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Effects of clinical and laboratory variables and of pretreatment with cardiovascular drugs in acute ischaemic stroke: A retrospective chart review from the GIFA study☆

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ABSTRACT

Background: Few studies have examined the role of cardiovascular drugs on acute ischaemic stroke prognosis.
Aims: To evaluate the relationship between a favourable outcome in patients with acute ischaemic stroke and specific demographic, clinical and laboratory variables and cardiovascular drug pretreatment.
Methods: The 1096 patients enrolled in the GIFA study (who had a main discharge diagnosis of ischaemic stroke) represent the final patient sample used in this analysis. Drugs considered in the analysis included angiotensin converting enzyme (ACE)-inhibitors, angiotensin II receptor blockers, statins, calcium channel blockers, anti-platelet drugs, vitamin K antagonists and heparins. The outcomes analyzed included in-hospital mortality, cognitive function evaluated by the Hodkinson Abbreviated Mental Test (HAMT), and functional status evaluated by activities of daily living (ADL). The definition of a good outcome was no in-hospital mortality, a HAMT score of ≥6 and no ADL impairment.
Results: Patients with no in-hospital mortality, a HAMT score of >6 and no ADL impairment were more likely to be younger at baseline and have a lower blood glucose level and a systolic blood pressure (SBP) between 120 and180 mmHg, a higher plasma total cholesterol level, a lower white blood cell count, and a lower Charlson Index (CI) score, a higher rate of pretreatment with ACE-inhibitors, calcium channel blockers and a lower rate of pretreatment with heparin.
Conclusions: Predictors of good outcome, in terms of in-hospital mortality and cognitive and functional performance at discharge, included higher SBP at admission between 120 and180 mmHg, a SBP plasma total cholesterol levels, a lower CI score, and pretreatment with ACE-inhibitors, calcium channel blockers and anti-platelets.

1. Introduction

Recognition of factors predictive of outcome in ischaemic stroke management seems essential for optimizing therapeutic procedures, especially those that are costly and time-consuming. Previous data have underlined the possible prognostic role of demographic and clinical variables at admission [1,2]. Data from a study by Selim et al. [3], comparing stroke severity in patients who were, or were not, taking ACE-inhibitors (ACE-I) before stroke onset, suggested that ACE-I may reduce the clinical severity of stroke, as measured by the National Institutes of Health Stroke Scale (NIHSS) scores. Furthermore, Sanossian et al. [4] showed that pre-stroke use of anti-platelet drugs (APLs) may be associated with a reduced severity of incident ischaemic strokes and an increased likelihood of a good discharge outcome, regardless of cerebrovascular event history, in those with no prior history of stroke or transient ischaemic attack.

All of these studies evaluated the effects of clinical/laboratory variables and cardiovascular drugs on NIHSS scores, but, to our knowledge, no study has evaluated their possible effects on in-hospital mortality or other outcomes, such as functional status and cognitive impairment.

The aim of this study was to evaluate the relationship between a favourable outcome in patients with acute ischaemic stroke and specific demographic, clinical and laboratory variables and pretreatment with cardiovascular drugs, such as angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), anti-platelet agents (APLs), vitamin K antagonists (VKAs) and heparins [low molecular weight heparins (LMWHs) and unfractioned heparin (UFH)].

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2. Methods

2.1. Patients and setting

The protocol of the GIFA (Italian Group of Pharmacoepidemiology in the Elderly) study has been published elsewhere [5]. Briefly, GIFA is a multicenter periodical survey of hospitalized elderly patients. All patients admitted to the 81 clinical centers, homogeneously distributed throughout Italy, were enrolled and followed-up until discharge. The study periods were the following: May 1 to June 30 and September 1 to December 31, 1988; May 15 to June 15, 1991; and May 1 to June 30 and September 1 to October 31 in 1993, 1995, 1997, and 1998. For each participant, a questionnaire was completed at admission and updated daily by a study physician who had received specific training. Data recorded included patient demographic characteristics, medications used before admission, during the pre-hospital period and those prescribed during hospital stay and at discharge, and admission and discharge diagnoses.

Our study population was limited to 17,377 patients for whom laboratory values were available; patients with a final diagnosis of acute ischaemic stroke comprised the final sample.

2.2. Disease prevalence and comorbidity

All diseases diagnosed by the physicians were classified according to the International Classification of Disease, 9th revision (ICD-9), with cases of ischaemic stroke identified on the basis of the ICD-9 code (434 to 434.9, 436, and 433.01, respectively). To estimate the global burden of disease, an index of comorbidity was calculated using the Charlson Index (CI) score, modified by Deyo et al. [6]. Patients were classified into three comorbidity groups based on a CI score of 0, 1–2 or >2.

2.3. Interventions

All drugs prescribed prior to hospital admission were obtained from hospital charts and codified according to the anatomical therapeutic chemical classification. Drugs considered in the analysis included ACE-I, ARBs, CCBs, APLs, VKAs and heparin.

2.4. Outcome measures

The primary outcomes of this study were in-hospital mortality, cognitive impairment at discharge and functional status at discharge.

Cognitive function was assessed using the Hodkinson Abbreviated Mental Test (HAMT), a 10-item screening test for dementia [7]. The presence of cognitive impairment was identified by the presence of ≥4 errors on the test administered at discharge, with a score of <6 suggesting cognitive impairment.

Functional status was evaluated using six basic activities of daily living (ADL), including transferring from bed to chair, walking in a small room, eating, bathing, using the toilet, and personal hygiene procedures. Patients were considered having severe disability if they needed intensive assistance in at least one ADL, and were considered having mild-to-moderate disability if they needed only supervision or limited assistance in at least one ADL at the time of hospital discharge. Patients were stratified by their level of ADL impairment into two groups based on disability grade: 0 (no ADL impairment) and 1–6 (with ADL impairment).

2.5. Statistical analysis

We assessed the association between outcome indicators of acute ischaemic stroke, some analysis variables (Table 1) and pretreatment with cardiovascular drugs, such as statins, ACE-I, ARBs, APLs, VKAs and heparin. This was primarily done by tabulating the outcome categories against each chosen potential predictive variable (yes versus no).

The proportions of patients with or without in-hospital mortality, with or without cognitive impairment and with or without ADL impairment were compared using contingency tables and the χ^2 test. A forward logistic regression analysis was performed with indexes of favourable outcome at discharge, such as no in-hospital mortality, a HAMT score of ≥6 and no ADL impairment, as the dependent variables (analyzed separately for each outcome indicator). Variables in this analysis were selected from univariate analysis (Student's *t*-test, contingency tables, and Mann–Whitney *U* test) when they reached a significance level of ≤0.05. For all statistical analyses, results were considered significant when $p<0.05$. All statistical analyses were performed with SPSS software.

Table 1
Analysis variables.

Parameter	Variable
In-hospital mortality	Yes vs. No
HAMT score	≥6 vs. <6
ADL-impairment	0 vs. 1–6
Demographic variables	
Age	(Years)
Gender	M vs. F
Laboratory variables	
Blood glucose levels	>200 mg/dL vs. <200 mg/dL
Plasma cholesterol levels	Serum, mg/dl
White blood cell count	>10,000 cells/mm^3 vs. <10,000 cells/mm^3
Systolic blood pressure	>140 mmHg vs. <140 mmHg
Diastolic blood pressure	>90 mmHg vs. <90 mmHg
Baseline clinical variables	
Charlson Index score	>2 vs. <2

3. Results

The demographic, clinical and laboratory variables of the 1096 patients with acute ischaemic stroke who were recruited are shown in Table 2. Data for HAMT score and ADL impairment were available for only 514 (46.89%) and 843 (76.91%) patients, respectively.

Information about duration of pre-hospital treatment was available in 987 subjects (90.05%); mean duration (±dS) was 2.5 ± 1.2 years for ACE-I, 3.7 ± years for CCBs, 2.8 ± 0.9 years for APLs and 9.2 ± 3.5 months for heparins.

Lack of some coprimary endpoints in a proportion of patients is consistent with the multicenter nature of our study due to registration problems in some peripheral centers.

3.1. Univariate analyses

Patients with no in-hospital mortality compared with patients with in-hospital mortality had: a lower age; a lower blood glucose level at admission; a lower percentage of patients with blood glucose levels >200 mg/dL; a higher systolic blood pressure (SBP) at admission; a higher percentage of patients with SBP ≥ 120 and ≤ 180 mmHg; a higher plasma level of total cholesterol; a lower WBC count; a lower CI score; a higher percentage of patients with a CI score <2; a higher percentage

Table 2
General and clinical characteristics in patients with acute ischaemic stroke.

Number of patients with acute ischaemic stroke	1096
Age, years	73.452 ± 6.2
Female, *n* (%)	580 (52.91)
Male, *n* (%)	515 (46.98)
Hypertension, *n* (%)	391 (35.67)
Diabetes mellitus, *n* (%)	198 (18.06)
Temperature at admission, °C	36.9 ± 0.72
Length of hospital stay, days	15.4 ± 6.4
Blood glucose, mg/dL	132.89 ± 65.17
SBP, mmHg	159.9 ± 28.73
SBP >140 mmHg, *n* (%)	420 (38.3)
DBP, mmHg	87.16 ± 13.2
DBP >90 mmHg, *n* (%)	177 (16.15)
WBC count at admission, cells/mm^3	8996 ± 3887
ESR, mm/h	28.4 ± 15.0
Plasma total cholesterol, mg/dL	213.6 ± 4.0
Plasma triglyceride, mg/dL	155.2 ± 76.1
Charlson Index score (mean/median)	2.95/3
Charlson Index score	
1–2, *n* (%)	333 (30.38)
>2, *n* (%)	763 (69.61)
In-hospital mortality, *n* (%)	247 (22.53)
HAMT score at discharge[a], *n* (%)	514 (46.89)
HAMT score <6, *n* (%)	237 (46.10)
HAMT score >6, *n* (%)	277 (53.89)
ADL at discharge[a], *n* (%)	843 (76.91)
No ADL impairment, *n* (%)	293 (34.75)
1–6 ADL impairment, *n* (%)	550 (65.24)
Pretreatment at admission	
Statin, *n* (%)	16 (1.45)
ACE-inhibitors, *n* (%)	431 (39.32)
Angiotensin II receptor blockers, *n* (%)	4 (0.36)
Anti-platelet drugs, *n* (%)	341 (31.11)
Anti-vitamin K drugs, *n* (%)	55 (5.01)
Calcium channel blockers, *n* (%)	565 (51.55)
Heparin, *n* (%)	307 (28.01)

ADL = activities of daily living; DBP = diastolic blood pressure; ESR = erythrocyte sedimentation rate; HAMT = Hodkinson Abbreviated Mental Test; SBP = systolic blood pressure; WBC = white blood cell.
Data given as mean ± standard deviation unless otherwise stated.
[a] Patients for whom the measurement was available.

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of patients with no ADL impairment; a higher percentage of patients pretreated with ACE-I, CCBs, APLs or VKAs; and a lower percentage of patients pretreated at admission with heparin (Table 3).

Patients with a HAMT score of ≥6 at discharge compared with patients with a HAMT score of <6 at discharge had: a lower age; a lower blood glucose level at admission; a higher percentage of patients with blood glucose levels >200 mg/dL; a higher percentage of patients with SBP ≥120 and ≤180 mmHg; a higher plasma total cholesterol level, a higher plasma triglyceride level; a lower WBC count; a higher percentage of patients with a CI score <2; a higher percentage of patients with no ADL impairment; and a higher percentage of patients pretreated at admission with ACE-I (Table 3).

Patients with no ADL impairment at discharge compared with patients with 1–6 ADL impairment at discharge had: a lower age; a lower blood glucose level at admission; a lower percentage of patients with blood glucose levels >200 mg/dL; a higher SBP at admission; a higher percentage of patients with SBP ≥120 and ≤180 mmHg; a lower WBC count; a lower CI score; a higher percentage of patients pretreated with ACE-I; and a lower percentage of patients pretreated with heparin (Table 3).

3.2. Logistic regression analyses

No in-hospital mortality was positively associated with SBP at admission, an SBP ≥120 and ≤180 mmHg at admission, plasma cholesterol levels, a CI score <2 and with ACE-I, CCB and APL pretreatment (Table 4).

A HAMT score of >6 at discharge was found to be positively associated with SBP at admission, an SBP ≥120 and ≤180 mmHg at admission, plasma cholesterol levels, a CI score <2 and with ACE-I and APL pretreatment (Table 5).

Furthermore, no ADL impairment at discharge was positively associated with an SBP ≥120 and ≤180 mmHg, a CI score <2 and with ACE-I and APL pretreatment (Table 6).

Table 4
Logistic regression with no in-hospital mortality as the dependent variable.

	Regression coefficient	Odds ratio	95% CI	*p*-value
Age, years	−0.11	0.91	0.92–0.99	0.024
SBP at admission	1.61	5.55	1.42–17.8	0.012
SBP ≥120 and ≤180 mmHg	1.48	2.78	1.97–3.35	<0.001
SBP >180 mmHg	−0.39	0.79	0.60–0.87	<0.005
SBP <120 mmHg	−0.38	0.77	0.61–0.85	<0.005
White blood cell count	−025	0.58	0.35–0.73	0.0110
Plasma cholesterol level	0.89	2.12	1.33–4.3	0.020
Blood glucose level >200 mg/dL	−0.32	0.75	0.65–0.80	<0.0001
Charlson Index score <2	1.02	4.12	1.42–17.8	0.012
Charlson Index score >2	−0.27	0.80	0.65–0.91	0.0231
ACE-inhibitors	1.61	3.42	1.88–8.1	0.012
Calcium channel blockers	1.55	5.12	1.92–12.8	0.014
Anti-platelet drugs	1.21	4.94	2.1–11.2	0.023
Heparin	−0.29	0.77	0.65–0.81	≤0.0001

ACE-I = ACE-inhibitors; SBP = systolic blood pressure.

4. Discussion

Our study suggests that higher baseline SBP and plasma total cholesterol level, a lower CI score and pretreatment with ACE-I, CCBs and APLs are predictors of a better short-term outcome, in terms of in-hospital mortality and cognitive and functional status at discharge, in patients with acute ischaemic stroke. Patients with baseline SBP ≥120 and ≤180 mmHg and lower total cholesterol level, a higher CI score, and those who did not receive cardiovascular drugs and were pretreated with heparin had a worse outcome.

Stroke case fatality has been used as a proxy measure of hospital performance and quality of care to compare across hospitals, provinces, and countries [8]. In addition, 7 day case fatality was recently implemented as an indicator of early stroke mortality, because the most important clinical decisions are made in the first week after hospital admission [9].

Table 3
Variables related to outcome (in-hospital mortality, disability and cognitive function) at discharge in patients with acute ischaemic stroke at univariate analysis.

	In-hospital mortality	No in-hospital mortaliy	*p*-value	HAMT >6	HAMT <6	*p*-value	No ADL-impairment	1–6 ADL-impairment	*p*-value
n (%)	247 (22.53)	849 (77.46)	<**0.0001**	277 (53.89)	237 (46.10)	<**0.001**	293 (34.75)	550 (65.24)	<**0.001**
Age, years	80.49 ± 7.35	75.65 ± 6.46	<**0.005**	79.23 ± 8.66	81.33 ± 7.23	**0.041**	72.85 ± .38	78.49 ± 9.25	<**0.005**
Males, *n* (%)	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, mg/dL	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
Blood glucose >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, mmHg	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, mmHg	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 mmHg	72 (29.14)	513 (60.42)	<**0.0001**	65 (23.46)	41 (17.29)	**0.021**	65 (22.18)	93 (16.90)	<**0.005**
SBP <120 mmHg	94 (29.95)	171 (20.14)	**0.029**	111 (40.07)	135 (56.96)	**0.038**	157 (53.58)	236 (42.90)	<**0.023**
SBP >180 mmHg	101 (40.89)	165 (19.43)	<**0.0001**	101 (36.46)	61 (25.73)	**0.021**	71 (24.23)	221(40.18)	<**0.005**
Plasma cholesterol, 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
Plasma triglyceride, 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
WBC count cells/mm^3	11001.27 ± 4408.8	8467 ± 3557.8	<**0.0001**	6 297 ± 4251	9495 ± 3029	0.011	8990 ± 2251	9840 ± 3251	**0.04**
WBC >10,000 cells/mm^3, *n* (%)	41 (16.59)	90 (10.61)	<**0.05**	74 (26.71)	74 (31.22)	**0.021**	44 (15.01)	143 (26)	<**0.005**
Charlson Index score (mean)	3.9	3.1	**0.035**	3.76	3.83	0.87	3.9 / 4	4/4.2	<**0.005**
Charlson Index score <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 score >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 (%)	69 (28.39)	236 (31.42)	0.55	–	–	–	172 (58.70)	323 (58.72)	0.70
AMTD <6 (%)	46 (23.95)	231 (30.75)	**0.021**	–	–	–	175 (59.72)	226 (41.09)	0.56
No ADL impairment, *n* (%)	76 (30.71)	414 (55.1)	<**0.0001**	91 (32.85)	48 (20.25)	<**0.005**	–	–	–
1–6 ADL impairment, *n* (%)	36 (18.75)	337 (44.87)	<**0.0001**	186 (67.14)	193 (81.43)	<**0.005**	–	–	–
Pre-hospital drug use									
Statin, *n* (%)	–	–	–	–	–	–	–	–	–
ACE-I, *n* (%)	18 (6.5)	125 (14.7)	<**0.0001**	63 (22.74)	39 (16.45)	**0.023**	81 (27.64)	101 (18.36)	<**0.005**
ARBs, *n* (%)	–	–	–	–	–	–	–	–	–
CCBs, *n* (%)	58 (12.36)	411 (87.63)	<**0.0001**	71 (25.63)	57 (24.05)	0.71	71 (24.23)	129 (23.45)	0.31
APLs, *n* (%)	16 (6.47)	204 (24.02)	<**0.0001**	43 (15.51)	35 (14.76)	0.57	41 (13.93)	82 (14.90)	0.89
VKAs, *n* (%)	1 (0.41)	42 (4.94)	<**0.0001**	14 (5.04)	12 (5.06)	0.44	9 (3.07)	15 (2.7)	0.91
Heparin, *n* (%)	89 (36.62)	218 (25.67)	<**0.05**	16 (5.77)	14 (5.90)	0.37	11 (3.75)	31 (5.6)	**0.041**

ACE-I = ACE-inhibitors; ADL = activities of daily living; AMTD = adjusted mean treatment difference; APLs = antiplatelets drugs; ARBs = Angiotensin II receptor blockers; CCBs = calcium channel blockers; DBP = diastolic blood pressure; ESR = erythrocyte sedimentation rate; HAMT = Hodkinson Abbreviated Mental Test; SBP = systolic blood pressure; WBC = white blood cell; VKA = vitamin K antagonist.
p-values of significance ($p<0.05$) are in bold.
Data given as mean ± standard deviation unless otherwise stated.

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Table 5
Logistic regression with HAMT score >6 at discharge as the dependent variable.

	Regression coefficient	Odds ratio	95% CI	*p*-value
Age	−0.19	0.84	0.72–0.95	0.035
Blood glucose level >200 mg/dL	−0.35	0.81	0.56–0.87	<0.05
SBP ≥ 120 and ≤ 180 mmHg	1.44	2.35	1.68–5.2	0.012
SBP >180 mmHg	−0.30	0.82	0.65–0.93	0.031
SBP<120 mmHg	−0.29	0.70	0.62–0.89	0.029
Plasma cholesterol level	0.69	1.78	1.41–4.6	0.022
Blood glucose level >200 mg/dL	1.23	4.64	1.55–11.8	0.020
White blood cell count	−0.21	0.79	0.61–0.93	0.012
Charlson Index score <2	1.31	3.11	1.88–5.1	0.010
Charlson Index score >2	−0.32	0.86	0.69–0.92	0.020
ACE-inhibitors	1.44	5.55	2.34–12.9	<0.0001
Anti-platelet drugs	1.39	4.79	2.11–8.81	<0.05
Heparin	−0.37	0.79	0.41–0.91	0.018

ACE-I = ACE-inhibitors; SBP = systolic blood pressure.

A transient increase in arterial BP frequently occurs in patients with acute stroke [10–12]. This could be a physiological response to maintain or enhance perfusion of a reversibly damaged cerebrum when normal autoregulatory mechanisms are impaired.

In a recent overview, Bath [13] reported that some studies failed to establish a relationship between admission BP and outcome, although others suggested that low or high SBP may be associated with poor outcome [14]. In our study, patients with an SBP ≥ 120 and ≤ 180 mmHg at admission and a higher mean SBP at admission had better outcomes (no in-hospital mortality, a HAMT score of >6 and no ADL impairment at discharge). This could represent an interesting observation that may alter the management of acute ischaemic stroke.

These findings confirm that the relationship of our outcome indicators to the SBP-on admission may follow a U-shaped curve as reported by other studies [15]. Nevertheless our findings could indicate a larger nadir or U-point of the curve that occurred in the range of 120–180 mmHg for SBP values, respectively. Indeed our findings showed that only SBP ≥ 120 and ≤ 180 mmHg is associated with no mortality, no cognitive impairment and no ADL impaired whereas both SBP <120 and >180 mmHg are associated with intrahospital mortality and cognitive impairment.

Although the association between serum cholesterol levels and cerebrovascular disorders has been extensively studied, the relationship between cholesterol levels and outcome following ischaemic stroke has been investigated in only a few studies. Vauthey et al. [16] showed that, compared with patients with normal cholesterol levels, patients with high cholesterol levels had a 2.2-fold lower risk of death and a 2.1-fold lower risk of a poor functional outcome at 1 month. More recently, a population study [17] reported that serum cholesterol was inversely and almost linearly related to stroke severity.

Table 6
Logistic regression with no ADL impairment at discharge as the dependent variable.

	Regression coefficient	Odds ratio	95% CI	*p*-value
Age	−0.16	0.88	0.77–0.96	0.021
Blood glucose level >200 mg/dL	−0.37	0.83	0.37–0.78	<0.05
SBP ≥ 120 and ≤ 180 mmHg	1.43	2.12	1.54–2.79	≤0.0001
SBP >180 mmHg	−0.37	0.71	0.68–0.86	0.018
SBP<120 mmHg	−0.34	0.77	0.66–0.867	0.019
White blood cell count	−0.31	0.75	0.61–0.86	0.015
White blood cell count >10,000 cells/mm^3	−0.24	0.77	0.55–0.86	0.022
Charlson Index >2	−0.31	0.82	0.61–0.88	<0.05
Charlson Index <2	1.34	2.51	1.78–9.6	<0.0001
ACE-inhibitors	1.41	2.25	1.65–6.99	<0.05
Anti-platelet drugs	1.35	2.95	1.98–9.87	<0.0001
Heparin	−0.25	0.80	0.64–0.91	0.013

ACE-I = ACE-inhibitors; SBP = systolic blood pressure.

Our finding concerning the association between higher plasma total cholesterol levels and lower rates of in-hospital mortality, cognitive impairment and disability at discharge, is an interesting observation that, to our knowledge, has not been reported before. It is conceivable that low cholesterol levels may reflect a state of general malnutrition [18] and that inflammatory markers may impact on plasma cholesterol levels, with acute-phase markers being independently associated with low levels of total and high density lipoprotein-cholesterol [19]. So, our finding of a better outcome in patients with higher plasma cholesterol levels could be related to a lower rate of acute immuno-inflammatory activation after acute ischaemic stroke.

We reported that WBC count is significantly associated with in-hospital mortality, cognitive impairment and disability at discharge, confirming the data of Kazmierski et al. [20] who reported that an increased WBC count within the first 12 h of onset of an ischaemic stroke is a prognostic factor for in-hospital mortality, probably owing to the fact that WBC count may reflect the extent of ischaemic damage and the magnitude of the inflammatory response to the ischaemic event.

Moreover, our study shows (using univariate and logistic regression analyses) that patients receiving ACE-I, CCBs and APLs before the onset of stroke were less likely to experience in-hospital mortality. In fact, ACE-I pretreatment was associated with each of the good outcome indicators (no in-hospital mortality, a HAMT score of >6 and no ADL impairment). The mechanisms by which these drugs provide clinical benefit in patients with acute ischaemic stroke remain speculative, although are thought likely to be multifactorial, such as anti-inflammatory [21], neuroprotective [22], pro-fibrinolytic [23] and improving cerebral basal flow (CBF) [24] properties.

Saposnik et al. showed that not using antithrombotics during hospital admission was one of the most consistent predictors of case fatality at 7 days, 30 days, and 1 year after stroke [25]. APLs and ACE-I are commonly used for stroke prevention.

Although some trials have assessed the role of CCBs in the acute stroke setting [26], few have addressed their safety and efficacy in secondary prevention. It is widely accepted that N-methyl-D-aspartic acid-mediated calcium influx contributes to cell death following cerebrovascular ischaemia. 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. [27] showed in a cohort from the registry of the Canadian Stroke Network that patients who were admitted on CCBs had improved outcomes at 6 months if they were also discharged on CCBs, compared with those who had their CCBs discontinued. To our knowledge, no study has previously evaluated the role of CCB treatment in acute stroke prognosis, so our findings appear novel in this regard.

Our findings concerning heparin pretreatment are especially interesting. A considerable number of our patients had been pretreated with heparin at the time of admission and we found an association between reported heparin use and increased in-hospital mortality. The exact role of heparins in the hyper-acute stage of ischaemic stroke is still unclear. A recent Cochrane analysis [32] showed no benefits, but there are insufficient data to ascertain their effects on other important outcomes, including death and intracranial haemorrhage. Nevertheless, our findings may suggest a disadvantage, perhaps linked to a higher rate of haemorrhagic transformation, although we currently do not have data to support this theory.

Some possible limitations of our study include the fact that we used two uncommonly used functional measures of stroke outcome (HAMT and ADL impairment). These were chosen because measures of acute neurological deficit, such as the NIHSS or Scandinavian Stroke Scale, or measures of disability, such as the Rankin or the Barthel

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Index, were not evaluated in the GIFA study. Furthermore, given the short time frame of evaluation (discharge), the HAMT score may not accurately reflect the long-term cognitive impact of stroke, after accounting for stroke recovery in the chronic stage. Similarly, the ADL score at discharge may not accurately reflect stroke recovery. So, an extended follow-up is probably necessary to assess long-term outcomes. Nevertheless, HAMT is an effective screening tool for cognitive impairment in older, community-dwelling, hospitalized or institutionalized adults, as well as acute cerebrovascular patients [28] whereas ADL evaluation [29] has been used to determine the influence of initially lowered orientation on rehabilitation outcomes in stroke patients.

Other possible limitations of our study include its retrospective nature, the paucity of HAMT data and the almost complete absence of patients treated with statins, owing to the fact that the data analyzed were obtained from 1993 to 1998, a period of less wide-spread statin use. Nevertheless, in our opinion, this latter limitation represents a possible advantage, since our study evaluated the relationship of some cardiovascular drugs, such as ACE-I, CCBs and APLs, in patients not treated with statins, and hence shows the real effects of these drugs on stroke prognosis independent of statin treatment which, in the last few years, has shown positive effects on stroke outcome [30,31].

A further limitation is that in GIFA Database there were no available NIHSS and TOAST subtype data owing to the fact that GIFA was not a stroke patient database but is a multicenter periodical survey of hospitalized elderly patients with several admissions from whom we choose to analyze stroke patients extracted on the basis of ICD-9 code.

In conclusion, we found that the use of ACE-I, CCBs and APLs before an acute ischaemic stroke may improve patient outcome, whereas heparin use may worsen outcome. However, definitive recommendations for the use of these drugs in stroke patients must await further experimental and clinical data.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [33].

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