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Antithrombotic medications and the etiology of intracerebral hemorrhage

MUCH-Italy

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ABSTRACT

Objective: To test the hypothesis that the effect of antithrombotic medications on the risk of intracerebral hemorrhage (ICH) varies according to the location of the hematoma.

Methods: Consecutive patients with ICH were enrolled as part of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy). Multivariable logistic regression models served to examine whether risk factors for ICH and location of the hematoma (deep vs lobar) predict treatment-specific ICH subgroups (antiplatelets-related ICH and oral anticoagulants [OACs]-related ICH).

Results: A total of 870 (313 lobar ICH, 557 deep ICH) subjects were included. Of these, 223 (25.6%) were taking antiplatelets and 77 (8.8%) OACs at the time of stroke. The odds of antiplatelet-related ICH increased with aging (odds ratio [OR] 1.05; 95% confidence interval [CI] 1.03–1.07) and hypertension (OR 1.86; 95% CI 1.22–2.85) but had no relation with the anatomical location of ICH. Conversely, lobar location of the hematoma was associated with the subgroup of OAC-related ICH (OR 1.70; 95% CI 1.03–2.81) when compared to the subgroup of patients taking no antithrombotic medications. Within the subgroup of patients taking OACs, international normalized ratio (INR) values were higher in those with lobar ICH as compared to those with deep ICH (2.8 ± 1.1 vs 2.2 ± 0.8 ; $p = 0.011$). The proportion of patients with lobar hematoma increased with increasing intensity of anticoagulation, with a ~2-fold increased odds of lobar compared to deep ICH (odds 2.17; $p = 0.03$) in those exposed to overanticoagulation (INR values >3.0).

Conclusions: OACs, as opposed to antiplatelets, predispose to lobar location of brain hematomas according to a dose-response relationship. *Neurology*® 2014;82:529–535

GLOSSARY

BMI = body mass index; **BP** = blood pressure; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **ICH** = intracerebral hemorrhage; **INR** = international normalized ratio; **MUCH-Italy** = Multicenter Study on Cerebral Hemorrhage in Italy; **OAC** = oral anticoagulant.

Antithrombotic medications are a highly effective therapy for the prevention of thromboembolic strokes in common clinical situations. However, the increasing use of both antiplatelet and oral anticoagulant (OAC) agents in an aging population has been associated with an increased risk of intracerebral hemorrhage (ICH),^{1–4} with the annual incidence ranging from 0.02% to 0.47% in patients taking a single antiplatelet agent to 0.3%–0.6% in those on OAC therapy.^{5,6} The prevention of ICH in patients with antithrombotic medications is therefore critical, and the identification of risk factors for bleeding is an important practical issue. Data are needed to determine how specific markers may contribute to individualized risk prediction in order to make antithrombotics as safe and effective as possible. Several lines of evidence support the hypothesis that age-related disorders of cerebral small vessels are closely linked to this rare but devastating complication of antithrombotics use. In other terms, antithrombotic medications

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per se might not cause ICH if cerebral vessels are intact, but the presence of microangiopathy, rendering small vessels brittle and fragile, is a plausible causal or predisposing factor for bleeding. In this regard, sparse reports have suggested that cerebral amyloid angiopathy (CAA) may be a stronger predictor of antithrombotic-associated ICH than hypertensive microangiopathy,^{7–10} but some recent observations have questioned this assumption.^{11,12} Thus, any specific relation has not yet been established. The Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy) provides the opportunity to investigate this issue owing to its large sample size, the homogeneous demographic characteristics and clinical phenotype of the subjects included, and the standard diagnostic workup. Therefore, we aimed to evaluate whether 1) antithrombotic medications have differential influence on specific small cerebral vessel pathology, using hemorrhage location (deep vs lobar) to categorize the likely etiology, and 2) any dose-effect relationship of anticoagulation may further predispose to bleeding, in a cohort of Italian stroke patients with ICH.

METHODS Study group. MUCH-Italy is a countrywide network of neurologic centers aimed at recruiting patients with cerebral hemorrhage in the setting of a hospital-based, multicenter, observational study, as previously described.¹³ For the purpose of the present analysis, we screened datasets from patients with acute ICH consecutively admitted to 4 hospitals between January 2002 and July 2011. Eligibility for study participation required neuroimaging (CT or MRI) confirmation of hemorrhagic stroke. Exclusion criteria included the presence of trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other perceived cause of secondary ICH. ICH location was assigned based on admission CT scan by stroke neurologists at each participating center. ICH isolated to the cortex (with or without involvement of subcortical white matter) and cerebellar hematomas were defined as lobar ICH, while ICH selectively involving the thalamus, basal ganglia, or brainstem was defined as deep (nonlobar) ICH. Multiple concurrent bleeds involving deep and lobar territories were defined as mixed ICH and represented an exclusion criterion. Demographic and clinical information, as well as neuroimaging data, were collected prospectively and ascertained by neurologists in each center. International normalized ratio (INR) was determined in each patient at admission as part of routine laboratory testing.

Standard protocol approvals, registrations, and patient consents. The study was approved by relevant local authorities at each study site. Written informed consent was obtained from all patients (or next of kin).

Risk factor definition. Subjects were classified as current smokers if they were currently smoking one or more cigarettes per day on a regular basis. Hypertension was defined as systolic

blood pressure (BP) >140 mm Hg or diastolic BP >90 mm Hg out of the acute phase or using pharmacologic treatment for hypertension. Hypercholesterolemia was considered as cholesterol >240 mg/dL out of the acute phase or using pharmacologic treatment to lower blood lipids. Diabetes was defined as fasting glucose levels >125 mg/dL out of the acute phase or current treatment with antidiabetic drugs. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2) and subjects dichotomized into obese ($\text{BMI} \geq 30.0 \text{ kg}/\text{m}^2$) and nonobese ($\text{BMI} < 30.0 \text{ kg}/\text{m}^2$). Based on daily alcohol consumption, subjects were dichotomized into excessive drinkers (>45 g of alcohol) and light to moderate drinkers/nondrinkers. We also collected information on atrial fibrillation (medical history or electrocardiographic findings at admission), atherosclerotic peripheral arterial disease (medical history), coronary artery disease (medical history of angina, myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty), history of previous stroke or TIA (based on clinical history), and pre-ICH medications (warfarin, aspirin or other antiplatelet agents, antihypertensive agents, oral hypoglycemic agents or insulin, and statins).¹³ Data were obtained from interviews with patients, next of kin, or attending physicians or general practitioners.

Statistical analyses. Differences among the treatment groups (ICHs unrelated to antithrombotic medications, antiplatelet-related ICHs, and OAC-related ICHs) were examined with the χ^2 test, median test, and analysis of variance *F* test, when appropriate. Categorical (multinomial) logistic regression model was performed to examine the conditional effect of risk factors (hypertension, diabetes, hypercholesterolemia, smoking, alcohol consumption) and location of the hematoma (deep vs lobar) in the prediction of ICH subgroups, adjusted for age and sex (model 1). Since both CAA and hypertensive vasculopathy may be involved in the pathogenesis of cerebellar hemorrhages,¹⁴ we conducted a separate analysis after exclusion of the cerebellar ICH cases from the study group, to minimize their potentially confounding effect (model 2). Finally, in order to investigate any dose effect of anticoagulant medications, we tested the impact of specific INR categories ($\text{INR} \leq 1.2$; $1.2 < \text{INR} \leq 2.0$; $2.0 < \text{INR} \leq 3.0$; $\text{INR} > 3.0$) on the location of the hematoma within the subgroup of patients with OAC-related ICH using the 4×2 frequency table. Results are given as ORs (as measures of disease risk for ICH–covariate associations) with 95% confidence intervals (CIs). A *p* value < 0.05 on 2-sided test was considered significant. Data were analyzed using SPSS v. 16 (www.spss.com).

RESULTS A total of 870 patients with ICH fulfilled the inclusion criteria (mean age 72.4 ± 13.0 years; 55.7% male). A total of 313 (36.0%) had lobar ICH, while 557 (64.0%) had deep ICH. A total of 300 (34.5%) patients were on treatment with antithrombotic medications at the time of stroke occurrence, including 223 (25.6%) patients taking antiplatelet drugs and 77 (8.8%) taking OACs (5 patients using a combination of antiplatelet agents and OACs were categorized as OAC users). No patient was on treatment with other antithrombotic agents (i.e., heparin) before admission. The characteristics of the study group are summarized in table 1, stratified by antithrombotic medications. Overall, patients treated with antithrombotics were older and more frequently

Table 1 Demographic and clinical characteristics of the study group

	No antithrombotic therapy (n = 570)	Antiplatelet-related ICH (n = 223)	OAC-related ICH (n = 77)	p Value
Age, y, mean ± SD	69.8 ± 13.9	77.2 ± 9.5	78.1 ± 8.8	0.002
Female	239 (41.9)	111 (49.8)	35 (45.5)	0.132
BMI ≥30 kg/m ²	202 (35.8)	72 (32.3)	25 (32.5)	0.592
Coronary artery disease	48 (8.5)	69 (31.1)	16 (20.8)	<0.001
Brain ischemia	20 (3.5)	44 (19.8)	17 (22.1)	<0.001
Atrial fibrillation	20 (3.5)	48 (21.6)	50 (66.7)	<0.001
Peripheral arterial disease	13 (2.3)	5 (2.2)	6 (7.8)	0.019
Hypertension				<0.001
Nonhypertensive	152 (26.8)	34 (15.2)	16 (20.8)	
Hypertensive on treatment	299 (52.7)	172 (77.1)	52 (67.5)	
Hypertensive not on treatment	116 (20.5)	17 (7.6)	9 (11.7)	
Diabetes				0.642
Nondiabetic	470 (82.9)	180 (80.7)	59 (76.6)	
Diabetic on treatment	69 (12.2)	32 (14.3)	12 (15.6)	
Diabetic not on treatment	28 (4.9)	11 (4.9)	6 (7.8)	
Cholesterolemia				0.012
Nonhypercholesterolemic	455 (80.2)	171 (76.7)	66 (85.7)	
Hypercholesterolemic on treatment with statins	51 (9.0)	36 (16.1)	9 (11.7)	
Hypercholesterolemic not on treatment	59 (10.4)	16 (7.2)	2 (2.6)	
Current smoking	83 (14.7)	28 (12.6)	5 (6.5)	0.128
Alcohol, excessive drinking	93 (16.3)	30 (13.5)	11 (14.3)	0.580
ICH location				
Deep	377 (66.1)	139 (62.3)	41 (53.2)	0.072
Lobar	193 (33.9)	84 (37.7)	36 (46.8)	

Abbreviations: BMI = body mass index; ICH = intracerebral hemorrhage; OAC = oral anticoagulant. Data are n (%) unless otherwise noted.

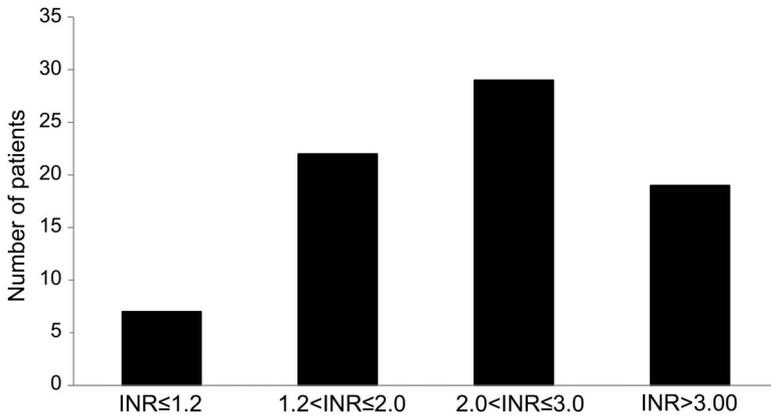
female and had a higher prevalence of risk factors (in particular, hypertension) and comorbidities (previous brain ischemia, ischemic heart disease, and atrial fibrillation) than patients who were not on treatment.

The majority of antiplatelet users were on treatment with aspirin (n = 207, 90.8%; ticlopidine, n = 17, 7.5%; clopidogrel, n = 3, 1.3%; aspirin plus dipyridamole, n = 1, 0.4%). Among OAC users, 7 (9.1%) had INR values ≤1.2, 22 (28.6%) had INR values 1.2–2.0, 29 (37.7%) had INR values 2.0–3.0, and 19 (24.7%) had INR values >3.0 (figure 1). The mean INR value in this subgroup was 2.5 ± 1.0 and was higher in patients with lobar ICH as compared to those with deep ICH (2.8 ± 1.1 vs 2.2 ± 0.8; p = 0.011). The mean INR value in the subgroup of patients exposed to overanticoagulation (INR > 3) was 4.0 ± 0.8.

As summarized in table 2, aging had a similar effect on increasing the risk of disease in the group of antiplatelet-related ICH (OR 1.05; 95% CI 1.03–1.07) as well as in that of OAC-related ICH (OR

1.06; 95% CI 1.03–1.09) when compared to the reference group of patients who were taking no antithrombotic medications at the time of stroke occurrence. In addition, we observed an increase in the risk of ICH with hypertension, which was significant only in the subgroup of patients with antiplatelet-related ICH (OR 1.86; 95% CI 1.22–2.85). None of the other traditional vascular risk factors had any independent influence on the risk of antithrombotic-related ICH. Lobar location of the hematoma was associated with the subgroup of OAC-related ICH (OR 1.70; 95% CI 1.03–2.81), as opposed to what was observed for deep ICH, while hemorrhage location had no significant association with the subgroup of antiplatelet-related ICH (model 1). Results remained substantially unchanged when data were reanalyzed after removing the subgroup of patients with cerebellar hemorrhages (model 2, not shown). Within the subgroup of OAC-related ICH, the frequency of ICH increased in both deep and lobar brain regions with increasing INR values up to 3.0, with no difference between the 2

Figure 1 Proportion of patients in various categories of international normalized ratio values at admission



Within the subgroup of oral anticoagulant-related intracerebral hemorrhage. INR = international normalized ratio.

groups ($p > 0.05$), but it decreased in deep structures when INR values were >3.0 ($p < 0.05$; figure 2A). The proportion of patients with lobar ICH increased with increasing intensity of anticoagulation according to a direct dose-response relationship (figure 2B), which resulted in a ~ 2 -fold increased odds of lobar ICH compared to deep ICH (odds 2.17; $p = 0.03$) in the subgroup with the highest level of anticoagulation (INR > 3.0).

DISCUSSION The precise contribution of antithrombotic medications to the location of ICH has not yet been determined. Our study, involving a large cohort of patients with ICH, indicates that antiplatelet agents have a negligible influence on the site of bleeding, their effect probably being overcome by that of other predisposing conditions, such as aging and hypertension, while, conversely, the use of OACs predisposes to lobar location of brain hematomas.

These findings confirm and extend those of previous studies on the relation between antithrombotic medications and hemorrhagic stroke and add further

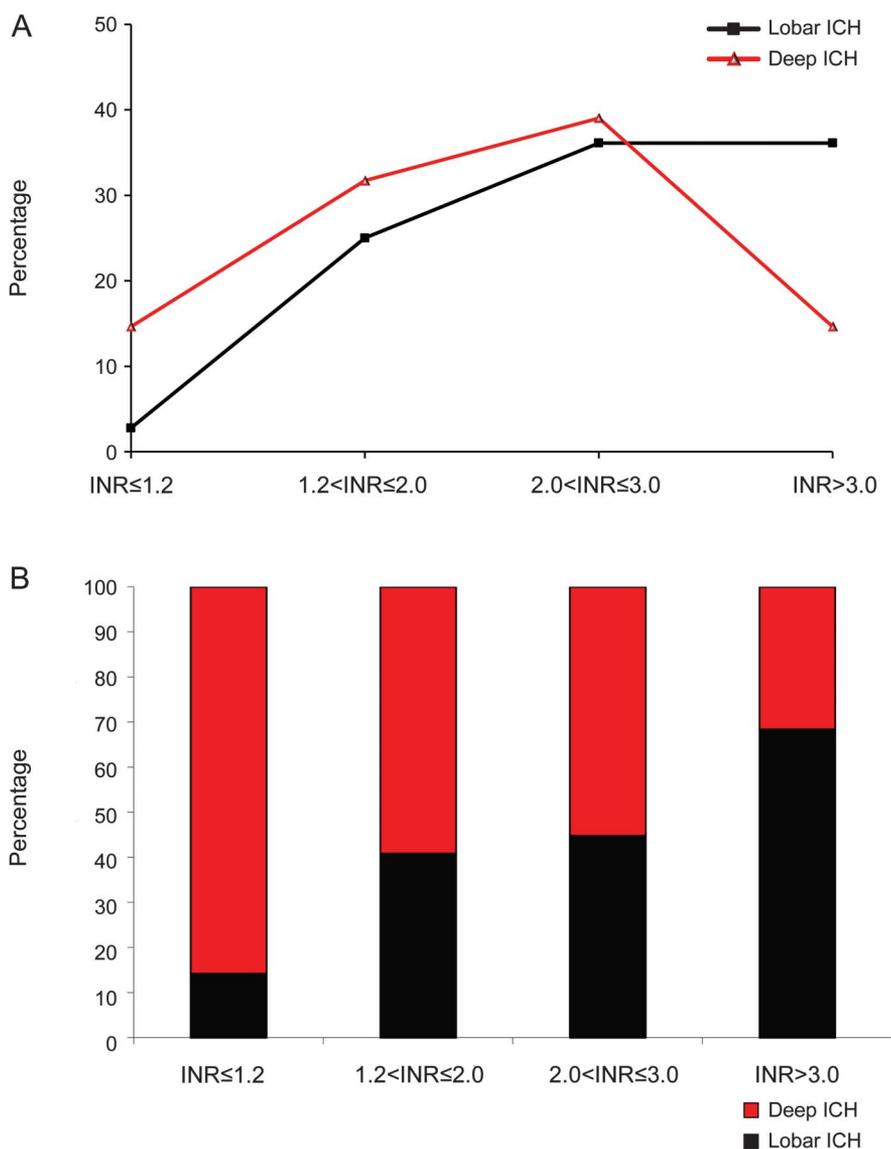
data on the question of whether the contribution of these agents, especially OACs, to cerebral bleeding might vary by anatomical location. First, they confirm that ICH is common in patients treated with antithrombotic drugs, independent of the anatomical location of bleeding. Furthermore, in our series like in prior studies,^{8,15,16} a relevant proportion of ICH among those on OACs occurred when the INR values were in the therapeutic range. Second, they support previous observations that OAC-related ICHs occur with a slightly more frequent lobar location.⁷⁻¹⁰ However, data on the impact of specific small-vessel arteriopathies on OAC-related ICH are scarce, mainly derived from studies including small case series, sometimes recording individual history of OAC use without taking into consideration the intensity of anticoagulation,⁷ including patients receiving heparin at the time of stroke,^{8,11} or aimed at addressing different issues,^{8,9,11} with only a few notable exceptions.^{10,12} In this regard, a novel finding from our data is the evidence of a direct dose-response relationship between OAC treatment and lobar ICH, as illustrated by the increasing number of patients in this subgroup as the INR values increase. We speculate that OACs affect CAA and hypertensive arteriolosclerosis equally when INR values are within the therapeutic range, but that they exert a differential impact on the 2 cerebral microangiopathies, with a greater effect on cortical-subcortical vessels, in case of excessive anticoagulation. As a consequence of this, there might be an individual threshold of INR values over which the influence of OACs on hematoma location becomes more evident. It remains unclear whether this is a causal association, or, more likely, the end result of a dynamic interplay among several conditions including the underlying bleeding-prone small-vessel disease, the direct effect of these agents on the clotting cascade, and other unknown factors. Though unproven, a number of histologic findings provide biologic support to this view. Arteriolar wall thinning, interposition of amyloid deposits between smooth muscle cells, dilated perivascular spaces, and microaneurysms are frequent findings in CAA involving lobar brain regions, whereas thickening of the vessel wall caused by lipohyalinosis in response to chronic hypertension is the pathologic marker of arteriolosclerosis in deep regions. It is likely that these abnormalities might render cortical-subcortical vessels more vulnerable to rupture and with less potential for tamponade compared to deep perforating arteries in the presence of excessive anticoagulation.^{17,18} In addition, evidence supporting a link between CAA and OAC-ICH includes the demonstration that the *APOE* $\epsilon 2$ allele, a known genetic risk factor of CAA-related lobar ICH,^{19,20} is more common in warfarin-associated ICH than in control patients on

Table 2 Conditional effect of age, sex, risk factors (hypertension, diabetes, hypercholesterolemia, smoking, alcohol consumption), and location of the hematoma (deep ICH vs lobar ICH) in the prediction of antiplatelet-related ICH and oral anticoagulant-related ICH (model 1)

Model 1	Antiplatelet-related ICHs vs non-antithrombotic-related ICHs		Oral anticoagulant-related ICHs vs non-antithrombotic-related ICHs	
	OR	95% CI	OR	95% CI
Age, per year	1.05	1.03-1.07	1.06	1.03-1.09
Hypertension	1.86	1.22-2.85	1.31	0.72-2.38
ICH location, lobar vs deep	1.17	0.83-1.64	1.70	1.03-2.81

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; OR = odds ratio. Only significant values are reported.

Figure 2 Relation between anatomical location of the hematoma and international normalized ratio values



(A) Percentage of international normalized ratio (INR) values conditional to the location of the hematoma. (B) Percentage of lobar and deep intracerebral hemorrhages (ICHs) conditional to INR values. (C) 4 × 2 frequency table of lobar/deep ICH by INR values with odds ratio (OR), 95% confidence interval (CI), and p values for lobar/deep.

warfarin without ICH,⁸ and that individual cases of ICH following anticoagulation or coronary thrombolysis revealed advanced CAA on autopsy.^{21,22} Our findings are in apparent disagreement with those derived from the PITCH study by Dequatre-Ponchelle et al.¹² who found no influence of OACs on the anatomical distribution of ICH but a significant effect of these compounds on the volume of deep brain hematomas. This would support the conclusion

that deep perforating arteries are more sensitive to anticoagulation than cortical-subcortical vessels. Such a discrepancy might be explained by the slightly different definition of deep and lobar ICH in the 2 studies, as well as by the potential biases in the measurement of hematoma volumes, as pointed out by the authors themselves, and, even more important, by the fact that regression models in the PITCH study did not include adjustment for hypertension.¹²

Furthermore, because existing evidence suggests that both CAA and hypertension can be responsible for intracranial bleeding in the cerebellum,¹⁴ analyses on the relation between risk factors and ICH location should consider cerebellar hemorrhages as a potential source of bias and take account of this.

Several strengths of the present study should be noted, including the large number of participants, the homogeneous demographic characteristics and clinical phenotype of the cohort, and the standardized diagnostic workup and evaluation of risk factors. Some limitations also should be considered. First, because the MUCH-Italy is a hospital-based study, the results might be susceptible to hospital referral selection bias. However, inaccurate capture of the incident cases is highly unlikely as all patients with acute cerebral hemorrhage in the geographic areas involved in the study are usually referred to the participating centers. Second, because of the relatively small numbers of subjects in specific subgroups, such as in the upper INR strata, some results should be viewed with caution. Third, recruitment time period was long, during which improvement in diagnostic facilities and preventive medications has occurred. In particular, because brain MRI was not part of the routine imaging protocol during the first years of the study, only a small proportion of patients have these data available. This precluded the inclusion of neuroradiologic markers that could be of interest, such as brain microbleeds,²³ in the final analysis. Fourth, we cannot theoretically exclude a classification bias in categorizing patients' medical history or the potential influence of other, undetected medical conditions (i.e., chronic kidney disease) on the results of the study.

In spite of these limitations, our findings provide evidence that OACs, as opposed to antiplatelet agents, increase the propensity to cerebral bleeding to a higher degree in lobar than in deep brain regions. This differential effect should be considered in future trials with new antithrombotic agents, as well as with any new molecules interfering with clot formation and, in clinical practice, when the potential benefits of OACs as regards stroke prevention are to be balanced against their bleeding risk. We hypothesize that a similar effect will be seen with novel OACs or with multiple antithrombotic therapies, but further dedicated studies are needed.

AUTHOR CONTRIBUTIONS

Dr. Pezzini: manuscript drafting/revising, study design, data analysis and interpretation, data acquisition, statistical analysis, study supervision. Dr. Grassi, Dr. Pepe: data analysis and interpretation, statistical analysis. Dr. Paciaroni, Dr. Zini, Dr. Silvestrelli: manuscript drafting/revising, study design, data acquisition. Dr. Del Zotto, Dr. Caso, Dr. Dell'Acqua, Dr. Giossi, Dr. Volonghi, Dr. Simone, Dr. Lanari, Dr. Costa, Dr. Poli, Dr. Gamba,

Dr. Morotti, Dr. De Giuli, Dr. Ciccone, Dr. Ritelli, Dr. Colombi, Dr. Agnelli: manuscript drafting/revising, data acquisition. Dr. Padovani: manuscript drafting/revising, study design, study supervision.

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Alessandro Pezzini, Mario Grassi, Maurizio Paciaroni, et al.
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