Serum cholesterol levels, HMG-CoA reductase inhibitors and the risk of intracerebral haemorrhage. The Multicenter Study on Cerebral Haemorrhage in Italy (MUCH-Italy).

Serum Cholesterol Levels, HMG-CoA Reductase Inhibitors and the Risk of Intracerebral Hemorrhage. The MUCH-Italy

Alessandro Pezzini MD, Mario Grassi, PhD, Licia Iacoviello MD, PhD, Marialuisa Zedde MD, Simona Marcheselli MD, Giorgio Silvestrelli MD, Maria Luisa DeLodovici MD, Maria Sessa MD, Andrea Zini MD, Maurizio Paciaroni MD, Cristiano Azzini MD, Massimo Gamba MD, Massimo Del Sette MD, Antonella Toriello MD, Carlo Gandolfo MD, Domenico Marco Bonifati MD, Rossana Tassi MD, Anna Cavallini MD, Alberto Chiti MD, Rocco Salvatore Calabrò MD, Rossella Musolino MD, Paolo Bovi MD, Giampaolo Tomelleri MD, Augusto Di Castelnuovo PhD, Laura Vandelli MD, Marco Ritelli PhD, Giancarlo Agnelli MD, PhD, Alessandro De Vito MD, Nicola Pugliese MD, Giuseppe Martini MD, Alessia Lanari MD, Alfonso Ciccone MD, Corrado Lodigiani MD, PhD, Giovanni Malferrari MD, Elisabetta Del Zotto MD, PhD, Andrea Morotti MD, Paolo Costa MD, Loris Poli MD, Valeria De Giuli MD, Silvia Bonaiti MD, Paolo La Spina MD, Norina Marcello MD, Giuseppe Micieli MD, Giovanni de Gaetano MD, PhD, Marina Colombi PhD, Alessandro Padovani MD, PhD,

on behalf of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy) Investigators

Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia, Italia (APezzini, AM, PC, LP, VDG, SB, APadovani)
Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Unità di Statistica Medica e Genomica, Università di Pavia, Italia (MG)
Laboratorio di Epidemiologia Molecolare e Nutrizionale, Dipartimento di Epidemiologia e Prevenzione, IRCCS Istituto Neurologico Mediterraneo, NEUROMED, Pozzilli, Italia (LI, ADC, GDG)
S.C. Neurologia, IRCCS - Arcispedale Santa Maria Nuova, Reggio Emilia, Italia (MZ, GM, NM)
Neurologia d'Urgenza and Stroke Unit, IRCCS Istituto Clinico Humanitas, Rozzano-Milano, Italia (SM)
Stroke Unit, Dipartimento di Neuroscienze, Ospedale Carlo Poma, Mantova, Italia (GS, AL, AC)
Unità di Neurologia, Ospedale di Circolo, Università dell'Insubria, Varese, Italia (MLDL)
Stroke Unit, U.O Neurologia, IRCCS Ospedale S. Raffaele, Milano, Italia (MS)
Stroke Unit, Clinica Neurologica, Nuovo Ospedale Civile "S. Agostino Estense", AUSL Modena, Italia (AZ, LV)
Stroke Unit and Divisione di Medicina Cardiovascolare, Università di Perugia, Italia (MP, GA)
Stroke Unit, Divisione di Neurologia, Dipartimento di Neuroscienze e Riabilitazione, Azienda Ospedaliero-Universitaria di Ferrara, Italia (CA, ADV)
Stroke Unit, Neurologia Vascolare, Spedali Civili di Brescia, Italia (MG)
Unità di Neurologia, E.O. Ospedali Galliera, Genova, Italia (MDS)
U.O.C. Neurologia, A.O Universitaria "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italia (AT, NP)
Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Università di Genova, Italia (CG)
Stroke Unit, U.O Neurologia, Ospedale "S. Chiara", Trento, Italia (DMB)
Stroke Unit, AOU Senese, Siena, Italia (RT, GM)

U.C Malattie Cerebrovascolari e Stroke Unit and U.C Neurologia d'Urgenza, IRCCS Fondazione Istituto Neurologico Nazionale "C. Mondino," Pavia, Italia (AC, GM)
Neurologia, Azienda Ospedaliero Universitaria Pisana, Pisa, Italia (AC)
Istituto di Ricovero e Cura a Carattere Scientifico, Centro Neurolesi Bonino-Pulejo, Messina, Italia (RSC)
Dipartimento di Neuroscienze, Scienze Psichiatriche e Anestesiologiche Clinica Neurologica, Università di Messina, Italia (RM, PLS)
USD Stroke Unit, DAI di Neuroscienze, Azienda Ospedaliera Universitaria Integrata Verona**,** Italia (PB, GT)
Centro Trombosi, IRCCS Istituto Clinico Humanitas, Rozzano-Milano, Italia (CL)
U.O. di Recupero e Rieducazione Funzionale, IRCCS Fondazione Don Gnocchi, Rovato, Italia (EDZ)
Divisione di Biologia e Genetica, Dipartimento di Medicina Molecolare e Traslazionale, Università degli Studi di Brescia, Italia (MR, MC)

Correspondence to:

Alessandro Pezzini
Dipartimento di Scienze Cliniche e Sperimentali
Clinica Neurologica
Università degli Studi di Brescia
P.le Spedali Civili, 1
25123 Brescia
Italia
Tel: +39.030.3384086
Fax: +39.030. 3384086
e-mail: ale_pezzini@hotmail.com
alessandro.pezzini@unibs.it

Serum Cholesterol Levels, HMG-CoA Reductase Inhibitors and the Risk of Intracerebral Hemorrhage.

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Dr. Alessandro Pezzini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Alessandro Pezzini, Mario Grassi. Acquisition of data: All authors. Interpretation of data: Alessandro Pezzini, Mario Grassi. Drafting of the manuscript: Alessandro Pezzini. Critical revision of the manuscript for important intellectual content: All authors. Data analysis: Alessandro Pezzini, Mario Grassi. Statistical analysis: Alessandro Pezzini, Mario Grassi. Administrative, technical, or material support: Alessandro Pezzini. Study supervision: Alessandro Pezzini, Alessandro Padovani

Abstract

Background and Purpose – Although a concern exists that HMG-CoA reductase inhibitors (statins) might increase the risk of intracerebral hemorrhage (ICH), the contribute of these agents on the relation between serum cholesterol and disease occurrence has been poorly investigated.

Methods – We compared consecutive patients with ICH with age and sex-matched stroke-free control subjects in a case-control analysis, as part of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy), and tested the presence of interaction effects between total serum cholesterol levels and statins on the risk of ICH.

Results - A total of 3,492 cases (mean age, 73.0±12.7 years; males, 56.6%) and 3,492 control subjects were enrolled. Increasing total serum cholesterol levels were confirmed inversely associated with ICH. We observed 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]. Increasing levels of total serum cholesterol were associated with a decreased risk of ICH within statin strata [average OR, 0.88; 95% CI, 0.86 – 0.89 for every increase of 0.26 mmol/l of total serum cholesterol concentrations], while statin use was associated with an increased risk (OR, 1.51; 95% CI, 1.29 – 1.75 at the average level of total serum cholesterol). The protective effect of serum cholesterol against ICH was reduced by statins in strictly lobar brain regions more than in non-lobar ones.

Conclusions – Statin therapy and total serum cholesterol levels exhibit interaction effects towards the risk of ICH. The magnitude of such effects appears higher in lobar brain regions.

Introduction

Increasing evidence has suggested that serum cholesterol is inversely associated to the risk of intracerebral hemorrhage (ICH)[1]. In the recent years, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have emerged as the most important class of cholesterol lowering agents, and among the most commonly prescribed drugs worldwide[2]. In spite of the proven benefits of statins in reducing the risk of cardiovascular and cerebrovascular disease, the results of several studies have raised concerns about the risk of hemorrhagic stroke, mainly ICH, in people treated with these agents[3,4], which is presumed to be the consequence of decreased serum cholesterol concentrations. Some of the pleiotropic effects of statins, including decreased platelet aggregation and decreased thrombogenesis, could further increase the risk of cerebral bleeding[5]. Although this potential risk, if any, is likely to be overshadowed by the large benefits in terms of reduction of individual susceptibility to cardiovascular disease, the clinical implications would be relevant, and clinicians would be asked to carefully consider this relation when prescribing statin therapy targeting low cholesterol goals. So far, the contribute of these agents on the link between serum cholesterol and ICH has been poorly investigated and the existing reports conflict with one another. Therefore, in the present study we aimed at elucidating whether 1) there is a relation between statin therapy and serum cholesterol, or *vice versa*, towards the risk of intra-cerebral bleeding, and 2) such a relation might vary according to the presumed mechanism of cerebral hemorrhage, in a cohort of Italian patients with ICH.

Material and Methods

Study Group and Design

The Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy) is a countrywide network of neurological centers designed to investigate epidemiology, risk factors and consequences of ICH in the setting of a hospital-based, multi-center, prospectively-recruiting, observational study, coordinated by the University of Brescia[6]. The MUCH-Italy study consists also of a biostatistical core (University of Pavia) and 19 Italian clinical recruiting centers. Institutional review board at each participating study center provided approval for the study. Written informed consent was obtained from all subjects (or next of kin). For the purpose of the present analysis, we screened data sets from patients with acute ICH consecutively admitted from January 1, 2002 to July 31, 2014.

Cases

Criteria for patient selection, risk factor definition, diagnostic procedures and assessment of hematoma location have been previously described[6].

Control Subjects

Control subjects were enrolled from the Moli-sani project, an Italian population-based study recruiting citizens of the Molise region, an area placed between Central and Southern region, aimed at investigating the equilibrium between genetics and environment in the pathogenesis of cardiovascular, cerebrovascular and cancer disease[7]. Individuals included were frequency-matched with cases by sex and age (± 5 years), and were confirmed to have no medical history of stroke through interview and review of medical records.

Measurement of Serum Lipid Levels

Fasting lipids measurements were carried out on venous blood samples in each participating center, using comparable enzymatic procedures. Hypercholesterolemia was defined as total serum cholesterol levels >6.2 mmol per liter out of the acute phase or using pharmacological treatment to lower blood lipids. Statin use included any of the following: atorvastatin, fluvastatin, lovastatin,

pravastatin, rosuvastatin, or simvastatin, or a combination medications that included a statin. Current use of these cholesterol-lowering medications was defined as filling a prescription for such medications in the 6 months prior to the index date. Subjects were classified as non-hypercholesterolemic, hypercholesterolemic under treatment with statins, or hypercholesterolemic not under treatment with statins. Data were obtained from interviews with patients, next of kin and/or attending physicians or general practitioners.

Statistical Analyses

We compared the characteristics of patients with ICH and control subjects using the χ^2 test for categorical variables, and the independent-samples *t*-test for continuous variables. Despite the matching criteria adopted for the selection of control individuals, this group was, on average, 3 years younger than that of cases. All multivariable analyses were, therefore, adjusted for age. We performed unconditional to matching logistic regression models to examine the effect of selected risk factors in the prediction of disease status (case/control) in each of the 3 study subgroups (overall ICH, deep ICH, and lobar ICH). In particular, we adjusted for those variables which might potentially influence the risk of cerebral bleeding, including age, hypertension (yes/no), diabetes mellitus (yes/no), hypercholesterolemia (yes/no), current smoking (yes/no), and antithrombotic medications use (yes/no). As statin treatment might modify the association between total serum cholesterol levels and ICH, we investigated whether this relation differed across strata of statin use, and tested the presence of interaction or modification effects. The modelling strategy assumed disease status (case/control) as outcome variable (Y), and total serum cholesterol concentrations (X) and statin use (Z) as predictors. In particular, we tested all the possible total serum cholesterol-statin use interaction logistic regression models (Supplemental Figure I). The assessment of interaction models was performed without and with adjustment for the following covariates: age, systolic blood pressure values, serum glucose levels, smoking habit, and use of antiplatelet agents and oral anticoagulants. To compare these competing models, we computed the Akaike's Information

Criterion (AIC= –2×model log-likelihood + 2×number of model parameters), and the Bayesian Information Criterion (BIC = –2×model log-likelihood + log(n)×number of model parameters). The selected model was the one minimizing either AIC or BIC[8]. The regression parameter estimates were re-expressed as Odds Ratios (ORs) and Interaction Odds Ratios [IOR= OR(group1)/OR(group2)], and 95% Confidence Intervals (95% CIs), using robust standard errors. For visualizing main effects and interaction of total serum cholesterol levels (X) and statin use (Z) with covariates, we consider the "covariate contribution" (CC = the sum of the covariates, excluding X and Z, multiplied by their corresponding logit coefficient) as suggested by Mitchell and Chen[9]. This reflects the aggregate contribution of covariates when the predicted probabilities of outcome (Y) in the logistic model are represented in two-dimensional plot. In particular, the probability plot displays the outcome probability Y as a function of the continuous variable X and the binary variable Z for low (20^{th} percentile) and high (80^{th} percentile) of CC. The threshold of statistical significance was set at $P < 0.05$ for all analyses. Data were analyzed using the SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL) package (www.spss.com) and our codes in R[10].

Results

A total of 3,492 patients with ICH (mean age, 73.0±12.7 years; males, 56.6%) and 3,492 control subjects (mean age, 70.6±10.5 years; males, 56.6%) were eligible for inclusion in the present study. All subjects were white. Based on the location of the hematoma, 1,604 (45.9%) patients were categorized as lobar ICH cases, while 1,888 (54.1%) as deep (non-lobar) ICH cases. Demographic and baseline clinical characteristics of the study group are summarized in Table 1, stratified by hematoma location. Compared to control subjects, cases were more likely to have a pre-ICH history of coronary artery disease, hypertension and diabetes, and to be prescribed anti-thrombotic medications. Their mean serum glucose levels, as well as systolic and diastolic blood pressure

values at the time of presentation were also higher. Conversely, they were less likely to have a history of hypercholesterolemia and their mean serum total cholesterol concentration was lower.

Table 1 about here

Table 2 summarises the associations between selected predisposing factors and the risk of ICH. The effect of hypertension and diabetes mellitus in increasing the risk of cerebral bleeding was prominent in non-lobar regions, whereas the use of antithrombotic medications was more strongly associated with lobar location of the hematoma. In contrast, we did not detect any association between current smoking and ICH, regardless of hemorrhage location. Of note, the protective effect of hypercholesterolemia was apparently attenuated by statin use, especially in the subgroup of patients with lobar ICH.

Table 2 about here

Akaike Information Criterion index and Bayesian Information Criterion index signed the "total serum cholesterol-statin use complete interaction model" (Supplemental Figure I, Model 8) as the best in predicting the effect of statins and total serum cholesterol levels on ICH risk (Supplemental Table I and Table II). Effects estimates for the interaction between statin use and total serum cholesterol levels, re-expressed as ORs, are displayed in Table 3. The interaction between total serum cholesterol levels and statin use for the risk of hemorrhage was statistically significant (IOR, 1.08; 95% CI, 1.05–1.12 for ICH regardless of hemorrhage location; IOR, 1.12; 95% CI, 1.07–1.17 for strictly lobar ICH; IOR, 1.07; 95% CI, 1.02–1.12 for deep ICH). Therefore, the effects of cholesterol and statins were not conditionally independent, but average effects. Overall, increasing levels of total serum cholesterol were associated with a decreased risk of ICH within statin strata [average OR, 0.88; 95% CI, 0.86–0.89 for every increase of 0.26 mmol per liter of total serum

cholesterol concentrations], an average effect that did not change substantially according to the location of cerebral hematoma (OR, 0.87; 95% CI, 0.85–0.89 for strictly lobar ICH; OR, 0.88; 95% CI, 0.87–0.90 for deep ICH). Conversely, statin use was associated with an increased risk of ICH at the average level of total serum cholesterol [5.7 mmol per liter: OR, 1.51; 95% CI, 1.29–1.75 for ICH regardless of hemorrhage location; OR, 1.46; 95% CI, 1.19–1.90 for strictly lobar ICH; OR, 1.48; 95% CI, 1.19–1.84 for deep ICH). These findings were not substantially affected by adjustment for covariates, except for the effect of statins on the risk of ICH which was strongly attenuated and became non-significant in multivariable model. Statin use resulted in a less dramatic change in the risk of cerebral bleeding across cholesterol values compared to non-statin use, and showed different association with disease risk according to serum cholesterol concentration. While marked reduction of cholesterol with statins was associated with a lower risk of ICH than naturally occurring low cholesterol, less severe reduction appeared to increase this risk.

Table 3 about here

Statin use, in particular, turned out to reduce the protective effect of total serum cholesterol against ICH (Figure 1), especially in strictly lobar brain regions (Figure 2) more than in non-lobar ones (Figure 3). After adjustment for potential confounders by covariate contributions we observed a direct, linear, slightly increased predicted probability of lobar ICH with increasing serum concentrations of total cholesterol in the subgroup of patients under treatment with statins (Figure 2B and 2C), an effect that was not detected neither in the whole cohort of patients with ICH (Figure 1B and 1C), nor in the subgroup of patients with non-lobar ICH (Figure 3B and 3C).

Figure 1, 2, and 3 about here

Discussion

The question of whether cholesterol-lowering drugs might be involved in the relationship between serum lipids, including cholesterol, and ICH has been matter of long debate. In particular, it is still unclear whether statin use may confer an increased risk of cerebral bleeding. The results of our study provide, therefore, further information on this theme and novel insights into the role of serum lipids in the etiology of ICH.

In line with a number of prior reports[1], we confirmed that total serum cholesterol concentrations are inversely associated with the risk of ICH. Although it still remains unclear how hypercholesterolemia might be protective against ICH occurrence, this relation appears biologically plausible and convincingly supported by the results of *in vitro* as well as animal studies. Because of the observational nature of our analysis, however, the extent to which serum cholesterol can be judged causal in the occurrence of ICH is difficult to assess. It could be theoretically argued that low cholesterol levels might be just an epiphenomenon of the individual propensity to cerebral hemorrhage rather than being causally related to the disease. Although we cannot definitively rule out this alternative interpretation, the dose-dependent relation we found (~12% decreased risk of ICH for every increase of 0.26 mmol/l in total serum cholesterol concentration) might be considered, however, an argument in favor of the hypothesis of a pathogenic link between serum cholesterol and cerebral hemorrhage.

Our findings also suggest that statin use before the index event might be related to intra-cerebral bleeding. A number of previous studies have highlighted the fact that statins, besides their effects as cholesterol-lowering agents, exhibit a wide range of anti-thrombotic properties, as a consequence of their modulatory effects on profibrinolytic mechanisms, blood coagulation cascade and platelet functions[5,11,12]. These effects could theoretically account for an increased risk of bleeding complications. Based on our data, the contribute of statins on the risk of cerebral bleeding might occur, at least in part, through their effect on serum total cholesterol levels. In particular, aggressive

statin treatment to low level of cholesterol is associated with a lower risk than naturally occurring low cholesterol, while less aggressive use of statins seems to reduce the strength of the inverse association between cholesterol and ICH, so that any protective influence of hypercholesterolemia might be attenuated by the cholesterol-lowering effect of these agents. These findings, indirectly, reinforce the assumption that total cholesterol might be related to the occurrence of brain hemorrhage, and make unlikely the influence of confounders, such as general medical or nutritional status[13]. On the other side, however, they are at odds with the results of previous meta-analyses of statin therapy which found no increased risk of hemorrhagic stroke in subjects taking these medications[14-17]. In particular, the inconsistency between the results from randomized clinical trials[16,17] and our findings is substantial, and calls for further investigation on how exactly cholesterol and statins affect stroke risk in order to explain this striking discrepancy. It should be noted, in this regard, that most of the previous studies on this topic were based on conventional regression models which allow to quantify the strength of the independent association of each factor (i.e, statins use or cholesterol level) with disease risk but do not allow to evaluate the interactions effects among these factors. What distinguishes our study from others is the application of a regression model which is able to explore and quantify the cholesterol-statins interactions and illustrate how these interactions influence outcome.

Another finding from our data is the differential patterns of association depending on the location of the hematoma, the strongest effect of statins being detected in the subgroup of patients with strictly lobar hemorrhage, likely related to cerebral amyloid angiopathy[18]. In agreement with our findings, statin therapy has been associated to an increased prevalence and severity of cerebral microbleeds, subclinical markers of vessel fragility and precursors of intra-cerebral bleeding, particularly in cortical-subcortical brain regions[19,20], as well as to higher propensity to lobar ICH in a recent epidemiologic study with the same case-control design of ours [21]. This supports the hypothesis of a different susceptibility of cerebral small vessels to the effect of serum lipids and statins.

The MUCH-Italy collaborative study differs from previous epidemiologic analyses on this topic in several ways that increase its reliability and precision: it is large, involving more than twice the number of subjects included in previous observational studies with the same design; it is based on a rigorous case-control matching and racial homogeneity; fasting total serum cholesterol levels are available for most of the participants, which implicates the ability to perform adequate interaction analyses; and it has the advantages of hospital-based recruitment, including a detailed and standardized data collection with few missing information, and complete radiologic data allowing to explore the effect of confounders on the cholesterol-statins-ICH relation. Nevertheless, we are aware of several limitations. We did not control for statin dosing, duration of treatment, or compliance because these data were not collected. The same is for the lack of cholesterol fractions, such as high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations, as well as for the absence of repeated measures of cholesterol, which does not allow to rule out intra-individual fluctuations in serum levels over time. Another caveat is the possibility that vascular disease can itself directly or indirectly affect blood cholesterol concentration. Although these drawbacks are noteworthy, we believe they do not alter the obvious clinical implication of our findings.

Conclusions

Although 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[2], clinicians should carefully consider bleeding susceptibility when prescribing statin therapy targeting reduced cardiovascular risk. Identification of those statin users who are more prone to develop this complication will be the goal of future research.

Disclosures

None

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Tables and Figure

Table 1

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

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

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 (20^{th} percentile, B), and high (80^{th} percentile, C) of covariate contribution.

Figure 2

Predicted probability (risk) of lobar ICH for total cholesterol and statin use (A), by low (20^{th} percentile, B), and high (80^{th} percentile, C) of covariate contribution.

Figure 3

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

	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 (8.0)	<0.001	283 (15.0)	146 (7.8)	<0.001
Hypertension			<0.001			<0.001			<0.001
Non-hypertensive	861 (24.7)	1574 (45.1)		430 (26.8)	707 (44.1)		431 (22.9)	867 (45.9)	
Hypertensive under treatment	2166 (62.1)	1822 (52.2)		998 (62.3)	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)	
Systolic blood pressure, mm Hg	165.6 ± 29.8	152.9 ± 21.6	<0.001	161.6 ± 28.8	152.8 ± 21.5	<0.001	169.2 ± 29.8	153.0 ± 21.7	<0.001
Diastolic blood pressure, mm Hg	89.7 ± 18.4	81.6 ± 9.9	<0.001	87.0 ± 17.6	81.1 ± 10.1	<0.001	92.0 ± 18.3	81.9 ± 9.7	<0.001
Diabetes			<0.001			<0.001			
Non-diabetic	2846 (81.6)	3069 (87.8)		1327 (82.8)	1417 (88.4)		1519 (80.6)	1652 (87.5)	
Diabetic under treatment	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)		66 (3.5)	19 (1.0)	
Serum glucose, mmol/l	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
Hypercholesterolemia			<0.001			<0.001			<0.001
Non-hypercholesterolemic	2617 (75.2)	2506 (71.8)		1210 (75.6)	1139 (71.0)		1406 (74.6)	1367 (72.4)	
Hypercholesterolemic under treatment with statins	587 (16.8)	437 (12.5)		276 (17.3)	207 (12.9)		311 (16.5)	230 (12.2)	
Hypercholesterolemic not under treatment	280 (8.0)	549 (15.7)		113 (7.1)	258 (16.1)		167 (8.9)	291 (15.4)	

Serum total cholesterol, mmol/l	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
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	1138 (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

	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 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 not 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			
Diabetic 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 not 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 under treatment with statins	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 not under treatment	0.42 (0.35 - 0.50)	<0.001	0.39 (0.30 - 0.50)	<0.001	0.45 (0.36 - 0.57)	<0.001
Current smoking	1.10 (0.94 - 1.29)	0.220	1.06 (0.82 - 1.36)	0.648	1.13 (0.92 - 1.40)	0.228
Antiplatelet agents	3.31 (2.90 - 3.78)	<0.001	3.68 (3.03 - 4.47)	<0.001	3.08 (2.57 - 3.69)	<0.001
Oral anticoagulants	19.83 (13.57 - 28.98)	<0.001	25.42 (14.63 - 44.15)	<0.001	15.84 (9.38 - 26.76)	<0.001

Table 2

	All ICH				Lobar ICH				Deep ICH			
	Crude OR (95% CI)	***P*-value interaction**	**Adjusted OR (95% CI)**	***P*-value interaction**	**Crude OR (95% CI)**	***P*-value interaction**	**Adjusted OR (95% CI)**	***P*-value interaction**	**Crude OR (95% CI)**	***P*-value interaction**	**Adjusted OR (95% CI)**	***P*-value interaction**
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 x 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

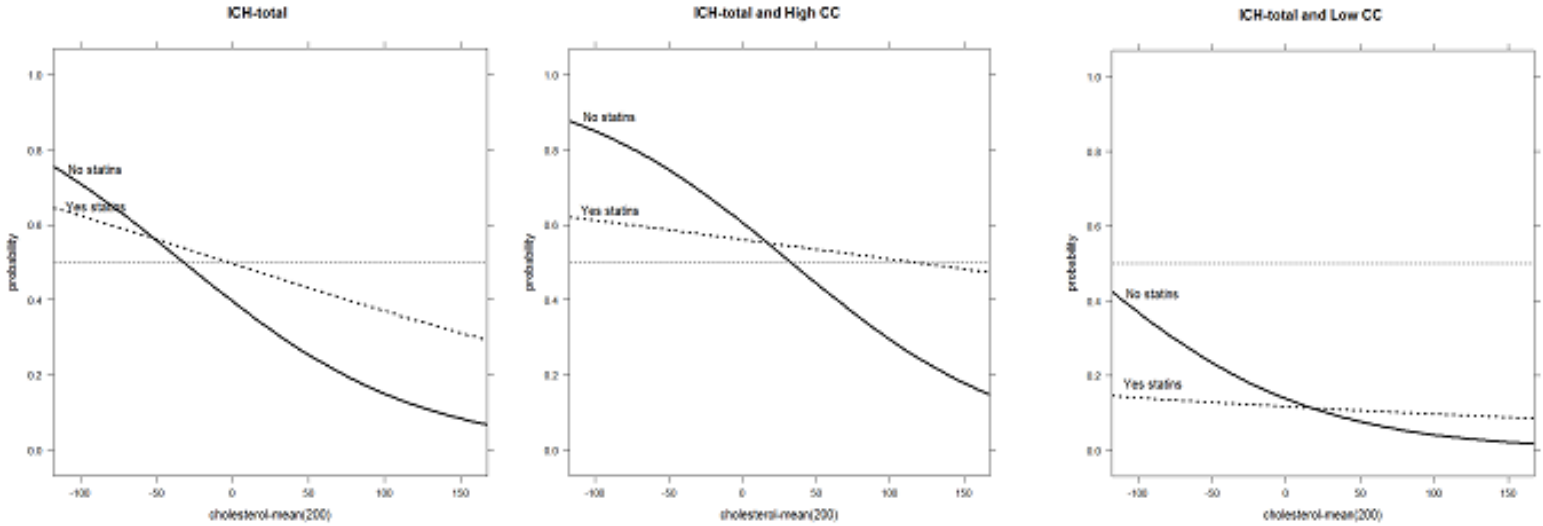
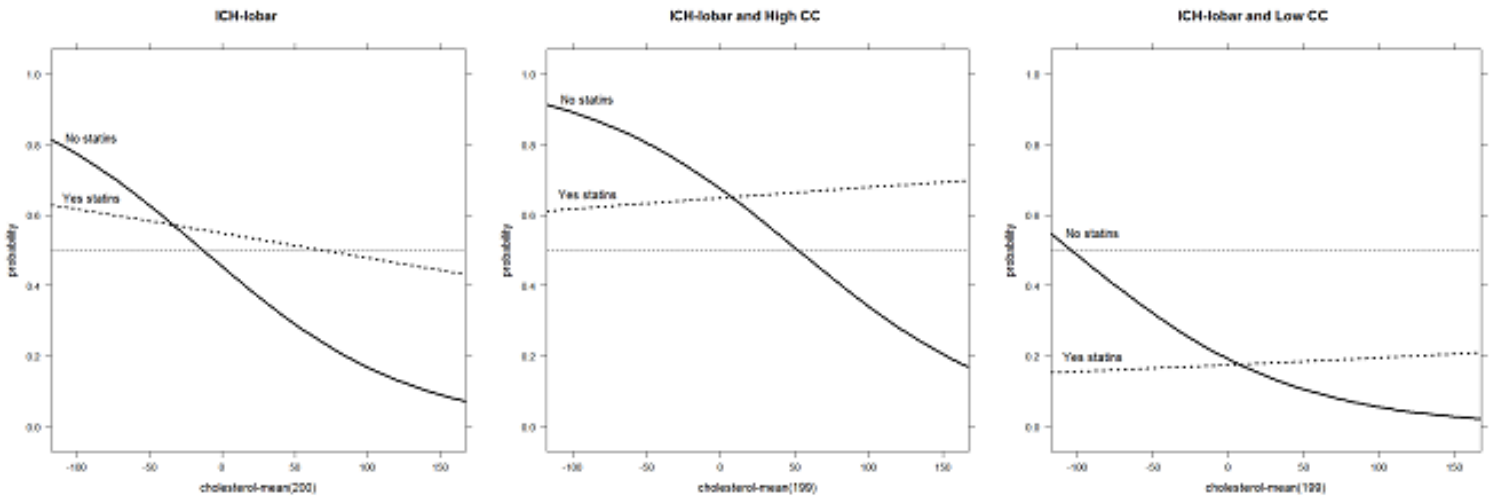

ICH-total
No statins
Yes statins
probability
cholesterol-mean(200)
A
ICH-total and High CC
No statins
Yes statins
probability
cholesterol-mean(200)
B
ICH-total and Low CC
No statins
Yes statins
probability
cholesterol-mean(200)
C

Figure 1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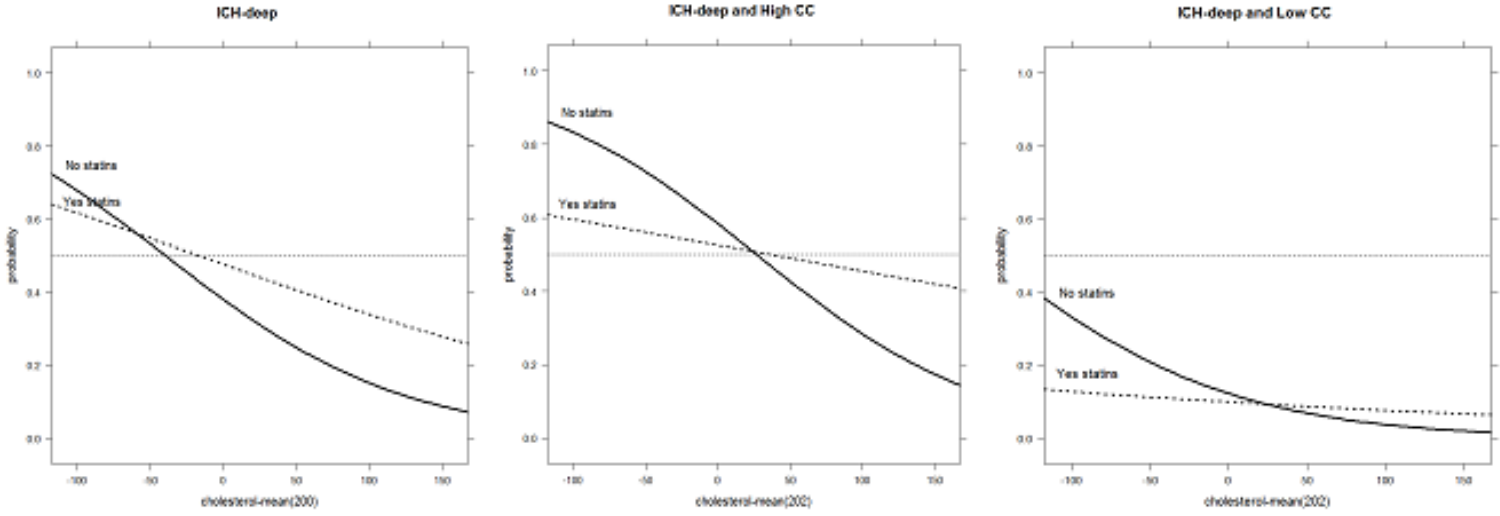
No statins
Yes statins
probability
cholesterol-mean(200)
ICH-lobar and High CC
No statins
Yes statins
probability
cholesterol-mean(199)
ICH-lobar and Low CC
No statins
Yes statins
probability
cholesterol-mean(199)

A **B** **C**

Figure 2


ICH-deep
No statins
Yes statins
probability
cholesterol-mean(200)
ICH-deep and High CC
No statins
Yes statins
probability
cholesterol-mean(202)
ICH-deep and Low CC
No statins
Yes statins
probability
cholesterol-mean(202)

A B C

Figure 3

Supplemental Material

Pezzini A, Grassi M, Iacoviello L, et al. Serum Cholesterol Levels, HMG-CoA Reductase Inhibitors and the Risk of Intracerebral Hemorrhage. The MUCH-Italy

Supplemental Figure I

Total serum cholesterol-statin therapy interaction logistic regression models.

Supplemental Table I

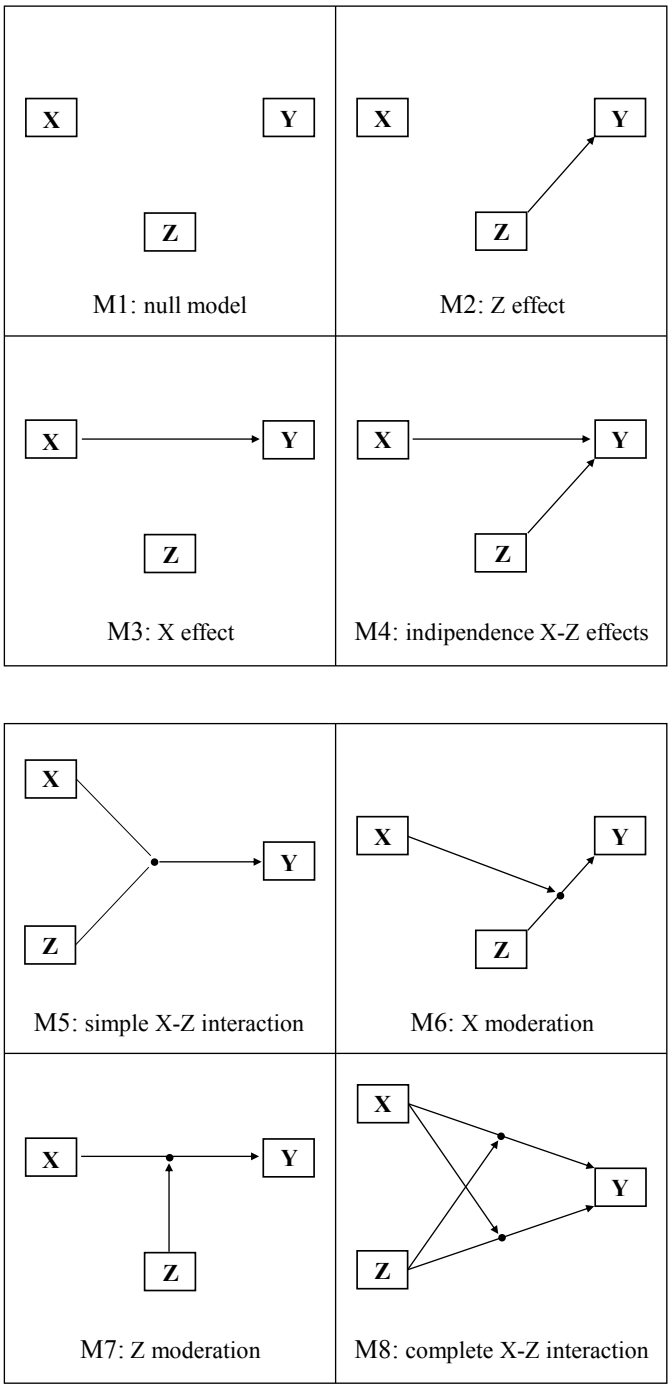
Goodness of fit statistics of the interaction logistic regression models (M1 - M8) without covariates.

Deviance = –2 × log-likelihood (M); t = number of parameters; AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion.

Supplemental Table II

Goodness of fit statistics of the interaction logistic regression models (M1 - M8) with covariates.

Deviance = –2 × log-likelihood (M); t = number of parameters; AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion. Covariates were age, systolic blood pressure values, serum glucose levels, smoking habit (current use), antiplatelet agents, and oral anticoagulants.



Supplemental Figure I

	Deviance	t	AIC	BIC
Deep ICH vs controls				
M1	4096.805	1	4098.805	4104.835
M2	4070.201	2	4074.201	4086.261
M3	3895.339	2	3899.339	3911.399
M4	3887.948	3	3893.948	3912.037
M5	4078.226	2	4082.226	4094.285
M6	4061.45	3	4067.45	4085.54
M7	3885.087	3	3891.087	3909.177
M8	3881.349	4	3889.349	3913.468
Lobar ICH vs controls				
M1	4053.386	1	4055.386	4061.372
M2	4035.501	2	4039.501	4051.473
M3	3809.285	2	3813.285	3825.258
M4	3802.245	3	3808.245	3826.203
M5	4040.927	2	4044.927	4056.9
M6	4030.561	3	4036.561	4054.519
M7	3796.149	3	3802.149	3820.108
M8	3780.204	4	3788.204	3812.149
Overall ICH vs controls				
M1	7844.745	1	7846.745	7853.414
M2	7795.54	2	7799.54	7812.879
M3	7416.537	2	7420.537	7433.876
M4	7401.157	3	7407.157	7427.165
M5	7841.545	2	7845.545	7858.884
M6	7779.904	3	7785.904	7805.912
M7	7408.829	3	7414.829	7434.837
M8	7381.585	4	7389.585	7416.263

Supplemental Table I

	Deviance	t	AIC	BIC
Deep ICH vs controls				
M1	2801.224	7	2815.224	2857.02
M2	2799.101	8	2815.1	2862.866
M3	2684.951	8	2700.951	2748.717
M4	2676.536	9	2694.536	2748.272
M5	2788.814	8	2804.814	2852.58
M6	2788.698	9	2806.698	2860.434
M7	2669.877	9	2687.877	2741.614
M8	2667.356	10	2687.356	2747.063
Lobar ICH vs controls				
M1	2885.201	7	2899.201	2940.639
M2	2884.464	8	2900.464	2947.822
M3	2744.206	8	2760.206	2807.563
M4	2740.877	9	2758.877	2812.155
M5	2863.61	8	2879.61	2926.967
M6	2863.595	9	2881.595	2934.873
M7	2714.38	9	2732.38	2785.657
M8	2713.712	10	2733.71	2792.909
Overall ICH vs controls				
M1	5392.807	7	5406.807	5453.055
M2	5390.179	8	5406.179	5459.034
M3	5155.532	8	5171.532	5224.386
M4	5143.262	9	5161.262	5220.724
M5	5368.985	8	5384.985	5437.84
M6	5368.881	9	5386.881	5446.342
M7	5122.638	9	5140.638	5200.099
M8	5119.469	10	5139.469	5205.538

Supplemental Table II

Appendix

MUCH-Italy Co-investigators (listed by participating centers)

Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia (Alessandro Pezzini, Andrea Morotti, Paolo Costa, Loris Poli, Valeria De Giuli, Silvia Bonaiti, Alessandro Padovani); Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Unità di Statistica Medica e Genomica, Università di Pavia (Mario Grassi); Stroke Unit and Divisione di Medicina Cardiovascolare, Università di Perugia (Maurizio Paciaroni, Cataldo d'Amore, Monica Acciarresi, Valeria Caso, Andrea Alberti, Michele Venti, Giancarlo Agnelli); Stroke Unit, Clinica Neurologica, Nuovo Ospedale Civile "S. Agostino Estense", AUSL Modena (Andrea Zini, Laura Vandelli, Maria Luisa Dell'Acqua, Anna Maria Simone, Paolo Frigio Nichelli); Stroke Unit, Dipartimento di Neuroscienze, Ospedale Carlo Poma, Mantova (Giorgio Silvestrelli, Alessia Lanari, Alfonso Ciccone); U.O. di Recupero e Rieducazione Funzionale, IRCCS Fondazione Don Gnocchi, Rovato (Elisabetta Del Zotto); Stroke Unit, Neurologia Vascolare, Spedali Civili, Brescia (Massimo Gamba, Nicola Gilberti, Mauro Magoni); Divisione di Biologia e Genetica, Dipartimento di Medicina Molecolare e Traslazionale, Università degli Studi di Brescia (Marco Ritelli, Marina Colombi); Centro Trombosi, IRCCS Istituto Clinico Humanitas, Rozzano-Milano (Corrado Lodigiani); Neurologia d'Urgenza - Stroke Unit, IRCCS Istituto Clinico Humanitas, Rozzano-Milano (Simona Marcheselli); Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Università di Genova (Gabriele Zucco, Davide Massucco, Cinzia Finocchi, Maurizio Balestrino, Carlo Gandolfo); USD Stroke Unit, DAI di Neuroscienze, Azienda Ospedaliera Universitaria Integrata Verona (Paolo Bovi, Giampaolo Tomelleri, Monica Carletti, Cecilia Zivelonghi); Dipartimento di Neuroscienze, Scienze Psichiatriche e Anestesiologiche Clinica Neurologica, Università di Messina (Rossella Musolino, Paolo La Spina); Istituto di Ricovero e Cura a Carattere Scientifico, Centro Neurolesi Bonino-Pulejo, Messina (Rocco Salvatore Calabrò, Placido Bramanti); Unità di Neurologia, Ospedale di

Circolo, Università dell'Insubria, Varese (Maria Luisa Delodovici, Lucia Princiotta Cariddi); Unità di Neurologia, Ospedale S. Andrea, La Spezia (Massimo Del Sette, Elisa Giorli); Unità di Neurologia, E.O. Ospedali Galliera, Genova, Italia (Massimo Del Sette); Stroke Unit, U.O Neurologia, IRCCS Ospedale S. Raffaele, Milano (Maria Sessa, Davide Strambo, Giacomo Giacalone); Laboratorio di Epidemiologia Molecolare e Nutrizionale, Dipartimento di Epidemiologia e Prevenzione, IRCCS Istituto Neurologico Mediterraneo NEUROMED, Pozzilli (Licia Iacoviello, Augusto Di Castelnuovo, Giovanni de Gaetano); U.O.C. Neurologia, A.O Universitaria "San Giovanni di Dio e Ruggi d'Aragona", Salerno (Antonella Toriello, Aurelio Glielmi, Giampiero Volpe, Nicola Pugliese); U.C Malattie Cerebrovascolari e Stroke Unit and U.C Neurologia d'Urgenza, IRCCS Fondazione Istituto Neurologico Nazionale "C. Mondino" Pavia (Anna Cavallini, Giuseppe Micieli); Neurologia, Azienda Ospedaliero Universitaria Pisana, Pisa (Alberto Chiti, Vincenzo Montano); Stroke Unit, Divisione di Neurologia, Dipartimento di Neuroscienze e Riabilitazione, Azienda Ospedaliero-Universitaria di Ferrara (Cristiano Azzini, Alessandro De Vito, Marina Padroni); Stroke Unit, AOU Senese, Siena (Rossana Tassi, Giovanna Marotta, Giuseppe Martini); S.C. Neurologia, IRCCS - Arcispedale Santa Maria Nuova, Reggio Emilia (Marialuisa Zedde, Giovanni Malferrari, Norina Marcello); Stroke Unit, U.O Neurologia, Ospedale "S. Chiara", Trento, Italia (Domenico Marco Bonifati)