Πρόγραμμα Μεταπτυχιακών Σπουδών ΕΚΠΑ
Καρδιομεταβολική Ιατρική
2024-2025

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

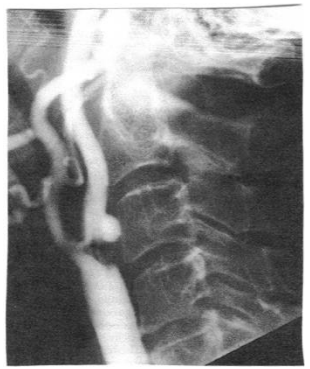
- Arterial hypertension 58%
- Diabetes 21%
- Coronary artery disease 19%
- Atrial fibrillation 18%
- Heart failure 7%

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

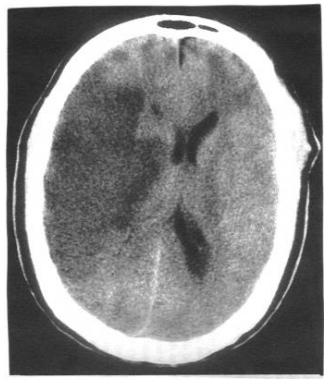
Source
IQVIA Medical Research Data (IMRD) 2018
Dataset includes all patients with a diagnosis of stroke on or before the 1st January 2018

Ischemic Stroke Classification based on etiology (TOAST criteria)

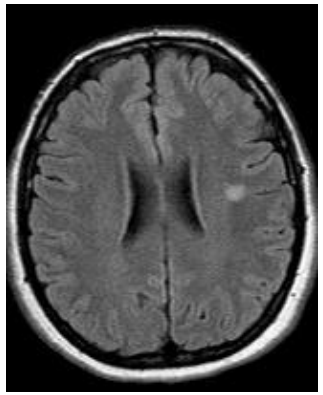
Atherosclerotic
15-25%



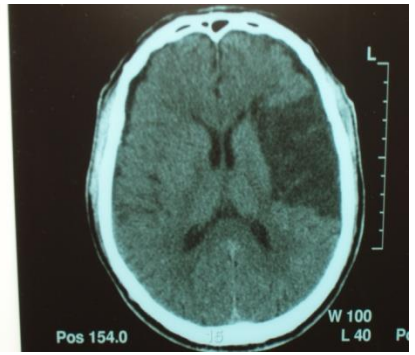
Cardioembolic
18-33%



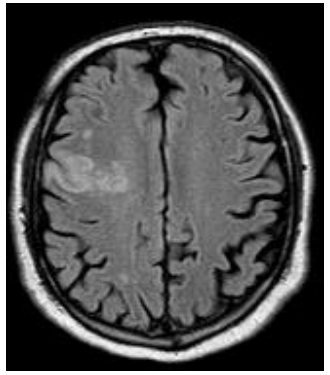
Lacunar
17-25%



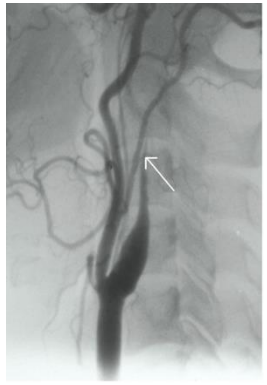
Cryptogenic
12-37%



E S U S



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



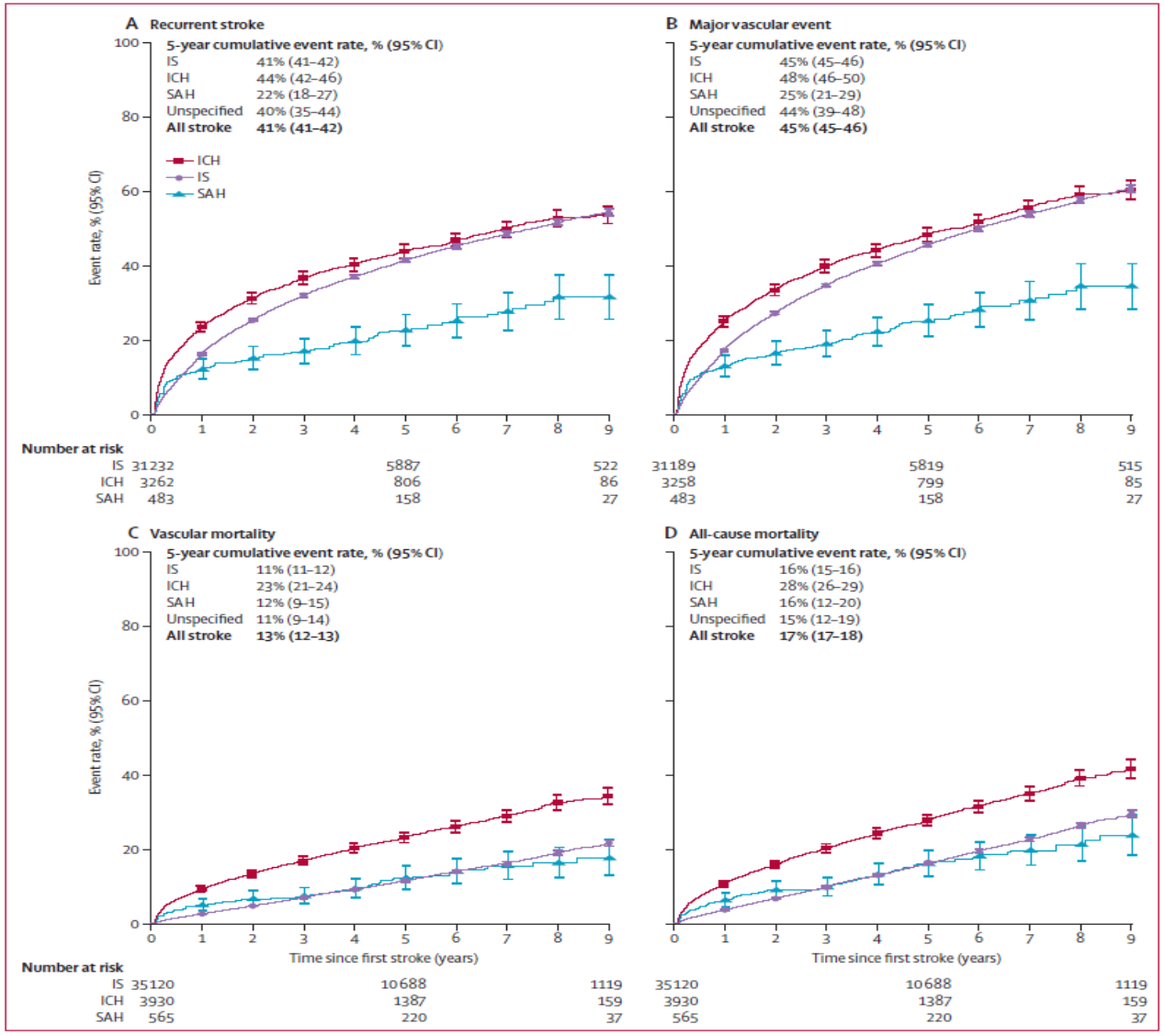
Αρχείο: "The Athens Stroke Data Bank"

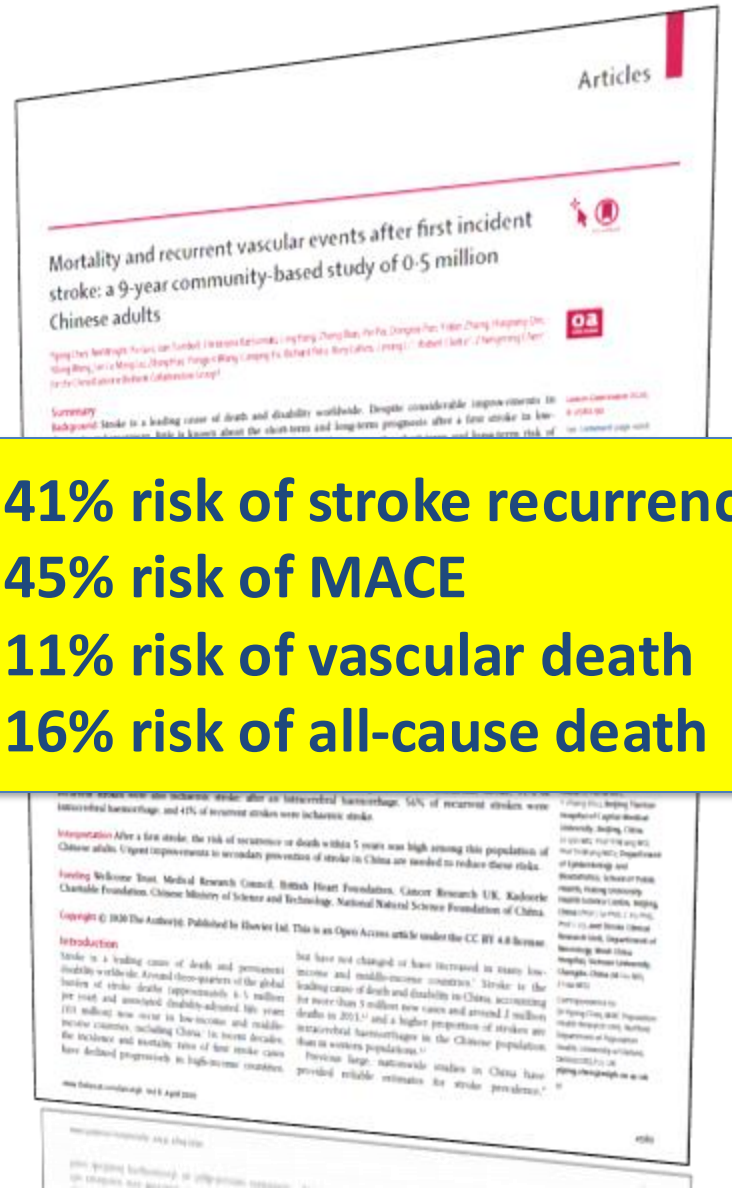
Patient with ischemic stroke

	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




Articles

Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0·5 million Chinese adults

- 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*

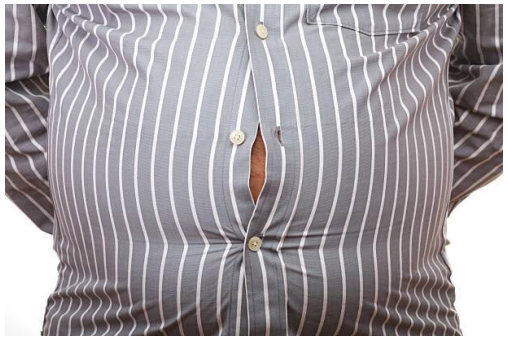
The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

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

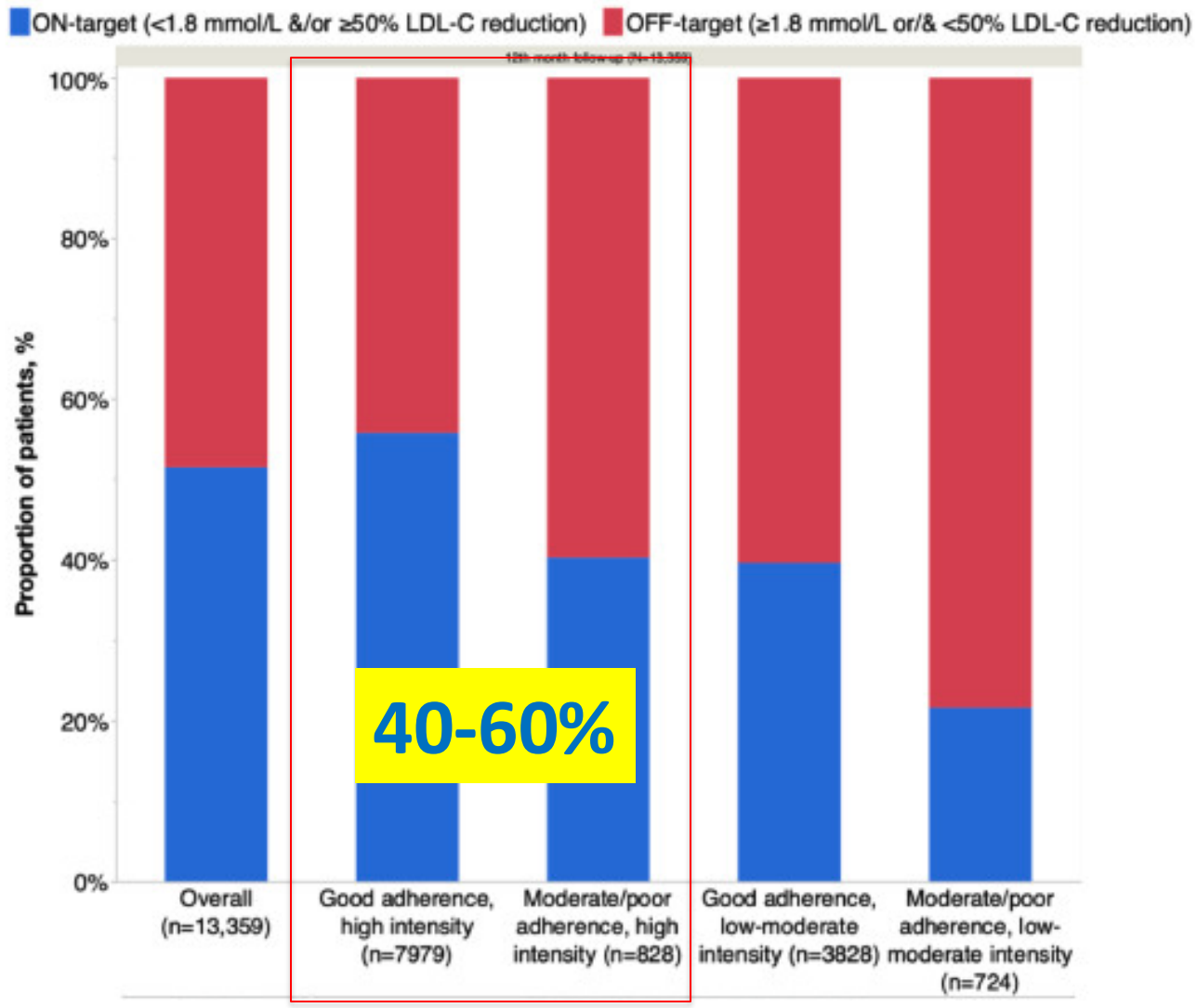
- 68 ετών
- N-STEMI + stent προ 7 ετίας
- Βαλσαρτάνη + HTZ
- Ασπιρινη
- Νεμπιβολόλη
- **Ατορβαστατίνη 40mg**



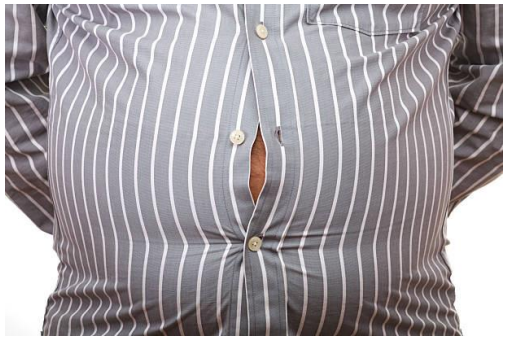
Δεξιά ημιπάρεση και ήπια αφασία εκπομπής

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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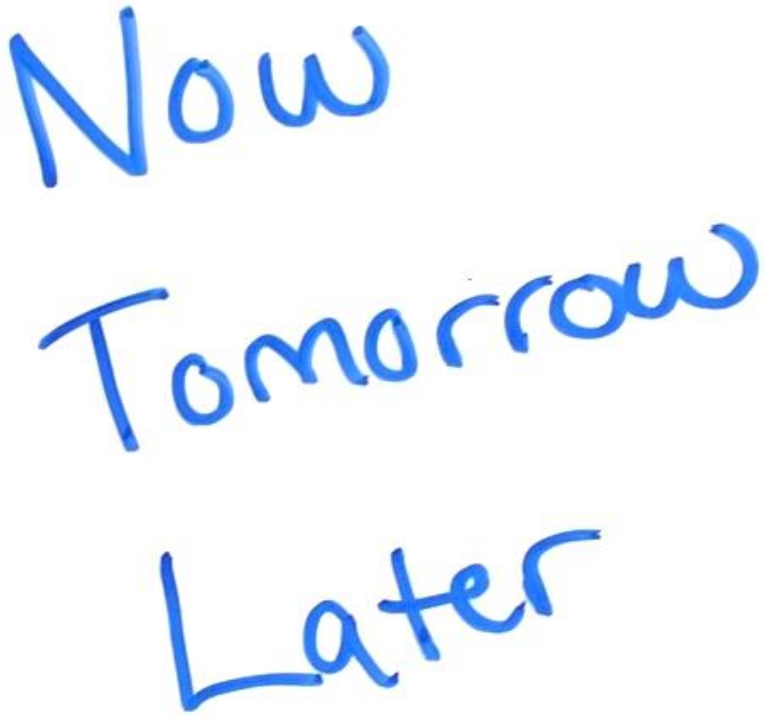
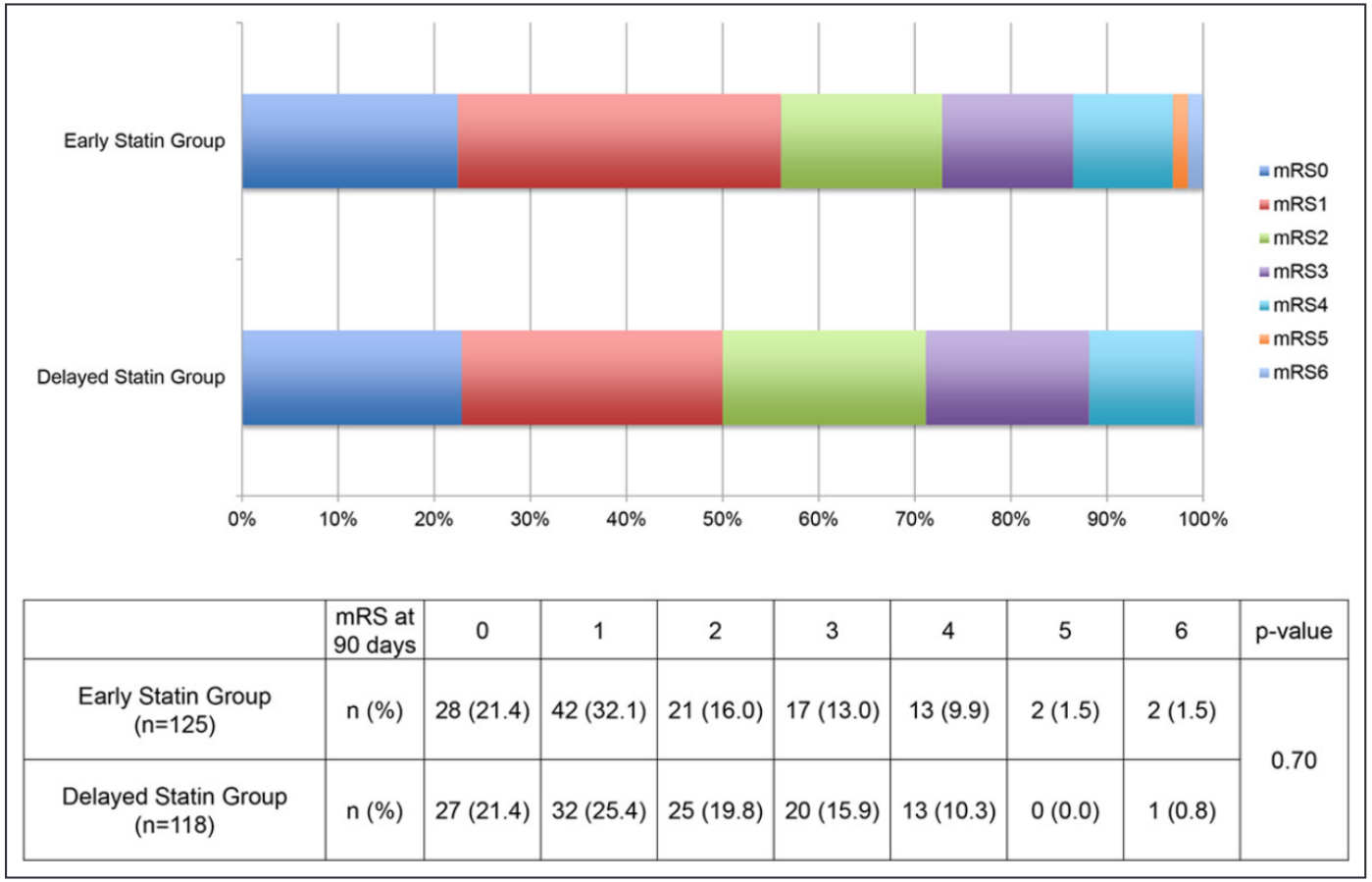
When to start?



When to start?

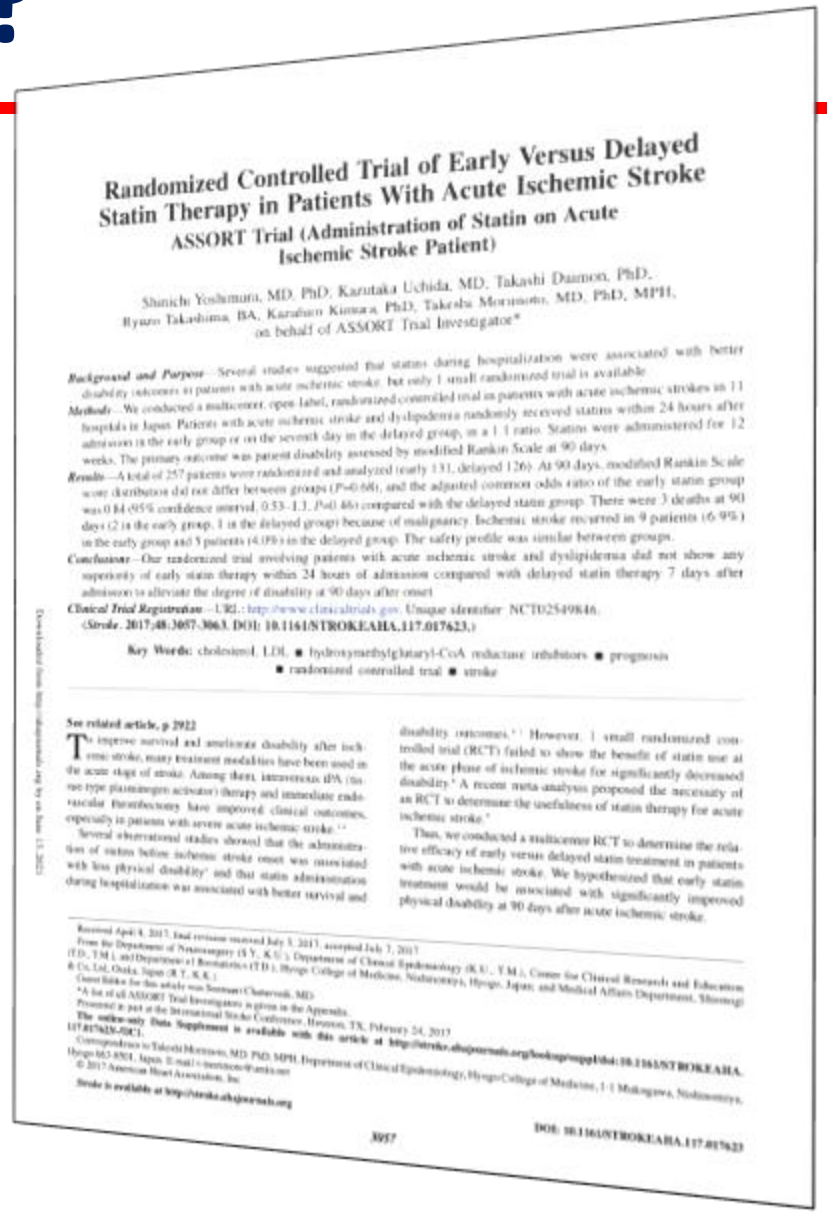
D1 Vs D7: Primary outcome mRS



	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



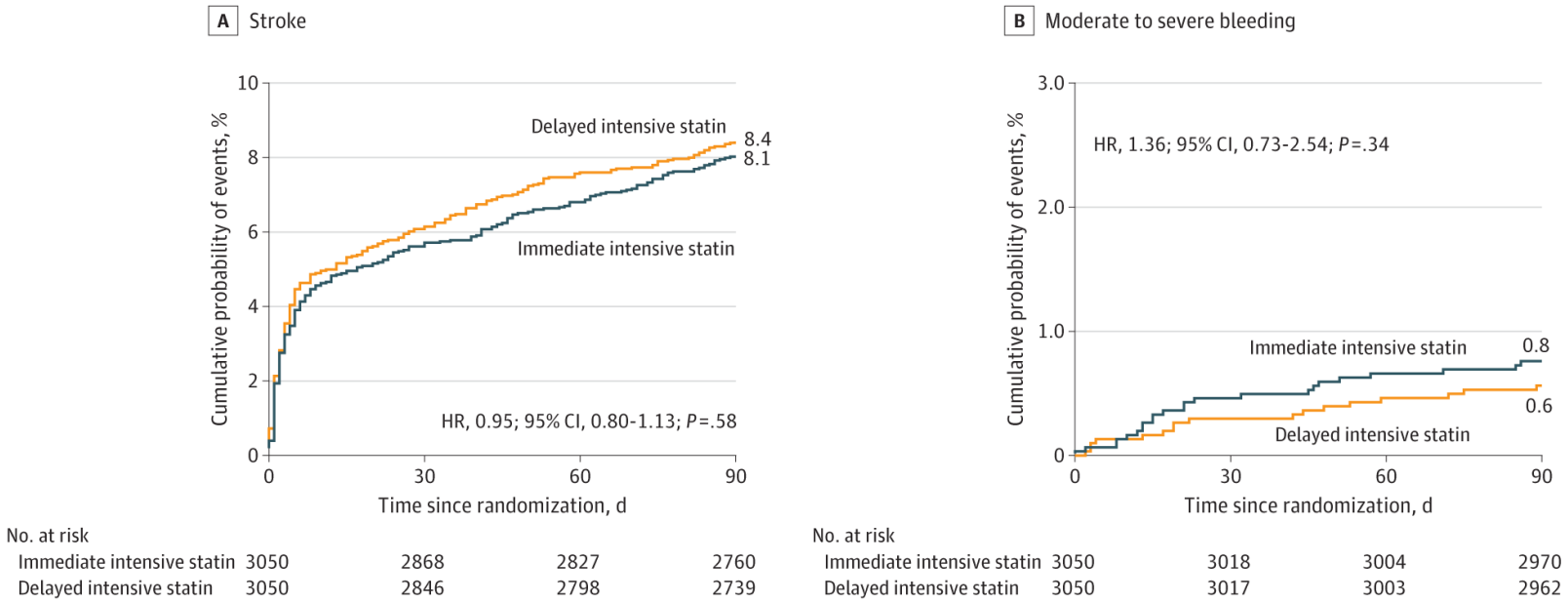
Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke

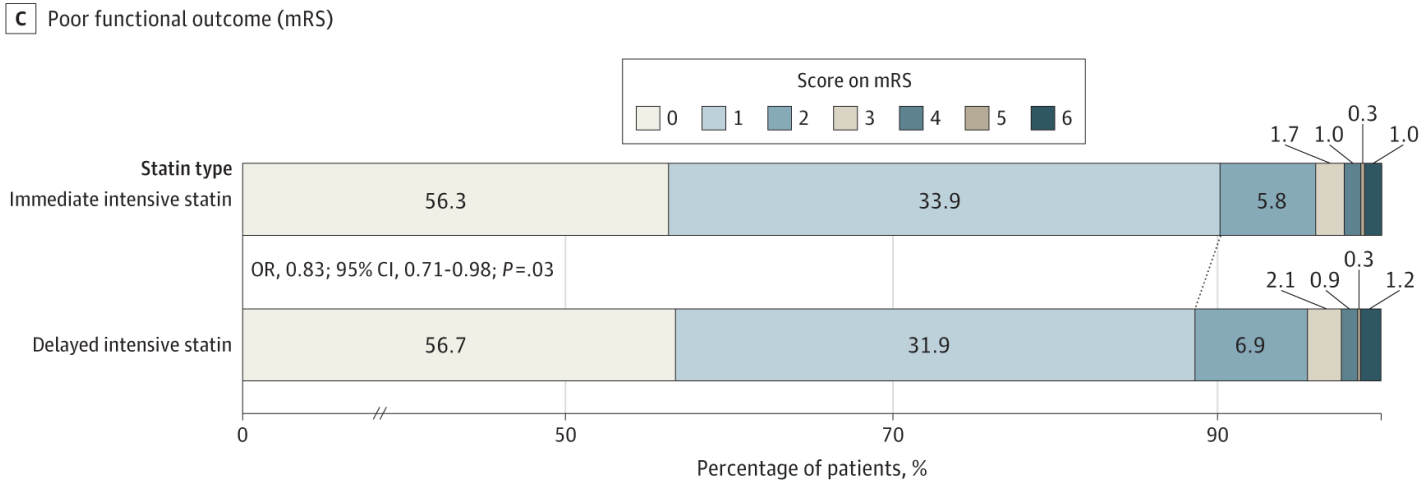
ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient)

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 Investigators*

Yoshimura et al; Stroke 2017

When to start?





- 6100 patients
- Age: 65 [57-71] years
- 3915 men [64.2%]
- Mild stroke or TIA
- 3050 assigned to each treatment group
- D1 Vs D4
- Primary: Stroke at 90d

INSPIRES trial / Gao et al; *JAMA Neurol.* 2024

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

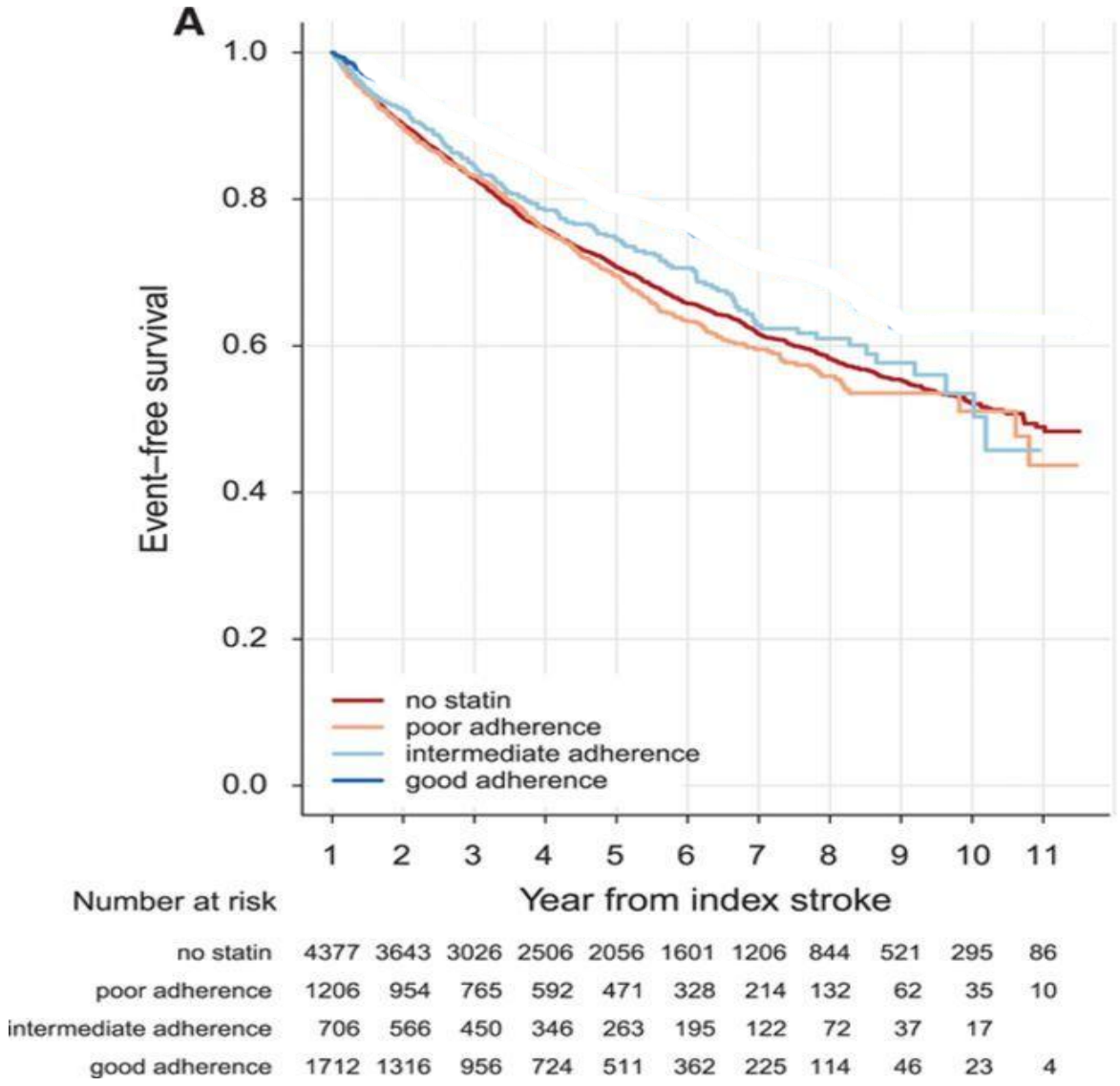
In-Hospital Initiation of Secondary Stroke Prevention Therapies Yields High Rates of Adherence at Follow-up

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



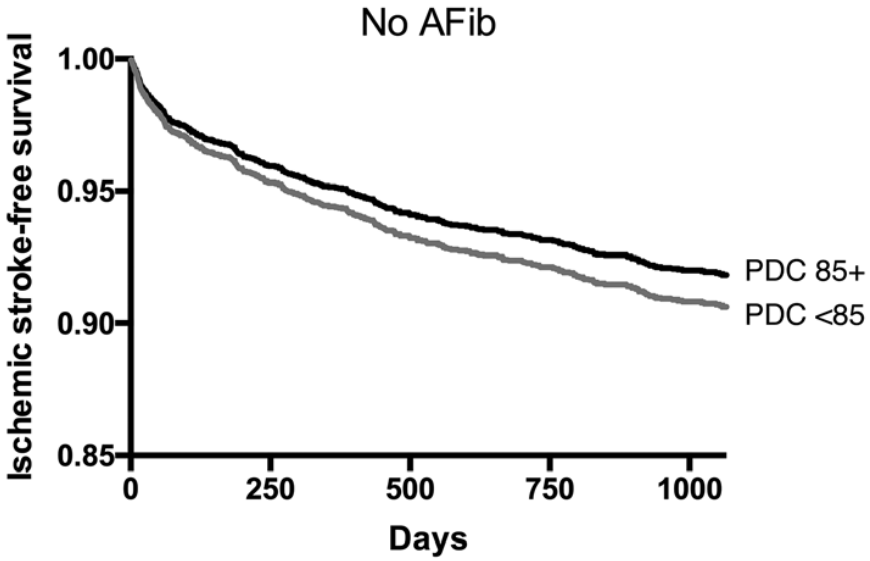
- **8001 acute ischemic stroke patients**
- **4.69±2.72 years**
- **2284 primary outcomes**

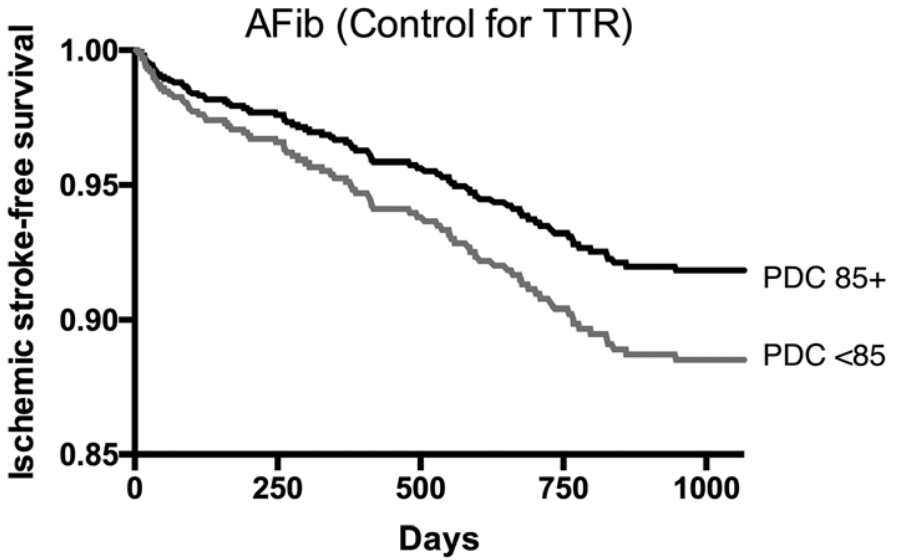
- **Adherence to statin treatment**
- **Statin intensity**

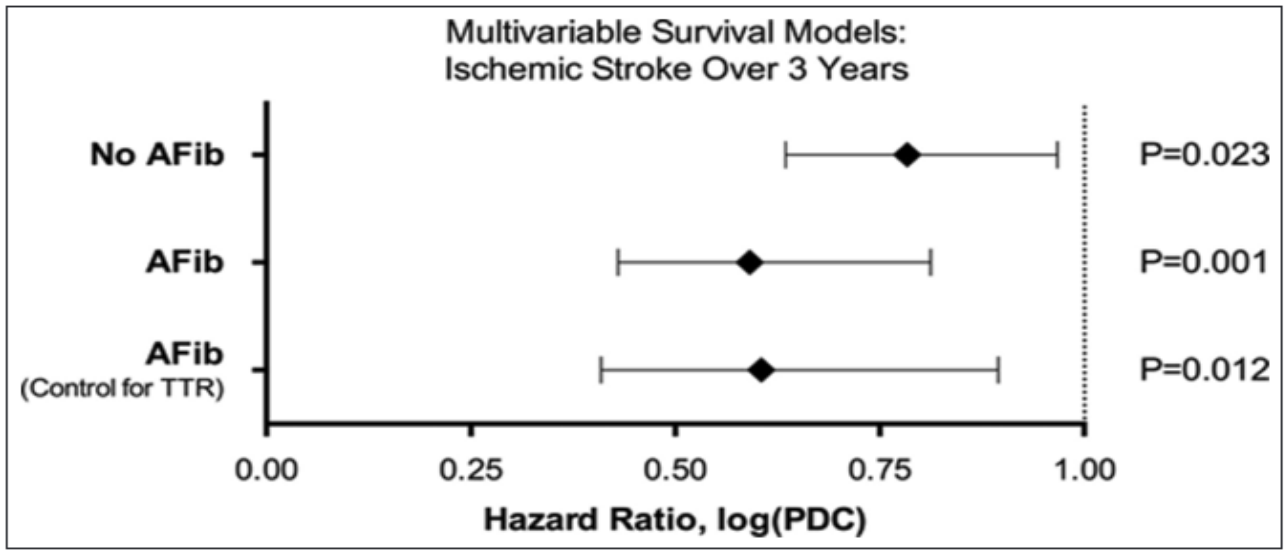
Adherence	Multivariate*	
	Adjusted HR (95% CI)	*P* Value
Adherence to statin		
No statin	Reference	
Poor	1.07 (0.95–1.20)	0.241
Intermediate adherence	0.93 (0.79–1.09)	0.383
Good adherence	0.74 (0.64–0.84)	<0.001

Kim et al. Stroke 2017

Adherence to treatment



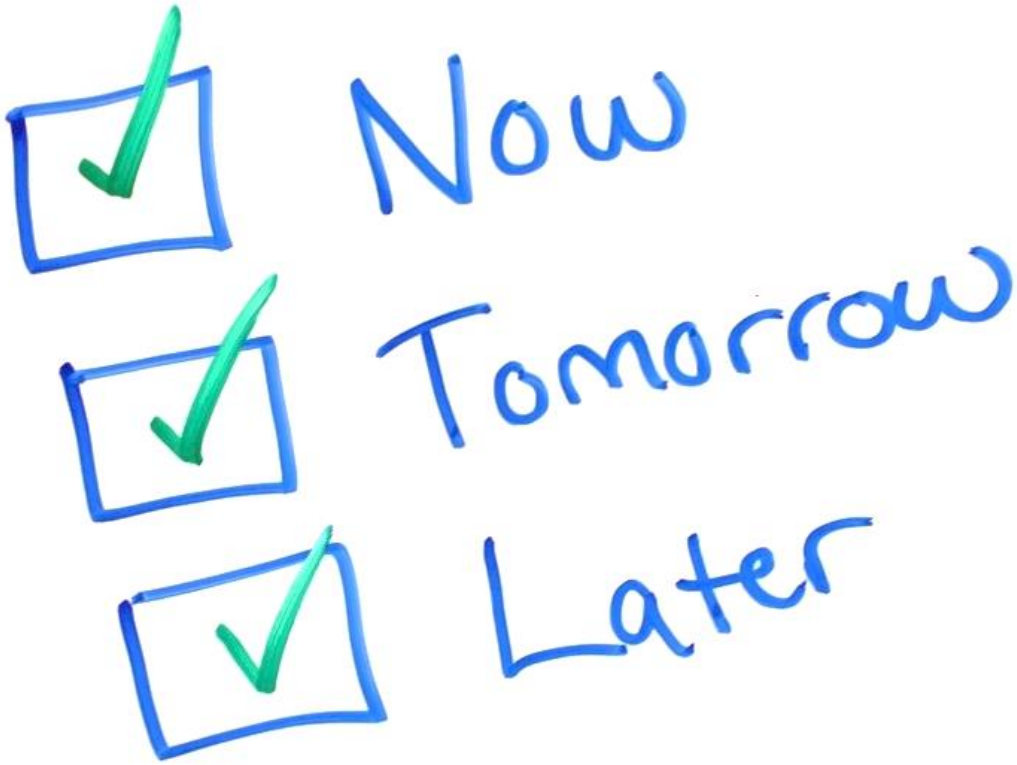




Higher adherence to statin therapy has been shown to be an independent predictor of stroke-free survival

Flint et al; Stroke 2017

When to start?



Better adherence

less future outcomes

Patient with ischemic stroke

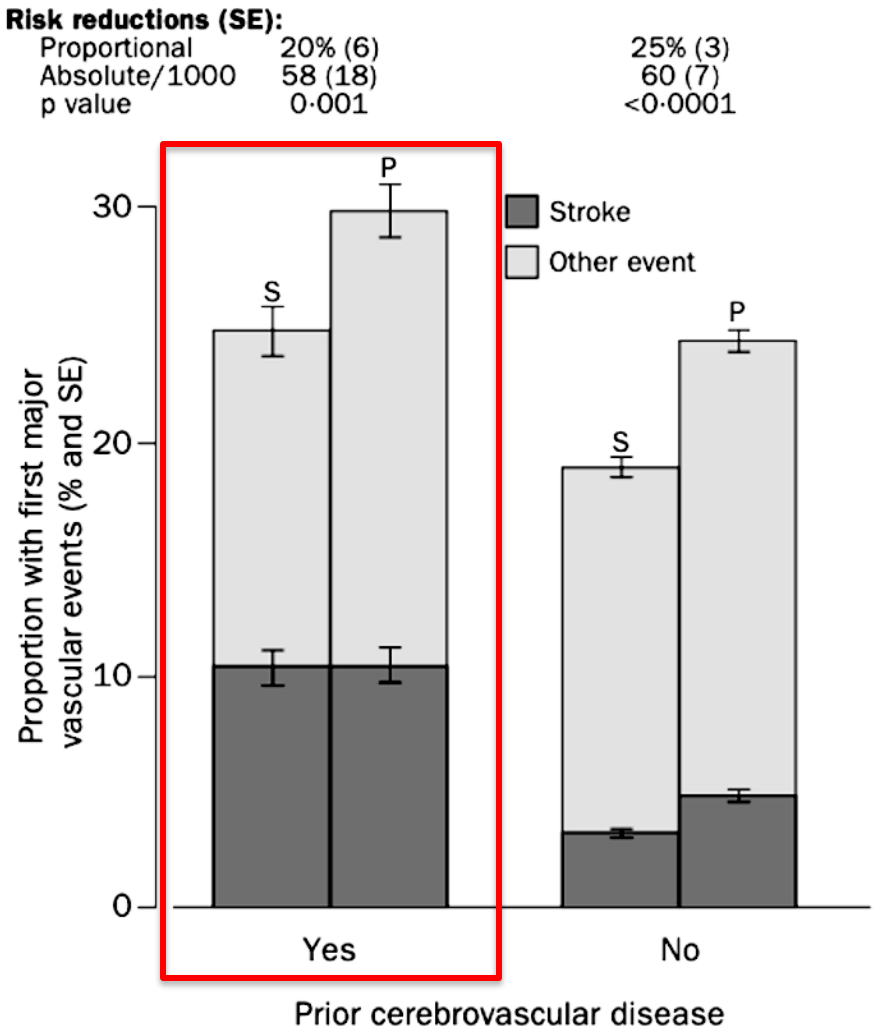
- ✓ **Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή**
- ✓ **Ποια υπολιπιδαιμική αγωγή πρέπει να χορηγήσω στον ασθενή με ισχαιμικό εγκεφαλικό επεισόδιο?**
- ✓ **Ποιος είναι ο στόχος μου ?**
- ✓ **Να φοβάμαι τις χαμηλές τιμές LDL?**

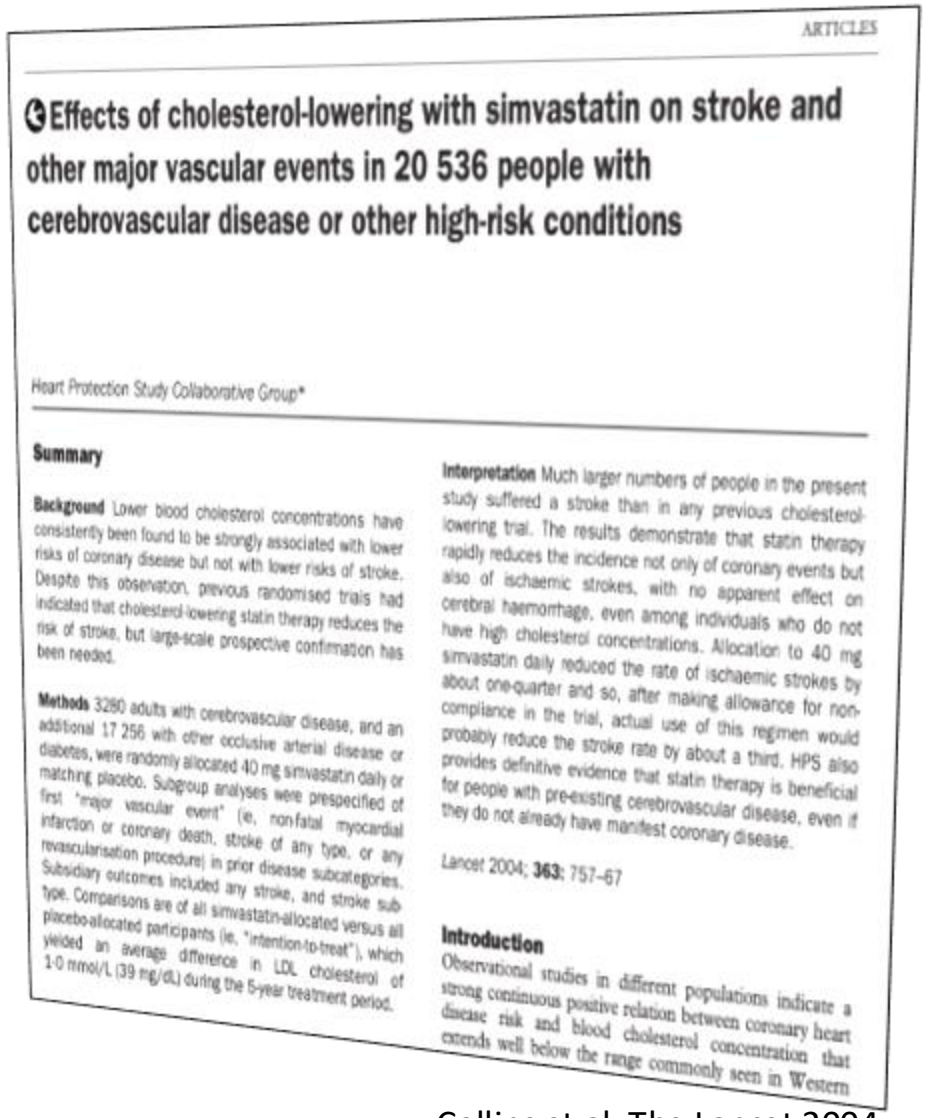
Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol

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

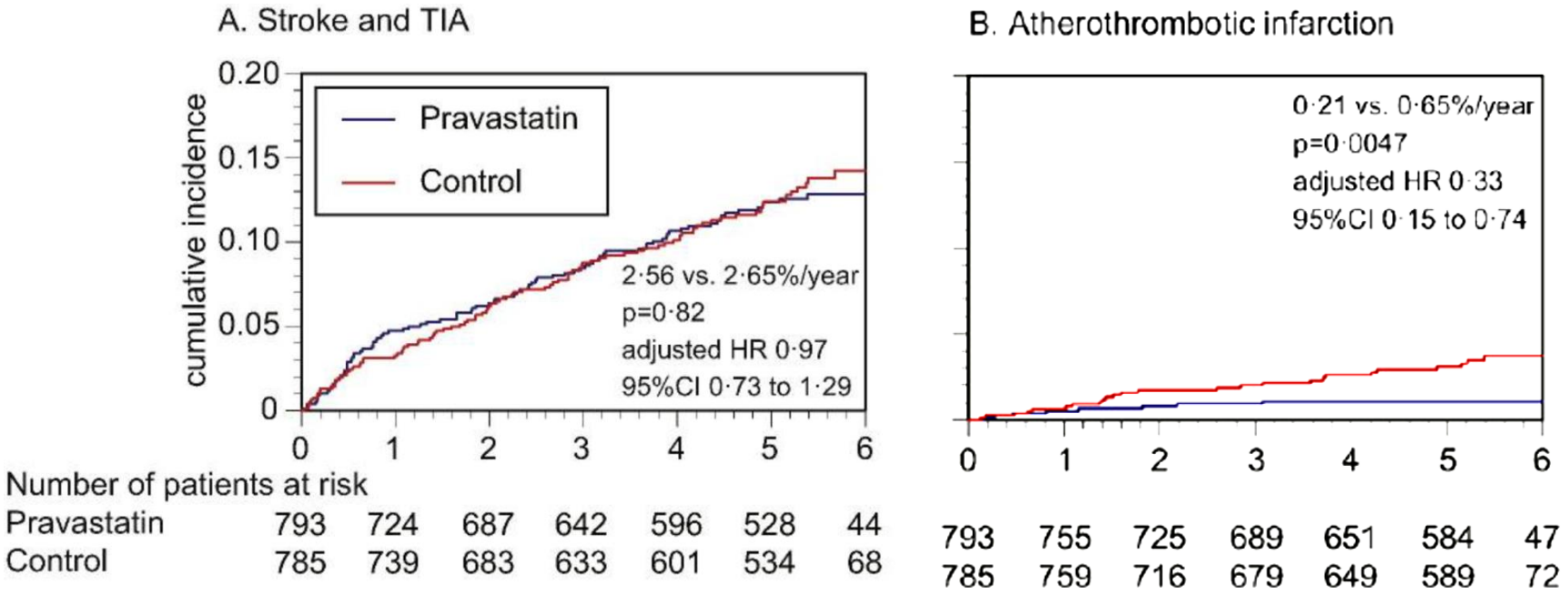
SPARCL: high-dose atorvastatin reduced stroke risk and CV events

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)

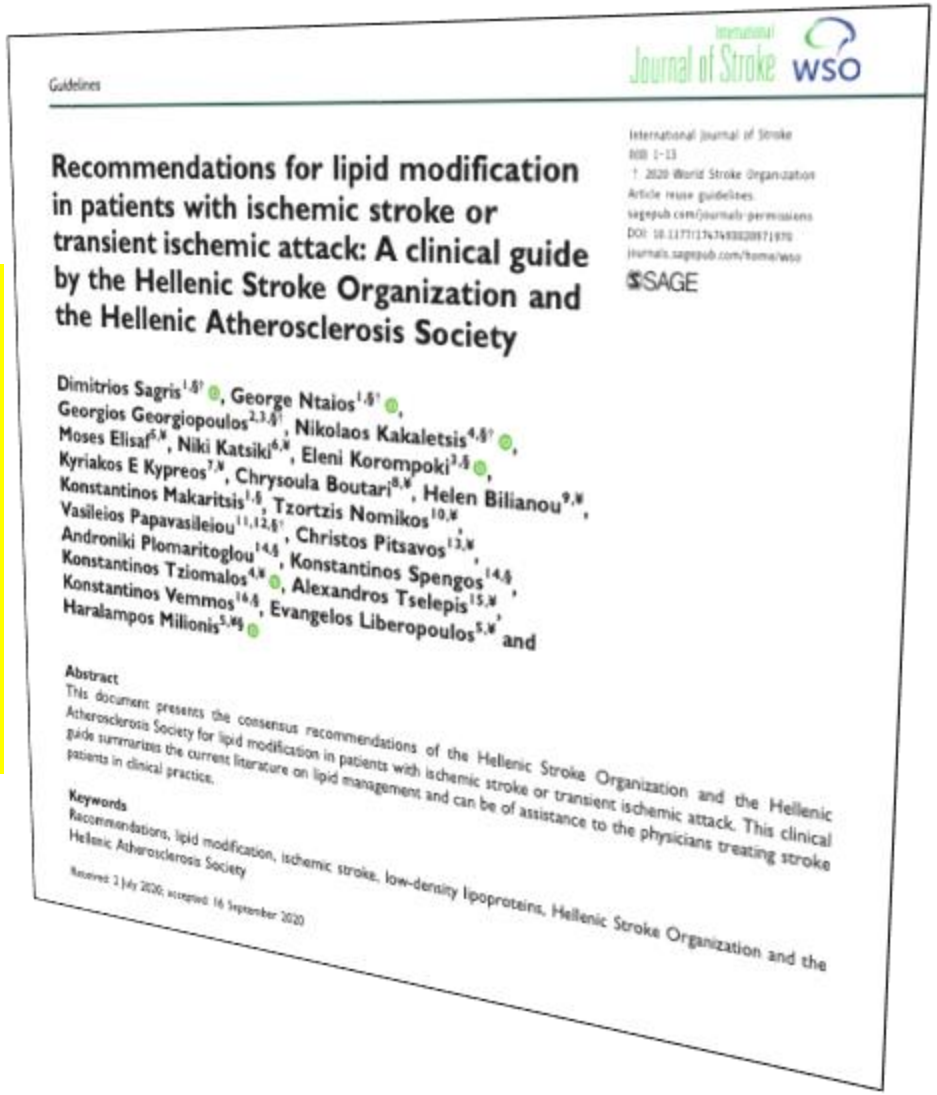
"…patients aged 45 to 80 years with a history of non-cardioembolic ischemic stroke …"

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).



Guidelines

International Journal of Stroke WSO

Recommendations for lipid modification in patients with ischemic stroke or transient ischemic attack: A clinical guide by the Hellenic Stroke Organization and the Hellenic Atherosclerosis Society

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Abstract

This document presents the consensus recommendations of the Hellenic Stroke Organization and the Hellenic Atherosclerosis Society for lipid modification in patients with ischemic stroke or transient ischemic attack. This clinical guide summarizes the current literature on lipid management and can be of assistance to the physicians treating stroke patients in clinical practice.

Keywords

Recommendations, lipid modification, ischemic stroke, low-density lipoproteins, Hellenic Stroke Organization and the Hellenic Atherosclerosis Society

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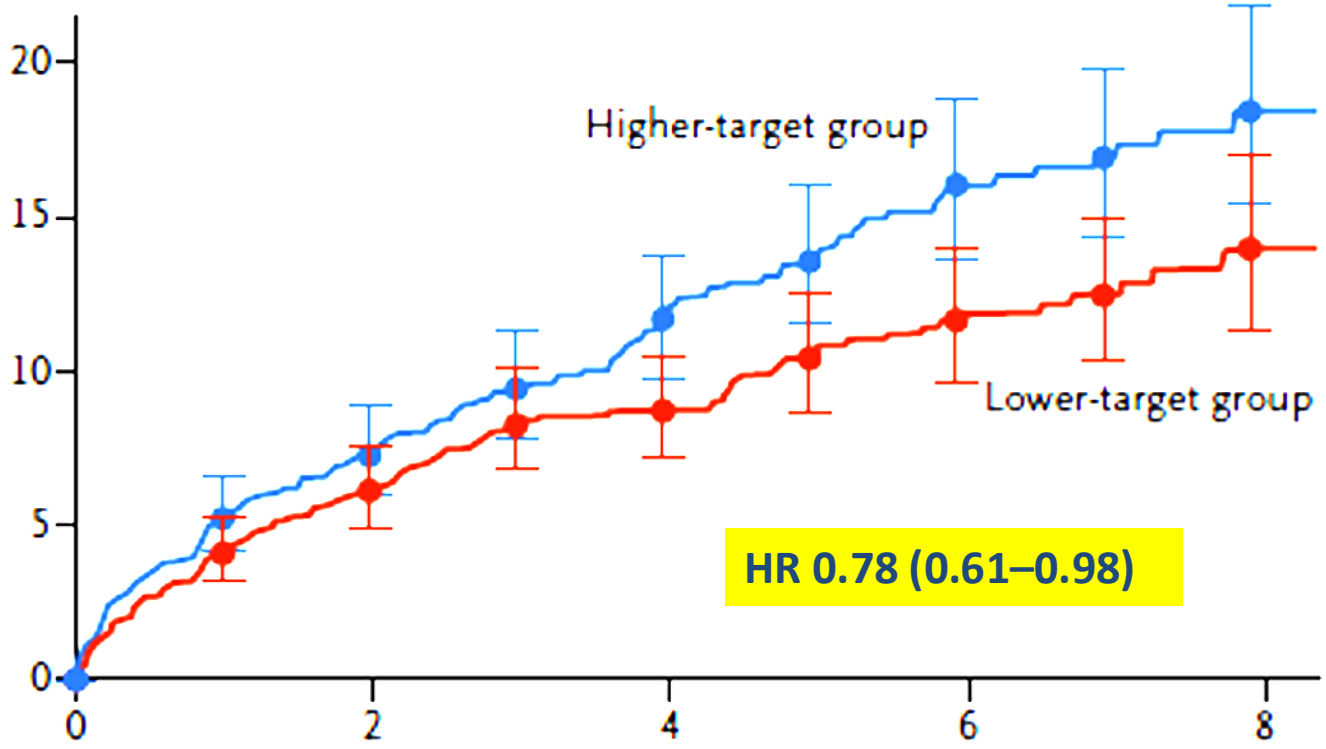
Sagris D et al. Int J Stroke 2020

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

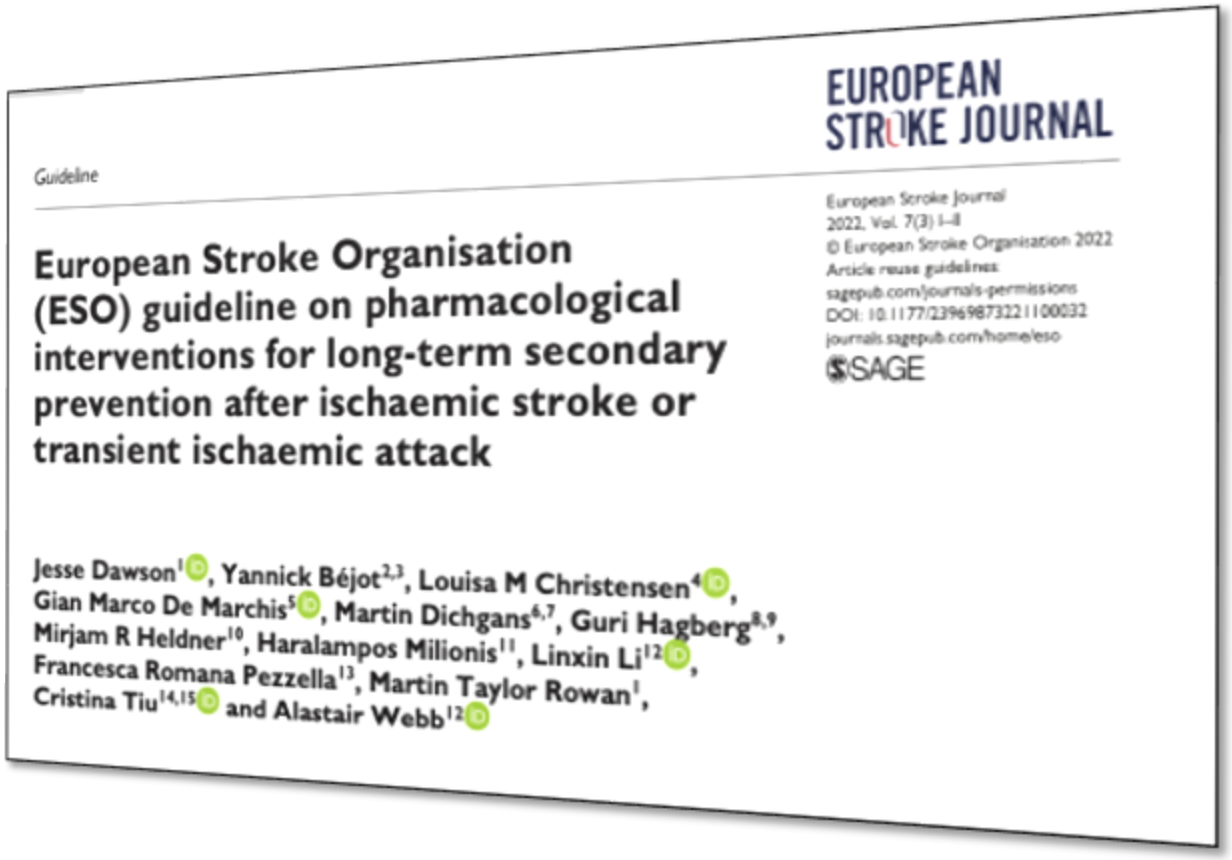
"…atherosclerotic disease that included stenosis of an extracranial or intracranial cerebral artery, ipsilateral or contralateral to the region of imputed brain ischemia…"

Amarenco et al ; n engl j med, 2019

LDL cholesterol treatment goals

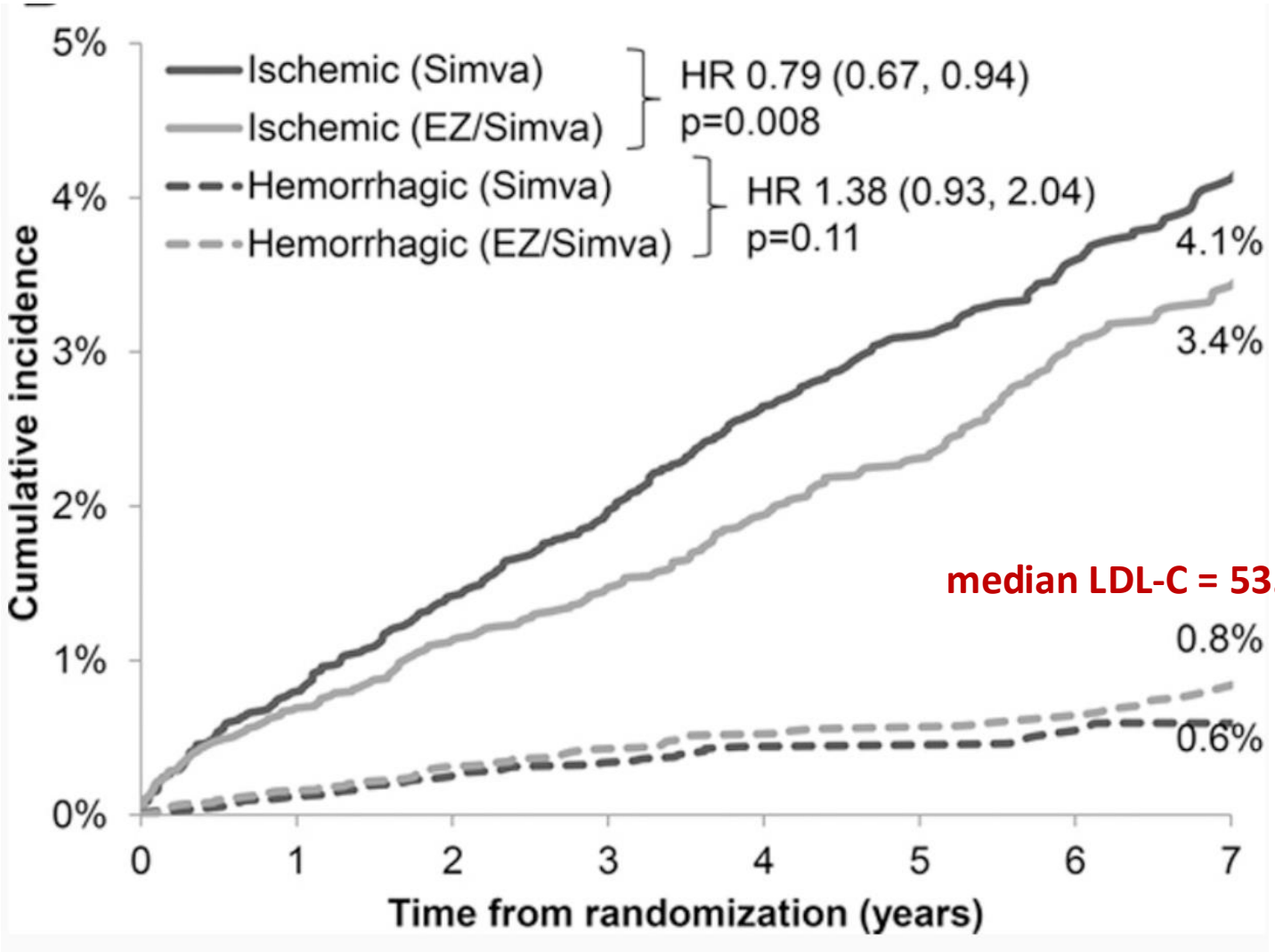
Evidence-based recommendation
In people with ischaemic stroke or TIA, we recommend aiming for an LDL cholesterol level of <1.8 mmol/l (70 mg/dl) to reduce the risk of major cardiovascular events.

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

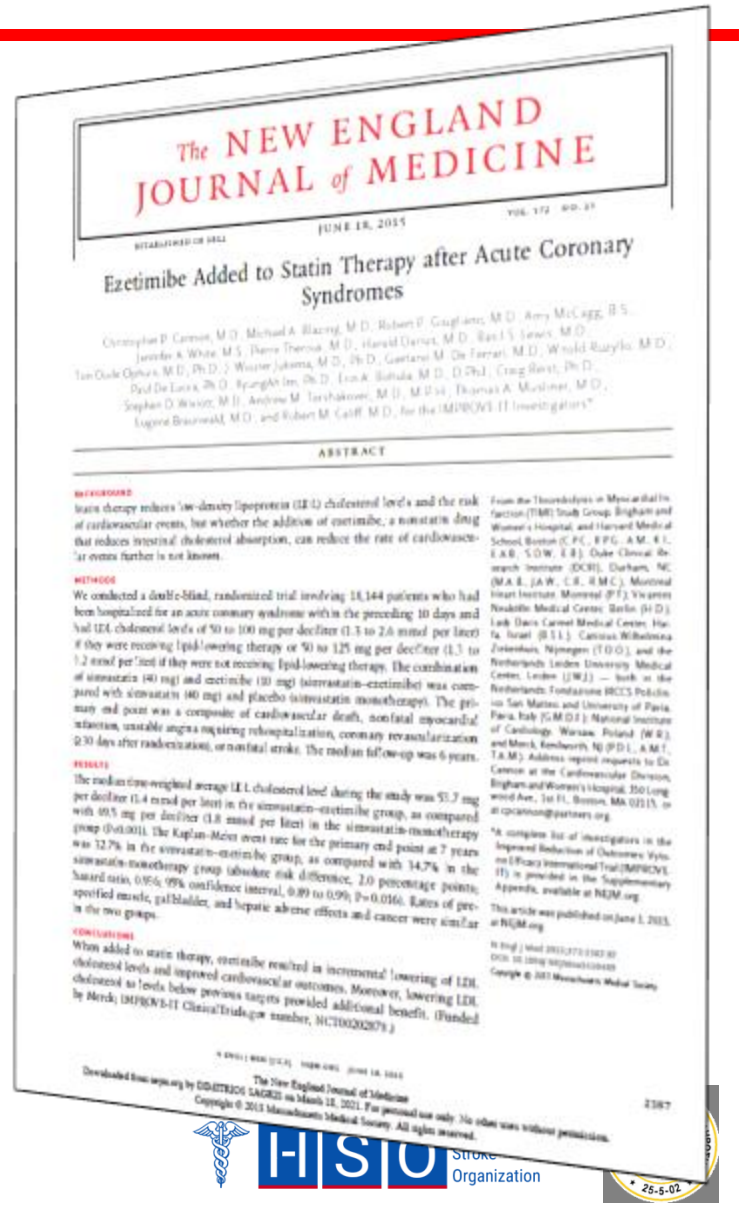


Γιατί μόνο <70?

LDL cholesterol treatment goals



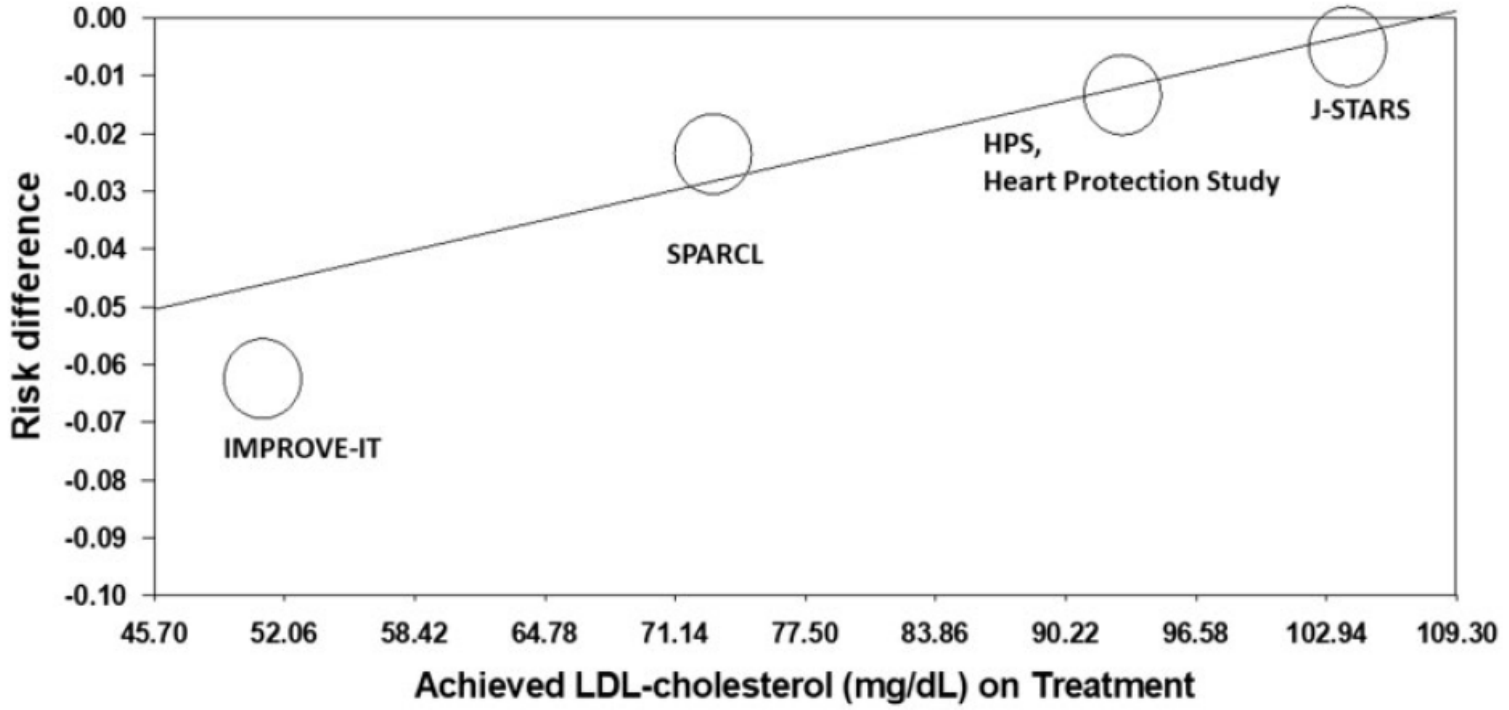
median LDL-C = 53.7 mg/dl



Bohula et al; Circulation 2017

Secondary stroke prevention: the lower, the better

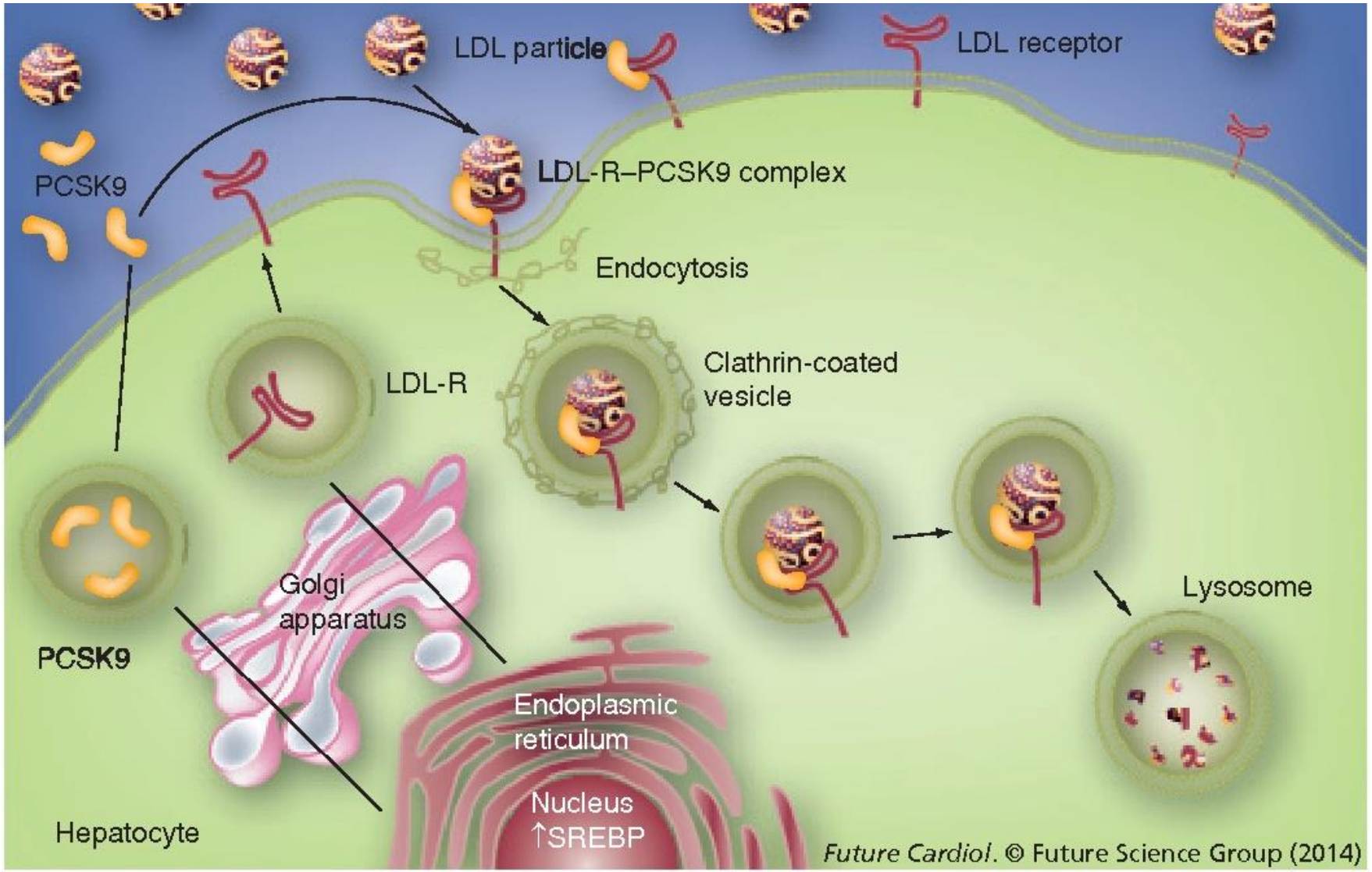
38mg/dl LDL reduction → 21% ↓Stroke reduction



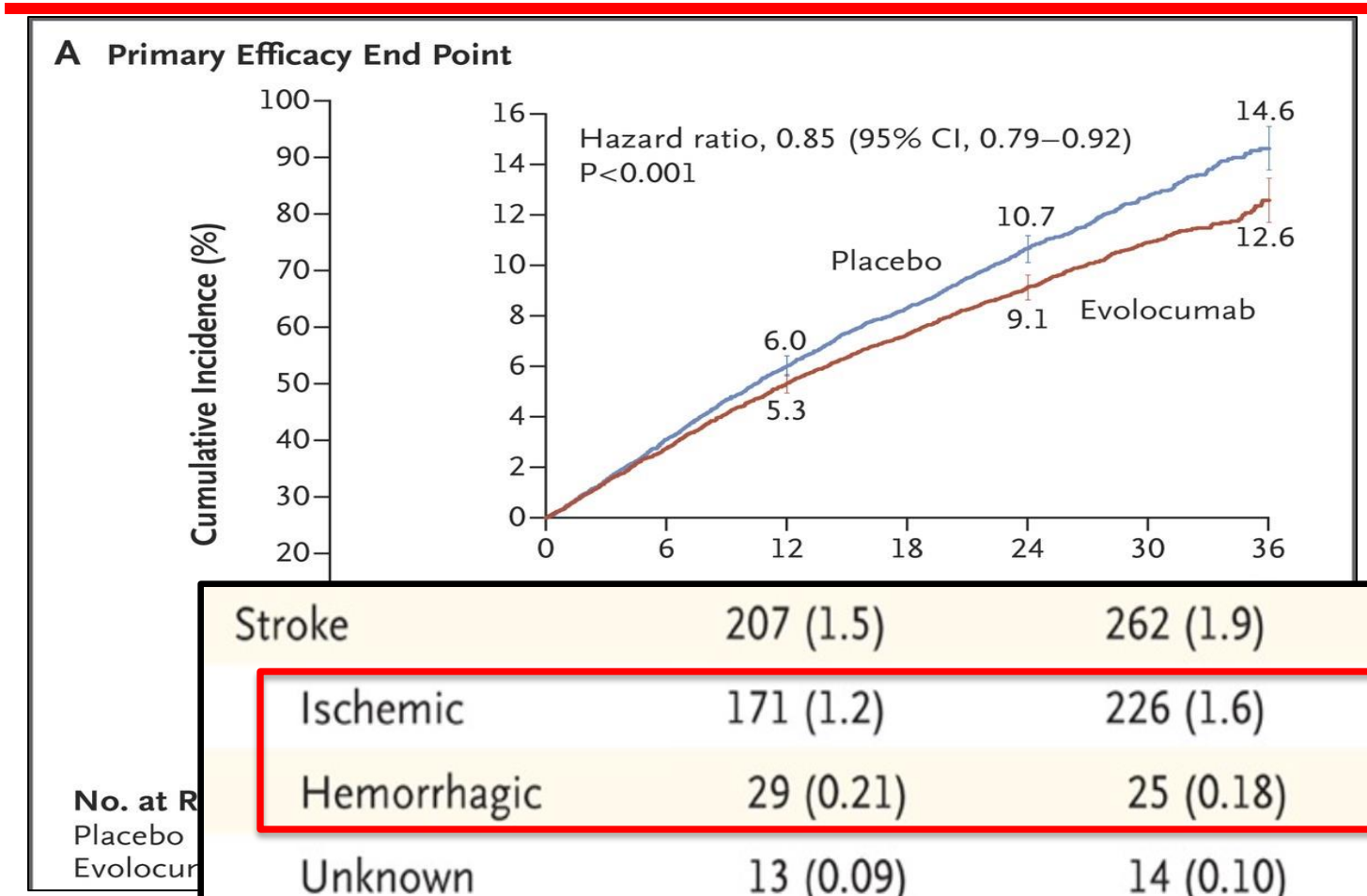

Statin-based therapy for primary and secondary prevention of ischemic stroke: A meta-analysis and critical overview

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

Proprotein convertase subtilisin/kexin type 9 (PCSK9)



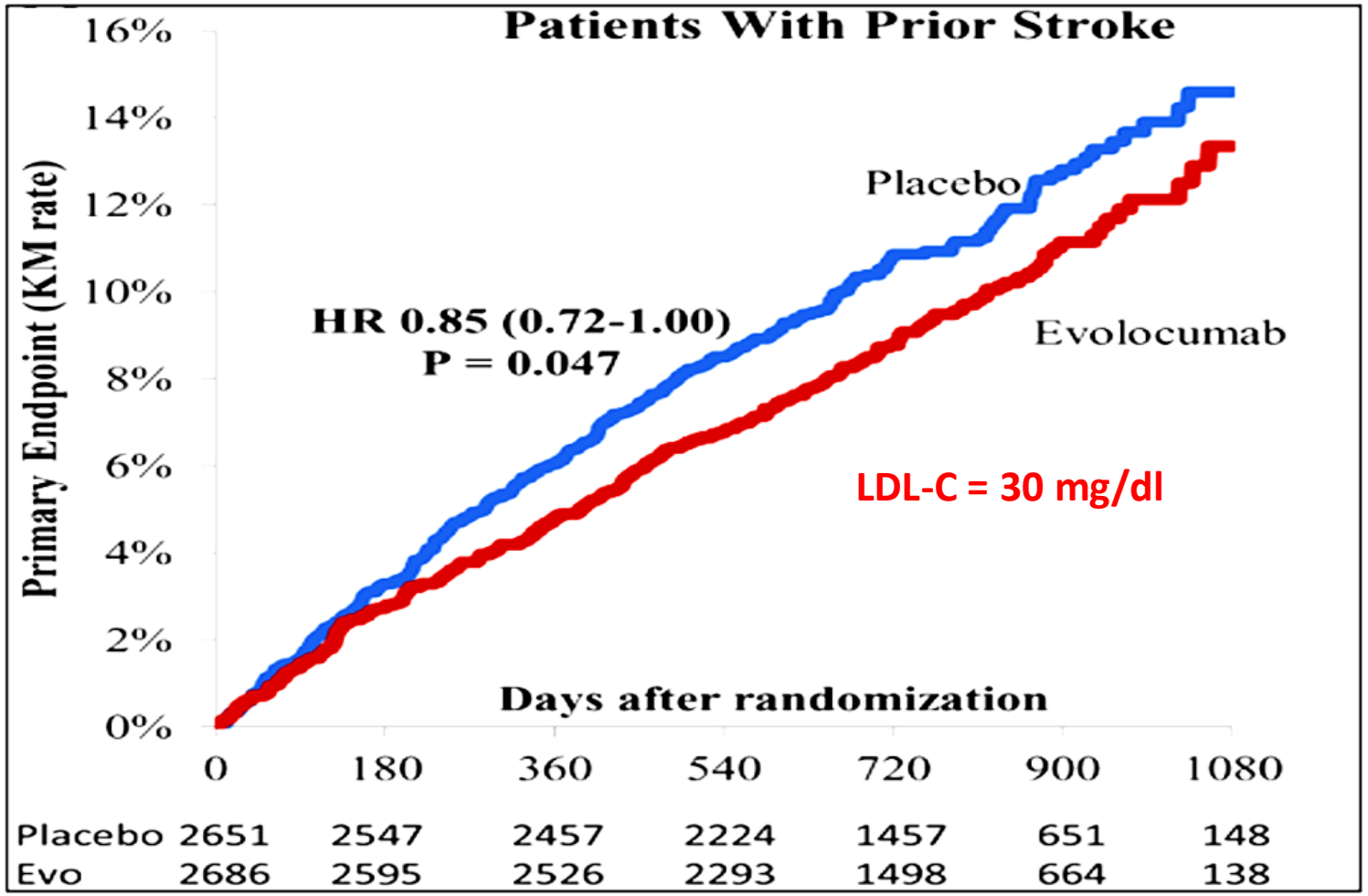
FOURIER (evolocumab)



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

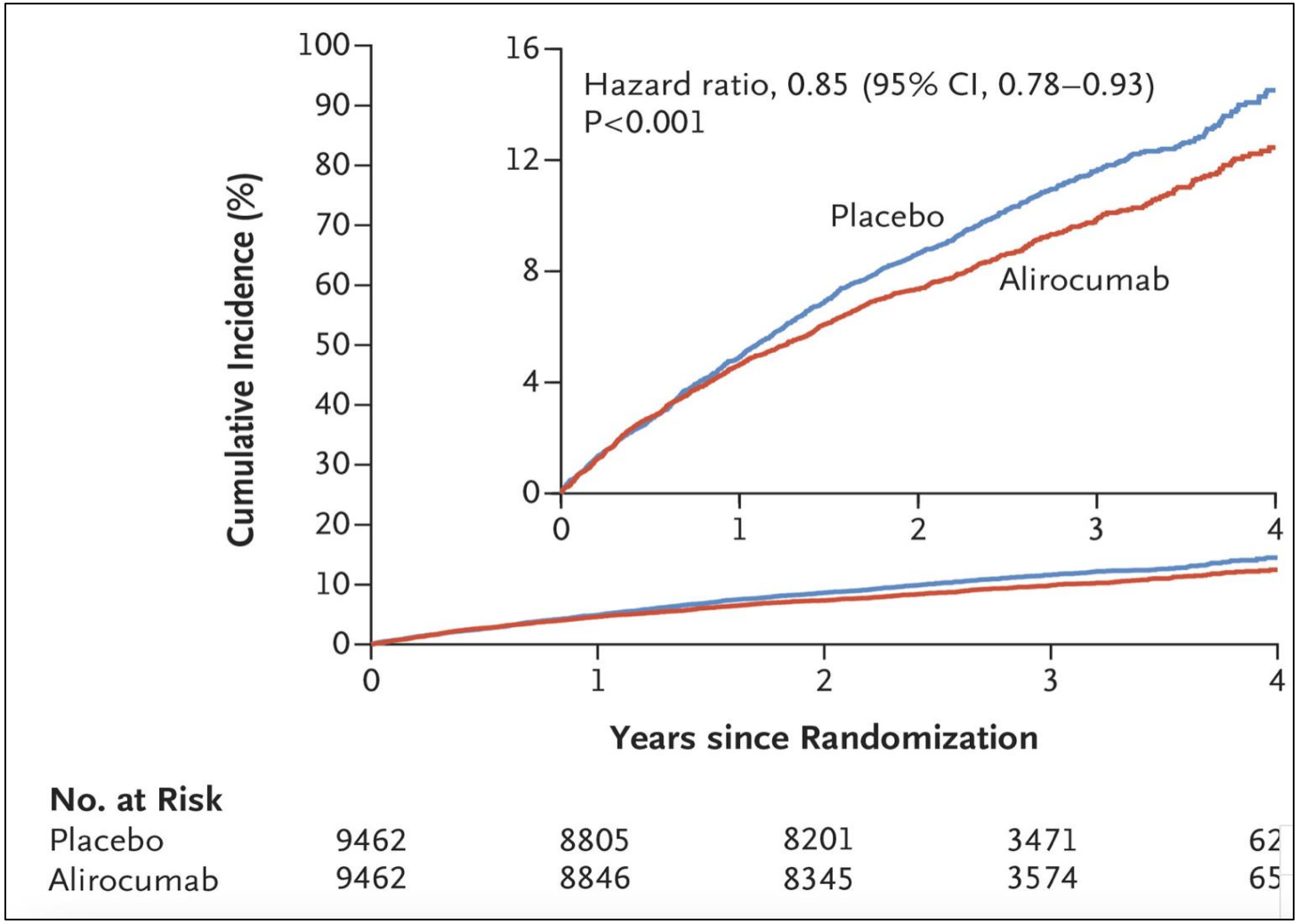
MAY 4, 2017

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

ABSTRACT

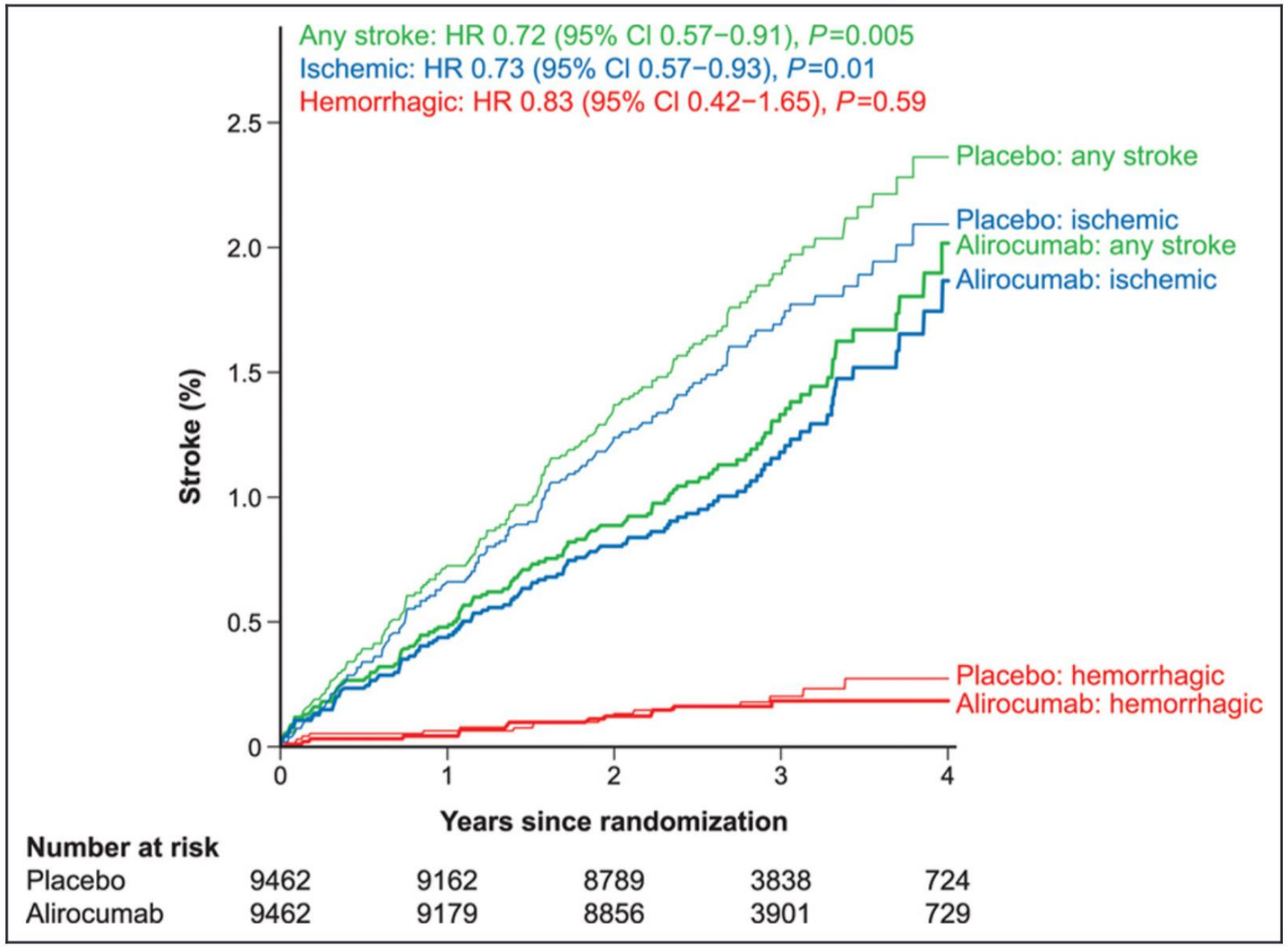
Giugliano et al; Stroke 2020

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

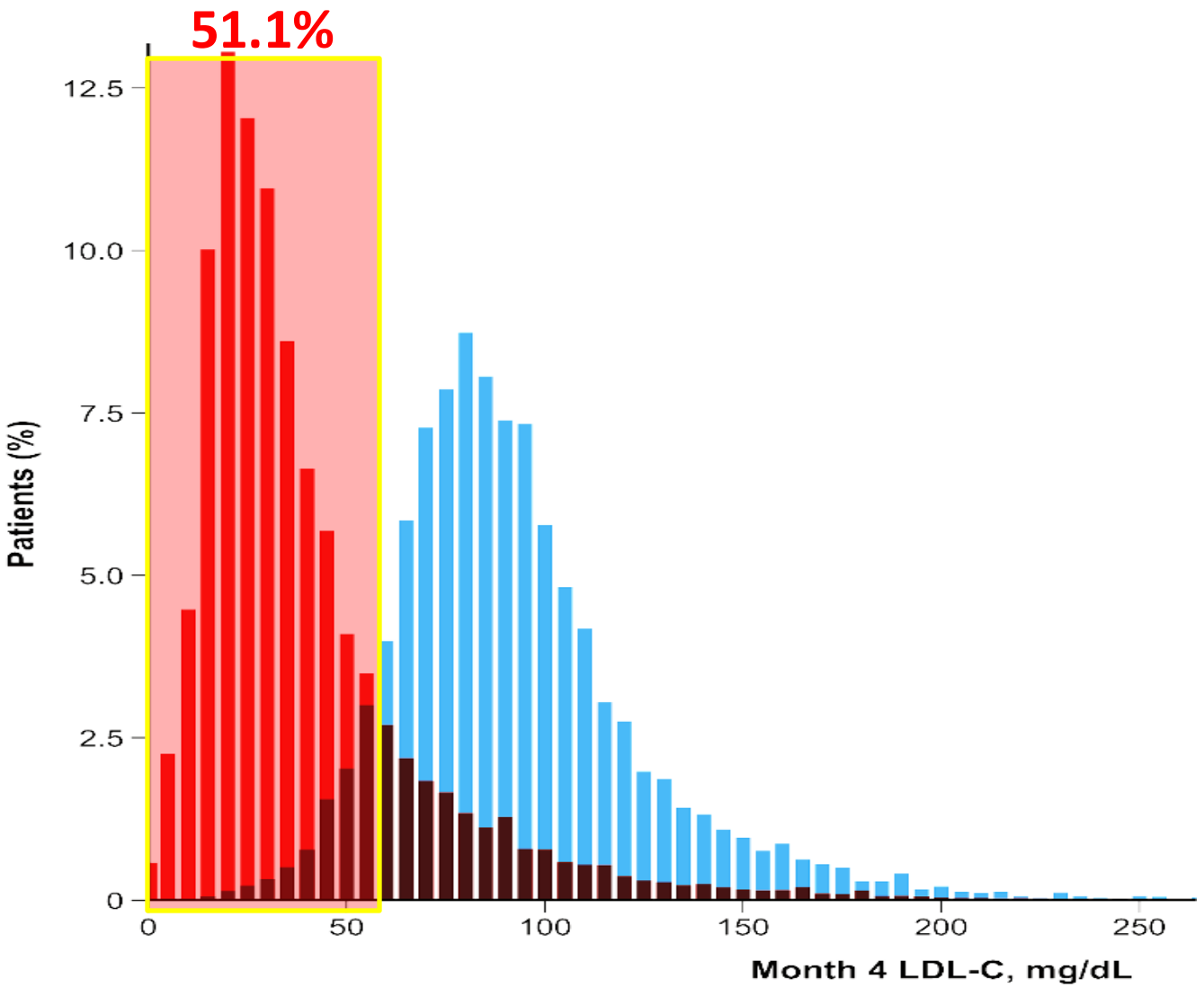
ODYSSEY OUTCOMES (alirocumab)



- 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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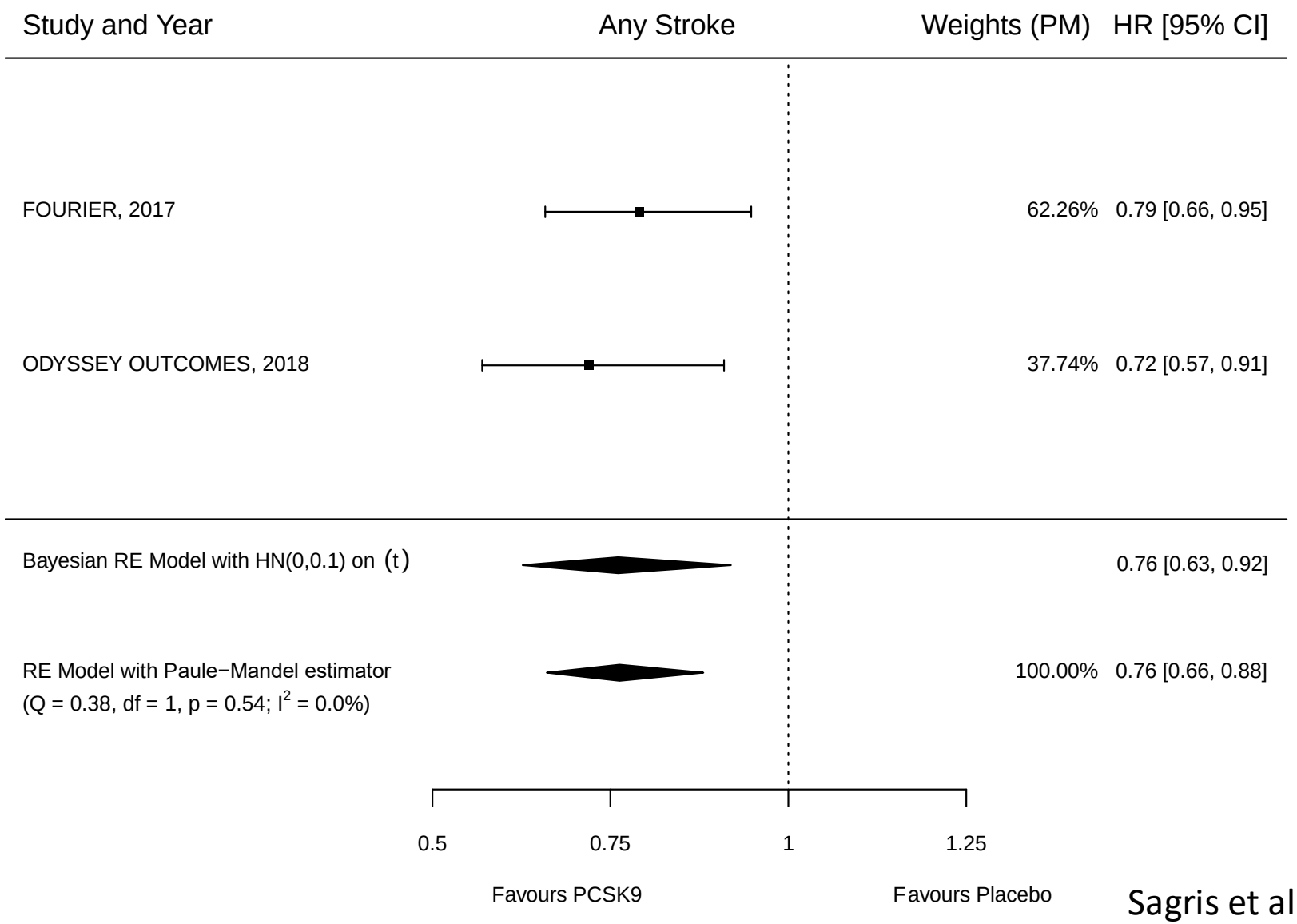
Jukema et al; Circulation. 2019

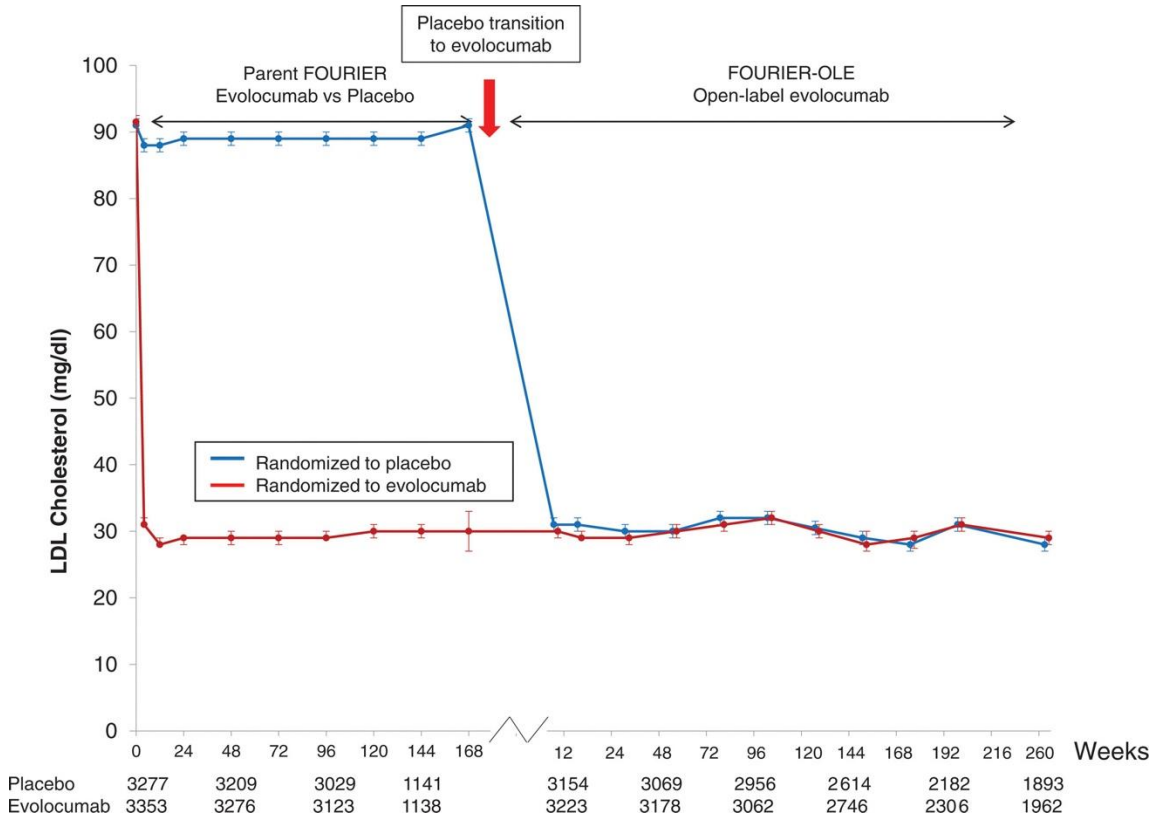
PCSK9 Inhibitors

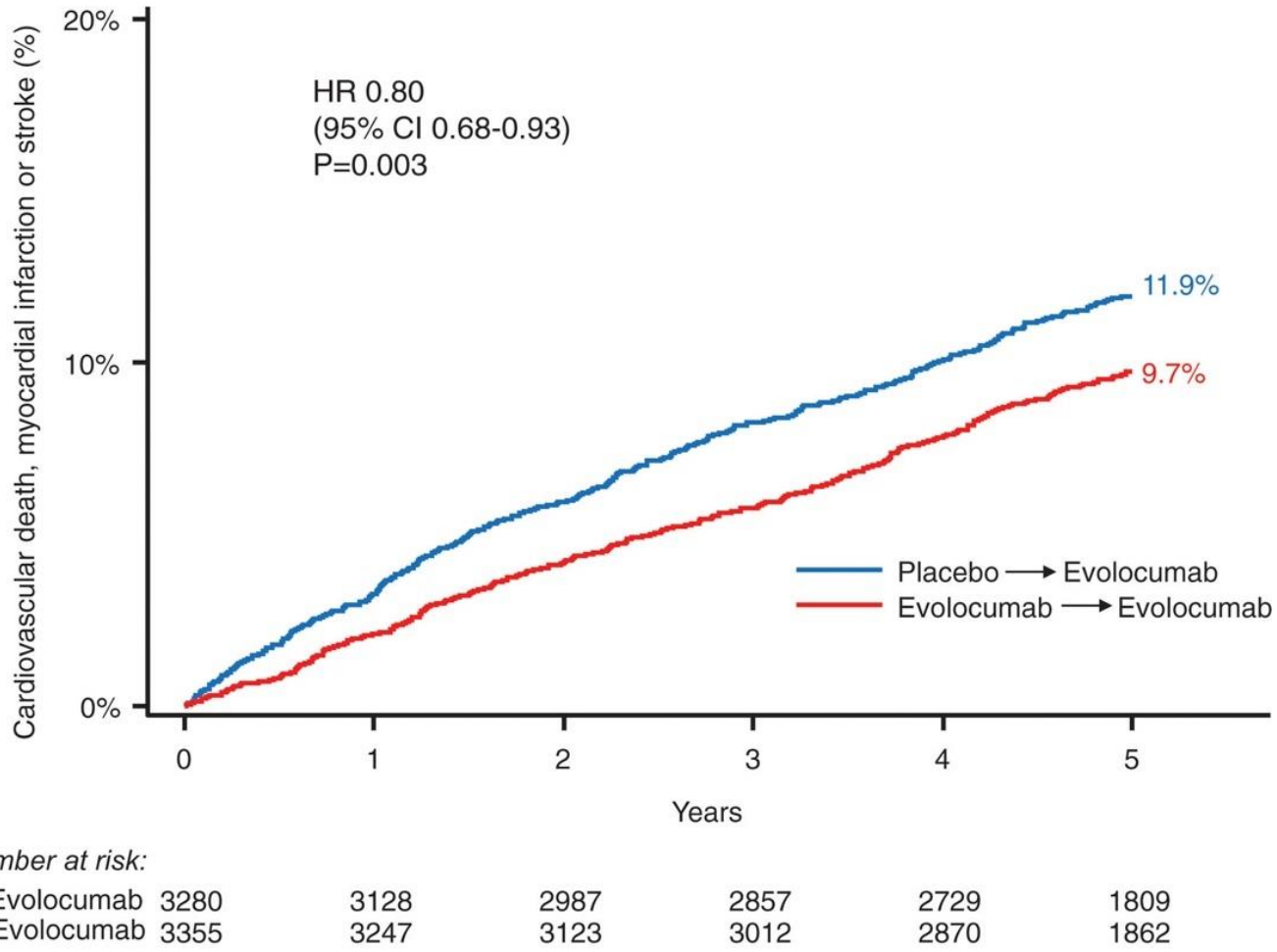


- **Median LDL-C before randomization: 93mg/dl**
- **Median time of randomization: 3 years**

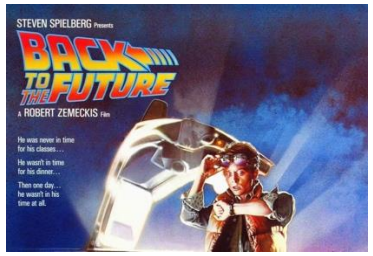
Sagris et al: European J int Medicine 2020

FOURIER - OLE (evolocumab)





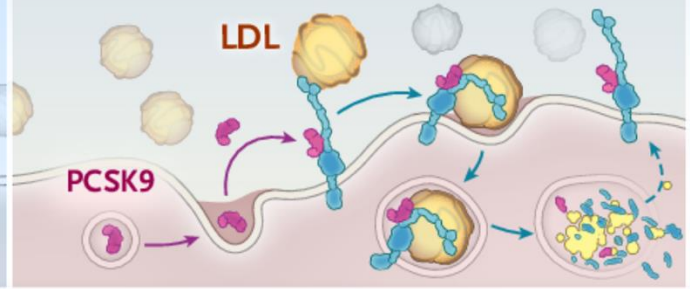
O'Donogoue et al; Circulation 2022



ORION-10 and 11 (inclisiran)

Inclisiran in Patients with Elevated LDL Cholesterol

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

ORION-10 (U.S.)	Adults with CVD and elevated LDL	ORION-11 (Europe and South Africa)
(N=1561)		(N=1617)
−51.3% with Inclisiran	Percentage change in LDL cholesterol at 510 days	−45.8% with Inclisiran
Difference, −52.3% (95% CI, −55.7 to −48.8; P<0.001)		Difference, −49.9% (95% CI, −53.1 to −46.6; P<0.001)
+1% with Placebo		+4% with Placebo

Ray et al NEJM 2020

Patient with ischemic stroke

- ✓ Πότε θα ξεκινήσουμε την υπολιπιδαιμική αγωγή
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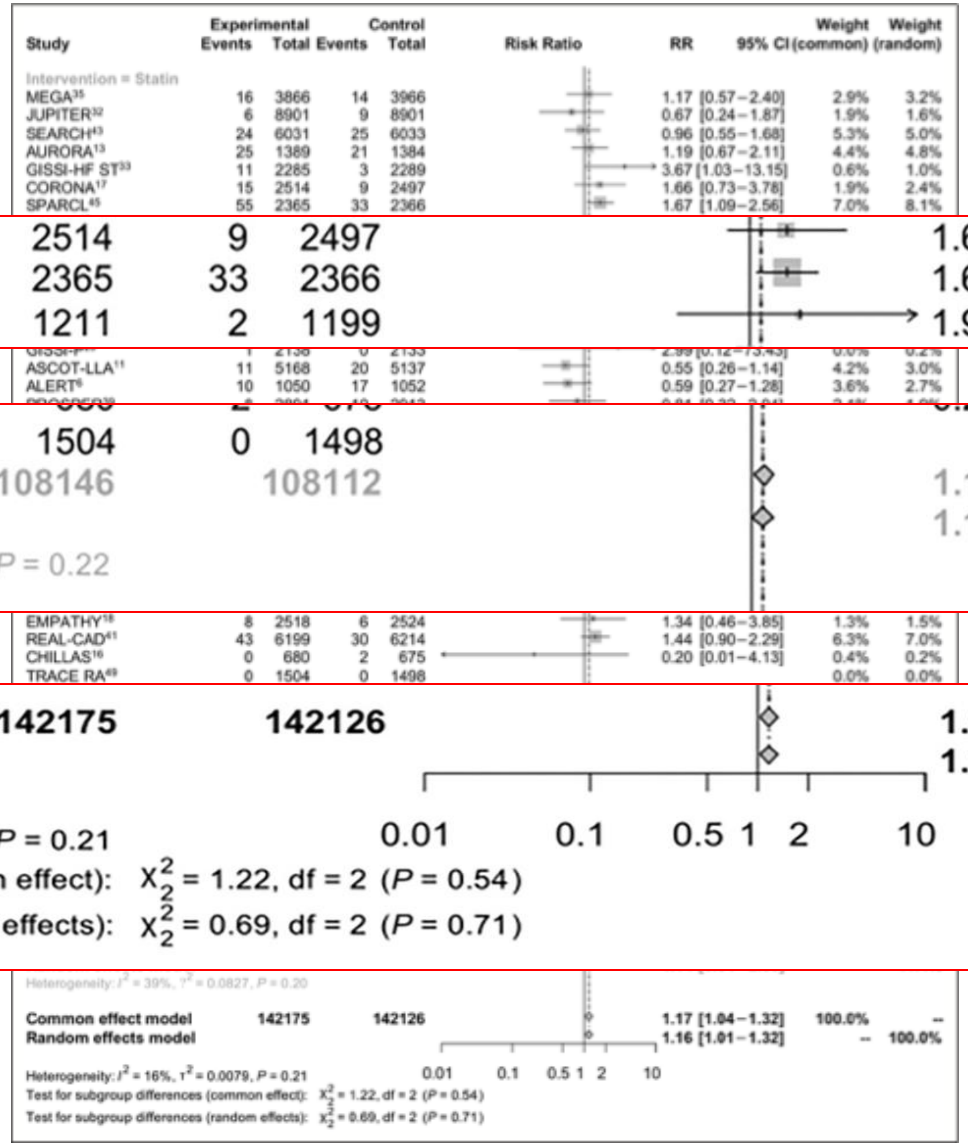
- ✓ Ποιος είναι ο στόχος μου ?
- ✓ Να φοβάμαι τις χαμηλές τιμές LDL?

Is there a risk of ICH?



CORONA[17]	15	2514	9	2497	1.66 [0.73–3.78]	1.9%	2.4%
SPARCL[45]	55	2365	33	2366	1.67 [1.09–2.56]	7.0%	8.1%
ASPEN[12]	4	1211	2	1199	1.98 [0.36–10.79]	0.4%	0.6%
TRACE RA[49]	0	1504	0	1498		0.0%	0.0%
Common effect model		108146		108112	1.19 [1.04–1.36]	79.9%	--
Random effects model					1.17 [1.01–1.36]	--	80.7%

Heterogeneity: I^2 = 16%, $?^2$ = 0.0128, P = 0.22

Common effect model	**142175**		**142126**		**1.17 [1.04–1.32]**	**100.0%**	**--**
Random effects model					**1.16 [1.01–1.32]**	**--**	**100.0%**

Heterogeneity: I^2 = 16%, τ^2 = 0.0079, P = 0.21

Test for subgroup differences (common effect): X^2_2 = 1.22, df = 2 (P = 0.54)

Test for subgroup differences (random effects): X^2_2 = 0.69, df = 2 (P = 0.71)

Bétrisey et al *J Am Heart As.* 2024

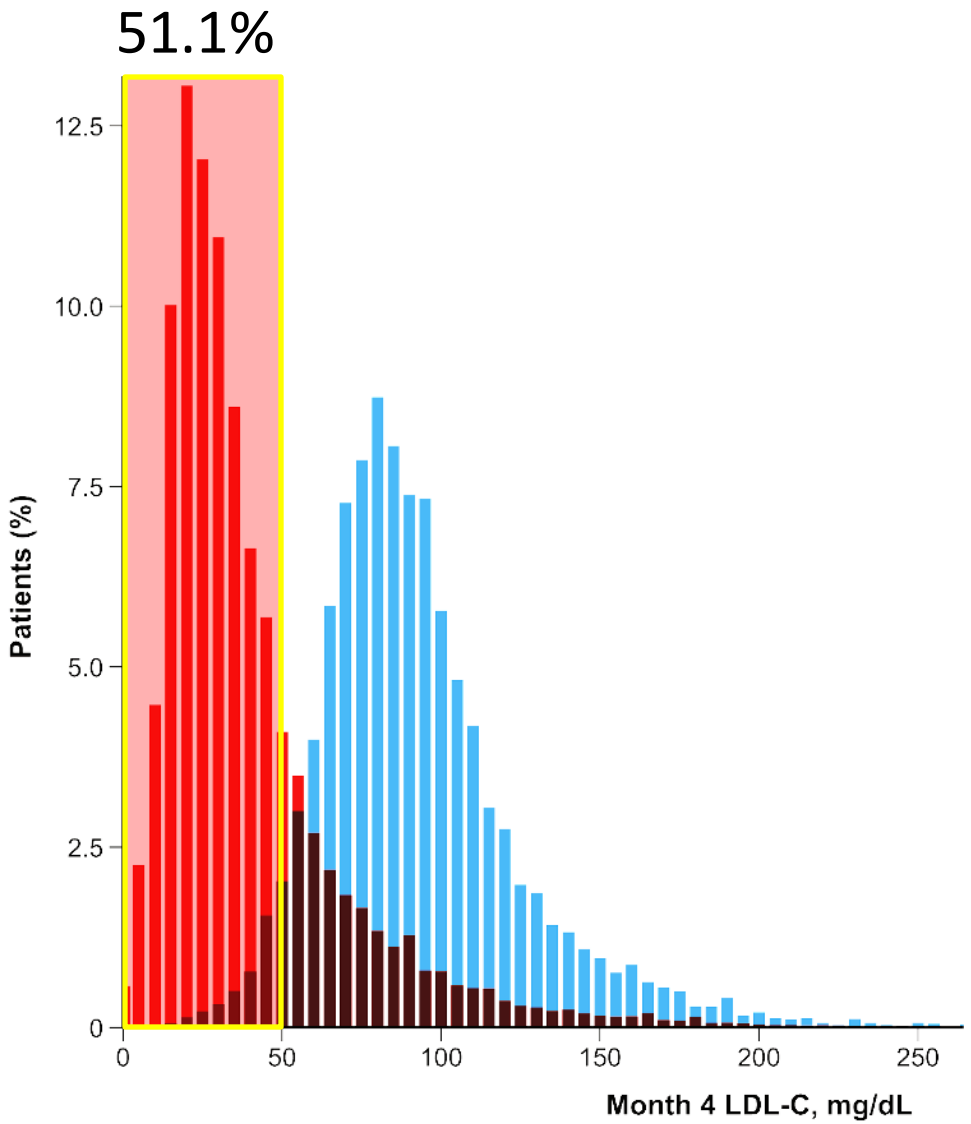
Is there a risk of ICH?

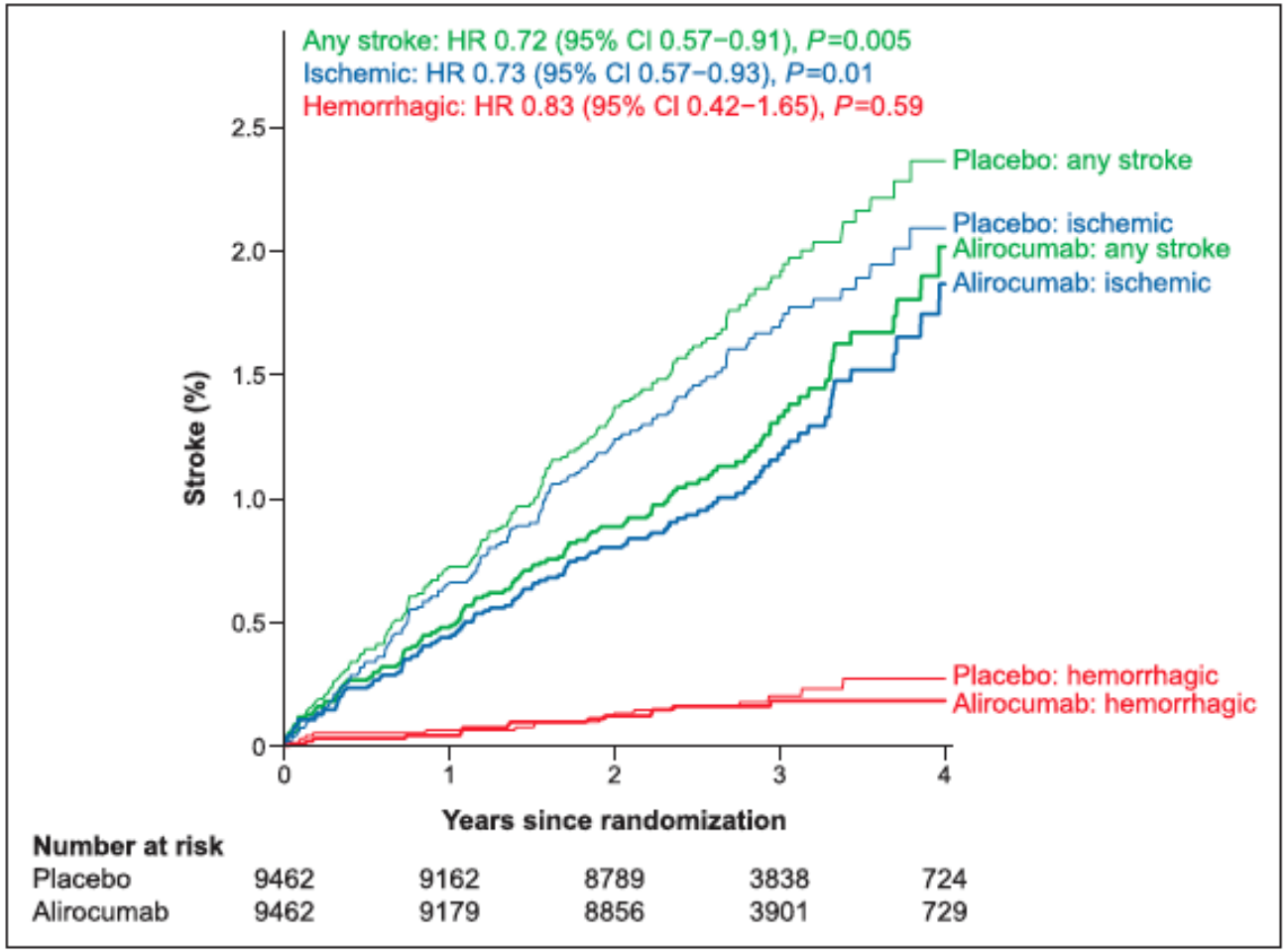
- *"The absolute risk of haemorrhagic stroke remained rare throughout the trials, and the absolute risk difference attributable to statin was low, with an estimated number needed to harm of 3333 for an average treatment length of 6.7 years."*

- *"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

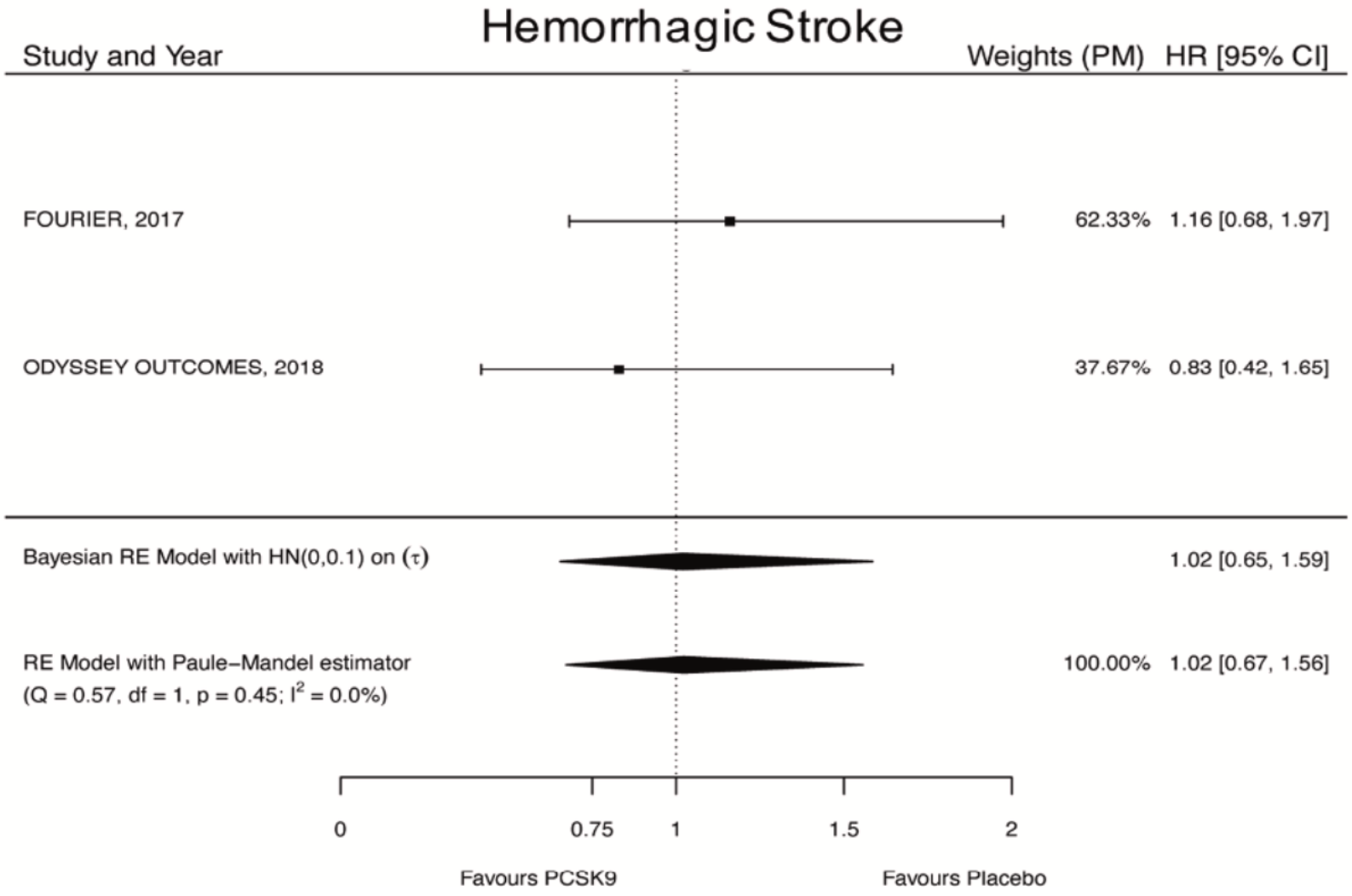
Is there a risk of ICH?





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!!!**

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*