

# SERUM CHOLESTEROL LEVELS, HMG-COA REDUCTASE INHIBITORS, AND THE RISK OF INTRACEREBRAL HEMORRHAGE. THE MULTICENTER STUDY ON CEREBRAL HEMORRHAGE IN ITALY (MUCH-ITALY)

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## Background

Low serum total cholesterol levels have been inconsistently associated with an increased risk of symptomatic intracranial hemorrhage (ICH), and the contribute of HMG-CoA reductase inhibitors (statins) therapy to this relationship is unclear.

## Methods and Results:

As part of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy) we compared 3,492 consecutive patients with ICH (mean age, 73.0 ± 12.7 years; males, 56.6%; 1,604 lobar ICH, 1,888 deep ICH) with 3,492 stroke-free control subjects frequency-matched with cases for sex and age. Hypercholesterolemia was inversely associated with ICH, independently of potential confounders. Increasing levels of cholesterol were associated with a decreased risk of ICH (average OR, 0.88; 95% CI, 0.86 – 0.89, for every increase of 0.26 mmol/l of total serum cholesterol concentrations). Conversely, statin use was directly associated with ICH risk (OR, 1.51; 95% CI, 1.29 – 1.75, at the average level of total serum cholesterol). There was statistical interaction between total serum cholesterol levels and statin use for the risk of hemorrhage [Interaction odds ratio (IOR), 1.08; 95% CI, 1.05–1.12, for ICH regardless of hematoma location] with no independent effect of statins. Statin therapy turned out to reduce the protective effect of total serum cholesterol against ICH, especially in cortico-subcortical regions.

## Discussion

The question of whether serum lipids, including cholesterol, might be linked to ICH, and whether cholesterol-lowering drugs might be involved in this relationship has been matter of long debate, and existing reports conflict with one another. In particular, it is still unclear whether statin use may confer an increased risk of cerebral bleeding. In line with a number of prior reports, we observed that total serum cholesterol concentrations were inversely associated with the risk of ICH.

Our findings also suggest that statin use before the index event might be associated with higher odds of intra-cerebral bleeding. Furthermore, we found differential patterns of associations depending on the location of the hematoma, the strongest effect of statins being detected in the subgroup of patients with strictly lobar haemorrhage.

We cannot dispute the fact that the potential risk of ICH associated with statin use, if any, is unlikely to overshadow the large benefits conferred by lipid-lowering medications in reducing cardiovascular events, including ischemic stroke. Nevertheless, clinicians should carefully consider bleeding risk when prescribing statin therapy targeting low cholesterol levels.

	All ICH			Lobar ICH			Deep ICH		
	Cases (n=3,492)	Control subjects (n=3,492)	P-value	Cases (n=1,604)	Control subjects (n=1,604)	P-value	Cases (n=1,888)	Control subjects (n=1,888)	P-value
Age, yrs ± SD	73.0 ± 12.7	70.6 ± 10.5	<0.001	73.9 ± 12.5	71.3 ± 10.4	<0.001	72.3 ± 12.7	70.0 ± 10.6	<0.001
Sex, Male	1978 (56.6)	1978 (56.6)		872 (54.4)	872 (54.4)		1106 (58.6)	1106 (58.6)	
Coronary artery disease	575 (16.5)	272 (7.8)	<0.001	294 (18.4)	126 (7.8)	<0.001	283 (15.0)	146 (7.8)	<0.001
Hypertension	861 (24.7)	1574 (45.1)	<0.001	430 (26.8)	707 (44.1)	<0.001	431 (22.9)	867 (45.9)	<0.001
Non-hypertensive	2166 (62.1)	1822 (52.2)		998 (62.1)	852 (53.1)		1168 (62.0)	970 (51.4)	
Hypertensive not under treatment	460 (13.2)	96 (2.7)		175 (10.9)	45 (2.8)		285 (15.1)	51 (2.7)	
Hypertensive under treatment	165.6 ± 29.8	152.9 ± 21.6	<0.001	161.6 ± 28.8	152.8 ± 21.5	<0.001	160.2 ± 29.8	153.0 ± 21.7	<0.001
Diastolic blood pressure, mm Hg	89.7 ± 18.4	81.6 ± 9.9	<0.001	87.8 ± 17.6	81.1 ± 10.1	<0.001	92.0 ± 18.3	81.9 ± 9.7	<0.001
Diabetes	2846 (81.6)	3069 (87.8)		1327 (82.8)	1417 (88.4)		1519 (80.6)	1652 (87.5)	
Non-diabetic	536 (15.4)	386 (11.1)		237 (14.8)	169 (10.5)		299 (15.9)	217 (11.5)	
Diabetic not under treatment	105 (3.0)	37 (1.1)		39 (2.4)	18 (1.1)		46 (2.5)	19 (1.0)	
Diabetic under treatment	7.72 ± 3.31	5.91 ± 1.61	<0.001	7.67 ± 3.46	5.86 ± 1.49	<0.001	7.60 ± 2.98	5.96 ± 1.69	<0.001
Serum glucose, mmol/l									
Hypercholesterolemia	2617 (75.2)	2506 (71.8)	<0.001	1210 (75.6)	1139 (71.0)	<0.001	1406 (74.6)	1367 (72.4)	<0.001
Non-hypercholesterolemic	587 (16.8)	471 (12.5)		276 (17.3)	207 (12.9)		311 (16.5)	230 (12.2)	
Hypercholesterolemic not under treatment	280 (8.0)	549 (15.7)	<0.001	113 (7.1)	258 (16.1)	<0.001	167 (8.9)	291 (15.4)	<0.001
Hypercholesterolemic under treatment with statins	4.74 ± 1.21	5.42 ± 1.09	<0.001	4.72 ± 1.18	5.42 ± 1.11	<0.001	4.77 ± 1.22	5.42 ± 1.09	<0.001
Serum total cholesterol, mmol/l									
Current smoking	411 (11.8)	450 (12.9)	0.188	163 (10.2)	194 (12.1)	0.096	248 (13.2)	256 (13.6)	0.755
Antiplatelet agents	1139 (32.6)	510 (14.6)	<0.001	553 (34.6)	236 (14.7)	<0.001	585 (31.1)	274 (14.5)	<0.001
Oral anticoagulants	432 (12.4)	30 (0.9)	<0.001	240 (15.0)	14 (0.9)	<0.001	192 (10.2)	16 (0.8)	<0.001

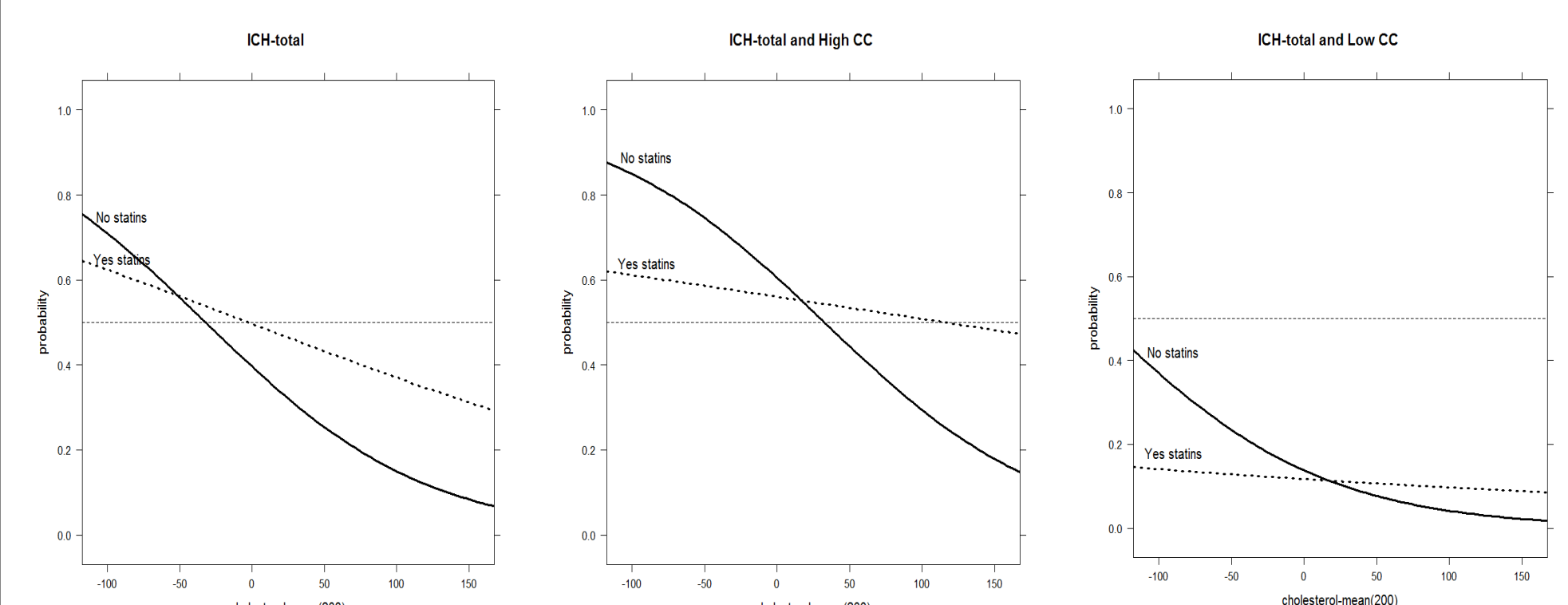
**Table 1**  
Baseline demographics and clinical characteristics of the MUCH-Italy study group according to hemorrhage location

	All ICH		Lobar ICH		Deep ICH	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, yrs	1.00 (0.99 - 1.00)	0.109	1.00 (0.99 - 1.01)	0.322	1.00 (0.99 - 1.01)	0.232
Hypertension						
Non-hypertensive	1		1		1	
Hypertensive not under treatment	1.56 (1.38 - 1.75)	<0.001	1.27 (1.06 - 1.51)	0.007	1.83 (1.56 - 2.15)	<0.001
Hypertensive under treatment	9.86 (7.73 - 12.5)	<0.001	6.72 (4.67 - 9.67)	<0.001	12.99 (9.34 - 18.01)	<0.001
Diabetes						
Non-diabetic	1		1		1	
Diabetic not under treatment	1.21 (1.03 - 1.41)	0.016	1.21 (0.95 - 1.53)	0.111	1.21 (0.98 - 1.49)	0.072
Diabetic under treatment	2.50 (1.65 - 3.78)	<0.001	2.30 (1.24 - 4.27)	0.008	2.60 (1.48 - 4.57)	0.001
Cholesterolemia						
Non-hypercholesterolemic	1		1		1	
Hypercholesterolemic not under treatment	0.79 (0.68 - 0.93)	0.005	0.83 (0.66 - 1.05)	0.132	0.76 (0.61 - 0.94)	0.015
Hypercholesterolemic under treatment with statins	0.42 (0.35 - 0.50)	<0.001	0.39 (0.30 - 0.50)	<0.001	0.45 (0.36 - 0.57)	<0.001
Hypercholesterolemic not under treatment	1.10 (0.94 - 1.29)	0.220	1.06 (0.82 - 1.36)	0.648	1.13 (0.92 - 1.40)	0.228
Current smoking	3.31 (2.90 - 3.78)	<0.001	3.68 (3.03 - 4.47)	<0.001	3.08 (2.57 - 3.69)	<0.001
Antiplatelet agents	19.83 (13.57 - 28.98)	<0.001	25.42 (14.63 - 44.15)	<0.001	15.84 (9.38 - 26.76)	<0.001
Oral anticoagulants						

**Table 2**  
Conditional effect of age, hypertension, diabetes mellitus, hypercholesterolemia, current smoking, and antithrombotic medications in the prediction of overall ICH, deep ICH, and lobar ICH. OR, odds ratio; CI, confidence intervals

	All ICH				Lobar ICH				Deep ICH			
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Total serum cholesterol	0.88 (0.86 - 0.89)	<0.001	0.88 (0.86 - 0.89)	<0.001	0.87 (0.85 - 0.89)	<0.001	0.87 (0.85 - 0.89)	<0.001	0.88 (0.87 - 0.90)	<0.001	0.88 (0.86 - 0.90)	<0.001
Statin use	1.51 (1.29 - 1.75)	<0.001	0.83 (0.68 - 1.02)	0.076	1.46 (1.19 - 1.90)	<0.001	0.90 (0.69 - 1.17)	0.415	1.48 (1.19 - 1.84)	<0.001	0.79 (0.59 - 1.06)	0.115
Total serum cholesterol × statin use	1.08 (1.05 - 1.12)	<0.001	1.12 (1.07 - 1.16)	<0.001	1.12 (1.07 - 1.17)	<0.001	1.16 (1.10 - 1.23)	<0.001	1.07 (1.02 - 1.12)	0.009	1.10 (1.04 - 1.17)	0.002

**Table 3**  
Interaction analysis of serum total cholesterol levels and statin therapy on the risk of intracerebral bleeding stratified by hemorrhage location.



**Figure 1**  
Predicted probability (risk) of overall ICH for total cholesterol and statin use (A), by low (20th percentile) (B), and high (80th percentile) (C) of covariate contribution.