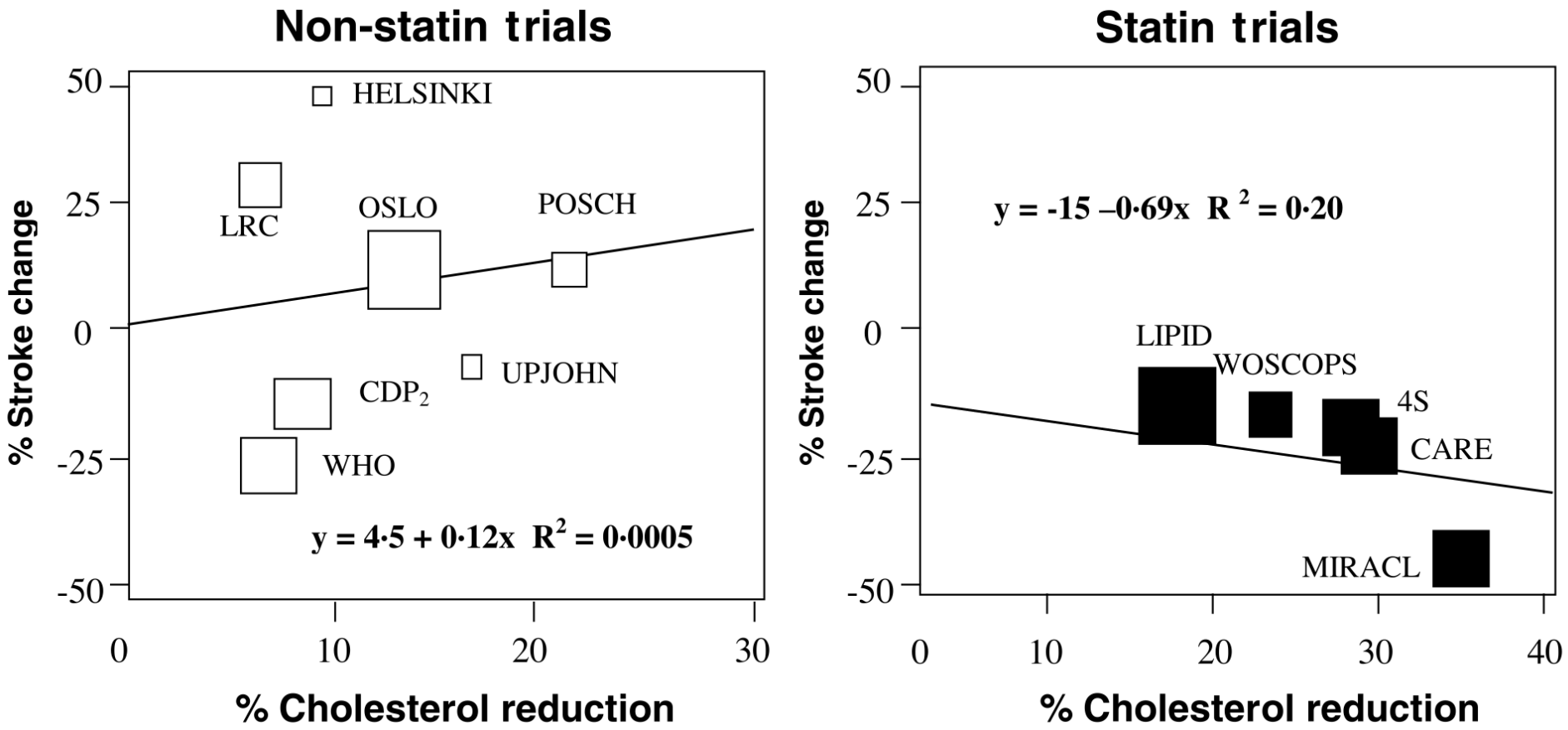
RUOLO DELLA RIDUZIONE DEI VALORI DI COLESTEROLEMIA NELLA PREVENZIONE DELL'ICTUS

BACKGROUND

- Cholesterol-lowering drugs and non pharmacological treatments significantly reduce morbidity from coronary heart disease, thus proving a causal role for cholesterol in coronary events
- The relationship between cholesterol levels and stroke has been much less clear
- Trials with statins have shown decreased stroke incidence in treated populations, but this had not been observed with nonstatin drugs or treatments, supporting the concept that such effects are attributable to statin- related "pleiotropism"—cholesterol-independent (neuro) protective properties related to the interference by statins with the mevalonate pathway

BACKGROUND



Eur Heart J 2002;23(24):1908–21

BENEFITS OF STATINS

Panel 1. Potential mechanism of benefit of statin in preventing stroke

LDL cholesterol reduction

Reduction in brain embolism in CHD patients (reduction of left ventricular thrombus with less myocardial infarction)

Blood pressure lowering effect

Regression of carotid or vertebral artery atherosclerosis and intima-media thickness

Anti-inflammatory effect

Plaque stabilisation (pleiotropic effects)

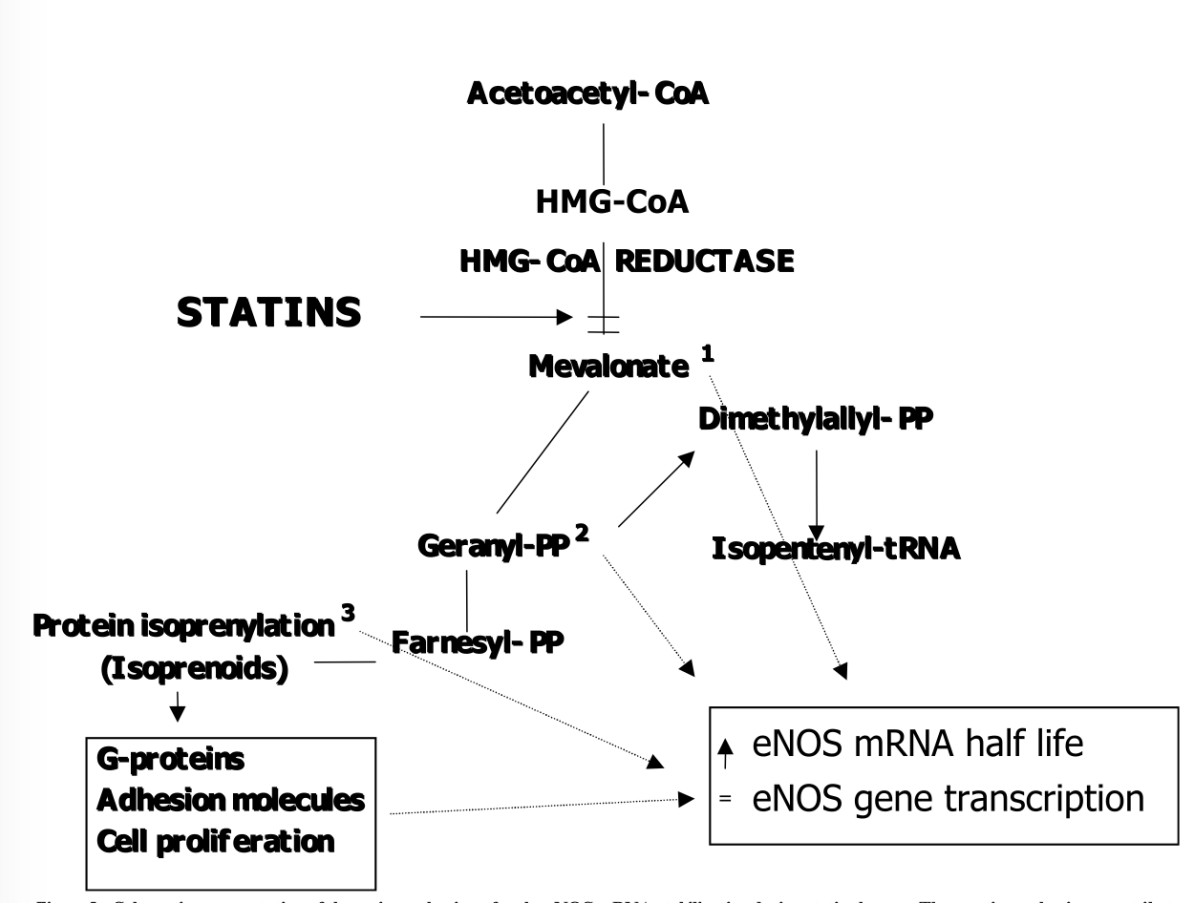
Improved endothelial dysfunction (with improved cerebral vasoreactivity)

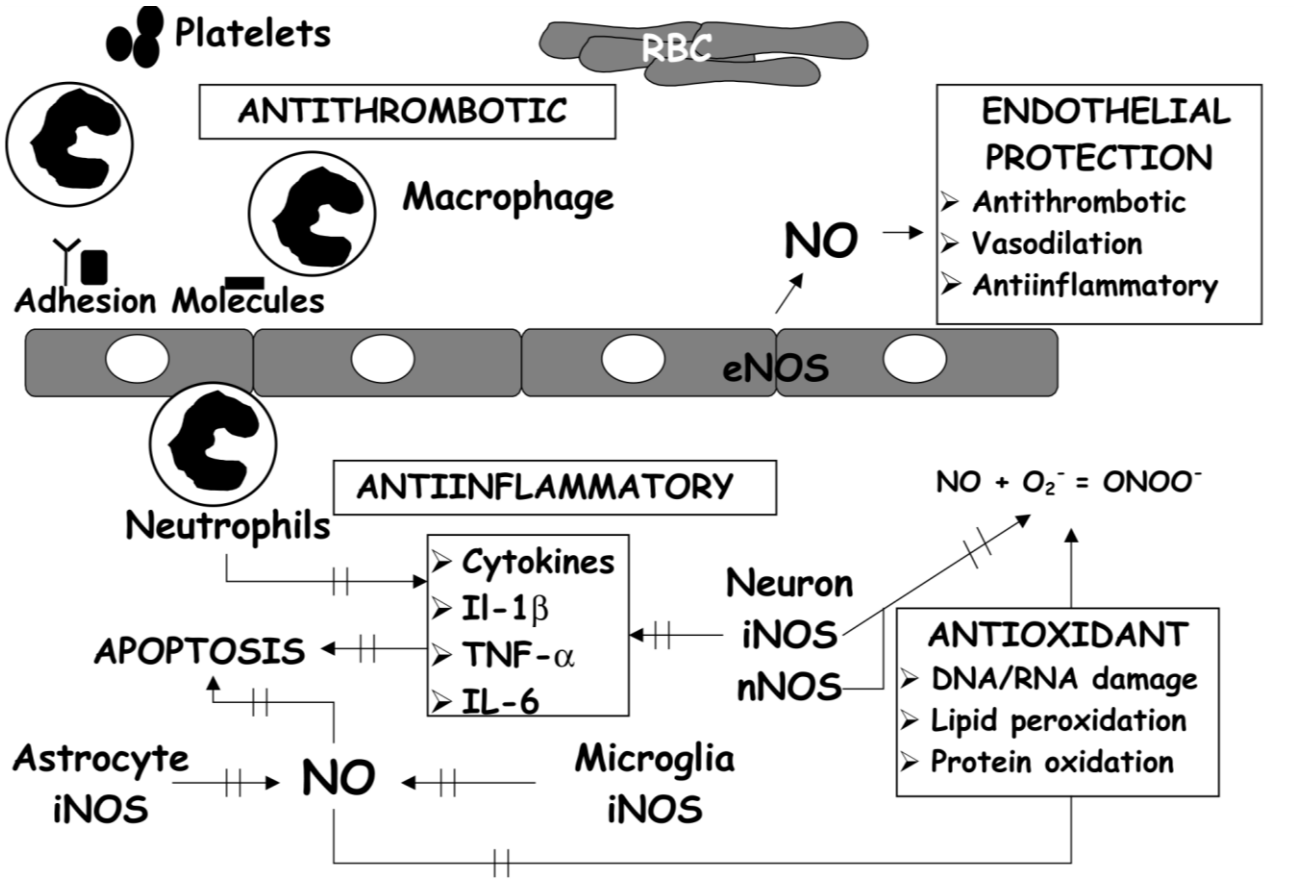
Positive effect on fibrinolytic system and platelet function

Neuroprotection (with upregulation of eNOS activity)

Lancet Neurol2004;3:271–78

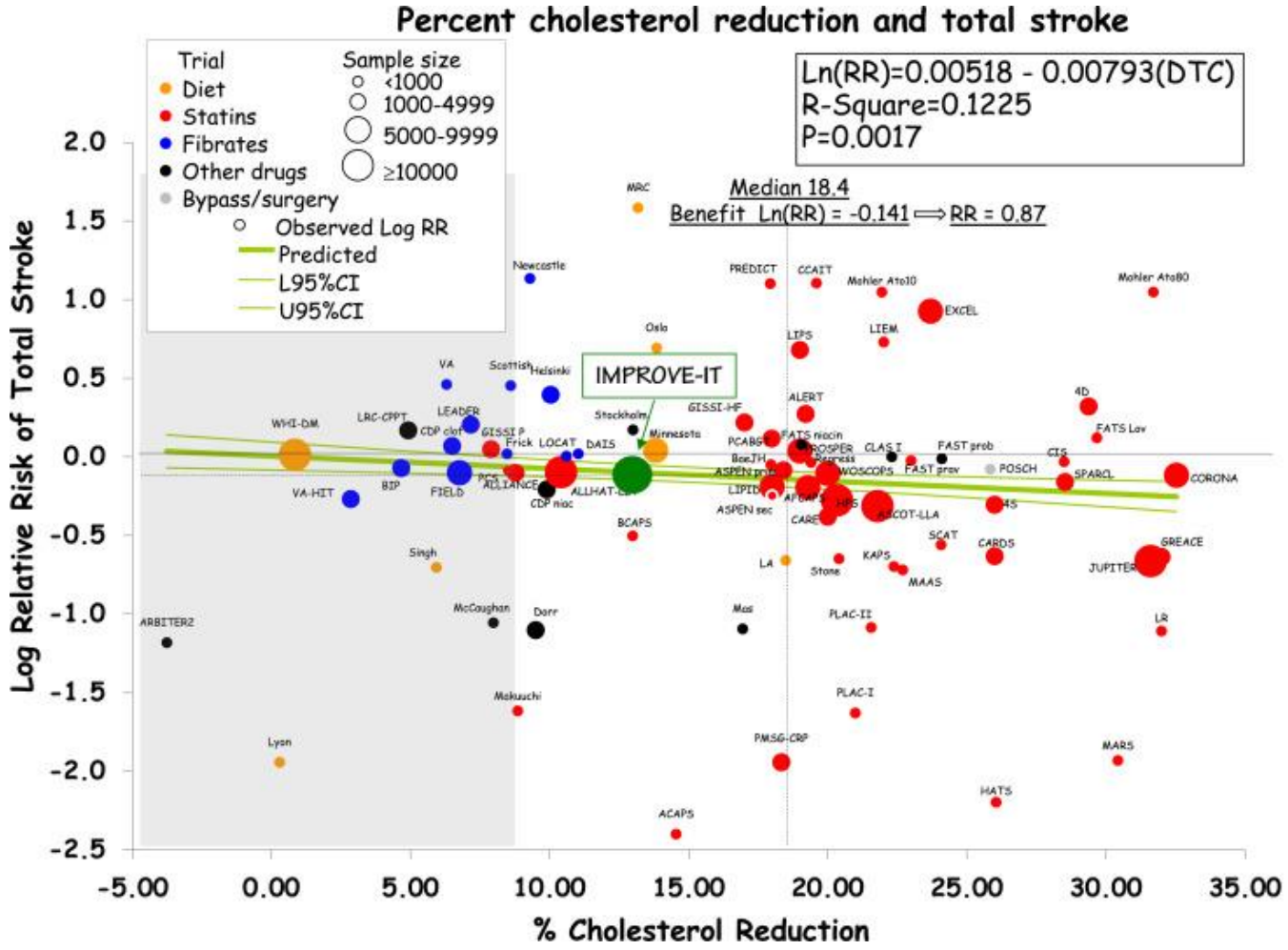
BENEFITS OF STATINS





Eur Heart J 2002;23(24):1908–21

META-REGRESSION WITHOUT PCSK9 INHIBITORS



R. De Caterina et al. Atherosclerosis 248 (2016) 216e218217

Cholesterol Lowering and Stroke: No Longer Room for Pleiotropic Effects of Statins — Confirmation from PCSK9 Inhibitor Studies

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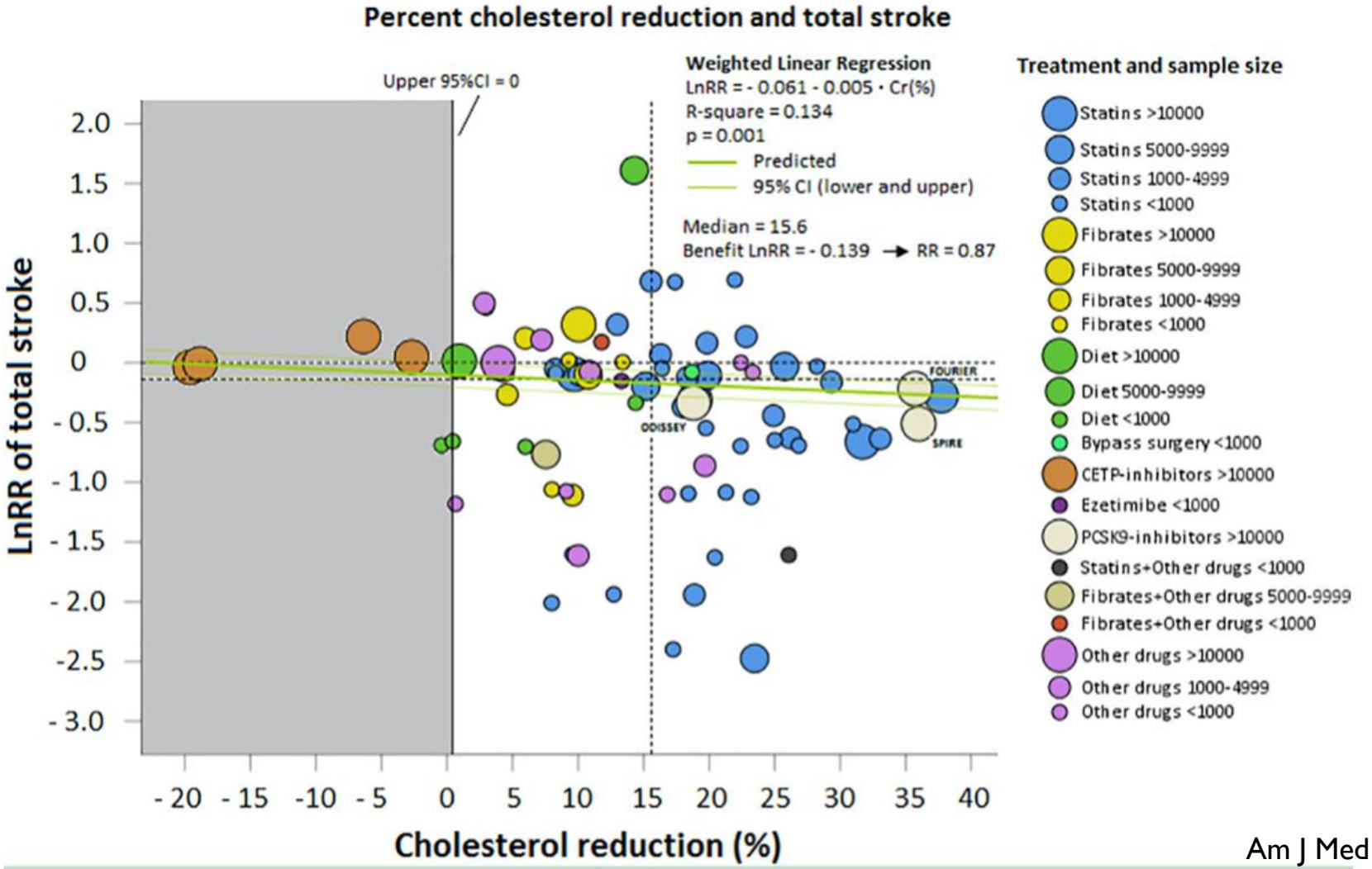
TOTAL CHOLESTEROL AND STROKE IN THE RANDOMIZATION GROUPS IN FOURIER, SPIRE-1/2, AND ODYSSEY OUTCOMES

	Total Cholesterol at Study End		Total Stroke		Observed Total Stroke RR in the Original Study Publication	Predicted Total Stroke RR in[11]	Predicted Total Stroke RR with the New Equation*
	mg/dL	Δ%	n	Δ%			
FOURIER[4]							
Placebo	168		262				
Evolocumab	108		207				
Δ = placebo - evolocumab	60	35.7	55	21.0			
RR					0.79	0.76	0.79
SPIRE-1 and -2[5]							
Placebo	164		75				
Bococizumab	105		45				
Δ = placebo - bococizumab	59	36	30	40			
RR					0.60	0.76	0.79
ODYSSEY OUTCOMES[6]							
Placebo	185		168				
Alirocumab	145		120				
Δ = placebo - alirocumab	40	21.6	48	28.6			
RR					0.79	0.85	0.84

HR = hazard ratio; RR = relative risk.
ln (Total Stroke RR) = 0.00518 − 0.00793 × (% total cholesterol reduction).
New equation: LnRR = −0.061 − 0.005*(% total cholesterol reduction).

Am J Med 2020 Jan;133(1):95-99.e6.

META-REGRESSION OF THE RELATIONSHIP BETWEEN % CHANGE IN TC ACHIEVED IN INTERVENTION TRIALS AND THE RR OF STROKE



Am J Med 2020 Jan;133(1):95-99.e6.

LIMITATIONS

- Use of total cholesterol and not LDL cholesterol
  - Only cholesterol-related parameter reported in older trials
- Use of total stroke as an endpoint due to the necessity of not excluding older trials, which did not report on adjudicated distinction of ischemic and hemorrhagic strokes
  - Cholesterol lowering related to an increase in hemorrhagic stroke?

Am J Med 2020 Jan;133(1):95-99.e6.

NO EXCESS IN HEMORRHAGIC STROKE IN FOURIER

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

Stroke. 2020;51:1546-1554

CONCLUSIONS

- No special property of any cholesterol-lowering intervention has to be invoked to explain the reduction in stroke, fitting a log-linear relationship
- Precise estimate of the expected results on stroke in future intervention trials affecting total cholesterol
- Favorable effects of cholesterol lowering on ischemic stroke far outweigh any possible detrimental effect on hemorrhagic stroke overall for most achieved cholesterol levels.