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Charles Foix Group for Clinical Trial in Stroke

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Benefit of a target LDL cholesterol of less than 70 mg/dL after an ischemic stroke of atherosclerotic origin
Results of the Treat Stroke to Target trial*

Amarenco P, Kim JS, Labreuche J, Charles H, Giroud M, Mahagne M-H, Nighoghossian N, Steg PG, Touboul PJ, Vicaut E, Bruckert E on behalf of the Treat Stroke to Target investigators

*Investigator intiated RCT
Conducted by the Charles Foix Group for Clinical Trial in Stroke (ARO) at Bichat hospital – University of Paris
Supported by the French Neurovascular Society
Funding : PHRC (French government), SOS-ATTAQUE CEERBRALE Association (NPO)
Unrestricted grant : Pfizer Europe, Astra-Zeneca, Merck, Pfizer global (Korea)

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Background

- The SPARCL trial[1] found a 16% relative risk reduction in stroke with atorvastatin 80 mg per day as compared to placebo in patients with stroke and no known coronary heart disease
- In the group with carotid stenosis[2] the relative risk reduction was 33%
- In SPARCL, patients achieving a LDL cholesterol of less than 70 mg/dL (1.8 mmol/L) had a 28% relative risk reduction as compared to patients who achieved 100 mg/dL (2.4 mmol/L) or above[3]
- Current AHA/ASA guidelines[4] recommend "intense" statin therapy after an ischemic stroke of atherosclerotic origin but does not stipulate a target level of LDL cholesterol because there is limited data on outcomes with different LDL-cholesterol lowering targets
- **Therefore, there is uncertainty about the target level of LDL cholesterol is appropriate to reduce cardiovascular events after stroke**

1. *SPARCL investigators. N Engl J Med. 2006;355:549-59*
2. Sillesen H, Amarenco P, Hennerici MG et al. *Stroke*. 2008 Dec;39(12):3297-302
3. Amarenco P, Goldstein LB, Szarek M, et al. *Stroke. 2007;38:3198-3204*
4. Kernan WN, Ovbiagele B, Black HR, et at. *Stroke*. 2014 ;45:2160-2236

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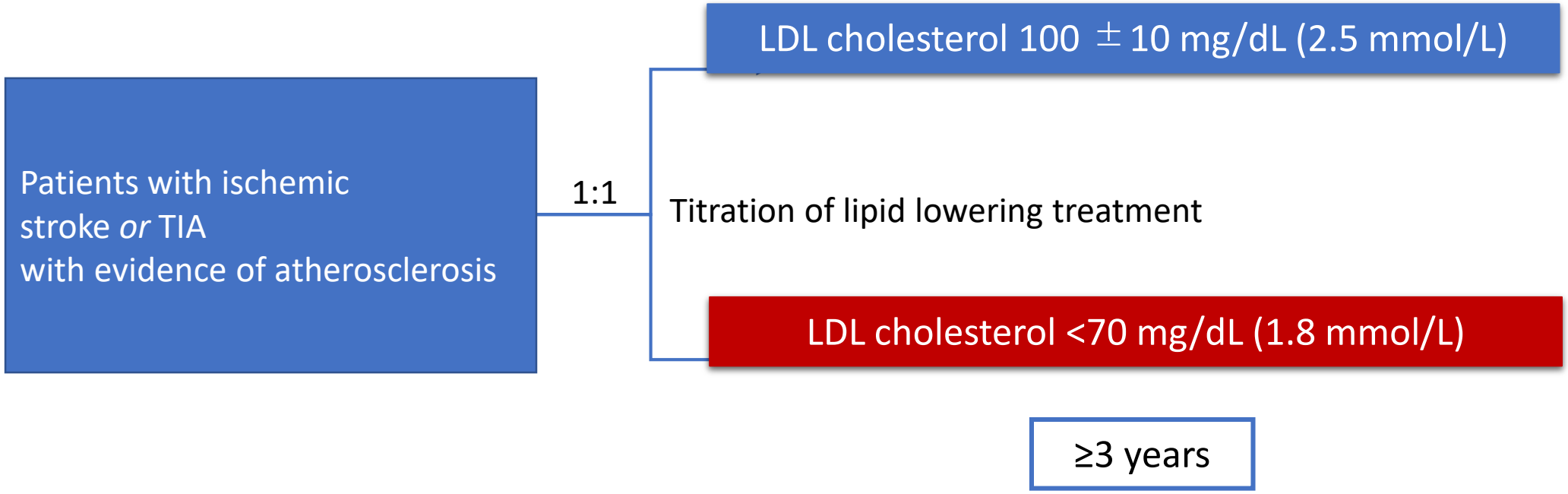
Study Design



Investigators used statin and dose of their choice in monotherapy or in combination with ezetimide or other drugs

CRAs in the trial unit contacted with patients 3 months before the next visit, making sure they were treated to the assigned target

Patients and investigators were not maintained blinded but the adjudication committee was fully blinded

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Primary End-Point

- Composite of :
  - non fatal ischemic stroke or undetermined stroke
  - non fatal MI
  - Unstable angina followed by urgent coronary revascularization
  - TIA followed by urgent carotid revascularization
  - and vascular death including sudden death

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Study specifications

- Patients were enrolled between March 15, 2010 to December 31, 2018
- We followed-up the patients until one year after last patients included
- It was an event driven trial until an accrual of 385 primary endpoints
- Follow-up visits occurred every 6 months
- The number of center was 61 in France, 16 in Korea (joined the trial in late 2015)
- **Trial was stopped on May 25, 2019 after allocated funds have been used, with 277 primary endpoints accrued**
- **Median follow-up 3.5 years (5.3 years in France, 2.0 years in Korea)**

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Randomized (**n=2873**)

Allocation

Assigned to LDL-c<70mg/dL target (**n=1440**)

- Did not meet the inclusion criteria (n=23)

Assigned to LDL-C 100±10 mg/dl target (**n=1433**)

- Did not meet the inclusion criteria (n=21)

Follow-up

Followed for endpoints though end of the study (**996**)

- lost to follow-up (n=78)
- No signed consent (n=10)
- withdrawn consent (n=221)
- Other reasons (n=135)
  - Serious adverse event (n=2)
  - investigator's decision (n=133)

Followed for endpoints though end of the study (**n=1023**)

- lost to follow-up (n=63)
- No signed consent (n=3)
- withdrawn consent (n=205)
- Other reasons (n=139)
  - Serious adverse event (n=4)
  - investigator's decision (n=135)

Primary Analysis

Analyzed (**n=1430**)

-excluded (n=10 no signed consent)

Analyzed (**n=1430**)

-excluded (n=3 no signed consent)

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Characteristics	LDL-c <70 mg/dL (N=1430)	LDLc 100±10 mg/dL (N=1430)
Age, years	66.4 (11.3)	67.0 (11.1)
Male sex, no/total no, (%)	971/1430 (67.9)	963/1430 (67.3)
Body-mass index, median (IQR)	25.6 (23.3-28.6)	25.5 (23.2-28.4)
Entry event		
Ischemic stroke	1220/1425 (**85.6**)	1229/1429 (**86.0**)
TIA	205/1425 (14.4)	200 /1429 (14.0)
Time since entry event, days, median (IQR)	6.0 (4.0-10.0)	6.0 (4.0-11.0)
Medical history		
Hypertension, no/total no, (%)	909/1422 (63.9)	959/1424 (67.3)
Diabetes, no/total no, (%)	328/1420 (23.1)	315/1421 (22.2)
Dyslipidemia, no/total no, (%)	878/1418 (61.9)	862/1420 (60.7)
Former smoker, no/total no, (%)	349/1420 (24.6)	306/1421 (21.5)
Current smoker, no/total no, (%)	446/1420 (31.4)	413/1421 (29.1)
Stroke or TIA, no/total no, (%)	169/1419 (11.9)	153/1420 (10.8)
Coronary artery disease, no/total no, (%)	263/1418 (18.5)	227/1419 (16.0)
Statin naïve (%)	800/1418 (**56.4**)	769/1420 (**54.2**)

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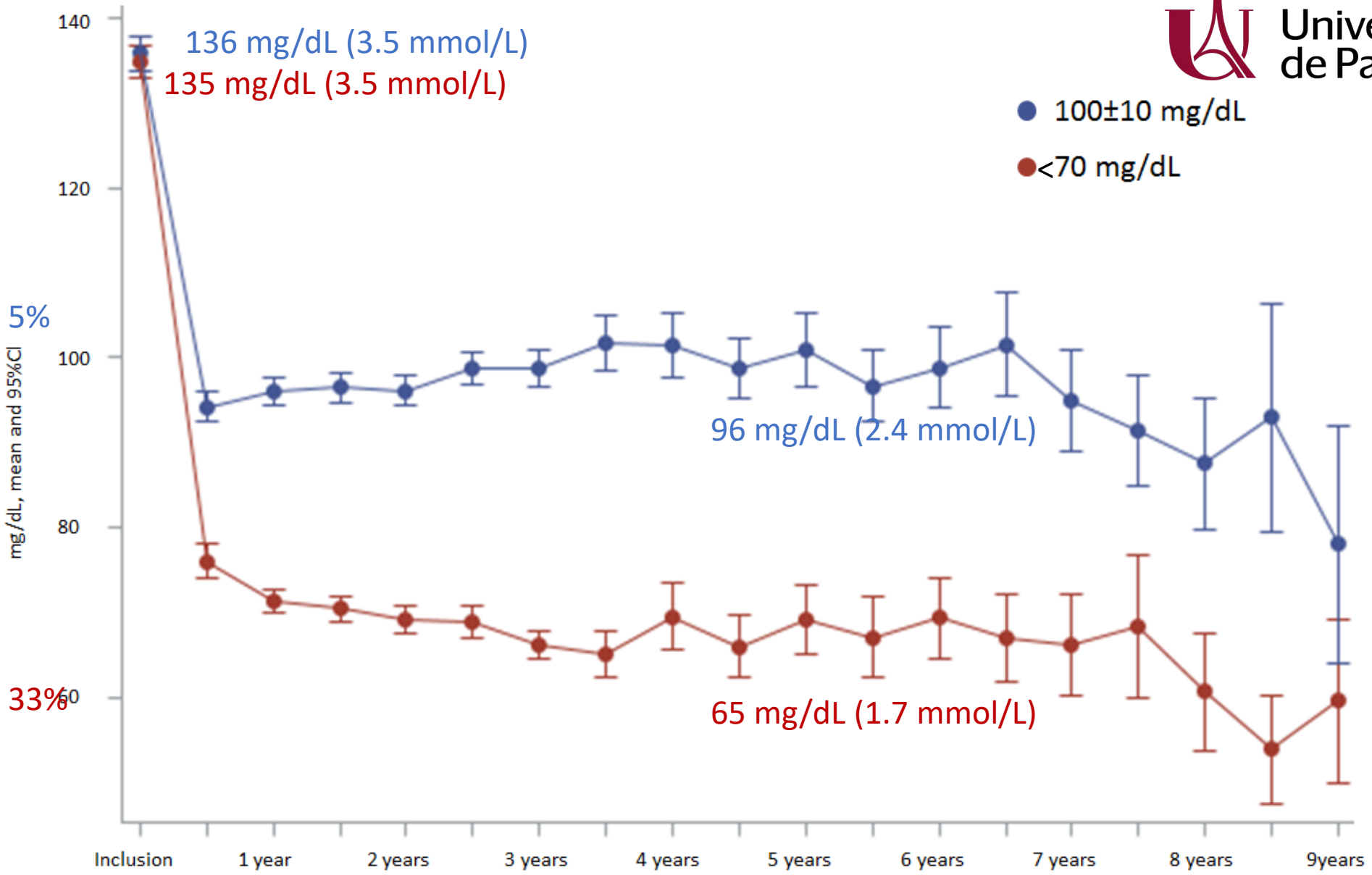
Statin only 94%
Statin+Ezetimibe 5%

Statin only 66%
Statin+Ezetimibe 33%



Number																			
100±10 mg/dL	1420	1115	989	787	792	681	598	292	242	185	164	133	114	80	83	67	31	22	5
<70 mg/dL	1414	1102	965	879	774	653	570	277	227	180	169	141	126	81	73	46	26	21	6
Absolute difference	-1.14	-18.3	-24.7	-26.1	-27.1	-29.8	-32.5	-36.6	-32.0	-32.8	-31.9	-29.5	-29.4	-34.6	-29.0	-23.2	-26.9	-39.2	-18.5

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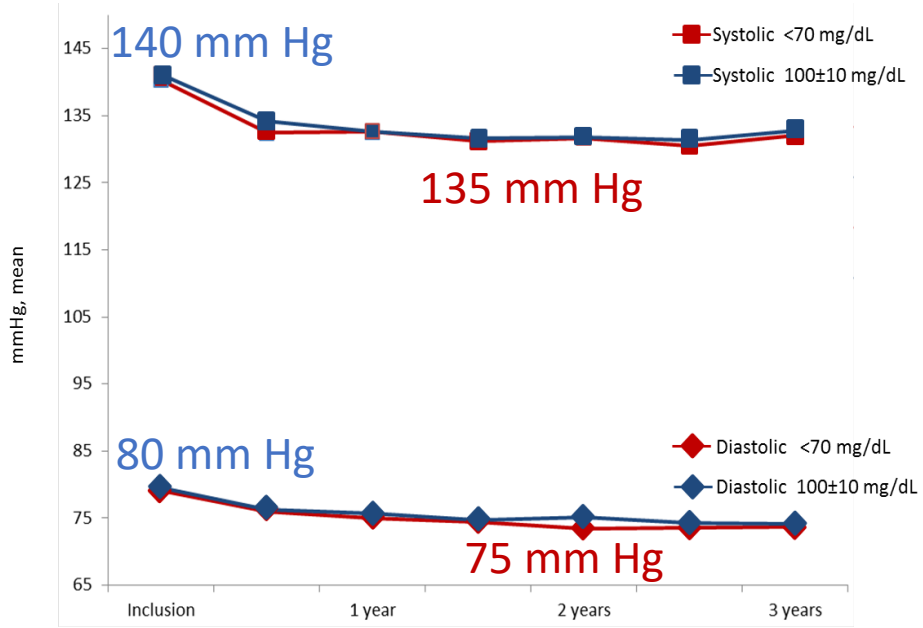
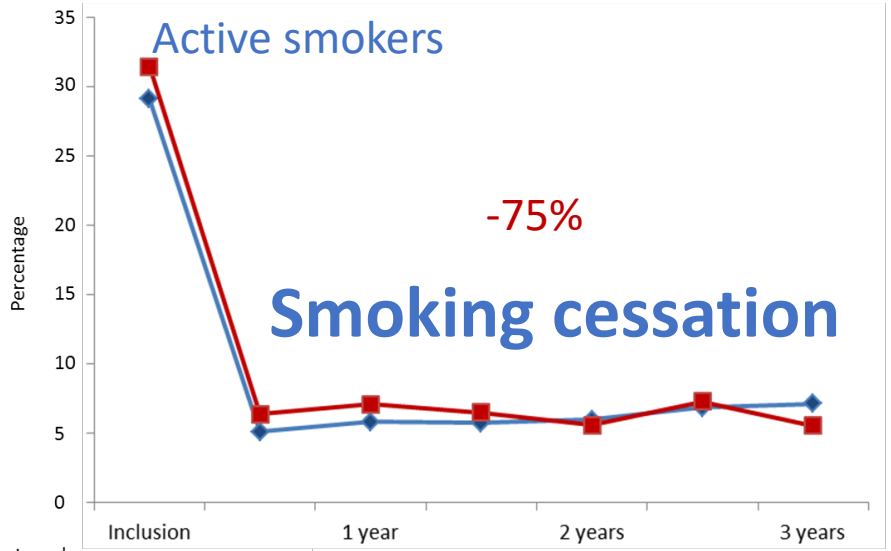
Achievement of prevention targets in the two treatment arms

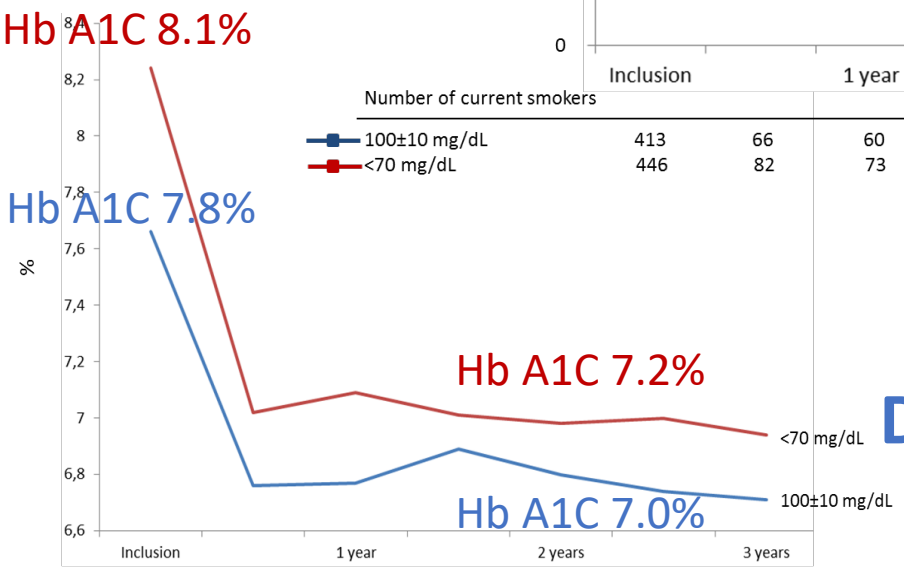


Number							
100±10 mg/dL	1414	1120	981	871	782	657	594
<70 mg/dL	1412	1132	968	872	769	640	578

Blood pressure lowering



Number of current smokers							
100±10 mg/dL	413	66	60	54	50	49	45
<70 mg/dL	446	82	73	61	47	52	35



Number							
100±10 mg/dL	304	109	193	94	133	80	98
<70 mg/dL	312	127	190	107	173	81	110

Diabetes control

23% Diabetics

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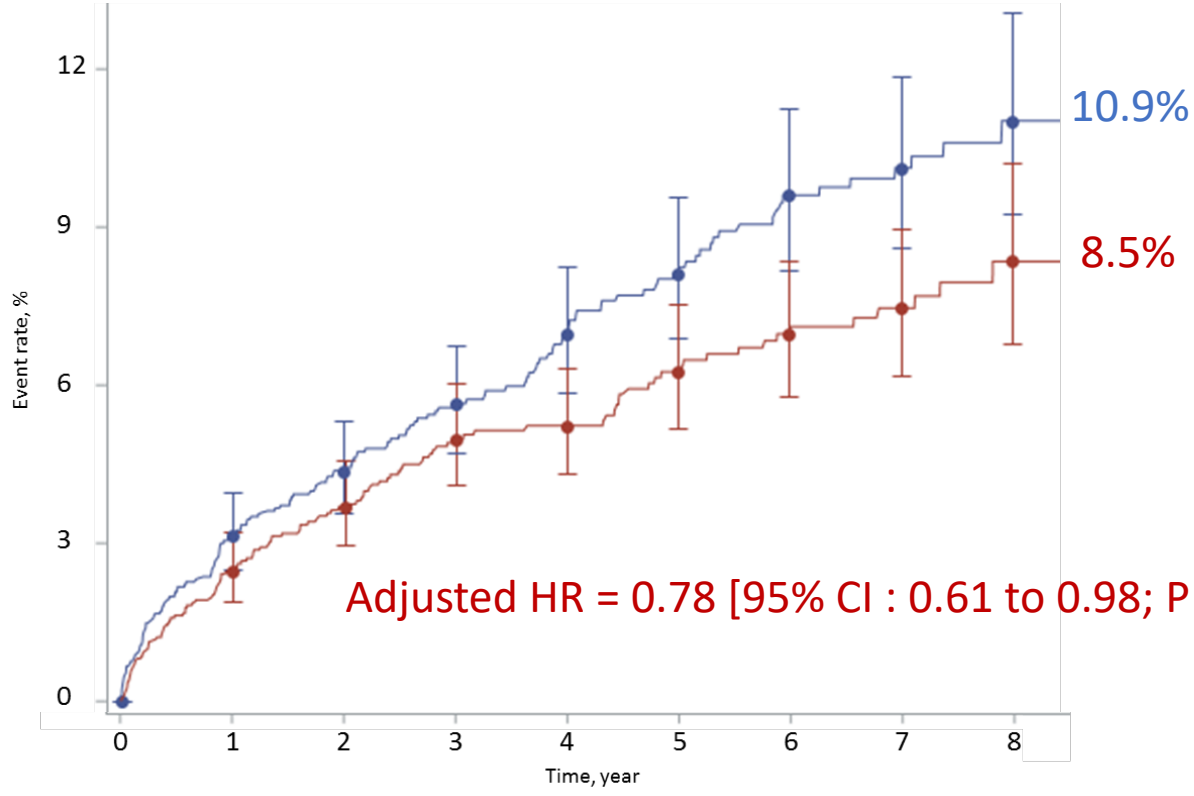
PRIMARY OUTCOME

Ischemic stroke or undetermined stroke, myocardial infarction, urgent coronary revascularization following unstable angina, urgent carotid revascularization following TIA, vascular death

PRE SPECIFIED COVARIATES ADJUSTMENTS
. Age
. Sex
. Entry event (ischemic stroke vs. TIA)
. Time from symptom onset to randomization
. Geographical region (France vs Korea)
(SPARCL trial adjustment)



22% RRR

Strategy									
<70 mg/dL	1430	1128	964	740	586	475	353	238	104
100±10 mg/dL	1430	1146	973	730	590	487	392	253	106

Non adjusted HR = 0.77 [95% CI; 0.61-0.97; P value = 0.029]

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Secondary Outcomes

	LDL <70 mg/dL (N=1430)	LDL 100±10 mg/dL (N=1430)	Hazard Ratio (95% CI)	P Value
myocardial infarction and urgent coronary revascularization	20/1430 (1.4)	31/1430 (2.2)	0.64 (0.37-1.13)	0.12*
cerebral infarction and urgent carotid and cerebral artery revascularization	88/1430 (6.2)	109/1430 (7.6)	0.81 (0.61-1.07)	
cerebral infarction or TIA	120/1430 (8.4)	139/1430 (9.7)	0.87 (0.68-1.11)	
any revascularization procedure (both urgent and elective)	94/1430 (6.6)	99/1430 (6.9)	0.93 (0.70-1.24)	
Carotid	17/94	23/99		
Coronary	44/94	51/99		
Peripheral	33/94	25/99		
vascular death	22/1430 (1.5)	32/1430 (2.2)	0.69 (0.40-1.18)	
all cause death	88/1430 (6.2)	93/1430 (6.5)	0.97 (0.73-1.30)	
Cerebral infarction or intracranial hemorrhage	103/1430 (7.2)	126/1430 (8.8)	0.82 (0.63-1.07)	
Intracranial hemorrhage	**18/1430 (1.3)**	**13/1430 (0.9)**	**1.38 (0.68-2.82)**	
Newly diagnosed diabetes	**103/1460 (7.2)**	**82/14**	**1.27 (0.95-1.70)**	
Primary outcome or intracranial hemorrhage	**133/1430 (9.3)**	**165/1430 (11.5)**	**0.80 (0.63-1.00)**	

* Hierarchical testing stopped

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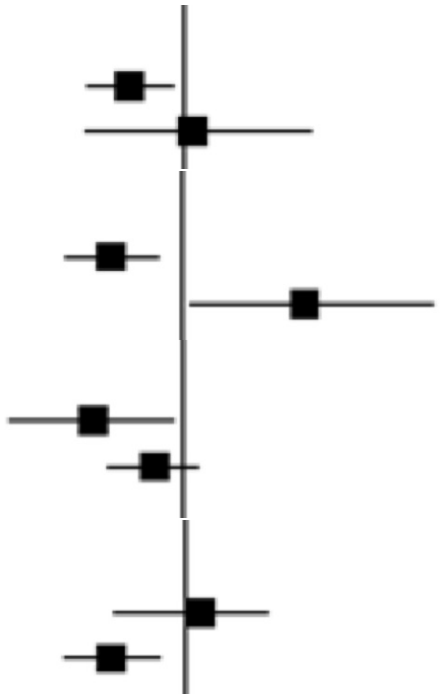
Key subgroups

Subgroup	<70 mg/dL (no. of primary outcome/total no.)	100±10 mg/dL (no. of primary outcome/total no.)	Hazard ratio (95%CI)	Nominal interaction P Value
Geographic region				
France	103/1073	139/1075	0.73 (0.57-0.95)	0.26
South Korea	18/357	17/355	1.11 (0.57-2.15)	
Diagnostic of index event				
Ischemic stroke	97/1220	144/1229	0.67 (0.52-0.87)	0.003
TIA	24/205	12/200	2.06 (1.03-4.12)	
Diabete mellitus at baseline				
Yes	27/328	44/315	0.60 (0.37-0.96)	0.16
No	93/1070	109/1085	0.85 (0.64-1.12)	
Time in therapeutic range per center*				
0%-49%	47/573	42/578	1.14 (0.75-1.73)	0.76
50%-100%	74/855	114/848	0.64 (0.48-0.85)	



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Conclusions

- With the limitation that we had to stop the trial when 277 primary endpoints were accrued whereas 385 were requested
- This trial shows that after an ischemic stroke with evidence of atherosclerosis, a target LDL cholesterol of less than 70 mg/dL (1.8 mmol/L) compared to 100±10 mg/dL (2.5 mmol/L), reduced the risk of subsequent cardiovascular events
- With no significant increase in intracranial hemorrhage
- And no increase in newly diagnosed diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

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