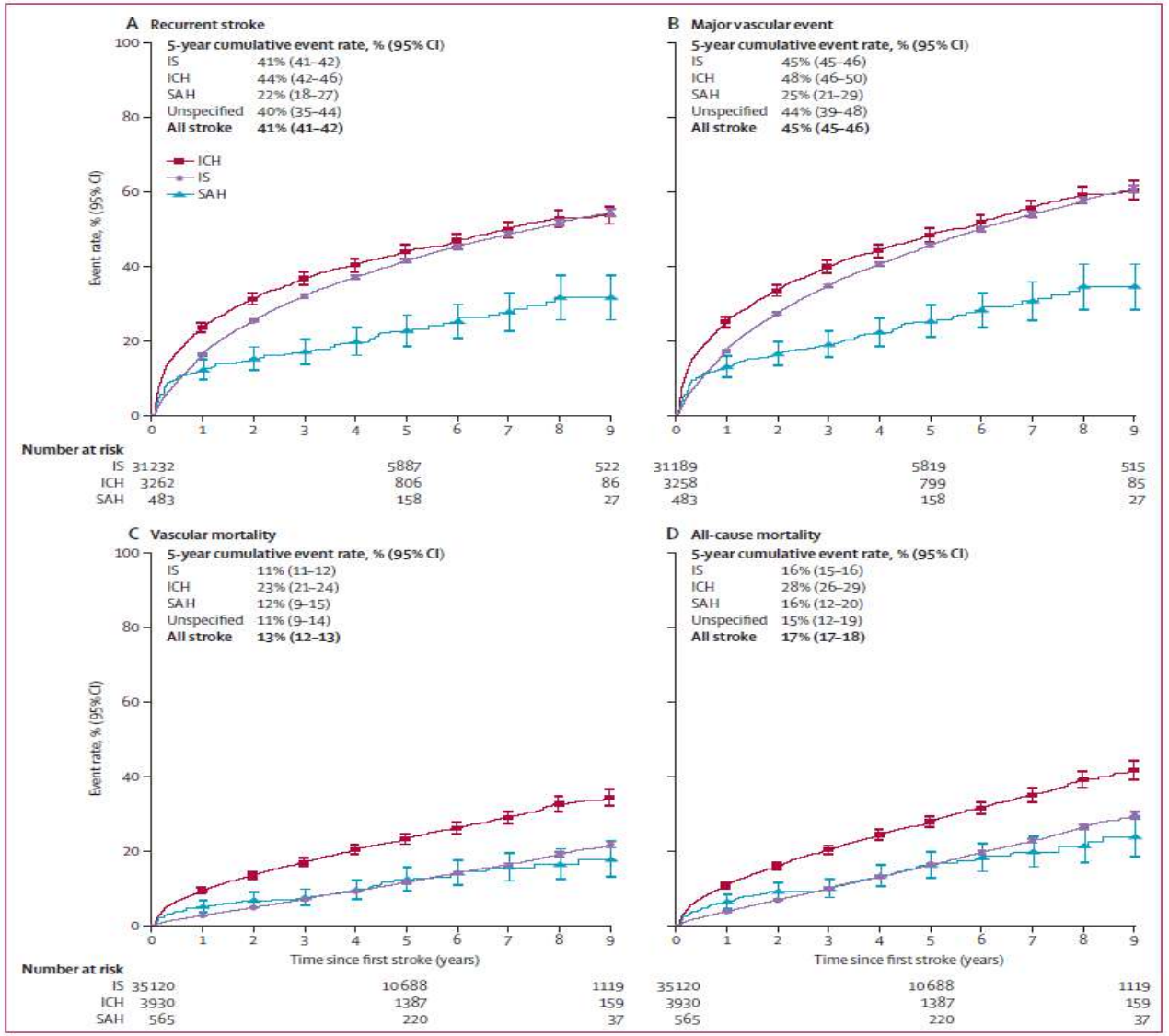
Αρχείο: "The Athens Stroke Data Bank"

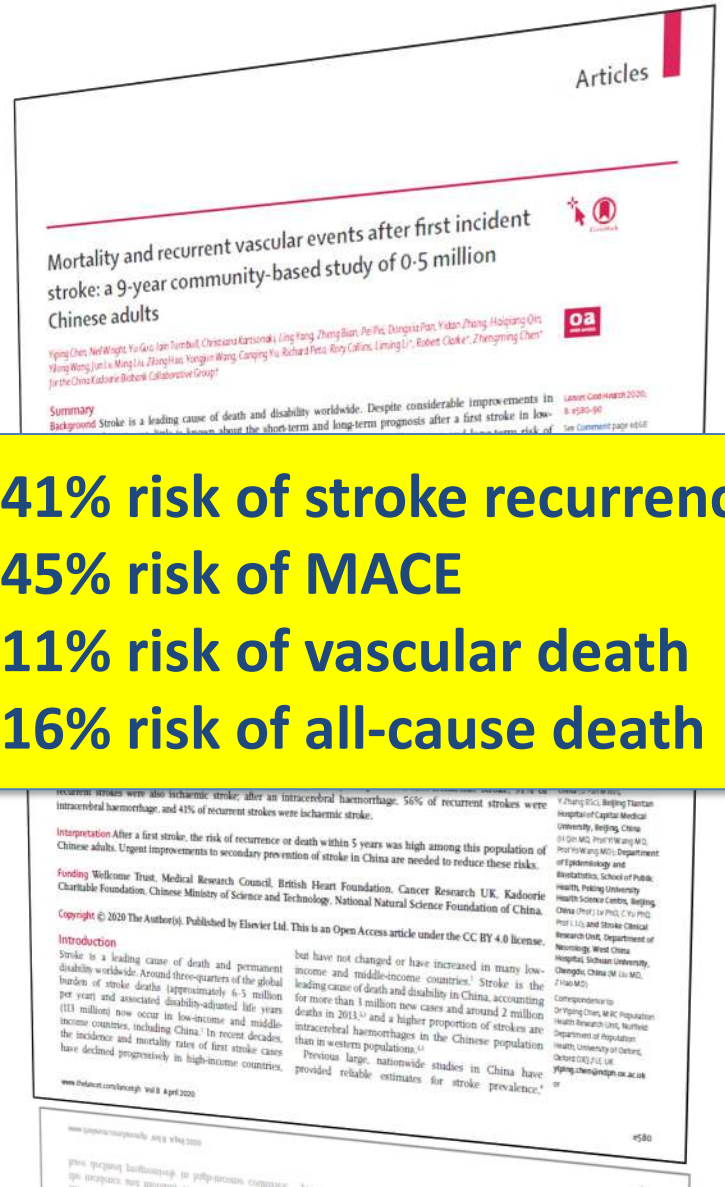
Patient with ischemic stroke

	ESUS (n=275)	Large-Artery Atherosclerotic (n=497)	Cardioembolic (n=869)	Lacunar (n=622)	Undetermined Other Than ESUS* (n=366)	Other Determined (n=102)
Comorbidities—risk factors						
Hypertension	178 (64.7%)	382 (76.9%)	631 (72.6%)	518 (83.3%)	259 (70.8%)	50 (49.0%)
Diabetes mellitus	65 (23.6%)	163 (32.8%)	192 (22.1%)	181 (29.1%)	115 (31.4%)	17 (16.7%)
Smoking	83 (30.2%)	251 (50.5%)	157 (18.1%)	235 (37.8%)	111 (30.3%)	39 (38.2%)
Previous TIA	27 (9.8%)	102 (20.5%)	53 (6.1%)	59 (9.5%)	39 (10.7%)	17 (16.7%)
Heart failure	22 (8.0%)	23 (4.6%)	139 (16.0%)	15 (2.4%)	31 (8.5%)	10 (9.8%)
Dyslipidemia	140 (50.9%)	273 (55.3%)	266 (30.7%)	306 (49.4%)	159 (43.6%)	40 (39.2%)
Coronary artery disease	65 (23.7%)	132 (26.8%)	169 (19.5%)	84 (13.6%)	86 (23.7%)	16 (15.7%)
Atrial fibrillation	0 (0.0%)	21 (4.2%)	774 (89.1%)	36 (5.8%)	41 (11.2%)	0 (0.0%)

Ntaios et al; Stroke. 2015

Stroke patients are at very high risk of MACE and death





- 41% risk of stroke recurrence
- 45% risk of MACE
- 11% risk of vascular death
- 16% risk of all-cause death

Chen Y, et al. Lancet Glob Health 2020;8: e580–90

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

ESC/EAS GUIDELINES

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)

Mach et al; European Heart Journal (2020)

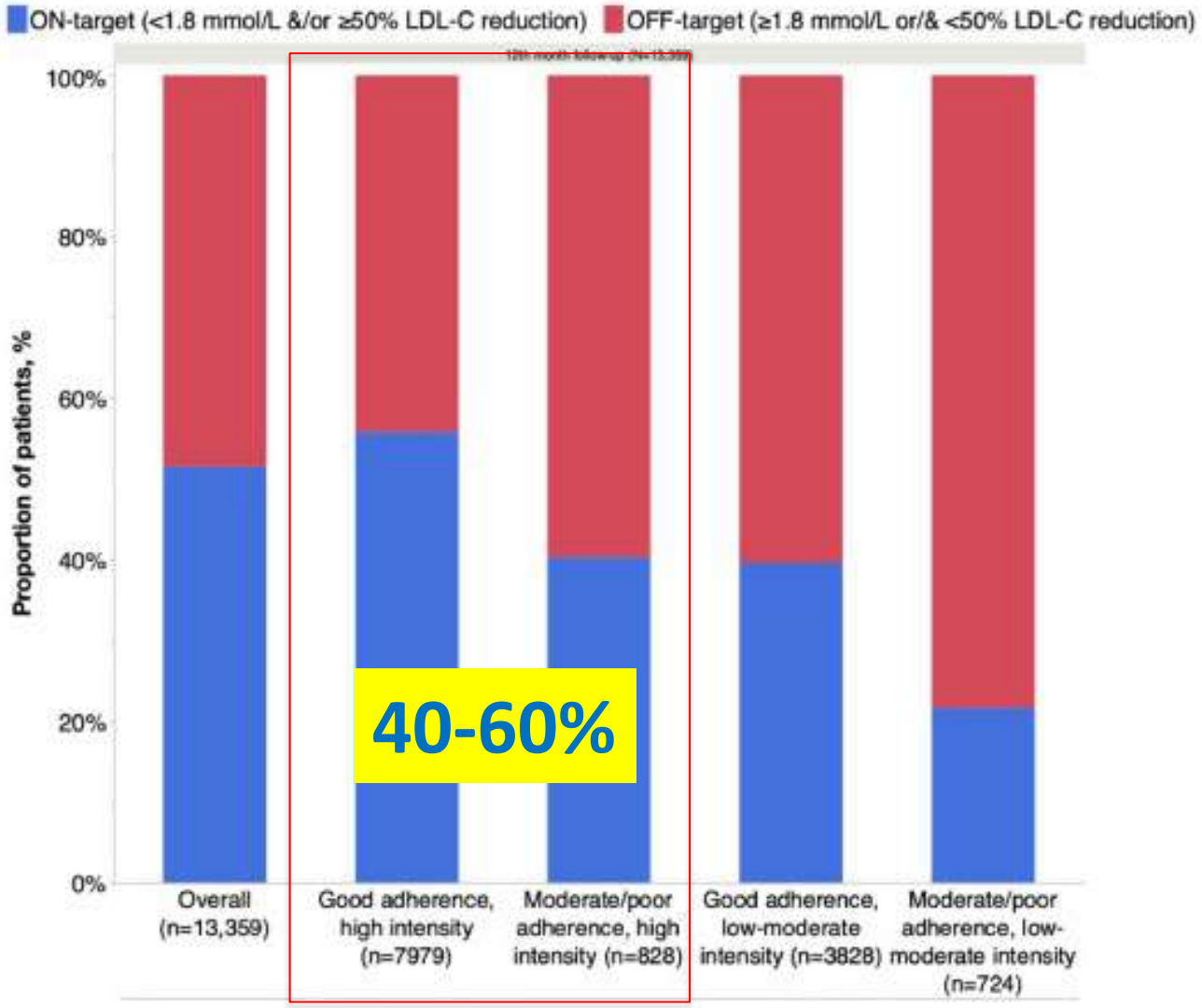
Ο Βαγγέλης

- 68 ετών
- N-STEMI + stent προ 7 ετίας
- Βαλσαρτάνη + HTZ
- Ασπιρινη
- Νεμπιβολόλη
- **Ατορβαστατίνη 40mg**

Δεξιά ημιπάρεση και ήπια αφασία εκπομπής

Χοληστερόλη (mg/dL) (φ.τ.: <200)	165
Τριγλυκερίδια (mg/dL) (φ.τ.: <150)	162
HDL (mg/dL) (φ.τ.: >45)	54
LDL (mg/dL)	**78**

Ο Βαγγέλης



Stockholm CREAtinine Measurements project: 26,768 patients

Mazhar et al American Heart J 2022

Patient with ischemic stroke

- ✓ Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή
- ✓ Ποια υπολιπιδαιμική αγωγή πρέπει να χορηγήσω στον ασθενή με ισχαιμικό εγκεφαλικό επεισόδιο?
- ✓ Ποιος είναι ο στόχος μου ?
- ✓ Να φοβάμαι τις χαμηλές τιμές LDL?

Patient with ischemic stroke

- ✓ **Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή**
- ✓ Ποια υπολιπιδαιμική αγωγή πρέπει να χορηγήσω στον ασθενή με ισχαιμικό εγκεφαλικό επεισόδιο?
- ✓ Ποιος είναι ο στόχος μου ?
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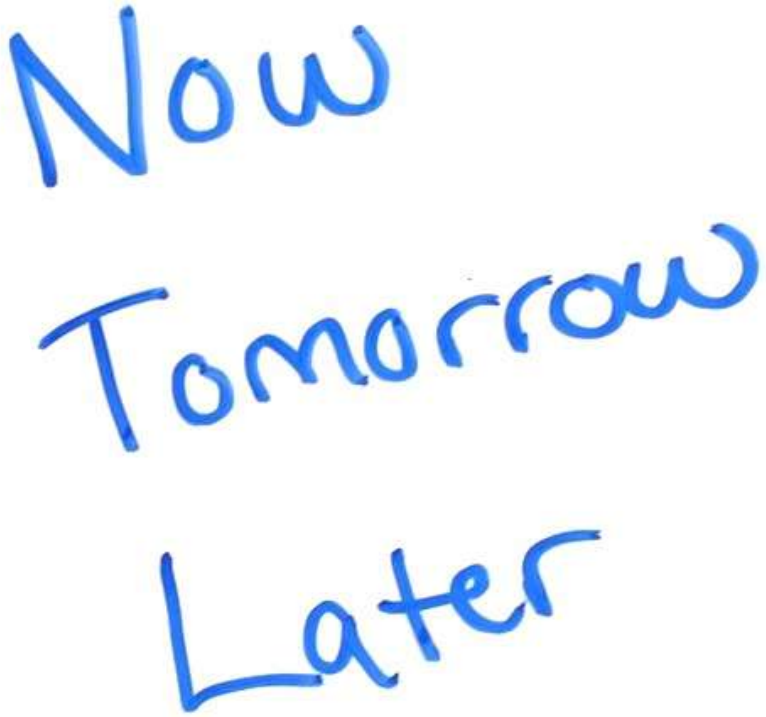
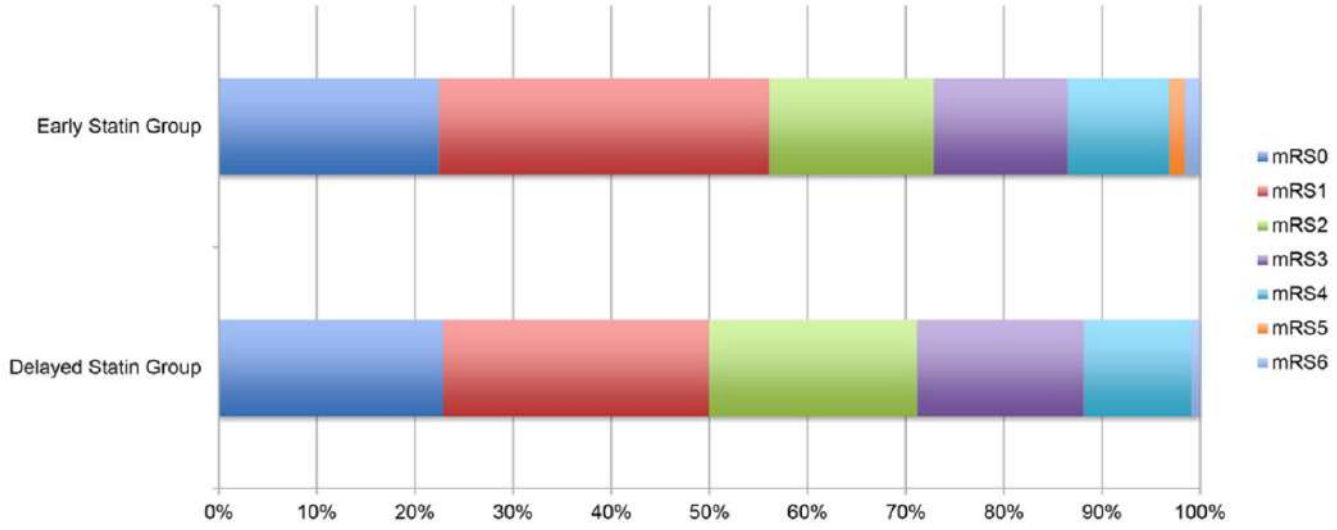
When to start?



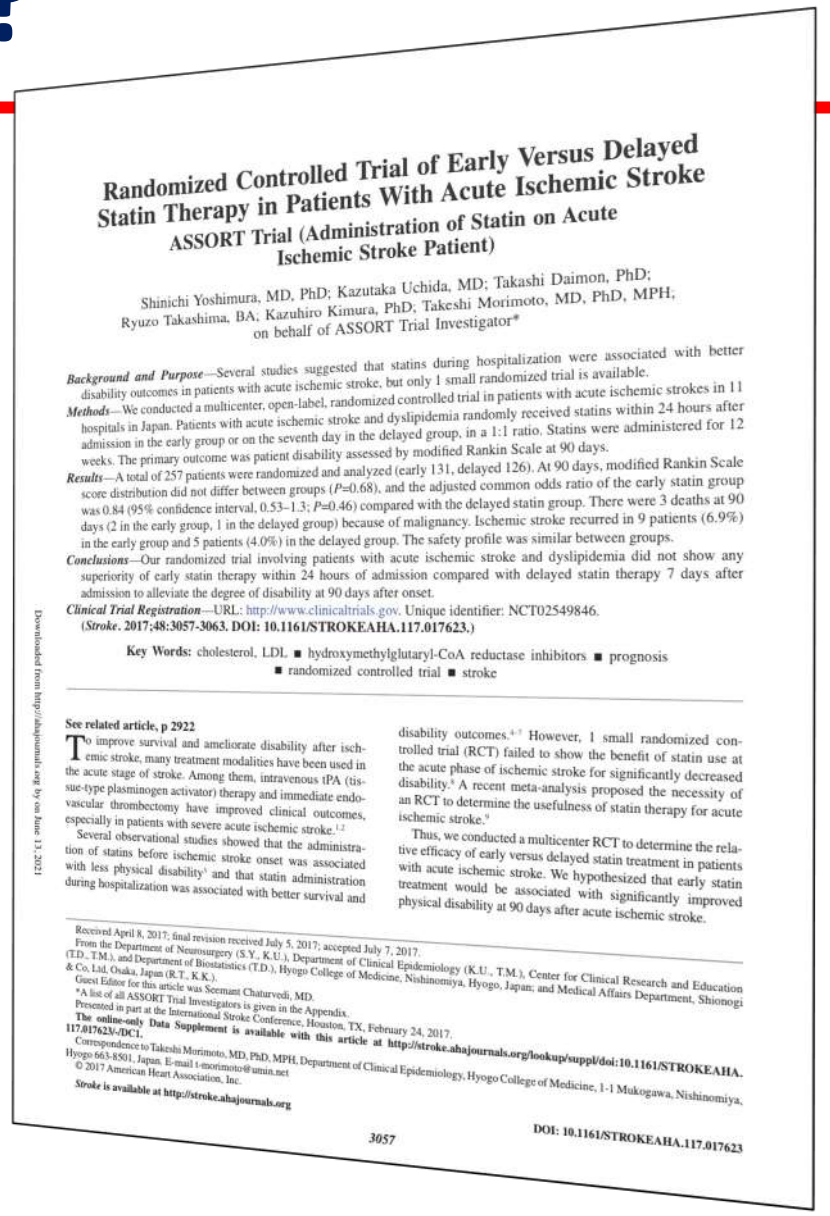
When to start?

D1 Vs D7: Primary outcome mRS



	mRS at 90 days	0	1	2	3	4	5	6	p-value
Early Statin Group (n=125)	n (%)	28 (21.4)	42 (32.1)	21 (16.0)	17 (13.0)	13 (9.9)	2 (1.5)	2 (1.5)	0.70
Delayed Statin Group (n=118)	n (%)	27 (21.4)	32 (25.4)	25 (19.8)	20 (15.9)	13 (10.3)	0 (0.0)	1 (0.8)	

No difference in stroke recurrence (9 Vs. 5)
No difference in safety profile



Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke
ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient)

Shinichi Yoshimura, MD, PhD; Kazutaka Uchida, MD; Takashi Daimon, PhD; Ryuzo Takashima, BA; Kazuhiro Kimura, PhD; Takeshi Morimoto, MD, PhD, MPH; on behalf of ASSORT Trial Investigator*

Background and Purpose—Several studies suggested that statins during hospitalization were associated with better disability outcomes in patients with acute ischemic stroke, but only 1 small randomized trial is available.

Methods—We conducted a multicenter, open-label, randomized controlled trial in patients with acute ischemic strokes in 11 hospitals in Japan. Patients with acute ischemic stroke and dyslipidemia randomly received statins within 24 hours after admission in the early group or on the seventh day in the delayed group, in a 1:1 ratio. Statins were administered for 12 weeks. The primary outcome was patient disability assessed by modified Rankin Scale at 90 days.

Results—A total of 257 patients were randomized and analyzed (early 131, delayed 126). At 90 days, modified Rankin Scale score distribution did not differ between groups (P=0.68), and the adjusted common odds ratio of the early statin group was 0.84 (95% confidence interval, 0.53–1.3; P=0.46) compared with the delayed statin group. There were 3 deaths at 90 days (2 in the early group, 1 in the delayed group) because of malignancy. Ischemic stroke recurred in 9 patients (6.9%) in the early group and 5 patients (4.0%) in the delayed group. The safety profile was similar between groups.

Conclusions—Our randomized trial involving patients with acute ischemic stroke and dyslipidemia did not show any superiority of early statin therapy within 24 hours of admission compared with delayed statin therapy 7 days after admission to alleviate the degree of disability at 90 days after onset.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02549846.

(*Stroke*. 2017;48:3057-3063. DOI: 10.1161/STROKEAHA.117.017623.)

Key Words: cholesterol, LDL ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ prognosis ■ randomized controlled trial ■ stroke

See related article, p 2922

To improve survival and ameliorate disability after ischemic stroke, many treatment modalities have been used in the acute stage of stroke. Among them, intravenous tPA (tissue-type plasminogen activator) therapy and immediate endovascular thrombectomy have improved clinical outcomes, especially in patients with severe acute ischemic stroke.[1,2]

Several observational studies showed that the administration of statins before ischemic stroke onset was associated with less physical disability[3] and that statin administration during hospitalization was associated with better survival and disability outcomes.[4–7] However, 1 small randomized controlled trial (RCT) failed to show the benefit of statin use at the acute phase of ischemic stroke for significantly decreased disability.[8] A recent meta-analysis proposed the necessity of an RCT to determine the usefulness of statin therapy for acute ischemic stroke.[9]

Thus, we conducted a multicenter RCT to determine the relative efficacy of early versus delayed statin treatment in patients with acute ischemic stroke. We hypothesized that early statin treatment would be associated with significantly improved physical disability at 90 days after acute ischemic stroke.

Received April 8, 2017; final revision received July 5, 2017; accepted July 7, 2017.

From the Department of Neurosurgery (S.Y., K.U.), Department of Clinical Epidemiology (K.U., T.M.), Center for Clinical Research and Education (T.D., T.M.), and Department of Biostatistics (T.D.), Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; and Medical Affairs Department, Shionogi & Co, Ltd, Osaka, Japan (R.T., K.K.).

Guest Editor for this article was Seemant Chaturvedi, MD.

*A list of all ASSORT Trial Investigators is given in the Appendix.

Presented in part at the International Stroke Conference, Houston, TX, February 24, 2017.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.017623/-/DC1.

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DOI: 10.1161/STROKEAHA.117.017623

Yoshimura et al; Stroke 2017

When to start?

August 2006

Achieving Target Cholesterol Goals After Stroke

Is In-Hospital Statin Initiation the Key?

Nerses Sanossian, MD; Jeffrey L. Saver, MD; David S. Liebeskind, MD; et al

» Author Affiliations | Article Information

Arch Neurol. 2006;63(8):1081-1083. doi:10.1001/archneur.63.8.1081

→ 93% statin adherence at 3m

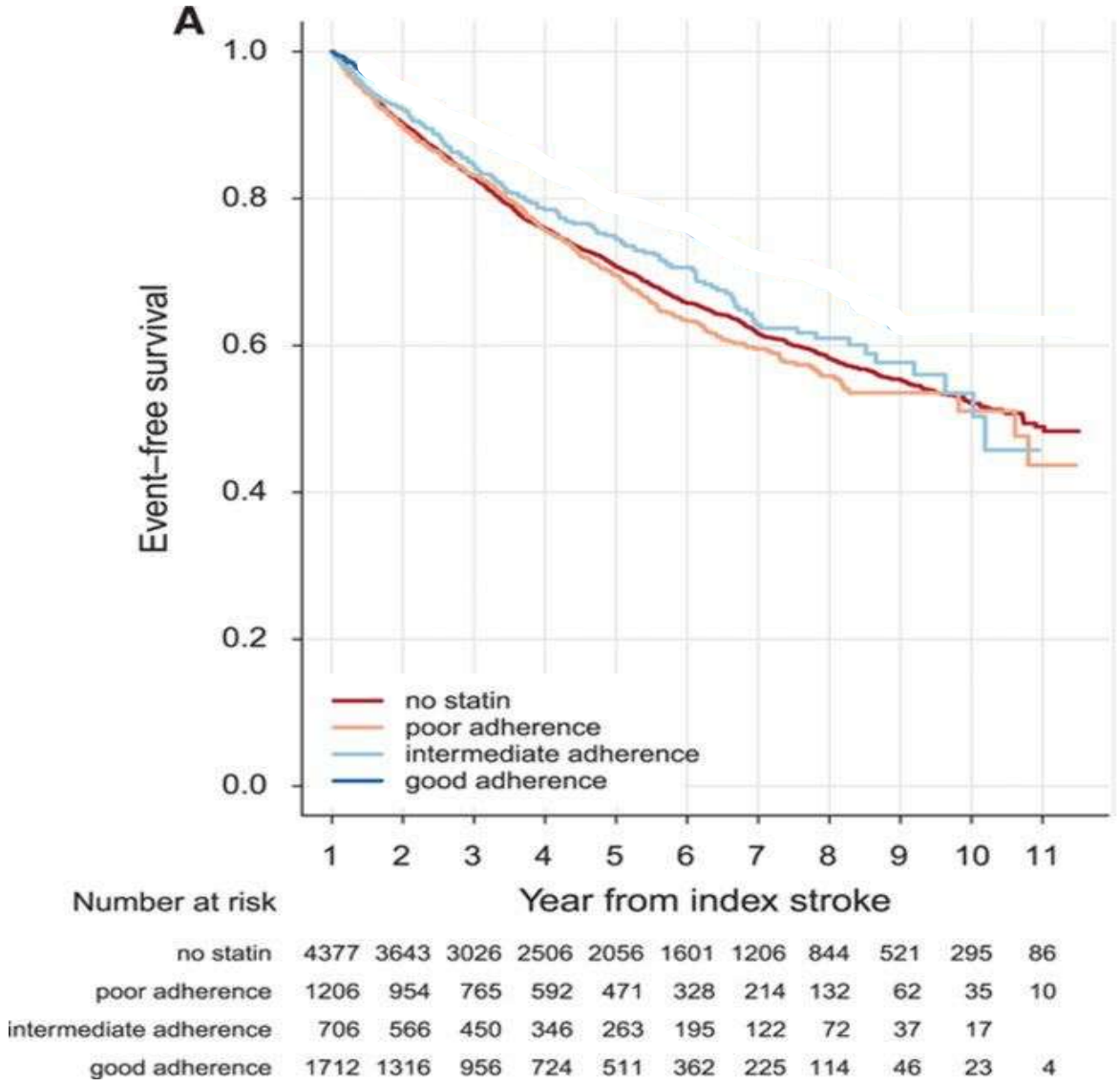
In-Hospital Initiation of Secondary Stroke Prevention Therapies Yields High Rates of Adherence at Follow-up

Bruce Ovbiagele, Jeffrey L. Saver, Andre Fredieu, Shuichi Suzuki, Scott Selco, Venkatakrishna Rajajee, Norma McNair, Tannaz Razinia and **Chelsea S. Kidwell**

Originally published 28 Oct 2004 | https://doi.org/10.1161/01.STR.0000147967.49567.d6 | Stroke. 2004;35:2879–2883

→ 99% statin adherence at 3m

Adherence to treatment



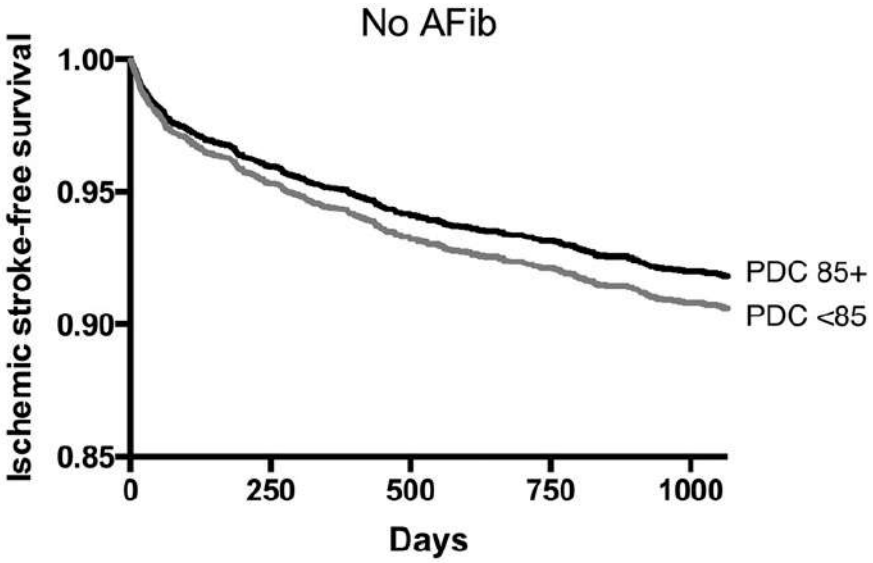
- **8001 acute ischemic stroke patients**
- **4.69±2.72 years**
- **2284 primary outcomes**

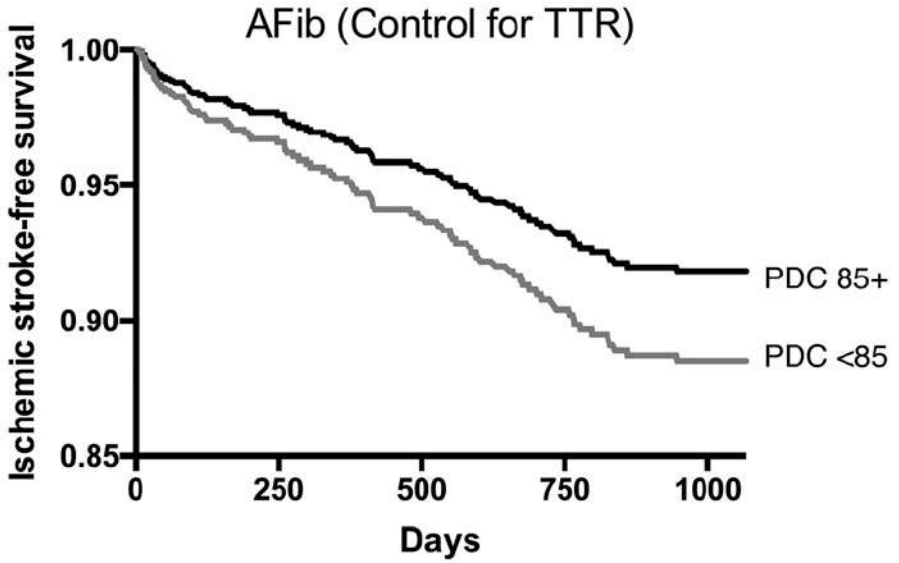
- **Adherence to statin treatment**
- **Statin intensity**

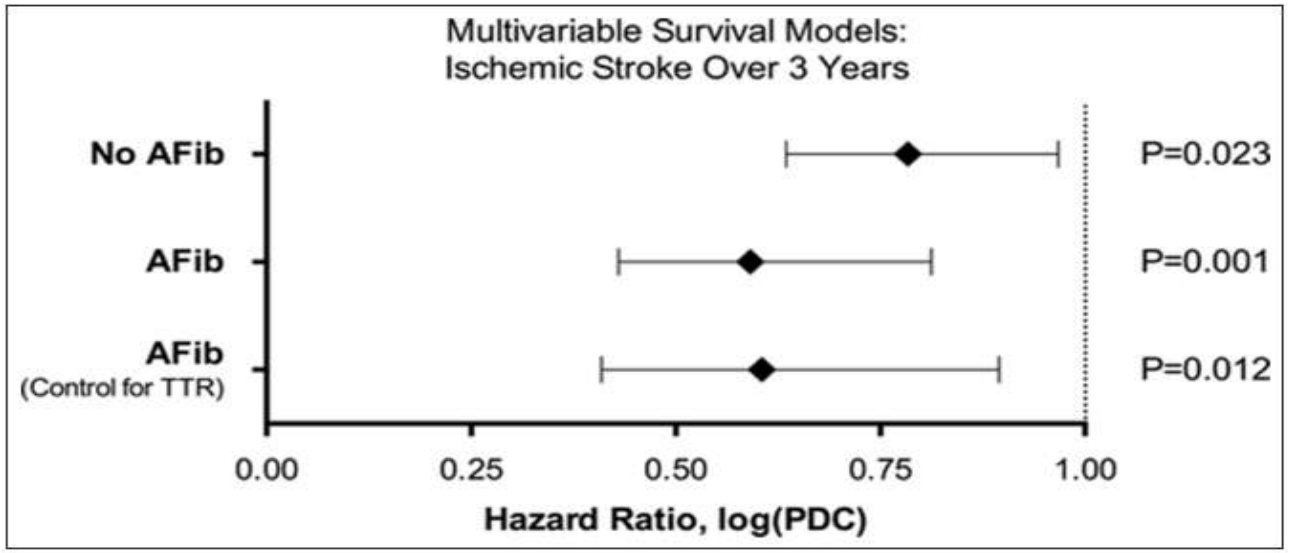
Adherence	Multivariate*	
	Adjusted HR (95% CI)	*P* Value
Adherence to statin		
No statin	Reference	
Poor	1.07 (0.95–1.20)	0.241
Intermediate adherence	0.93 (0.79–1.09)	0.383
Good adherence	0.74 (0.64–0.84)	<0.001

Kim et al. Stroke 2017

Adherence to treatment



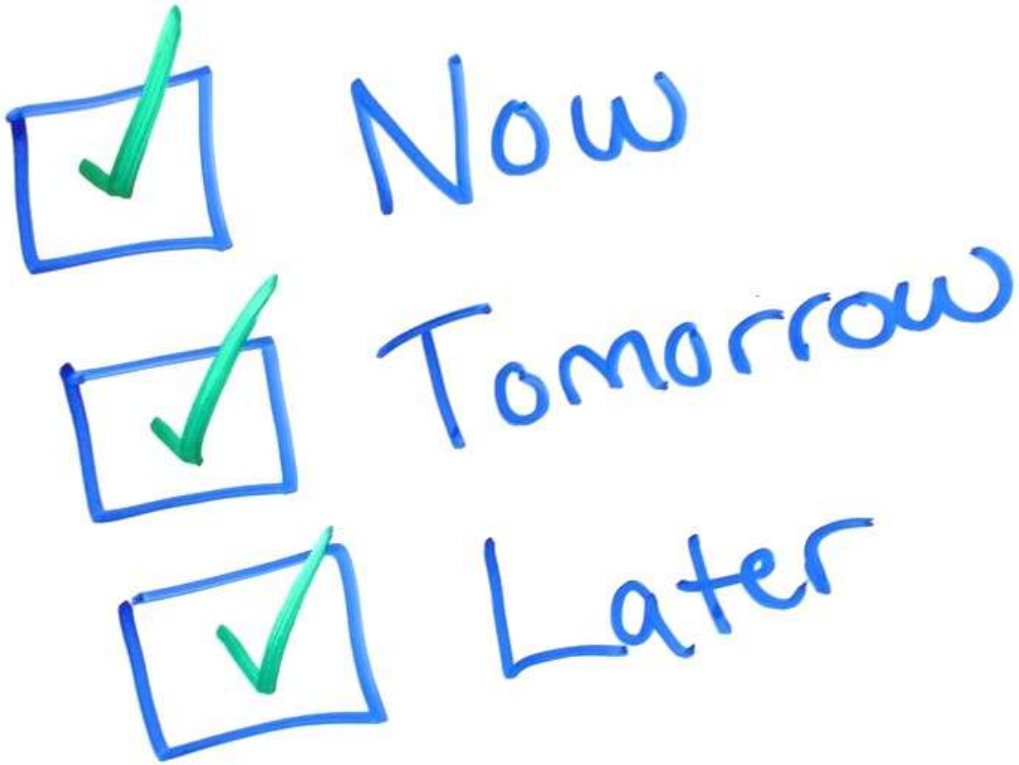




Higher adherence to statin therapy has been shown to be an independent predictor of stroke-free survival

Flint et al; Stroke 2017

When to start?



Better adherence

less future outcomes

Patient with ischemic stroke

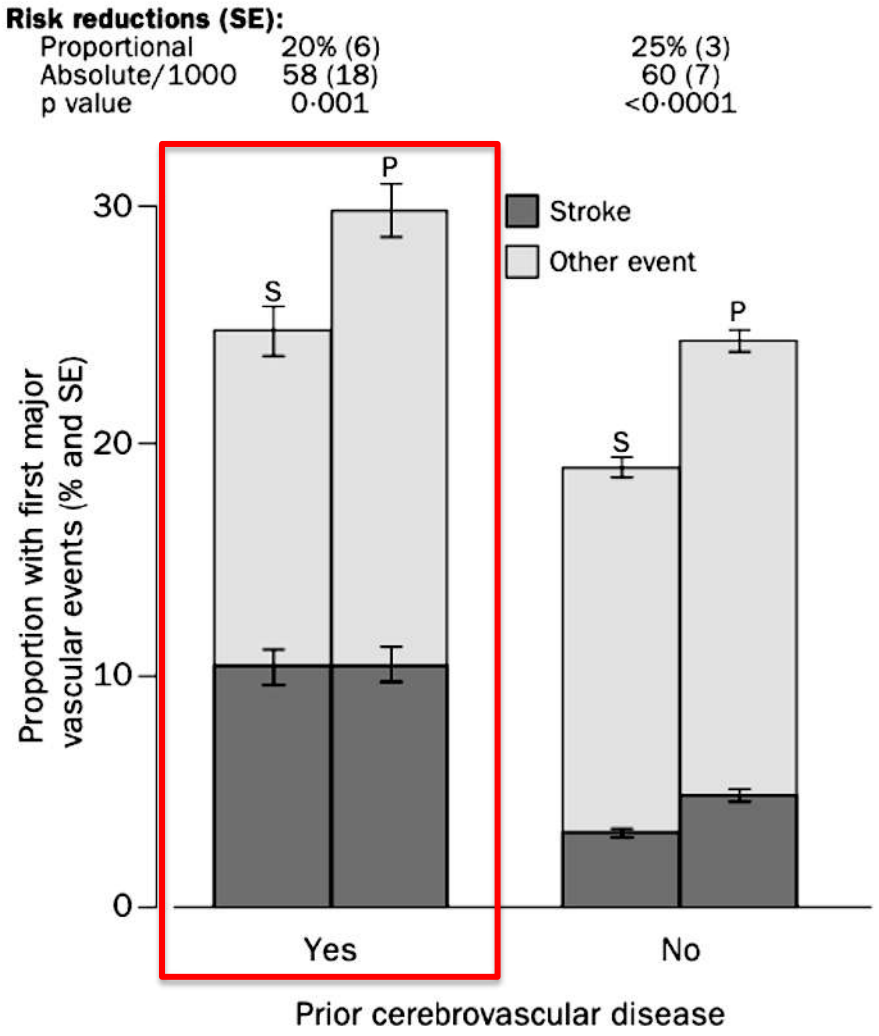
- ✓ **Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή**
- ✓ **Ποια υπολιπιδαιμική αγωγή πρέπει να χορηγήσω στον ασθενή με ισχαιμικό εγκεφαλικό επεισόδιο?**
- ✓ **Ποιος είναι ο στόχος μου ?**
- ✓ **Να φοβάμαι τις χαμηλές τιμές LDL?**

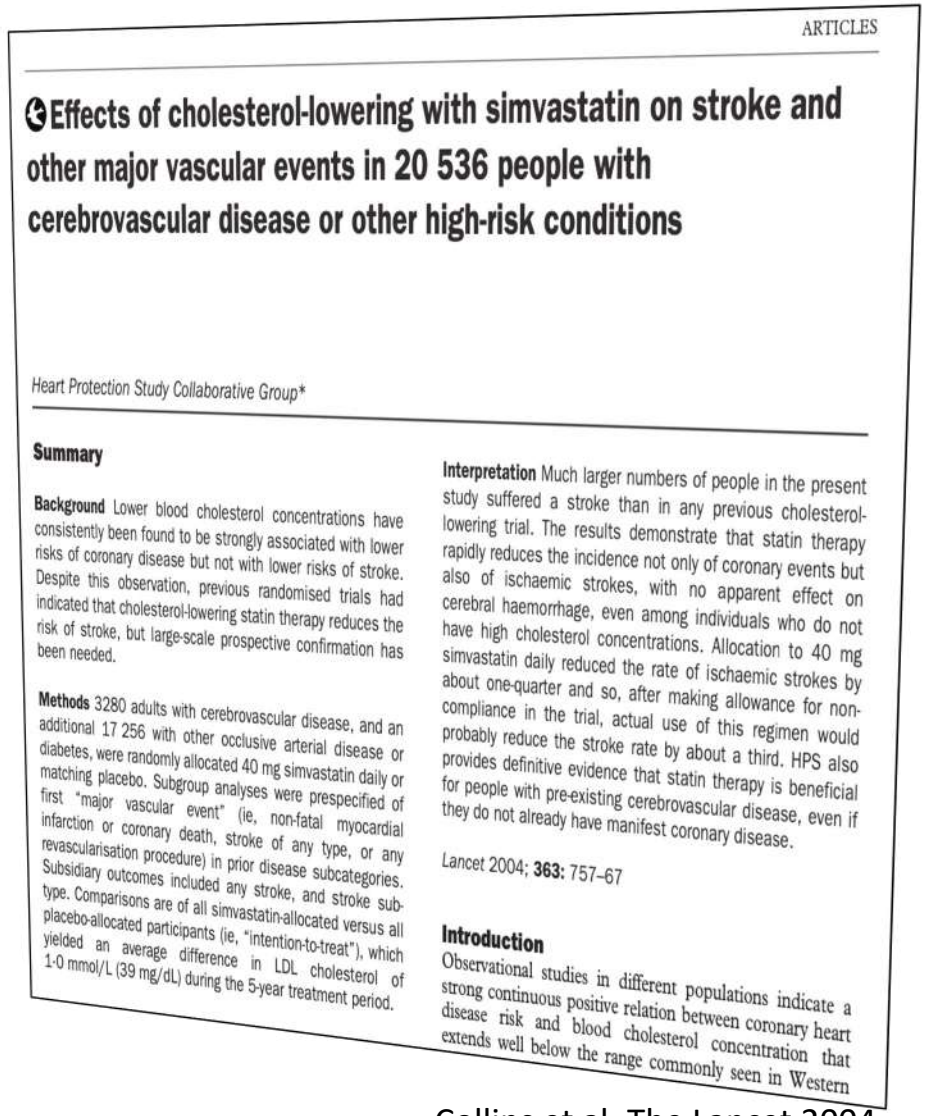
Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol

Study	Patients no.	Stroke patients no.	Treatment	Age, years (mean)	Follow-up, years (mean)	Baseline LDL-C, mg/dL (mean)	On treatment LDL-C, mg/dL (mean)	Ischemic stroke events (treatment/no treatment)
HPS, 2004	20,536	3280	Simvastatin	65	5.0	132	93	100/122
SPARCL, 2006	4731	4731	Atorvastatin	63	4.9	133	73	218/274
J-STARS, 2015	1578	1578	Pravastatin	66	4.9	130	104	62/66
FOURIER, 2017	27,564	5337	Evolocumab	63	2.2	86	30	171/226
TST, 2019	2860	2860	Statin ± Ezetimibe	67	3.5	135	65	120/139

Sagris D et al. Int J Stroke 2020

Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol





ARTICLES

Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions

*Heart Protection Study Collaborative Group**

Summary

Background Lower blood cholesterol concentrations have consistently been found to be strongly associated with lower risks of coronary disease but not with lower risks of stroke. Despite this observation, previous randomised trials had indicated that cholesterol-lowering statin therapy reduces the risk of stroke, but large-scale prospective confirmation has been needed.

Methods 3280 adults with cerebrovascular disease, and an additional 17 256 with other occlusive arterial disease or diabetes, were randomly allocated 40 mg simvastatin daily or matching placebo. Subgroup analyses were prespecified of first "major vascular event" (ie, non-fatal myocardial infarction or coronary death, stroke of any type, or any revascularisation procedure) in prior disease subcategories. Subsidiary outcomes included any stroke, and stroke subtype. Comparisons are of all simvastatin-allocated versus all placebo-allocated participants (ie, "intention-to-treat"), which yielded an average difference in LDL cholesterol of 1·0 mmol/L (39 mg/dL) during the 5-year treatment period.

Interpretation Much larger numbers of people in the present study suffered a stroke than in any previous cholesterol-lowering trial. The results demonstrate that statin therapy rapidly reduces the incidence not only of coronary events but also of ischaemic strokes, with no apparent effect on cerebral haemorrhage, even among individuals who do not have high cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rate of ischaemic strokes by about one-quarter and so, after making allowance for non-compliance in the trial, actual use of this regimen would probably reduce the stroke rate by about a third. HPS also provides definitive evidence that statin therapy is beneficial for people with pre-existing cerebrovascular disease, even if they do not already have manifest coronary disease.

Lancet 2004; **363:** 757–67

Introduction

Observational studies in different populations indicate a strong continuous positive relation between coronary heart disease risk and blood cholesterol concentration that extends well below the range commonly seen in Western

Collins et al; The Lancet 2004

Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol

Table 2. Estimates of the Hazard Ratio for the Primary and Secondary Efficacy Outcome Measures.

Outcome*	Atorvastatin (N=2365)	Placebo (N=2366)	Unadjusted P Value†	Prespecified Adjusted Model‡	
				HR (95% CI)	P Value
	no. (%)				
Primary outcome					
Nonfatal or fatal stroke§	265 (11.2)	311 (13.1)	0.05	0.84 (0.71–0.99)	0.03
Nonfatal stroke	247 (10.4)	280 (11.8)	0.14	0.87 (0.73–1.03)	0.11
Fatal stroke	24 (1.0)	41 (1.7)	0.04	0.57 (0.35–0.95)	0.03
Secondary outcomes					
Stroke or TIA	375 (15.9)	476 (20.1)	<0.001	0.77 (0.67–0.88)	<0.001
TIA	153 (6.5)	208 (8.8)	0.004	0.74 (0.60–0.91)	0.004
Major coronary event§	81 (3.4)	120 (5.1)	0.006	0.65 (0.49–0.87)	0.003
Death from cardiac causes	40 (1.7)	39 (1.6)	0.90	1.00 (0.64–1.56)	1.00
Nonfatal myocardial infarction	43 (1.8)	82 (3.5)	0.001	0.51 (0.35–0.74)	<0.001
Resuscitation after cardiac arrest	1 (<0.1)	1 (<0.1)	—	—	—
Major cardiovascular event	334 (14.1)	407 (17.2)	0.005	0.80 (0.69–0.92)	0.002

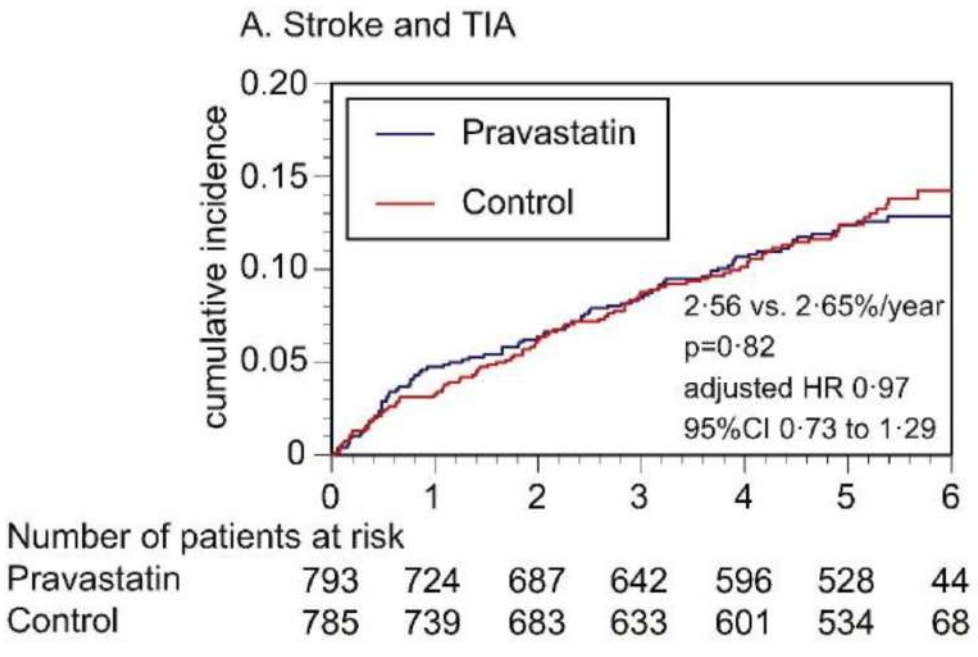
SPARCL: high-dose atorvastatin reduced stroke risk and CV events

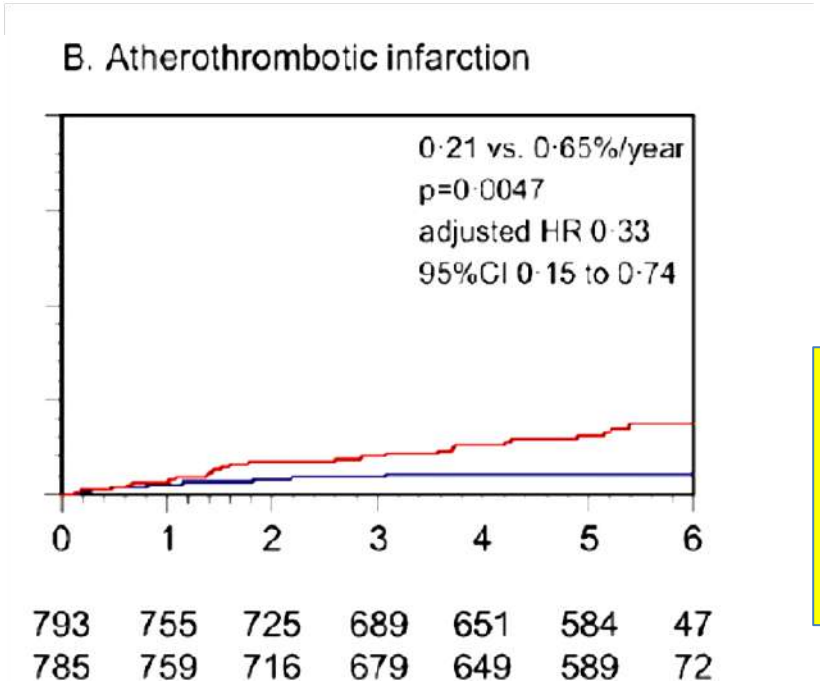
Hemorrhagic stroke
1.66 (95% CI 1.08 to 2.55)

No effect of LDL-C on ICH

Amarenco N Engl J Med 2006; 355:549-559

Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol





Lacunar stroke: 63%
Atherosclerotic stroke: 25%

J-Stars: pravastatin reduced atherothrombotic strokes but not total strokes (primary end-point)

"…patients aged 45 to 80 years with a history of non-cardioembolic ischemic stroke …"

LDL in statin arm: 104mg/dl

N. Hosomi et al. / EBioMedicine 2 (2015)

Lipid-lowering therapy

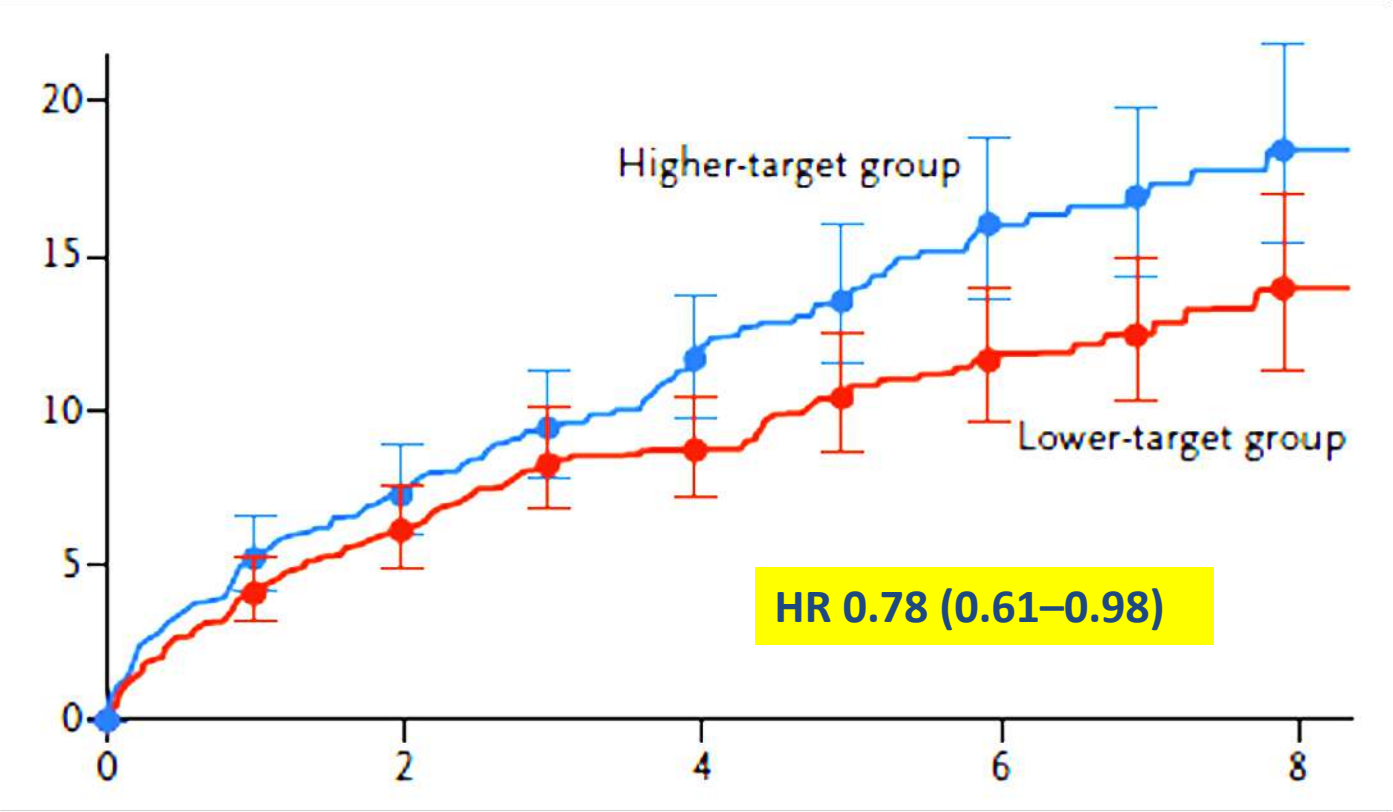
- Patients with ischemic stroke or TIA should receive lipid-modifying treatment with **high-intensity statin (1A)**.

Sagris D et al. Int J Stroke 2020

Patient with ischemic stroke

- ✓ Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή
- ✓ Ποια υπολιπιδαιμική αγωγή πρέπει να χορηγήσω στον ασθενή με ισχαιμικό εγκεφαλικό επεισόδιο?
- ✓ Ποιος είναι ο στόχος μου ?
- ✓ Να φοβάμαι τις χαμηλές τιμές LDL?

Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol



TST study: LDL≤70mg/dl after stroke reduced CV events

"…atherosclerotic disease that included stenosis of an extracranial or intracranial cerebral artery, ipsilateral or contralateral to the region of imputed brain ischemia…"

Amarenco et al ; n engl j med, 2019

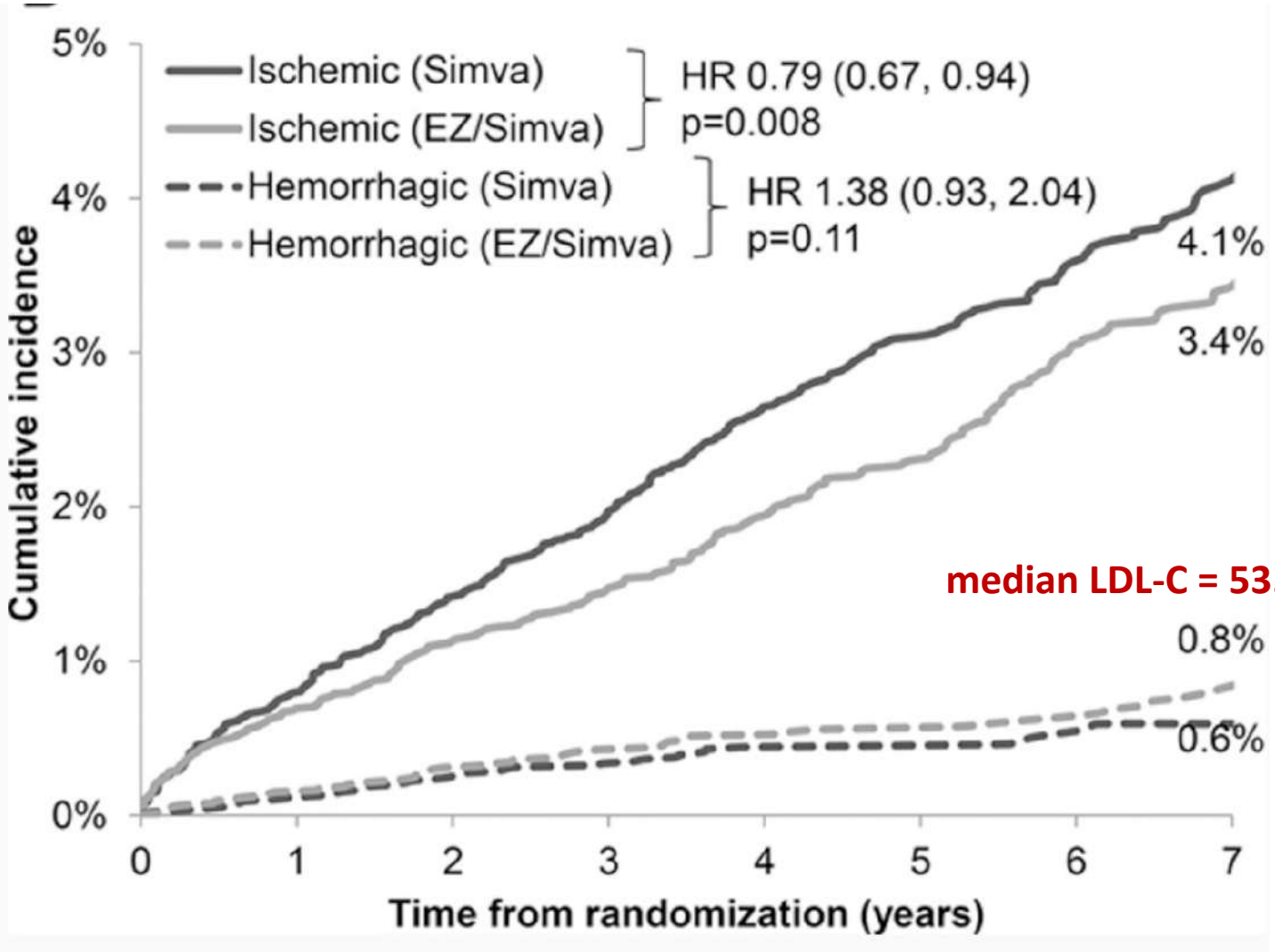
LDL cholesterol treatment goals

Evidence-based recommendation
In people with ischaemic stroke or TIA, we recommend aiming for an LDL cholesterol level of <1.8 mmol/l (70 mg/dl) to reduce the risk of major cardiovascular events.

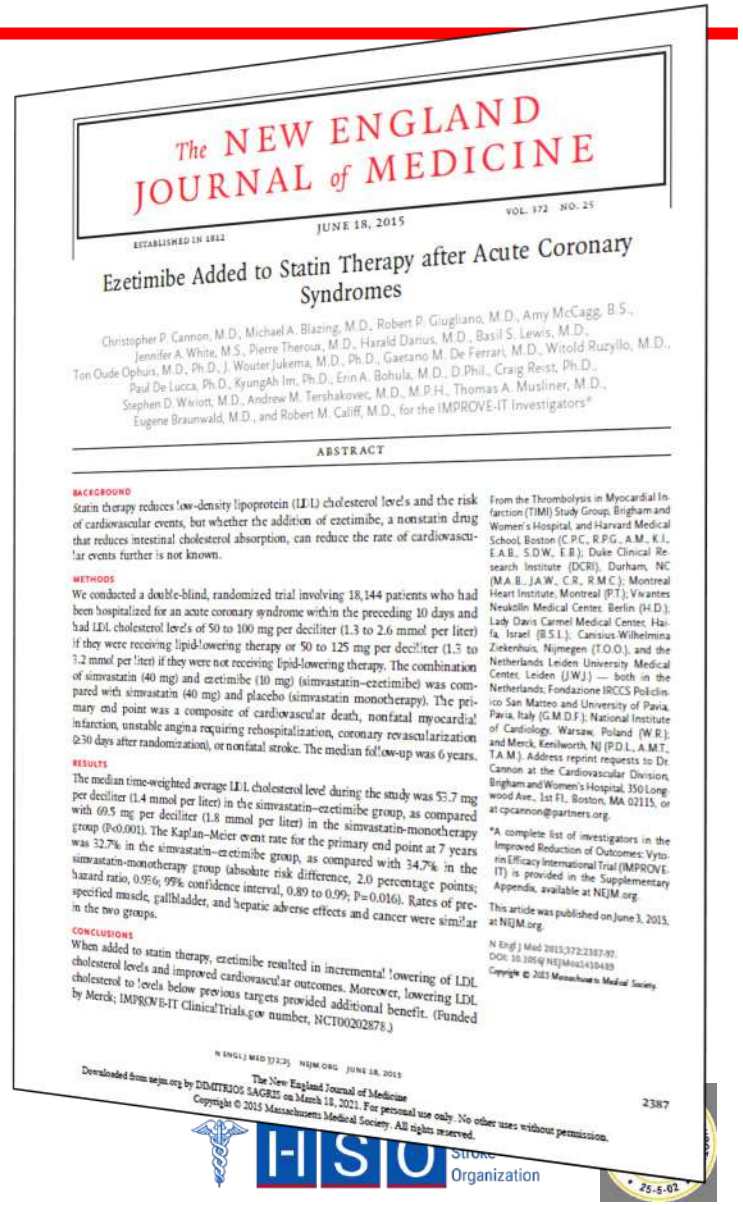
Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Strong for intervention** ↑↑

Γιατί μόνο <70?

LDL cholesterol treatment goals



median LDL-C = 53.7 mg/dl



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

ABSTRACT

BACKGROUND

Statin therapy reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe, a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known.

METHODS

We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin–ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS

The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group (P<0.001). The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 99% confidence interval, 0.89 to 0.99; P=0.016). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

CONCLUSIONS

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital, and Harvard Medical School, Boston (C.P.C., R.P.G., A.M., K.I., E.A.B., S.D.W., E.B.); Duke Clinical Research Institute (DCRI), Durham, NC (M.A.B., J.A.W., C.R., R.M.C.); Montreal Heart Institute, Montreal (P.T.); Vivantes Neukölln Medical Center, Berlin (H.D.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Canisius-Wilhelmina Ziekenhuis, Nijmegen (T.O.O.), and the Netherlands Leiden University Medical Center, Leiden (J.W.J.) — both in the Netherlands; Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy (G.M.D.F.); National Institute of Cardiology, Warsaw, Poland (W.R.); and Merck, Kenilworth, NJ (P.D.L., A.M.T., T.A.M.). Address reprint requests to Dr. Cannon at the Cardiovascular Division, Brigham and Women's Hospital, 350 Longwood Ave., 1st Fl., Boston, MA 02115, or at cpcannon@partners.org.

*A complete list of investigators in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is provided in the Supplementary Appendix, available at NEJM.org.

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N ENGL J MED 372;25 NEJM.ORG JUNE 18, 2015

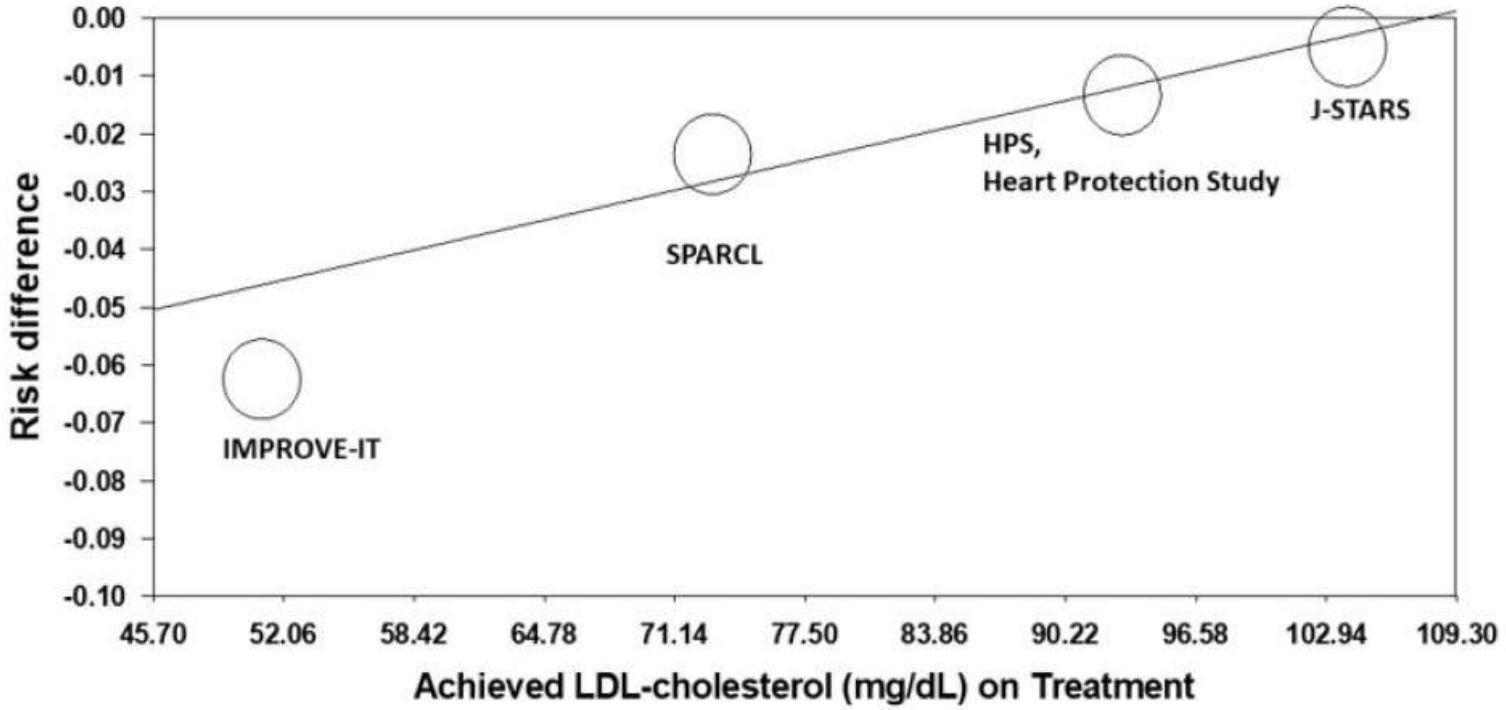
The New England Journal of Medicine

2387

Bohula et al; Circulation 2017

Secondary stroke prevention: the lower, the better

38mg/dl LDL reduction → 21% ↓Stroke reduction




Journal of Stroke WSO

Review

Statin-based therapy for primary and secondary prevention of ischemic stroke: A meta-analysis and critical overview

SAGE

Haralampos Milionis[1,2], George Ntaios[2,3], Eleni Korompoki[2,4,5], Konstantinos Vemmos[2] and Patrik Michel[6]

Abstract

Background and aims: To reassess the effect of statin-based lipid-lowering therapy on ischemic stroke in primary and secondary prevention trials with regard to achieved levels of low-density lipoprotein-cholesterol in view of the availability of novel potent hypolipidemic agents.

Methods: English literature was searched (up to November 2018) for publications restricted to trials with a minimum enrolment of 1000 and 500 subjects for primary and secondary prevention, respectively, meeting the following criteria: adult population, randomized controlled design, and recorded outcome data on ischemic stroke events. Data were meta-analyzed and curve-estimation procedure was applied to estimate regression statistics and produce related plots.

Results: Four primary prevention trials and four secondary prevention trials fulfilled the eligibility criteria. Lipid-lowering therapy was associated with a lower risk of ischemic stroke in primary (risk ratio, RR 0.70, 95% confidence interval, CI, 0.60–0.82; $p < 0.001$) and in the secondary prevention setting (RR 0.80, 95% CI 0.70–0.90; $p < 0.001$). Curve-estimation procedure revealed a linear relationship between the absolute risk reduction of ischemic stroke and active treatment-achieved low-density lipoprotein-cholesterol levels in secondary prevention (adjusted R-square 0.90) in support of "the lower the better" hypothesis for stroke survivors. On the other hand, the cubic model followed the observed data well in primary prevention (adjusted R-square 0.98), indicating greater absolute risk reduction in high-risk cardiovascular disease-free individuals.

Conclusions: Statin-based lipid-lowering is effective both for primary and secondary prevention of ischemic stroke. Most benefit derives from targeting disease-free individuals at high cardiovascular risk, and by achieving low treatment targets for low-density lipoprotein-cholesterol in stroke survivors.

Keywords

Cholesterol, ischemic stroke, lipid lowering, meta-analysis, prevention, statin

Received: 18 May 2019; accepted: 6 June 2019

Introduction

Low-density lipoprotein (LDL)-cholesterol has been validated as a modifiable risk factor for cardiovascular disease (CVD) since at least three decades, but the association between LDL-cholesterol and stroke has been long disputed.[1,2] Despite the evidence from statin (hydroxy-methyl-glutaryl, HMG-CoA reductase inhibitors) trials that LDL-cholesterol lowering reduces stroke risk in various groups of dyslipidemic or CVD patients, the implementation of intensive lipid-lowering therapy after stroke has been slow compared with coronary artery disease (CAD).[3] The heterogeneity of the underlying pathogenetic mechanisms of 'stroke' has been mostly incriminated.[3,4]

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[5]Division of Brain Diseases, Imperial College, London, UK
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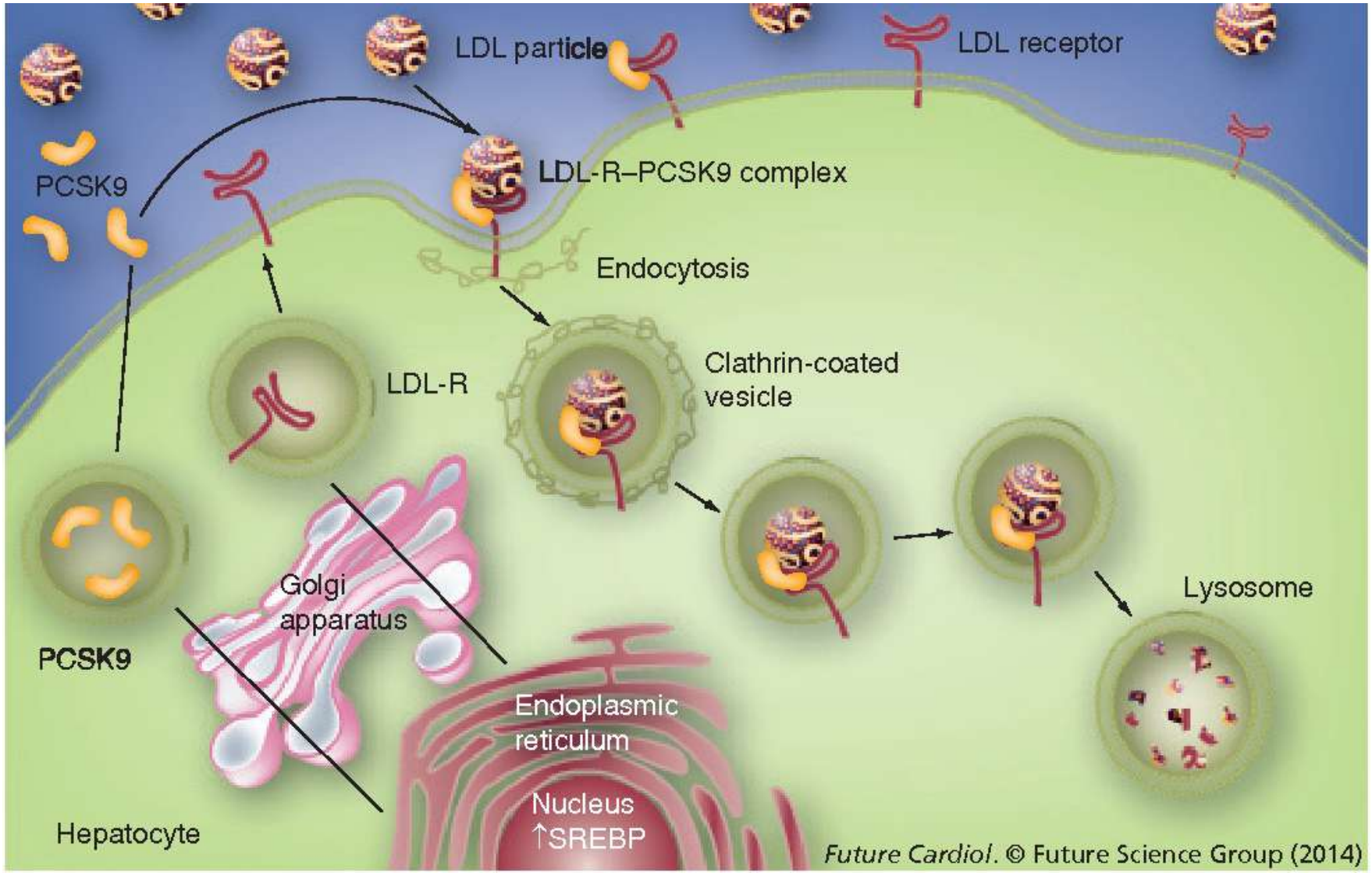
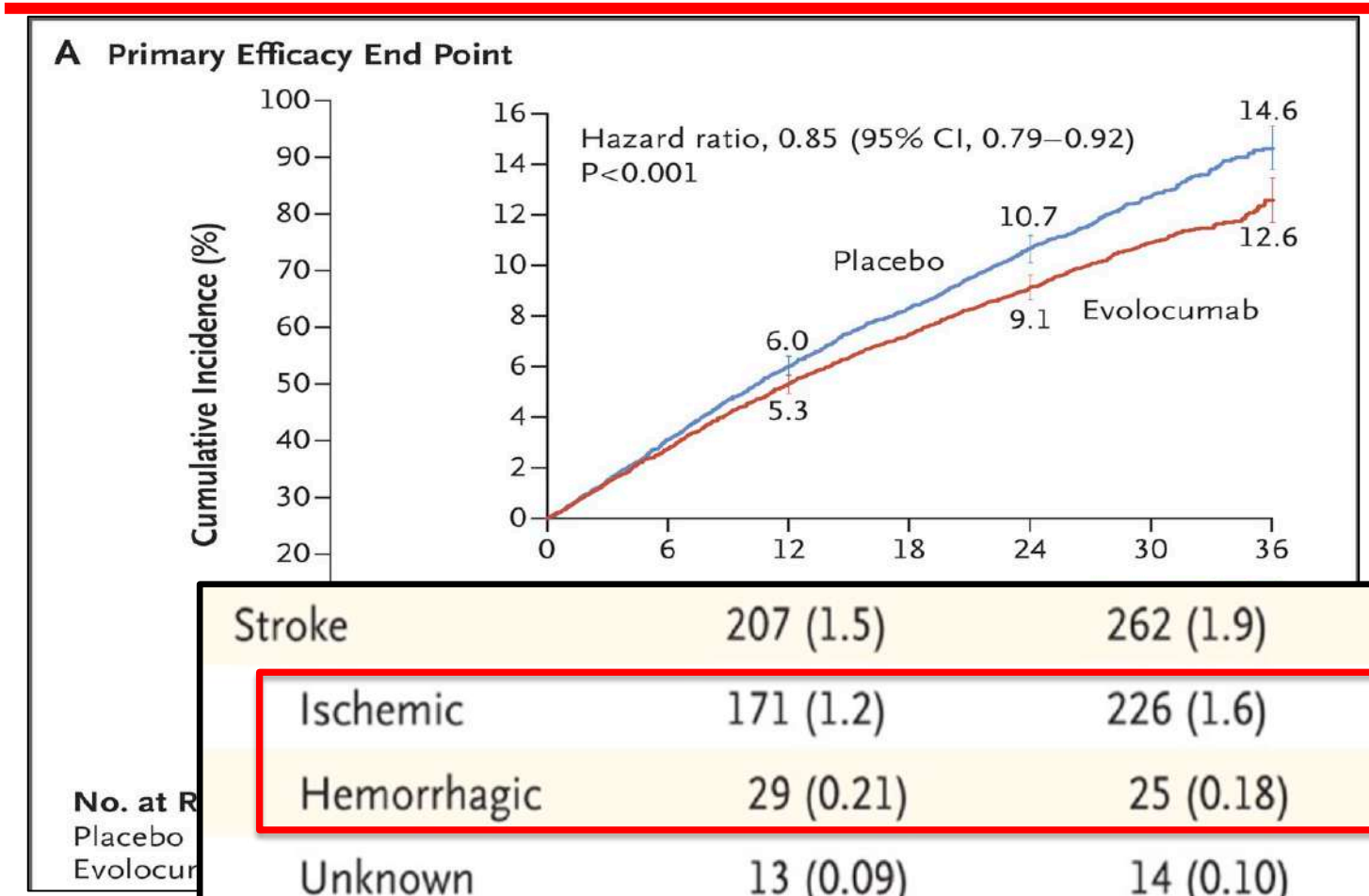
International Journal of Stroke, 15(4)

Milionis H, Ntaios G, et al. International Journal of Stroke 2020; 15:377-84

Proprotein convertase subtilisin/kexin type 9 (PCSK9)



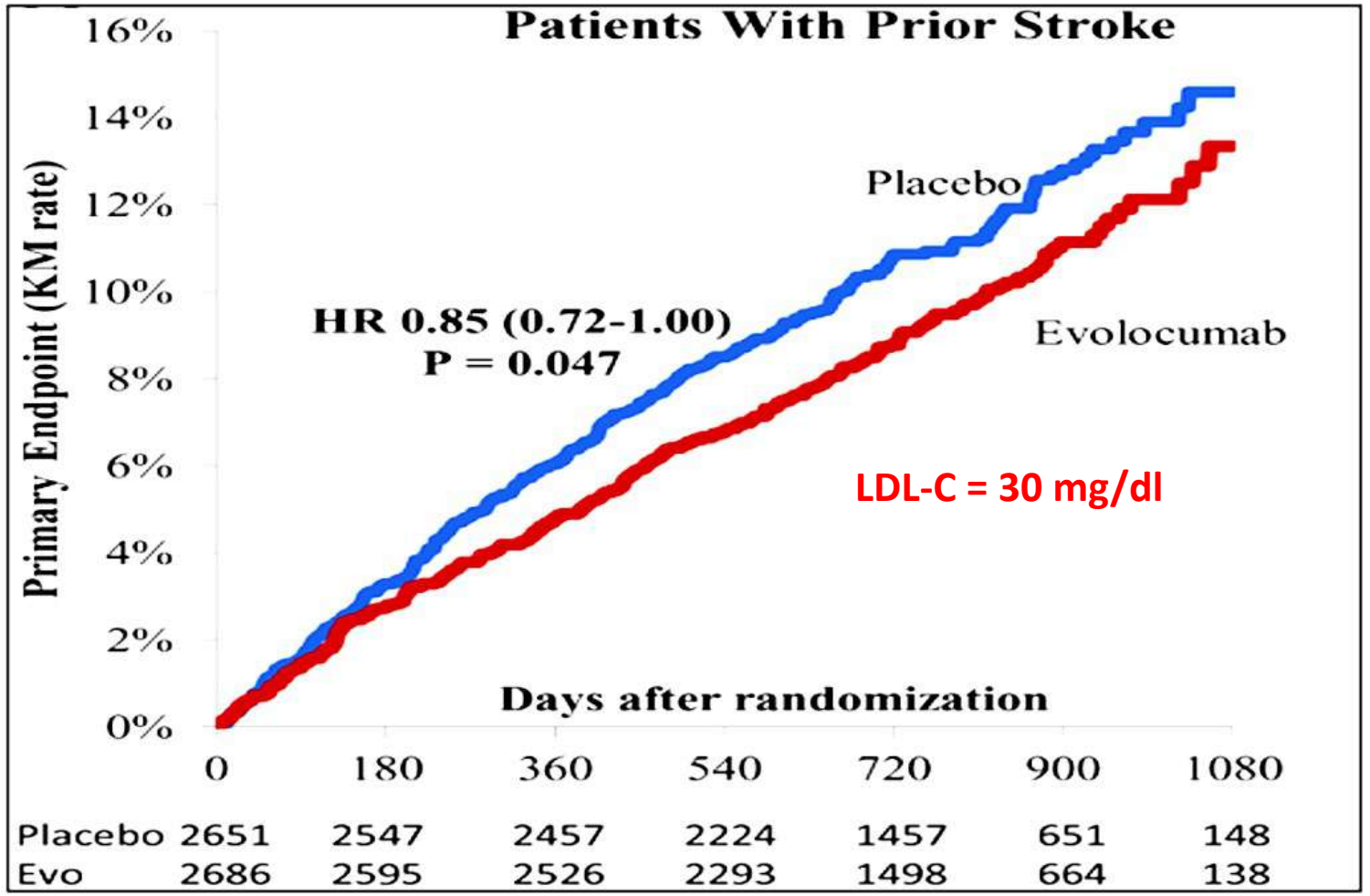
FOURIER (evolocumab)

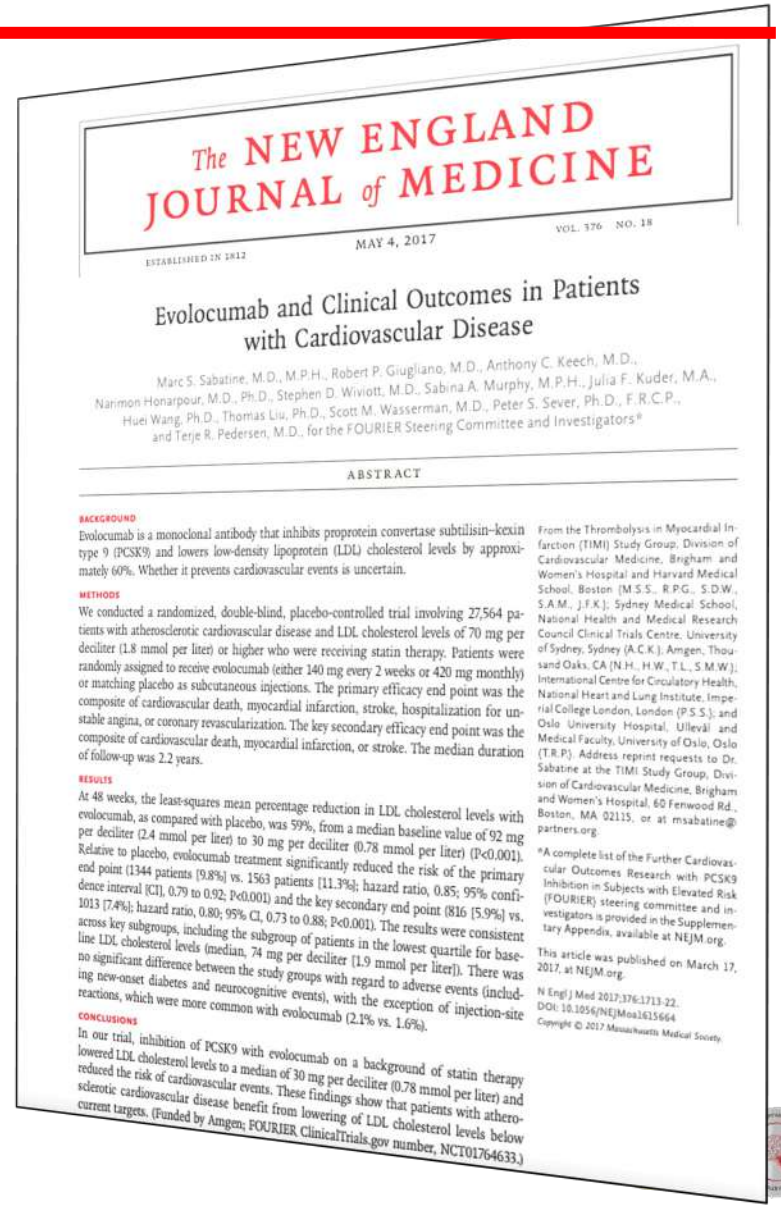


Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	

- 27,564 patients with atherosclerotic CV
- LDL ≥70 mg/dl under statin
- **Primary end-point**: CV death, talization for or coronary

FOURIER (evolocumab)





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ABSTRACT

BACKGROUND
Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

METHODS
We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

RESULTS
At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).

CONCLUSIONS
In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W., S.A.M., J.F.K.); Sydney Medical School, National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (A.C.K.); Amgen, Thousand Oaks, CA (N.H., H.W., T.L., S.M.W.); International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London (P.S.S.); and Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo (T.R.P.). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 60 Fenwood Rd., Boston, MA 02115, or at msabatine@partners.org.

*A complete list of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) steering committee and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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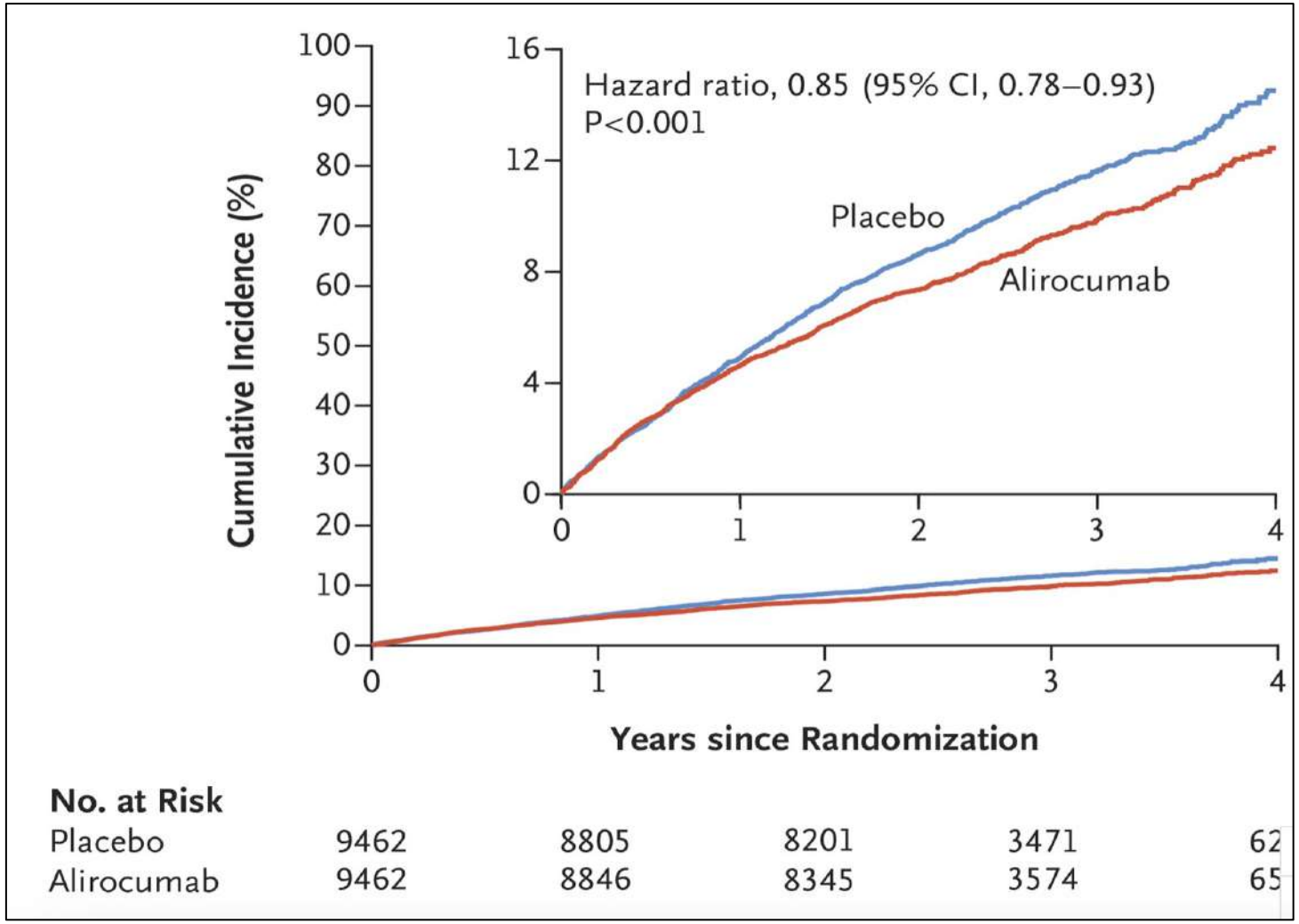
N Engl J Med 2017;376:1713-22.
DOI: 10.1056/NEJMoa1615664

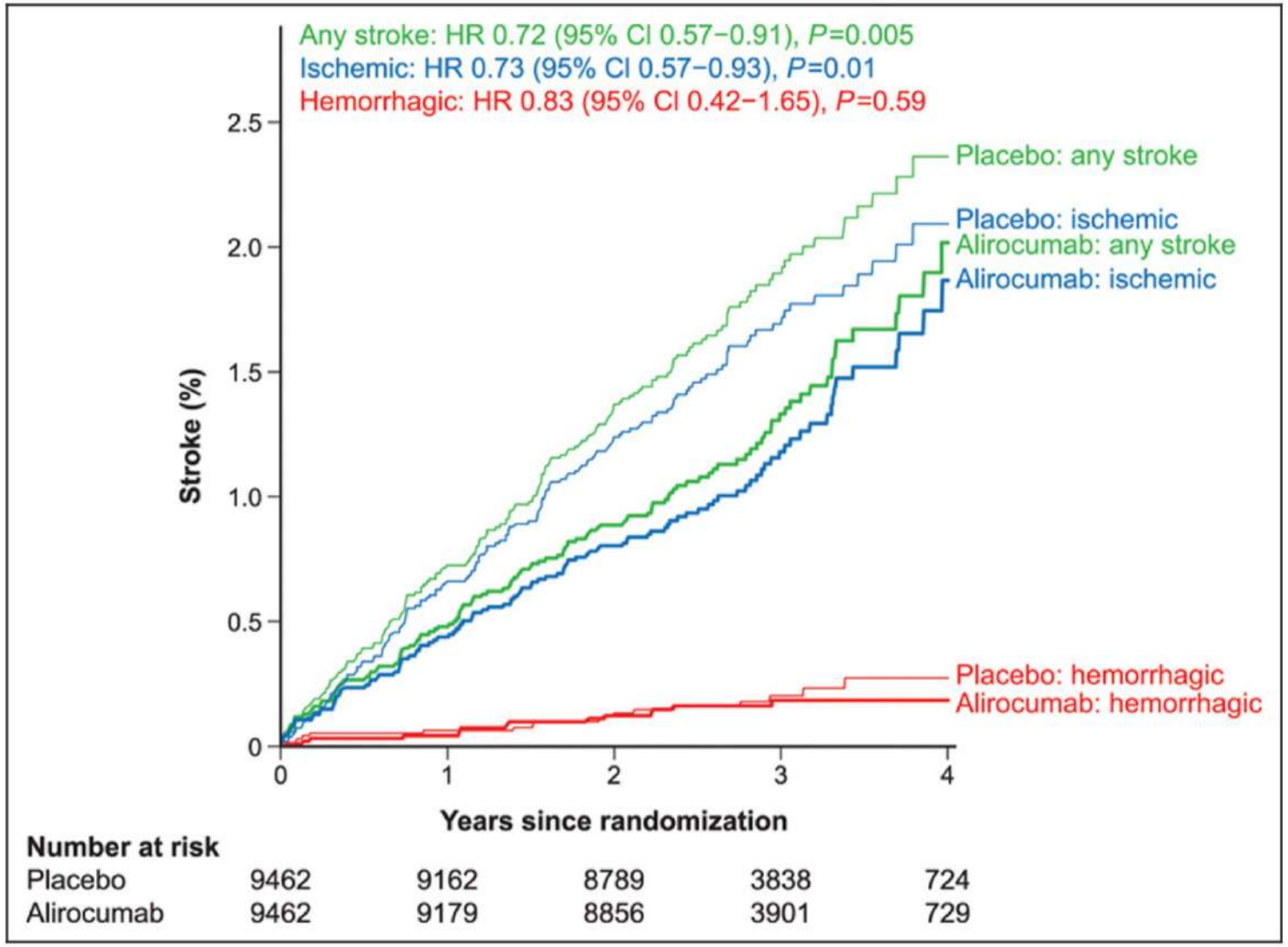
Giugliano et al; Stroke 2020

ODYSSEY OUTCOMES (alirocumab)



- 18,924 patients with ACS ≤12 months
- LDL ≥70 mg/dl under statin
- **Primary end-point**: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

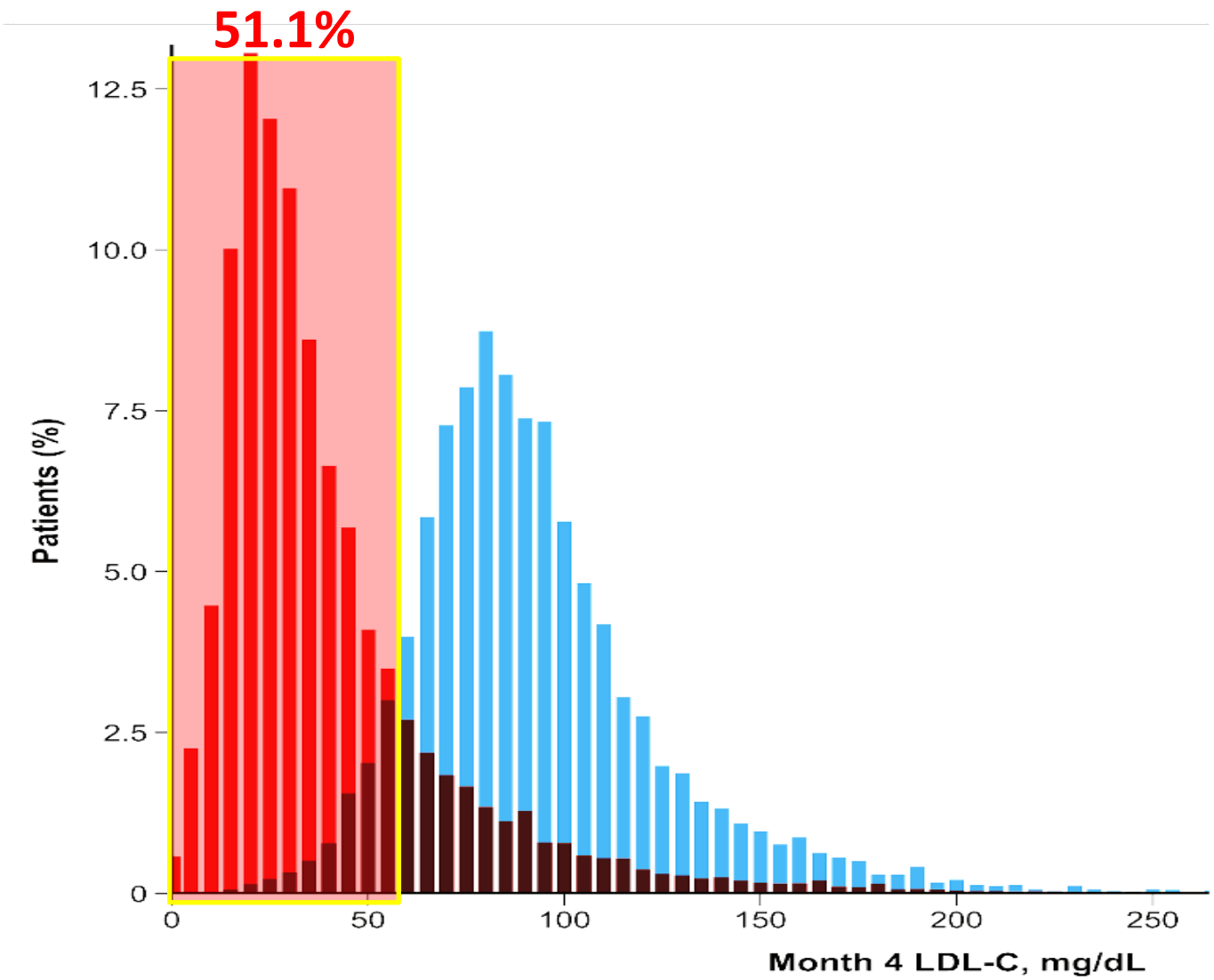
ODYSSEY OUTCOMES (alirocumab)



- 263 ischemic strokes and 33 hemorrhagic strokes
- Alirocumab significantly reduced the risk of ischemic stroke
- Did not increase the risk of hemorrhagic stroke

Jukema et al; Circulation. 2019

ODYSSEY OUTCOMES (alirocumab)



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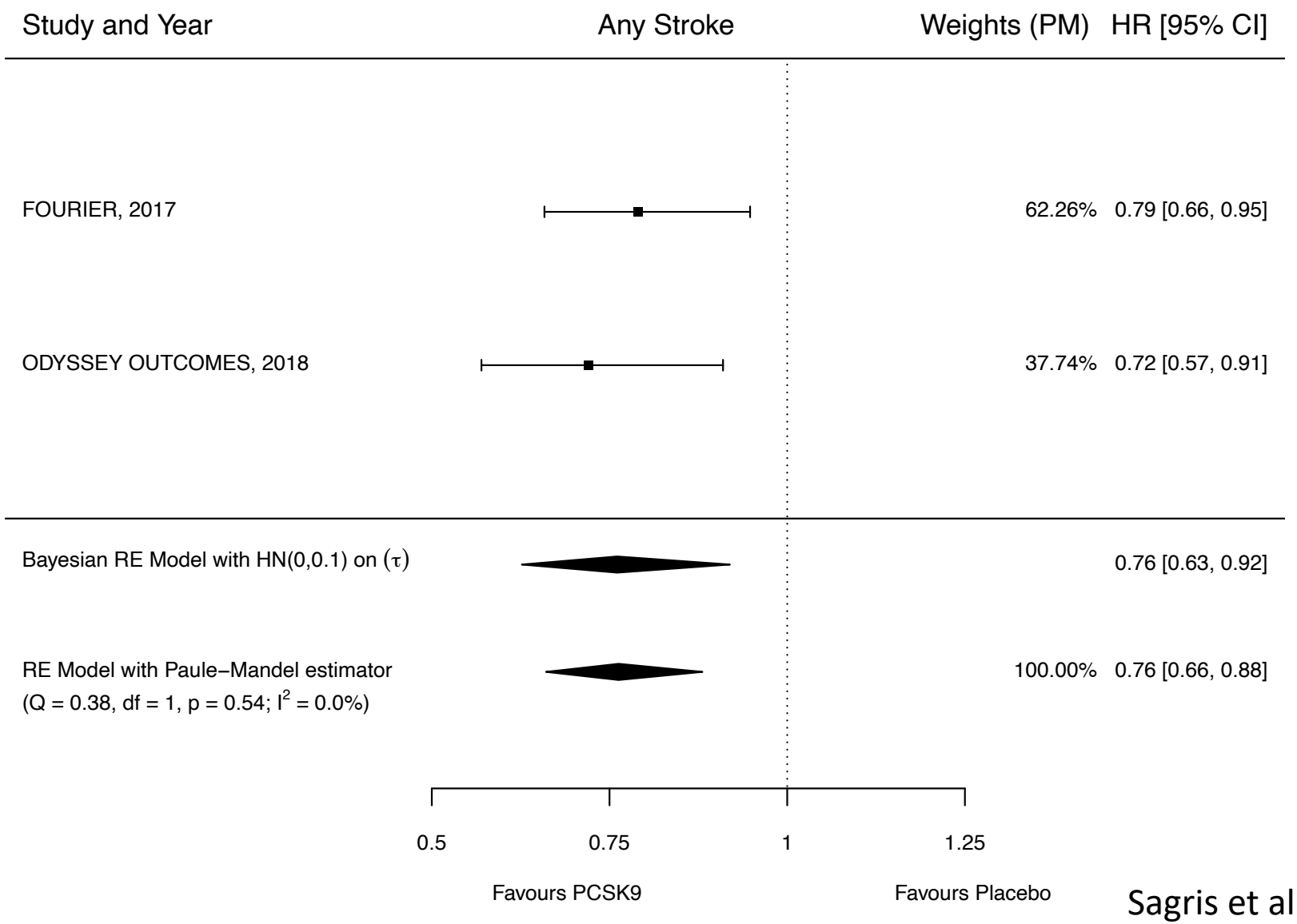
Jukema et al; Circulation. 2019

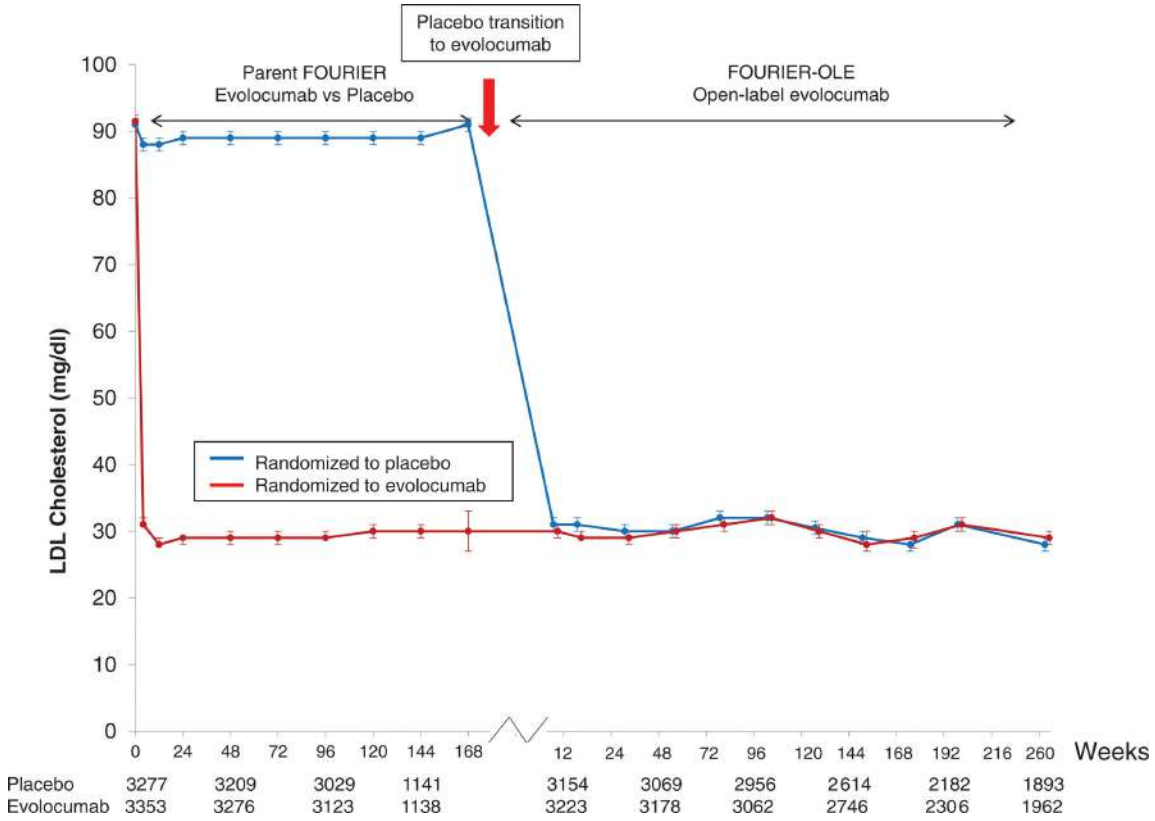
PCSK9 Inhibitors

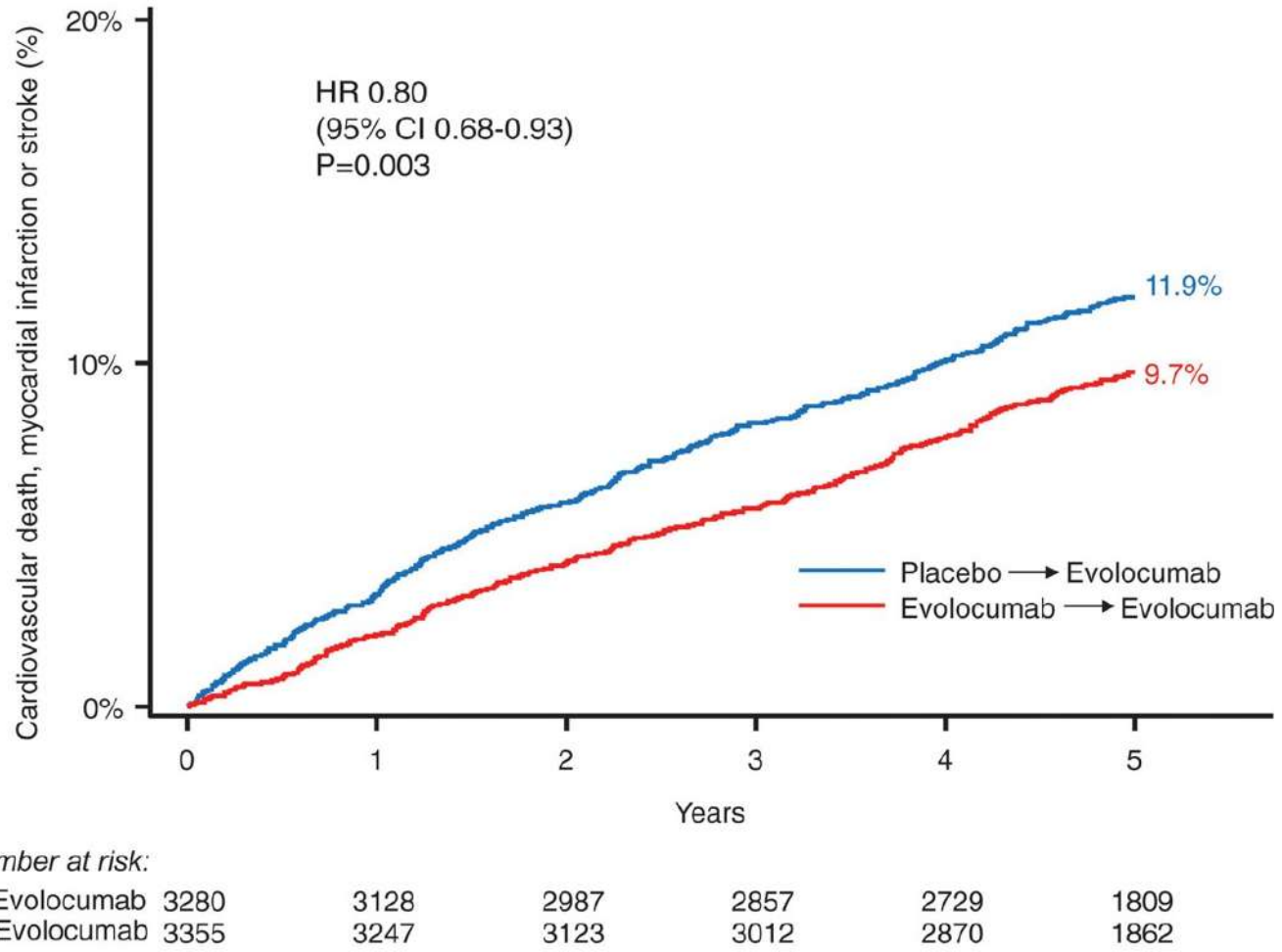


- **Median LDL-C before randomization: 93mg/dl**
- **Median time of randomization: 3 years**

Sagris et al: European J int Medicine 2020

FOURIER - OLE (evolocumab)





O'Donogoue et al; Circulation 2022

ORION-10 and 11 (inclisiran)

Inclisiran in Patients with Elevated LDL Cholesterol

TWO PHASE 3, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS

ORION-10
(U.S.)

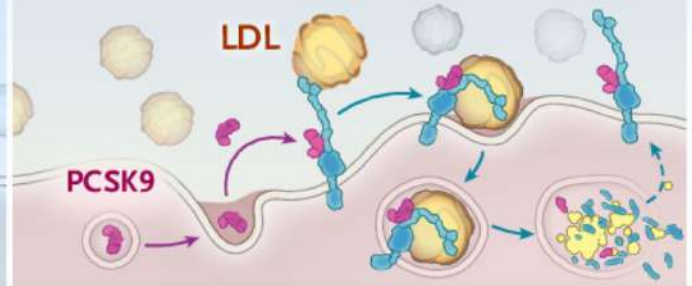
(N=1561)

–51.3% with Inclisiran

Difference, –52.3%
(95% CI, –55.7 to –48.8; P<0.001)

+1% with Placebo

Adults with CVD and elevated LDL



Percentage change in LDL cholesterol at 510 days

ORION-11
(Europe and South Africa)

(N=1617)

–45.8% with Inclisiran

Difference, –49.9%
(95% CI, –53.1 to –46.6; P<0.001)

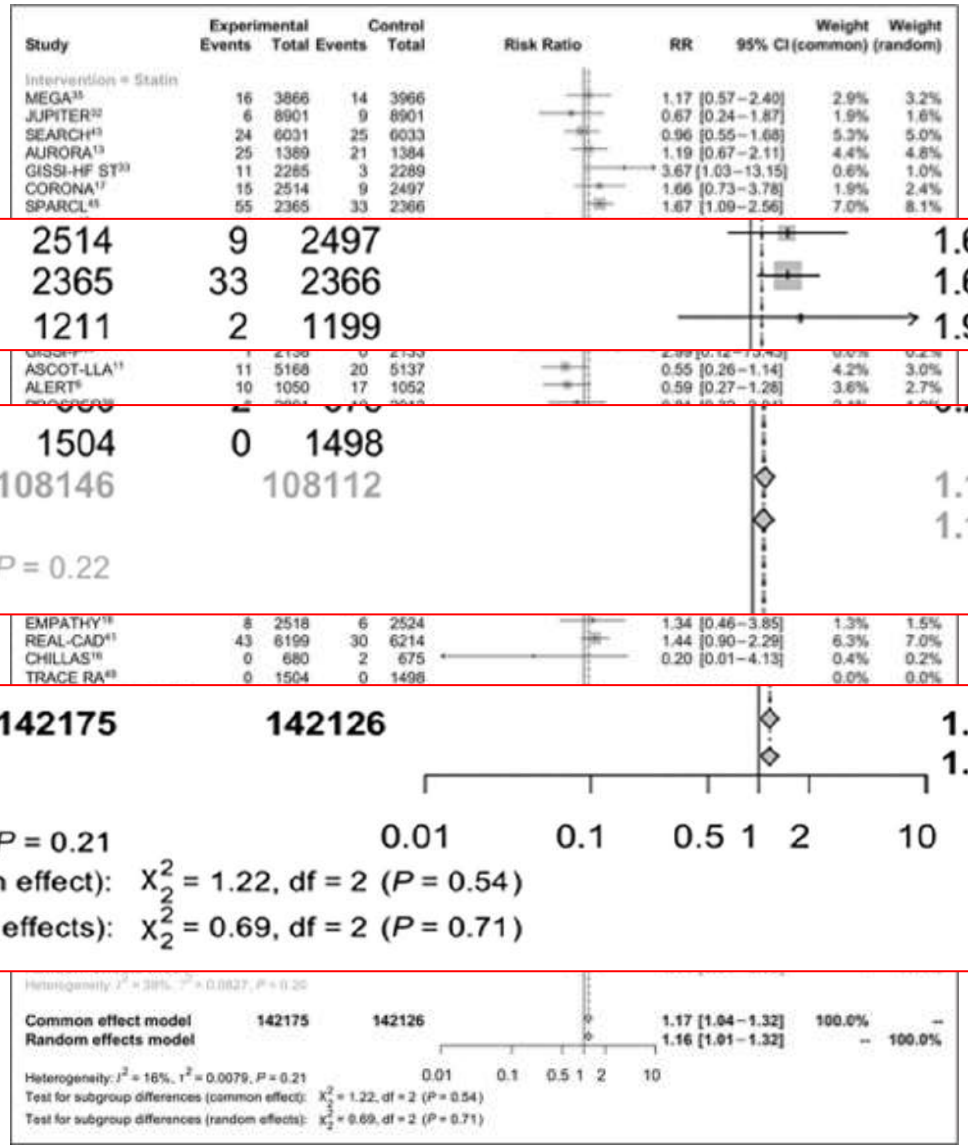
+4% with Placebo

Ray et al NEJM 2020

Patient with ischemic stroke

- ✓ Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή
- ✓ Ποια υπολιπιδαιμική αγωγή πρέπει να χορηγήσω στον ασθενή με ισχαιμικό εγκεφαλικό επεισόδιο?
- ✓ Ποιος είναι ο στόχος μου ?
- ✓ Να φοβάμαι τις χαμηλές τιμές LDL?

Is there a risk of ICH?



Bétrisey et al *J Am Heart As.* 2024

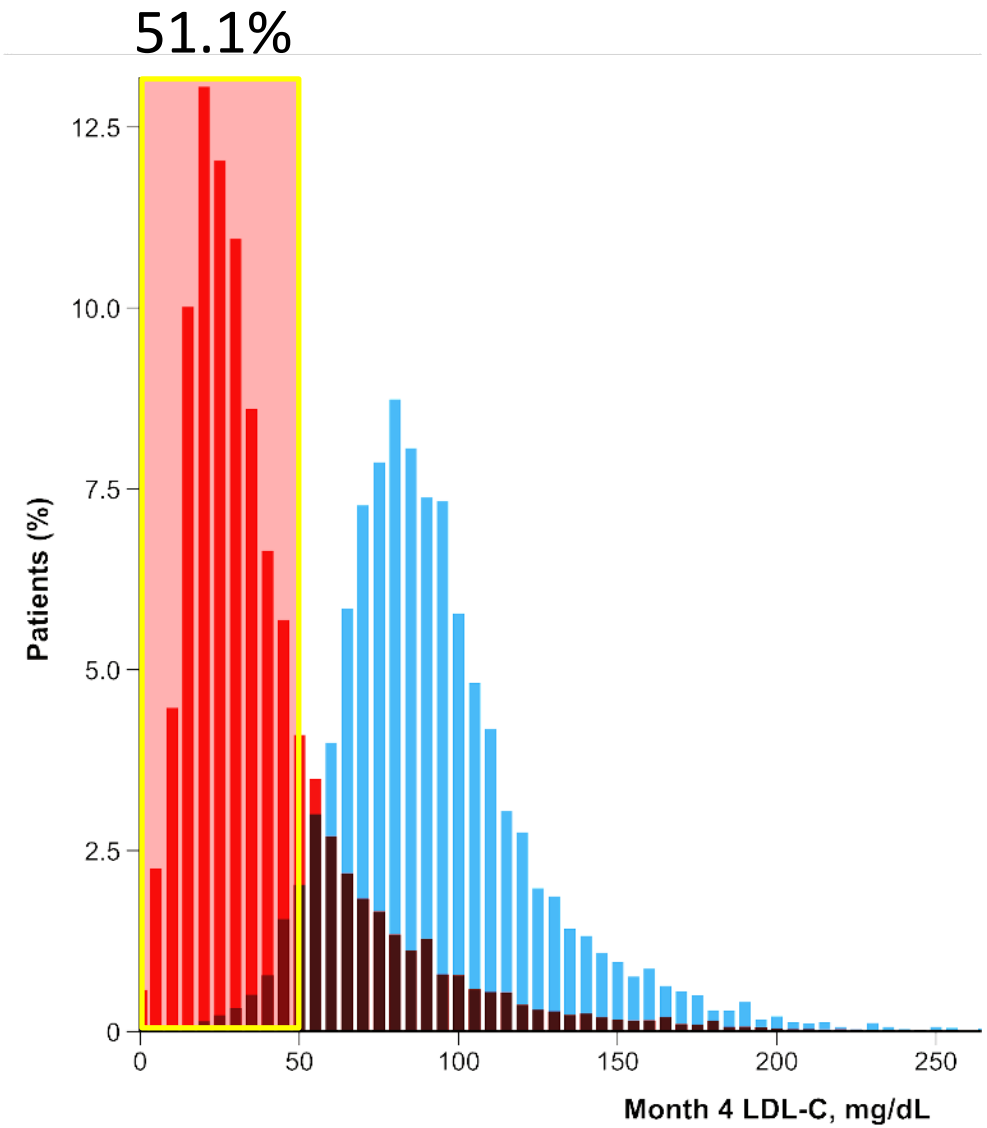
Is there a risk of ICH?

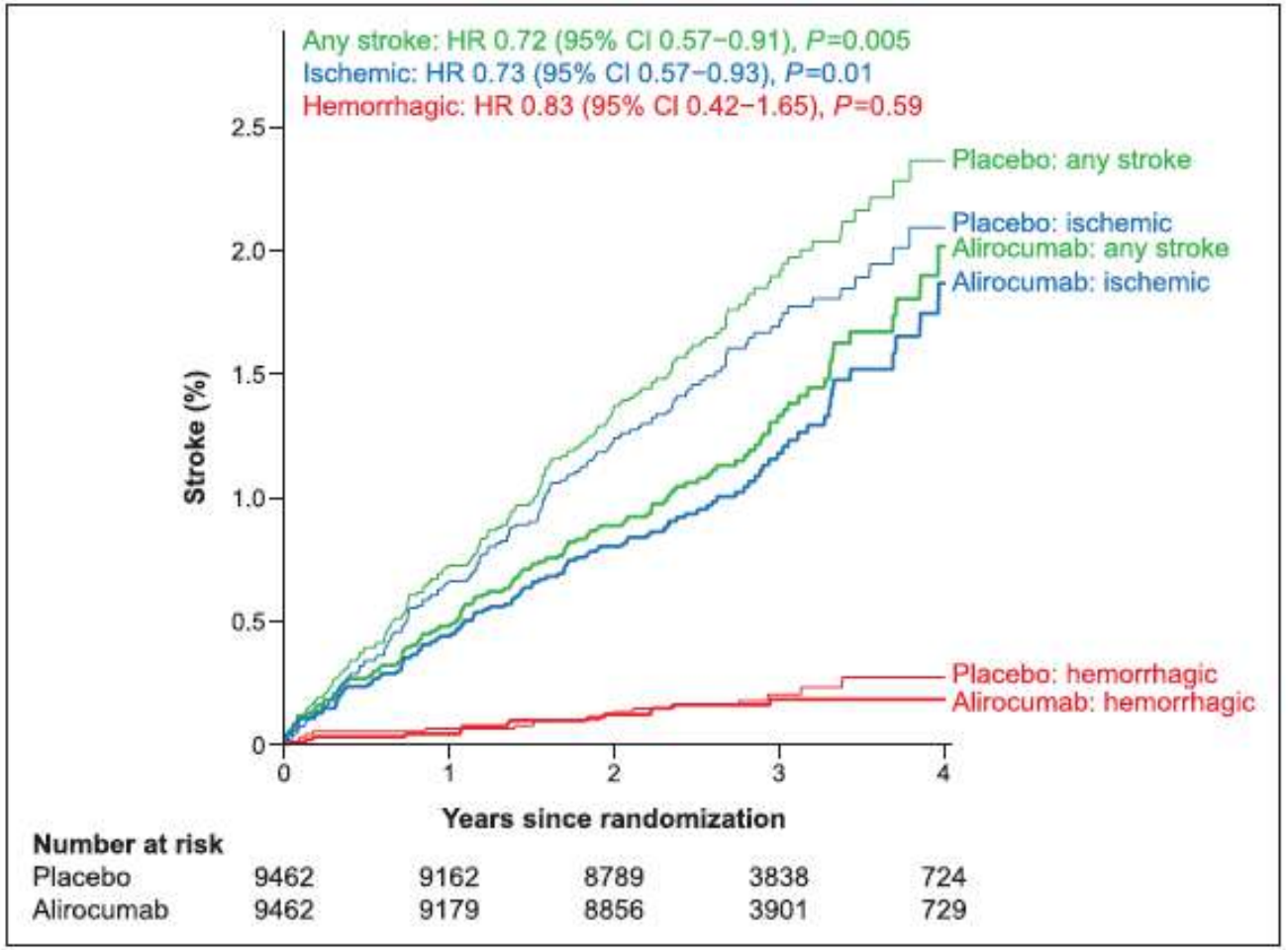
- *"The absolute risk of haemorrhagic stroke remained rare throughout the trials, and the absolute risk difference attributable to statin was low, with an estimated number needed to harm of 3333 for an average treatment length of 6.7 years."*

- *"The number needed to treat with statin to prevent 1 ischemic event over a period of 5 years is 49, so HS risk should not preclude statin use if clinically indicated."*

Bétrisey et al *J Am Heart As.* 2024

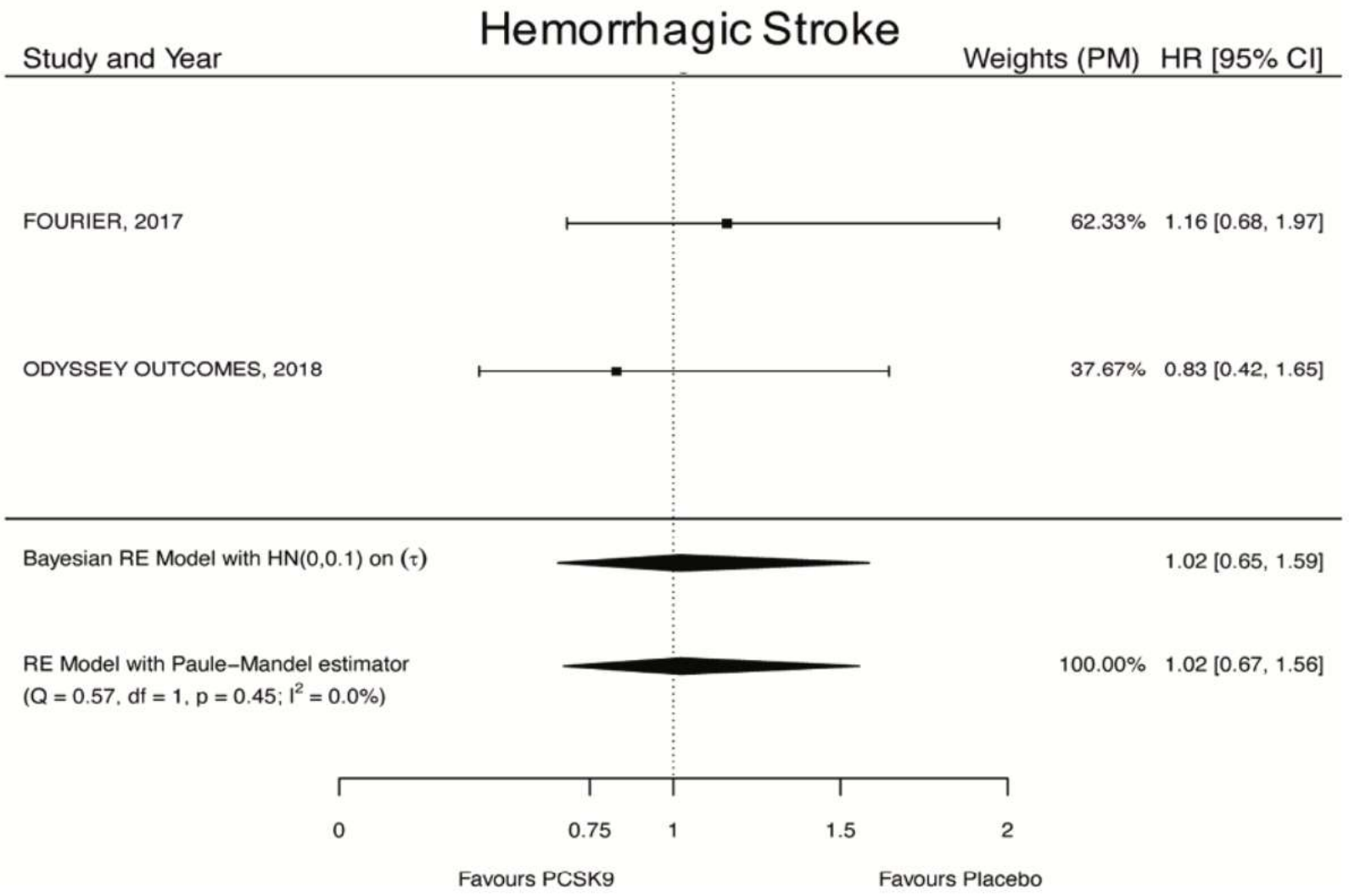
Is there a risk of ICH?





Jukema et al; Circulation. 2019

Is there a risk of ICH?

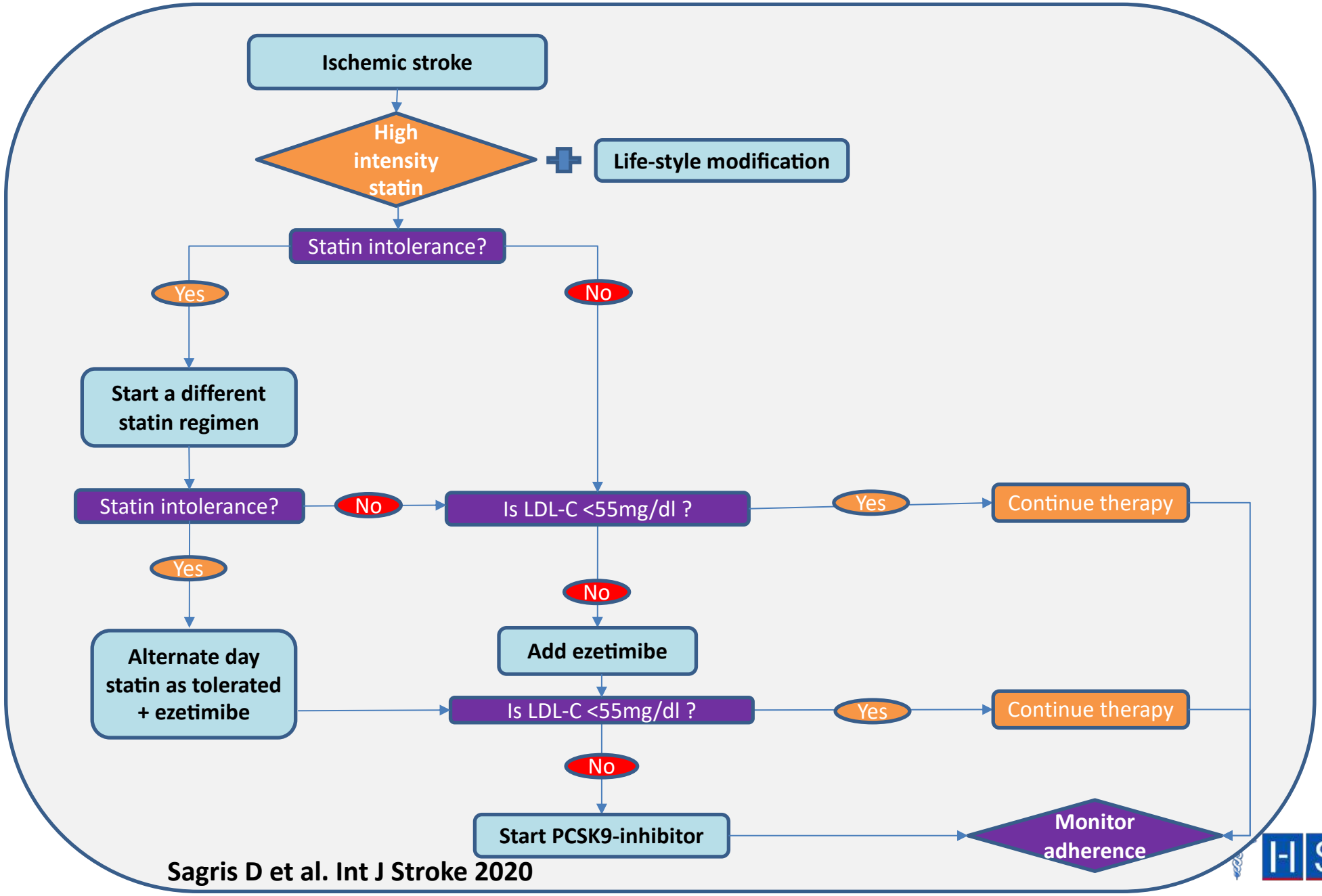


Sagris et al: European J int Medicine 2020

Patient with ischemic stroke

- ✓ **Πότε? → Από το νοσοκομείο**
- ✓ **Ποια? → Ισχυρή στατίνη (Ατορβα 40 ή Ροσου 20 +/- eze)**
- ✓ **Ποιος ο στόχος? → <55mg/dl + 50% μείωση**
- ✓ **Να φοβάμαι τις χαμηλές τιμές LDL? → Όχι!!!**

Step by step lipid lowering therapy in patients with ischemic stroke



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Ο Βαγγέλης

Stroke ward

Follow-up

Antithrombotic therapy

Lipid lowering therapy in ALL patients with stroke associated to CV risk factors

Rosu- 20 +ezetimibe 10mg

Reassess in 8 weeks if LDL-C <55mg/dl

Monitor adherence

Ezetimibe ± PCSK-9i

Diabetes Mellitus

Is the patient on metformin and/or Insulin?

HbA1c aim ≤ 7%

Atherosclerosis (Carotid, CAD, PAD)

CKD or HF

GLP-1 RA irrespective of HbA1c levels

SGLT-2i irrespective of HbA1c levels

CKD or HF

SGLT-2i irrespective of HbA1c levels or the presence of DM

Hypertension

Prior treatment if preexisting HTN

Aim <130/80 *

*Combination over single therapy

Sagris D, Ntaios G, Milionis H. *J Neurol Neurosurg Psychiatry, 2022*