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Effects of clinical and laboratory variables at admission and of in-hospital treatment with cardiovascular drugs on short term prognosis of ischemic stroke. The GIFA study

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Abstract *Introduction:* No information exists, to our knowledge, about the possible role of cardiovascular drug administration in the acute phase of ischemic stroke and possible effects on stroke outcome. The aim of our study was to evaluate the relationship between in-hospital treatment with cardiovascular drugs in patients with acute ischemic stroke and some outcome indicators.
Methods and Results: 1096 subjects enrolled in the GIFA study, who had a main discharge diagnosis of ischemic stroke represent the final sample. Drugs considered for the analysis were the following: ACE-inhibitors (ACEI), angiotensin II receptor blockers (ARBs), statins, calcium-channel-blockers (CCBs), antiplatelet (APL) drugs, antivitamin-k (VKAs), and heparins. As outcome indicators we choose in-hospital mortality, cognitive function evaluated by Hodkinson Abbreviated Mental Test (HAMT), and functional status evaluated by activity daily living (ADL). Indicators of a good outcome were: no in-hospital mortality, HAMT >6 and 0 ADL impaired. Patients with a good outcome showed a higher rate of in-hospital treatment with ACE-inhibitors, calcium-channel blockers and a lower rate of pre-treatment with heparin.
Conclusions: Our study suggests that if a patient with acute ischemic stroke has higher SBP at admission, higher total cholesterol plasma levels, a lower Charlson index and is treated with ACE-inhibitors, calcium channel blockers and antiplatelet drugs, the short term outcome is better

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in terms of in-hospital mortality and functional indicators such as cognitive and functional performance at discharge.

Introduction

Pre-treatment with several active cardiovascular drugs such as statins [1], antiplatelets [2] and ACE-inhibitors [3] are associated with a better outcome in subjects with acute ischemic stroke.

All these studies evaluated effects of these active cardiovascular drugs on NIHSS scores, but no study evaluated, to our knowledge, possible effects of in-hospital treatment with these drugs on in-hospital mortality or other outcome indicators such as indexes of functional and cognitive outcome.

Recently our group evaluated the relationship between a favourable outcome and cardiovascular drug pre-treatment prior of hospital admission [4]

On this basis our aim was to evaluate the relationship between in-hospital treatment with cardiovascular drugs such as ACE-inhibitors (ACEI), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), anti-platelet drugs (APL), anti-vitamin K (VKAs) drugs and heparin and a favourable outcome in subjects with acute ischemic stroke.

Methods

Patients and setting

The study protocol of the Italian Group of Pharmacoepidemiology in the Elderly (Gruppo Italiano di Farmacoepidemiologia nell'Anziano [GIFA]) study has been described elsewhere [5].

Briefly, the GIFA is a multicenter periodical survey of hospitalized older patients. All patients admitted to 81 clinical centers homogeneously distributed throughout Italy were enrolled and followed-up until discharge. For this project, only patients enrolled during 1993, 1995, 1997, and 1998 surveys were considered. Data collected in 1988 and 1991 were not included because most of the randomized clinical trials showing the protective effect of antithrombotic therapy were published in the 1990s.

Prevalent disease findings

All diseases diagnosed by the physicians were classified according to the International Classification of Disease, 9th revision (ICD-9). Cases of ischemic stroke were identified on the basis of the ICD-9 code (434—434.9, 436, 433.01, and 435 to 435.9, respectively).

To estimate the global burden of diseases, an index of co-morbidity was calculated using the Charlson index (CI) score, modified by Deyo et al. [6]. Subjects were classified into 2 co-morbidity groups as follows: Charlson index <2 and Charlson index >2. The Charlson co-morbidity index predicts the ten-year mortality for a patient who may have a range of co-morbid conditions such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned with a score of 1,2,3 or 6 depending on the risk of dying associated with this condition. Then the scores are summed up and given a total score which predicts mortality.

The clinical conditions and scores are as follow: 1 each: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease. 2 each: Hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukemia, lymphoma. 3 each: Moderate or severe liver disease. 6 each: Malignant tumor, metastasis, AIDS.

To estimate the burden of arterial blood pressure values at admission on stroke prognosis, enrolled subjects were classified into three different groups in relation of systolic blood pressure (SBP) values at admission: 1) SBP $\geq$120 and $\leq$180 mm/Hg; 2) SBP $<$120 mm/Hg; SBP $>$180 mmHg.

Ascertainment of drug prescription

All new prescribed drugs during hospital stay were abstracted from hospital charts and codified according to the anatomical therapeutic chemical classification. On this basis we excluded drugs also prescribed before hospital admission. Drugs considered for the analysis were the following: *ACE-inhibitors* (ACEI), *angiotensin calcium channel blockers* (*CCBs*), *antiplatelet drugs* (APL), vitamin K antagonists (*VKAs*) *drugs and heparin*.

Outcome measures

The primary outcomes of this study were: 1) in-hospital mortality; 2) cognitive impairment at discharge; 3) functional status at discharge.

Cognitive and functional status was assessed at the time of admission and at discharge. Cognitive function was assessed using the Hodkinson Abbreviated Mental Test (HAMT), a 10-item screening test for dementia [7]. The following questions are put to the patient. Each question correctly answered scores one point. A score of 6 or less suggests delirium or dementia, although further and more formal tests are necessary to confirm the diagnosis.

The presence of cognitive impairment was identified by the presence of $\geq$4 errors on the test administered at discharge.

Functional status was evaluated using 6 basic activities of daily living (ADL) [8]. Activities of Daily Living (ADLs) is a term used in healthcare to refer to daily self-care activities within an individual's place of residence, in outdoor environments, or both. Health professionals routinely refer to the ability or inability to perform ADLs as a measurement of the functional status of a person, particularly in regards

to people with disabilities and the elderly. ADLs are defined as "the things we normally do" such as feeding ourselves, bathing, dressing, grooming, work, homemaking, and leisure. They include transferring from bed to chair, walking in a small room, eating, bathing, using the toilet, and personal hygiene procedures. Patients were considered "severe disability" if they needed intensive assistance in at least one activity of daily living and were considered "mild–moderate disability" if they needed only supervision or limited assistance in at least one activity of daily living at the time of discharge from the hospital.

Statistical analysis

We intended to assess the association between outcome indicators of acute ischemic stroke *(no in-hospital mortality, in-hospital mortality,* HAMT >6, HAMT <6; *no ADL-impaired or* 1-2 *ADL*) with some potential predictive variables such as demographic data (age, male sex), laboratory variables (glucose blood levels, cholesterol plasma levels, white body cell count), clinical variables [systolic blood pressure (SBP) at admission, diastolic blood pressure (DBP) at admission, Charlson index score at admission] and in-hospital treatment with cardiovascular drugs such as statins, ACE-inhibitors, ARBs, antiplatelet drugs, antivitamin-k drugs and heparin.

This was primarily done by tabulating the outcome categories against each chosen potential predictive variable (yes vs. no). The proportions of patients with or without in-hospital mortality, with and without cognitive impairment and with and without 1–6 impaired ADL were compared using contingency tables and the χ^2 test. Therefore, we performed a forward logistic regression analysis respectively with indexes of favorable outcome at discharge such as no in-hospital mortality, HAMT >6 and 0 ADL impaired as the dependent variable (separately for each outcome indicator). Variables for this analysis were selected from univariate analysis (Student *t* test, contingency tables, and Mann–Whitney *U* test) when they reached a significance of $\leq$0.05. For all the statistical analyses, the results were considered significant when $P < 0.05$. All statistical analyses were performed with the SPSS software.

Results

Demographic, clinical and laboratory variables in recruited patients are shown in Table 1. We enrolled 1096 subjects with acute ischemic stroke; 516 were male and 580 female, 391 (41.4%) had a history of hypertension and 198 (20.98%) a history of diabetes.

Data for HAMT score at discharge was only available for 514 (46.89%) patients.

Data for n° of ADL impaired at discharge was only available for 843 (76.91%).

With regard to outcome indicators during hospital stay, there were 247 (22.53%) in-hospital death, 237 (46.10% of the 514 available) subjects showed a HAMT< 6 at discharge, whereas 550 (65.24% of the 843 available) had 1-6 ADL impaired at discharge.

Table 1 Selected general and clinical characteristics in patients with acute cerebrovascolar syndrome.

Pts with acute ischemic stroke	
Number	1096
Age (years)	73.452 ± 6.2
Female: (*n*) (%)	580 (52.91)
Male: (*n*) (%)	515 (46.98)
Hypertension (*n*) (%)	391 (41.4)
Diabetes (%) (*n*)	198 (20.9)
T° at admission (°C)	36.9 ± 0.72
Length of hospital stay (days)	15.4 ± 6.4
Glucose blood levels (mg/dl)	132.89 ± 65.17
SBP (mm/Hg)	159.9 ± 28.73
SBP >140 (%) (n)	420 (38.3)
DBP (mm/Hg)	87.16 ± 13.2
DBP >90 mm/Hg	177/16.16
WBC at admission (per mm^3)	8996 ± 3887
Neutrophils (%) at admission	74.0 ± 15.38
ESR (mm/h)	28.4 ± 15.0
Total cholesterol plasma level (mg/dl)	213.6 ± 4.0
Trigliceryde plasma level (mg/dl)	155.2 ± 76.1
Charlson index (mean/median)	2.95/3
Charlson index score	
• <2 (*n*) (%)	333 (30.38)
• >2 (*n*) (%)	763 (69.61)
In-hospital death (*n*) (%)	247 (22.53)
HAMT at discharge (total number*) (*n*) (%)	514 (46.89)
HAMT <6 (at discharge) (*n*) (%)	237 (46.10)
HAMT >6 (at discharge) (*n*) (%)	277 (53.89)
ADL (total number**) (*n*) (%)	843 (76.91)
• No ADL impaired	293 (34.75)
• 1–6 ADL impaired	550 (65.24)
Treatment during hospital stay	
• Statin	–
• Ace-inhibitors (*n*) (%)	180 (16.42)
• CCB	469 (42.79)
• AT-1 antagonists (*n*) (%)	–
• Antiplatelet drugs (*n*) (%)	220 (20.07)
• Anti-vitamin-k drugs (*n*) (%)	43 (3.9)
• Heparin e (*n*) (%)	398 (36.31)

Regarding the type of cardiovascular treatment during hospital stay, no patients were treated with statins, 180 (16.42%) were treated with ACE-inhibitors, no patients with ARBs, 220 (20.07%) were treated with antiplatelets, 469 (42.79%) with CCBs, 43 (3.9%) with AVK drugs and 398 (36.31%) with heparin.

At univariate analysis (see Table 2) patients with no in-hospital mortality compared to those with intra-hospital mortality were more likely to have: lower age, lower blood glucose level at admission, a lower percentage of subjects with blood glucose levels >200 mg/dl, a higher SBP at admission, a higher percentage of patients with SBP $\geq$120 mm/Hg and $\leq$180 mm/Hg, a higher percentage of subjects with DBP >90 mm/Hg, higher plasma levels of total cholesterol, a lower white body cell count a lower Charlson index score, a higher percentage of subjects with Charlson index score <2, a higher percentage of subjects with 0 ADL impaired, a higher percentage of subjects who

Table 2 Variables related to outcome (intra-hospital mortality, disability and cognitive function) at discharge in patients with acute ischemic stroke at univariate analysis.

	Intrahospital death	No intra-hospital death	*P*	HAMT >6	HAMT< 6	*P*	No ADL-impaired	1-2 ADL-impaired	*P*
n/%	247 (22.53)	849 (77.46)		277 (53.89)	237 (46.10)		293 (34.75)	550 (65.24)	
Age	80.49 ± 7.35	75.65 ± 6.46	<0.005	79.23 ± 8.66	81.33 ± 7.23	0.041	72.85 ± 0.38	78.49 ± 9.25	<0.005
Sex (% men)	113 (45.74)	391 (46.05%)	0.37	163 (58.84)	99 (41.77)	<0.001	164 (55.97)	297 (54)	0.038
Blood glucose at admission	158.29 ± 83.38	126.14 ± 57.62	<0.01	124.05 ± 61.81	143.16 ± 84.4	<0.001	123.74 ± 60.18	137.28 ± 73.31	0.021
Glucose blood levels >200 mg/dl (n/%)	35 (14.17)	63 (7.42)	<0.005	38 (13.71)	24 (10.12)	<0.001	34 (11.60)	111 (20.18)	<0.005
SBP at admission (mm/Hg)	148.80 ± 32.69	160.16 ± 27.87	<0.0001	151.18 ± 26.08	153.04 ± 27.52	0.06	154.28 ± 27.23	149.32 ± 28.13	0.045
DBP at admission (mm/Hg)	86.63 ± 15	87.26 ± 12.96	0.78	84.84 ± 14.04	85.85 ± 12.67	0.07	84.18 ± 13.53	85.89 ± 13.27	0.78
SBP ≥120 and ≤180 mm/Hg	72 (29.14)	458 (53.94)	<0.0001	86 (31.03)	55 (23.20)	0.021	91 (31.05)	123 (22.36)	<0.005
SBP <120 mm/Hg	77 (31.17)	191 (22.49)	0.022	100 (36.10)	99 (41.77)	0.041	104 (35.49)	228 (41.45)	0.031
SBP >180 mmHg	98 (39.67)	200 (29.51)	0.033	91 (32.85)	83 (35.83)	0.65	98 (33.44)	199 (36.18)	0.75
DBP >90 mm/Hg (n/%)	68 (27.93)	146 (17.19)	0.021	55 (19.85)	49 (20.67)	0.41	61 (20.81)	104 (18.90)	0.21
Cholesterol plasma levels (mg/dl)	191.74 ± 51.75	200.53 ± 50.92	0.039	202.32 ± 20.92	194.54 ± 31.75	0.038	199.74 ± 51.75	201.53 ± 50.92	0.43
Triglyceride plasma levels (mg/dl)	148.48 ± 91.01	145.74 ± 87.36	0.37	156.8 ± 57.01	145.74 ± 87.36	0.023	147.83 ± 91.01	144.54 ± 67.36	0.07
Diabetes mellitus (n/%)	39 (15.78)	147 (17.31)	0.38	53 (19.13)	44 (18.56)	0.61	55 (18.77)	102 (18.54)	0.45
White body cell (WBC)	11001.27 ± 4408.8	8467 ± 3557.8	<0.0001	6297 ± 4251	9495 ± 3029	0.011	8990 ± 2251	9.840 ± 3251	0.04
WBC >10,000	41 (16.59)	90 (10.61)	<0.05	74 (26.71)	74 (31.22)	0.021	44 (15.01)	143 [25]	<0.005
Charlson index (mean)	3.9	3.1	0.035	3.76	3.83	0.87	3.9/4	4/4.2	<0.005
Charlson index <2 (n/%)	166 (67.21)	728 (85.75)	<0.05	192 (69.31)	121 (51.05)	0.021	181 (61.77)	343(62.36)	0.71
Charlson index >2 (n/%)	81 (32.79)	121 (14.25)	<0.0001	86 (31.04)	47 (19.83)	<0.005	107 (36.51)	206 (37.45)	0.56
AMTD >6 (n/%)	69 (28.39)	236/31.42%	0.55	—	—		172 (58.70)	323 (58.72)	0.70
AMTD <6 (n/%)	46 (23.95)	231 (30.75)	0.021	—	—		175 (59.72)	226 (41.09)	0.56
0 ADL impaired (n/%)	76 (30.71)	414 (55.1)	<0.0001	91 (32.85)	48 (20.25)	<0.005	—	—	—
1-6 ADL impaired (n/%)	36 (18.75)	337 (44.87)	<0.0001	186 (67.14)	193 (81.43)	<0.005	—	—	—
Intra-hospital drugs									
Statin (n/%)	—	—		—	—				
Ace-inhibitors (n/%)	46 (18.62)	224 (26.38)	0.021	64 (23.10)	39 (16.45)	0.010	76 (27.43)	43 (18.14)	<0.005
AT1-antagonists (n/%)	—	—	—	—	—	—	—	—	—
Calcium-channel blockers (n/%)	77 (31.17)	398 (46.87)	<0.0001	75 (27)	46 (19.40)	0.011	54 (19.49)	55 (23.20)	0.06
Antiplatelet drugs (n/%)	24 (9.71)	267 (31.44)	<0.0001	45 (16.24)	35 (14.76)	0.41	37 (13.35)	35 (14.76)	0.11
Vitamin K antagonists (VKAs) (n/%)	21 (8.59)	77 (9.06)	0.41	9 (3.24)	8 (3.37)	0.22	12 (4.33)	7 (2.95)	0.067
Heparine (n/%)	99 (40.08)	198 (23.22)	<0.005	17 (6.13)	10 (4.21)	0.77	11 (3.97)	14 (5.90)	0.41

Table 3 Logistic regression with no-intrahospital mortality.

	Regression coefficient	Odds ratio	95% CI	*P*
Age	−0.11	0.91	0.92−0.99	0.024
SBP at admission (n/%)	1.61	5.55	1.42−17.8	0.012
SBP ≥ 120 and ≤180 mm/Hg	1.48	2.78	1.97−3.35	≤0.0001
SBP < 120 mm/Hg	−0.22	0.75	0.5−0.98	0.012
SBP >180 mmHg	−0.33	0.73	0.66−0.81	≤0.0001
White body cell (WBC)	−0.21	0.78	0.5−0.89	0.010
Cholesterol plasma levels	1.38	2.12	1.33−4.3	0.012
Glucose blood levels > 200 mg/dl	−0.32	0.75	0.65−0.80	≤0.0001
Charlson index <2 (n/%)	1.02	4.12	1.42−17.8	0.012
Charlson index >2 (n/%)	−0.27	0.80	0.65−0.91	0.022
Ace-inhibitors	1.92	3.88	1.89−8.2	<0.05
Calcium antagonists	1.71	5.56	1.77−9.4	0.010
Antiplatelet drugs	1.65	4.23	2.7−8.3	0.014
Heparin	−0.22	0.79	0.43−0.89	≤0.0001

Dependent variable: no intra-hospital mortality.

had in-hospital treatment with ACE-inhibitors, calcium-antagonist and antiplatelet drugs and a lower percentage of patients treated during hospital stay with heparine.

At univariate analysis (see Table 2) patients with HAMT <6 at discharge compared to those with HAMT >6 at discharge showed: a lower age, lower blood glucose level at admission, a lower percentage of subjects with blood glucose levels >200 mg/dl, a higher percentage of subjects with SBP ≥120 mm/Hg and ≤180 mm/Hg, higher levels of plasma total cholesterol, higher levels of plasma triglyceride, a lower white body cell count, a higher percentage of subjects with Charlson index score <2, a higher percentage of subjects with 0 ADL impaired, a higher percentage of subjects that had in-hospital treatment with ACE-inhibitors, a higher percentage of subjects that had in-hospital treatment with CCBs.

At univariate analysis (see Table 2) patients with 0 ADL impaired at discharge compared to those with >2 ADL at discharge were more likely to have: a lower age, lower blood glucose level, a lower percentage of subjects with blood glucose levels >200 mg/dl, a higher SBP at admission, a higher percentage of subjects with SBP ≥120 mm/Hg and ≤180 mm/Hg, a higher percentage of subjects with DBP >90 mm/Hg, a lower white body cell count, a lower Charlson index score, a higher percentage of subjects with Charlson index score <2, a higher percentage of subjects with 0 ADL impaired, a higher percentage of subjects that had a in-hospital treatment with ACE-inhibitors.

At logistic regression analysis no in-hospital mortality was significantly associated with SBP values at admission, with a SBP ≥120 and ≤180 mm/Hg at admission, cholesterol plasma levels, Charlson index <2 and with in-hospital

Table 4 Logistic regression with HAMT >6.

	Regression coefficient	Odds ratio	95% CI	*P*
Age	−0.16	0.88	0.70−0.91	0.035
Glucose blood levels >200 mg/dl	−0.29	0.85	0.46−0.79	<0.05
SBP ≥120 and ≤180 mm/Hg	1.52	2.41	1.48−4.7	0.012
SBP <120 mm/Hg	−0.17	0.87	0.67−0.94	0.025
SBP >180 mm/Hg	−0.29	0.85	0.46−0.79	<0.05
Cholesterol plasma levels (mg/dl)	−0.35	0.70	0.45−0.88	0.025
Diabetes mellitus	−0.30	0.79	0.56−0.93	0.021
White body cell (WBC)	−0.27	0.77	0.67−0.96	0.017
Charlson index <2	1.47	3.45	1.79−4.96	0.010
Charlson index >2	−0.29	0.88	0.59−0.96	0.032
0 ADL impaired	1.41	3.70	2.21−7.9	<0.05
1-6 ADL impaired	−0.27	0.81	0.63−0.80	0.019
Ace-inhibitors	1.81	3.99	2.11−8.3	<0.0001
Antiplatelet drugs	1.77	3.85	2.21−8.77	<0.05
Heparin	−0.69	0.70	0.29−0.88	0.020

Dependent variable: MMSE >6 at discharge.

Table 5 Logistic regression with no ADL impaired.

	Regression coefficient	Odds ratio	95% CI	*P*
Age	−0.11	0.87	0.70−0.95	0.030
Glucose blood levels >200 mg/dl	−0.31	0.82	0.29−0.81	<0.05
SBP ≥120 and ≤180 mm/Hg	1.51	2.07	1.64−2.66	≤0.0001
SBP <120 mm/Hg	0.33	0.85	0.39−0.81	<0.05
SBP >180 mmHg	0.88	0.98	0.44−1.01	0.021
White body cell (WBC)	−0.30	0.71	0.56−0.82	0.020
WBC >10,000	−0.29	0.69	0.50−0.83	0.019
Charlson index >2	−0.30	0.80	0.57−0.80	<0.05
Charlson index <2	1.37	2.44	1.70−8.5	≤0.0001
Ace-inhibitors	1.81	2.17	1.55−7.05	<0.05
Calcium-antagonist	1.60	2.88	1.44−8.11	≤0.0001
Antiplatelet drugs	1.59	2.77	1.88−8.21	≤0.0001
Heparin	−0.27	0.80	0.59−0.96	0.012

Dependent variable: no ADL impairment at discharge.

treatment with ACE-inhibitors, CCbs and antiplatelet drugs (see Table 3).

At logistic regression analysis HAMT <6 at discharge was significantly associated with SBP at admission, SBP ≥120 and ≤180 mm/Hg at admission, Cholesterol plasma levels, Charlson index <2 and with in-hospital treatment with ACE-inhibitors and antiplatelet drugs (see Table 4).

At logistic regression no ADL impaired at discharge was significantly associated with SBP ≥120 and ≤180 mm/Hg (n/%), Charlson index <2 and with intra-hospital treatment with ACE-inhibitors and antiplatelet drugs (see Table 5).

Discussion

Our study suggests that if a patient with acute ischemic stroke has, at admission, an SBP ≥120 and ≤180 mm/Hg, higher total cholesterol plasma levels, a lower Charlson index, the short term outcome in terms of in-hospital mortality and functional indicators such as cognitive and functional status at discharge is better.

Admission blood pressure (BP) and significant decreases in BP after acute stroke have been correlated with outcome. Few data are available on the impact of extreme values at any time point within the first 24 h but a recent study showed that diurnal BP variations influence the course of BP after acute stroke [9].

Extreme hypertension and hypotension on admission have both been correlated with adverse outcome in acute stroke patients [9−15]. However, there is no consensus of the "optimal range" of BP [16]. Elevations in systolic or diastolic blood pressure (BP) are observed in up to 80% of patients after an acute ischemic stroke, even in previous normotensives.

Our findings show a higher percentage of patients with SBP ≥120 and ≤180 mm/Hg in subjects with no in-hospital mortality, no cognitive impairment and no dependency at discharge and that at logistic regression all the outcome indicators that we evaluated (in-*hospital mortality*, *cognitive impairment at discharge*, *functional status at discharge*) were significantly associated with SBP values at admission and in particular with a SBP ≥120 and ≤180 mm/Hg at admission. The relationship between higher SBP values and a better outcome are not a novel finding, but no study, to our knowledge, evaluated cognitive impairment evaluated through HAMT score and functional status through ADL evaluation as outcome indicators in patients with acute ischemic stroke in relation to systolic blood pressure at admission.

Moreover, these findings could provide a possible confirmation of the latest recommendations of clinical guidelines from American Heart Association/American Stroke Association Stroke Council [17] indicating that rapid and steep reductions in blood pressure might be harmful and that antihypertensive treatment should be withheld unless the diastolic blood pressure is ≥120 mm Hg or unless the systolic blood pressure is ≥220 mm.

Our findings concerning higher median levels of plasma total cholesterol in subjects with better outcome after an acute ischemic stroke and the reported association at logistic regression between cholesterol plasma levels and no-intrahospital mortality are consistent with these previous reports.

Several studies evaluated the prognostic importance of various stroke characteristics and social, demographic, and medical factors in patients with the most severe strokes but few studies examined the role of medical treatment [18,19], but these studies have focused exclusively on tissue plasminogen activator (tPA). Although few studies examined the impact of pre-treatment with other medical treatment such as ACE-inhibitors, statins, and antiplatelet drugs [20−22], no study to our knowledge has addressed the role of in-hospital treatment with cardiovascular drugs such as antihypertensive, antiplatelet and hypocholesterolemic drugs used in the acute phase of stroke during the in-hospital stay on stroke outcome.

We report that patients with no in-hospital mortality had a higher percentage of patients that have in-hospital treatment with ACE-inhibitors, calcium-antagonist and antiplatelet drugs.

Our study also shows at univariate analysis and at logistic regression analyses that patients receiving ACE-inhibitors,

calcium channel blockers and antiplatelet drugs during hospital stay after an acute ischemic stroke were more likely to have no in-hospital mortality. In-hospital treatment with ACE-inhibitors and with antiplatelet in our patients was associated with all the good outcome indicators (no in-hospital mortality, HAMT >6 and 0 ADL impaired). These are interesting and, to our knowledge, novel findings. The role of antihypertensive drugs in the acute phase of ischemic stroke represents a controversial issue. In a recent study the administration of antihypertensives was more strongly associated with poor outcome than any BP threshold violation [22]. Nevertheless one study indicated that pre-stroke use of ACE-inhibitors may result in additive reduction in stroke severity, as measured by NIH Stroke Scale, and the volume of ischemic tissue at risk, as assessed by perfusion-weighted imaging—diffusion-weighted imaging mismatch [22].

We also reported a higher percentage of patients receiving treatment with calcium channel blockers in subjects with better outcome. Despite the advancing knowledge of calcium signalling in neurite outgrowth and recovery, little is known about the clinical effect of calcium antagonism during the recovery period following stroke. Recently Dowlatshahi et al. [21] showed in a cohort from the registry of the Canadian Stroke Network that in subjects with ischemic stroke there was no change in 6-month mortality in terms of treatment with ACEI, B-blockers or diuretics at discharge and that subjects that were admitted on CCBs had improved outcome at 6-months if they were also discharged on CCB, compared to patients who had their CCBs discontinued.

Our findings also show a lower percentage of patients treated with heparins in subjects with better outcome, underlining a possible association between heparine and poor outcome indicators.

The exact role of heparins in hyper-acute stage of ischemic stroke is still unclear. Nevertheless our findings may suggest a disadvantage, perhaps linked to an extension of the ischemic lesion or a higher rate of hemorrhagic transformation although we currently do not have bibliographic data in support of this finding.

Some possible limitations of our study are that we used two uncommonly used scores for functional measures of stroke outcome: HAMT score and ADL impairment score. We choose these scores because the GIFA Database did not evaluate scores of acute neurological deficit such as National Institute of Health Stroke Scale (NIHSS) or Scandinavian Stroke Scale Score (SSS), nor Rankin score or Barthel index as a disability score. Furthermore, given the short time frame at evaluation (discharge), the HAMT score may not accurately reflect long-term cognitive impact of stroke, after accounting for stroke recovery in the chronic stage. The ADL score, likewise, at discharge may not accurately reflect stroke recovery. So a delayed follow-up is necessary to assess long-term outcomes. Nevertheless, HAMT is effective as a screening tool for cognitive impairment with older, community dwelling, hospitalized and institutionalized adults even in acute cerebrovascular patients [23], whereas ADL evaluation [24] has been used to determine the influence of initially lowered orientation on rehabilitation outcome in stroke patients.

Other possible limitations of our study are the retrospective analysis, the availability of HAMT score only in 614 patients of the 1096 with acute ischemic stroke, and the almost complete absence of patients treated with statin because we analyzed data obtained from 1993 to 1998, which wasn't a period of wide-spread statin treatment. Nevertheless this limitation represents, in our opinion, a possible advantage since our study evaluated the relationship of some cardiovascular active drugs such as ACE-inhibitors, calcium-channel-blockers, antiplatelet drugs in subjects not treated with statins, and hence shows the real effects of these drugs on stroke prognosis independently of statin treatment that in the last years showed their positive effect on stroke outcome [25,26].

Finally another limitation is the possibility of a "reverse-causality" bias is most likely, since only those patients who were not severely-ill (e.g. were not comatose, dysphagic) might have been given some cardiovascular pills during hospital-stay.

Some conclusions can be drawn from our data nevertheless.

First, we found that some clinical and laboratory variables such as systolic blood pressure, cholesterol blood levels, and glucose blood levels are associated with prognosis in terms of in-hospital mortality, cognitive function and functional outcome.

Second, we report that the use of ACE-inhibitors, calcium channel blockers and antiplatelet drugs administered in the acute phase of ischemic stroke may improve the outcome of patients, whereas heparin use is associated with a worse short term outcome. Definitive recommendations for the use of these drugs in stroke patients must await further experimental and clinical data although our study suggests that for maximum benefit, this type of therapy should be initiated within the first few hours of an ischemic stroke with careful monitoring of blood pressure.

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