Early Hemorrhagic Transformation of Brain Infarction: Rate, Predictive Factors, and Influence on Clinical Outcome

Results of a Prospective Multicenter Study

Maurizio Paciaroni, MD; Giancarlo Agnelli, MD; Francesco Corea, MD, PhD; Walter Ageno, MD; Andrea Alberti, MD; Alessia Lanari, MD; Valeria Caso, MD, PhD; Sara Micheli, MD; Luca Bertolani, MD; Michele Venti, MD, PhD; Francesco Palmerini, MD; Sergio Biagini, MD; Giancarlo Comi, MD; Paolo Previdi, MD; Giorgio Silvestrelli, MD, PhD

Background and Purpose—Early hemorrhagic transformation (HT) is a complication of ischemic stroke but its effect on patient outcome is unclear. The aims of this study were to assess: (1) the rate of early HT in patients admitted for ischemic stroke, (2) the correlation between early HT and functional outcome at 3 months, and (3) the risk factors for early HT.

Methods—Consecutive patients with ischemic stroke were included in this prospective study in 4 study centers. Early HT was assessed by CT examination performed at day 5±2 after stroke onset. Study outcomes were 3-month mortality or disability. Disability was assessed using a modified Rankin score (≥3 indicating disabling stroke) by neurologists unaware of the occurrence of HT in the individual cases. Outcomes in patients with and without early HT were compared by χ^2 test. Multiple logistic regression analysis was used to identify predictors for HT.

Results—Among 1125 consecutive patients (median age 76.00 years), 98 (8.7%) had HT, 62 (5.5%) had hemorrhagic infarction, and 36 (3.2%) parenchymal hematoma. At 3 months, 455 patients (40.7%) were disabled or died. Death or disability was seen in 33 patients with parenchymal hematoma (91.7%), in 35 patients with hemorrhagic infarction (57.4%) as compared with 387 of the 1021 patients without HT (37.9%). At logistic regression analysis, parenchymal hematoma, but not hemorrhagic infarction, was independently associated with an increased risk for death or disability (OR 15.29; 95% CI 2.35 to 99.35). At logistic regression analysis, parenchymal hematoma was predicted by large lesions (OR 12.20, 95% CI 5.58 to 26.67), stroke attributable to cardioembolism (OR 5.25; 95% CI 2.27 to 12.14) or to other causes (OR 6.77; 95% CI 1.75 to 26.18), high levels of blood glucose (OR 1.01; 95% CI 1.00 to 1.01), and thrombolytic treatment (OR 3.54, 95% CI 1.04 to 11.95).

Conclusions—Early HT occurs in about 9% of patients. Parenchymal hematoma, seen in about 3% of patients, is associated with an adverse outcome. Parenchymal hematoma was predicted by large lesions attributable to cardioembolism or other causes, high blood glucose, and treatment with thrombolysis. **(*Stroke*. 2008;39:2249-2256.)**

Key Words: hemorrhagic infarction ■ ischemic stroke ■ outcome

Hemorrhagic transformation (HT) is a complication of ischemic stroke.[1] However, the incidence and risk factors for HT as well as the effect of HT on the outcome of patients with ischemic stroke are unclear.

Most of the previous studies on HT in patients with ischemic stroke were of limited sample size, had some methodological limitations, or were subgroup analyses of larger studies.[2–11] Furthermore, most of the information on the effect of early HT on clinical outcomes derives from studies on thrombolysis for ischemic stroke,[12–16] and data on early HT in patients not receiving thrombolysis mainly derives from patients randomized to placebo in the thrombolysis trials.[17,18]

The aims of this prospective study in consecutive patients were therefore to assess: (1) the rate of early HT in patients admitted for ischemic stroke, (2) the correlation between early HT and functional outcome at 3 months, and (3) the risk factors for early HT.

Methods

Consecutive patients admitted to 4 Italian hospitals with objectively diagnosed ischemic stroke between January 1st, 2006 and April 15th,

Received November 17, 2007; final revision received December 20, 2007; accepted January 3, 2008.

From the Stroke Unit, Division of Cardiovascular Medicine (M.P., G.A., A.A., V.C., M.V., F.P., S.B.), University of Perugia, Italy; the Stroke Unit, Division of Neurology (A.L., L.B., P.P., G.S.), Carlo Poma Hospital, Mantova, Italy; the Stroke Unit (S.M.), San Raffaele Hospital, University of Milan, Italy; the Department of Neurology (F.C., G.C.), Institute of Experimental Neurology, Scientific Institute San Raffaele, Milano, Italy; and the Department of Clinical Medicine (W.A.), University of Insubria, Varese, Italy.

Correspondence to Maurizio Paciaroni, Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Sant'Andrea delle Fratte, Perugia, 06126 Italy. E-mail mpaciaroni@med.unipg.it

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.107.510321**

2007 were included in this prospective cohort study. Patients with cerebral venous thrombosis, subarachnoid hemorrhage, or intracerebral bleeding on admission were excluded. All patients were assessed by a neurologist to determine the diagnosis of stroke (neurological deficit lasted >24 hours) and its pathological and etiologic subtypes.[19] On admission, stroke severity was assessed using the National Institutes of Health (NIH) Stroke Scale. Patients admitted within 3 hours were evaluated for thrombolysis treatment according SITS-MOST criteria.[20]

The 4 study centers provided stroke unit standard care for each patient. All patients were monitored for blood pressure, temperature, glucose level, heart rate, and blood gases in the first days after stroke.

Computed Tomography Scan Characteristics

In all patients cerebral computed tomography (CT) examination without contrast was performed on admission to exclude intracranial hemorrhage and to define both topography and extension of the ischemic lesion. Patients were admitted to the Stroke Unit within 12 hours from stroke onset. CT examination was performed within 2 hours from admission. The occurrence of early HT was investigated on repeated CT examination performed after 5 days (±2) from stroke onset or immediately in case of clinical worsening. Patients without repeated CT examination (eg, for early death) were excluded from the analysis unless they had an autopsy examination. Fourth generation CT scanner were used in all centers with 5 mm contiguous axial section for supratentorial images and 3 mm for images of posterior fossa. The study protocol recommended a window width of 80 to 100 Housfield units and a center level of 30 to 40 Housfield units. CT examination of patients with HT, as identified by the local investigators, were also independently adjudicated for study purpose by 2 members of the CT examination reading panel located in Perugia (M.P., V.C.). Disagreement was resolved by consensus. The members of the CT reading panel were unaware of the patient clinical outcome.

HT was defined as any degree of hyperdensity within the area of low attenuation, and it was categorized as hemorrhagic infarction or parenchymal hematoma.[21,22] Hemorrhagic infarction was defined as small petechiae along the margins of the infarct (HI-1) or as more confluent petechiae within the infarcted area but without space-occupying effect (HI-2). Parenchymal hematoma was defined as hematoma in ≤30% of the infarcted area with some slight space-occupying effect (PH-1) or as dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (PH-2). In cases of more than 1 hemorrhagic lesion on CT examination, the worst possible HT category was assumed.[14] For analysis purpose, we considered 2 groups of HT: hemorrhagic infarction HI-1 and HI-2 together and parenchymal hematoma PH-1 and PH-2 together.[17,18]

HT was considered symptomatic if it was not seen on a previous CT examination and there was, subsequently, either a suspicion of hemorrhage or a decline in neurological status.[23]

In addition, on repeated study CT examination, we assessed the site and size of the qualifying infarct. Based on standard templates,[24,25] the size of infarcts was quantified as: (1) small (lesion in the anterior or posterior circulation <1.5 cm), (2) medium (lesion in a cortical superficial branch of middle cerebral artery [MCA], or lesion involving the MCA deep branch, or lesion in internal borderzone territories, or lesion in a cortical superficial branch of posterior cerebral artery [PCA], or lesion involving the PCA branch or lesion in a cortical superficial branch of anterior cerebral artery [ACA]), (3) large anterior (lesion involving complete territory of ACM, ACP, or ACA or lesion involving 2 cortical superificial branches of MCA or lesion involving a cortical superficial branch of MCA associated to the MCA deep branch, or lesion involving more than 1 artery territory [eg, MCA associated to ACA territories]), (4) large posterior (lesion involving brain stem or cerebellum >1.5 cm).

Stroke Risk Factors

Data were collected on stroke risk factors: age, gender, history of hypertension (blood pressure of >140/90 mm Hg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (glucose level >126 mg/dL preprandial on 2 examinations, glucose level >200 mg/dL postprandial, or HbA_{1c}>8.5%, or under hypoglycemic treatment), current cigarette smoking, past smoking (cessation less than 5 years ago), history of hyperlipidemia (total cholesterol concentration >200 mg/dL or triglyceride concentration >140 mg/dL the day after admission or already under lipid lowering therapy), history of symptomatic ischemic heart disease (proven myocardial infarction, history of angina or existence of multiple lesions on thallium heart isotope screen or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; and ankle/arm systolic blood pressure ratio ≤0.85 in either leg and rest; or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), atrial fibrillation, alcohol abuse (>300 g per week), obesity (body mass index ≥30 kg/m^2), or previous stroke/transient ischemic attacks (TIAs). White matter changes (leukoaraiosis defined on the admission CT examination as ill-defined and moderately hypodense areas of ≥5 mm according to previously published criteria) were evaluated.[26] Leukoaraiosis in the deep white matter was dichotomized into absent versus mild, moderate, or severe.

Other baseline variables that were obtained at admission for each patient included: fasting serum glucose, fasting serum cholesterol (total, HDL, and LDL), platelet count, International Normalized Ratios (INR), activated thromboplastin times (aPTT), systolic blood pressure, and diastolic blood pressure.

Patients or proxies were interviewed to obtain information on treatment before the event (antiplatelet agents, prophylactic doses of anticoagulants, therapeutic doses of anticoagulants [heparin or warfarin], antihypertensive drugs, antidiabetic drugs, and statins). Treatments performed during hospitalization (antiplatelet agents, prophylactic doses of anticoagulants alone or associated with antiplatelet agents, therapeutic doses of anticoagulants [heparin or warfarin], thrombolytic [intravenous or intra-arterial]), were also analyzed.

Evaluation of Outcome

Patients were followed-up prospectively by face-to-face or telephone interview. Study outcomes were 3-month mortality or disability. Disability was assessed using a modified Rankin score (mRS) by neurologists unaware of the occurrence of HT in the individual cases. Stroke was defined as not disabling (mRS 0 to 2) or disabling (mRS 3 to 5).[27] The time of occurrence and the cause of death were recorded. The causes of death were divided into: neurological (recurrence of stroke, status epilepticus, edema, herniation), cardiovascular (myocardial infarction, heart failure, sudden death, other cardiovascular disease), and other causes (pneumonia, cancer, pulmonary embolus, and other causes).

Statistical Analysis

Outcomes in patients with and without early HT were compared by χ^2 test.

The first step of analysis was aimed at identifying predictors of adverse outcome (death or disability) at 3 months. Univariate tests were used to compare HT, clinical characteristics on admission, preexisting risk factors for stroke, CT findings, and therapies administered to alive and nondisabled patients in comparison to disabled or patients who died. All variables were subjected to multiple logistic regression analysis to identify independent predictors for death or disability.

The second step of analysis was aimed at identifying predictors of HT among baseline findings. Univariate tests were applied to compare clinical characteristics on admission, preexisting risk factors for stroke, CT findings, and therapies administered to HT and non-HT patients. All variables were subjected to multiple logistic regression analysis to identify independent predictors for HT.

Given the high number of variables evaluated in both analyses, the stepwise forward conditional model[28] was used for the logistic regression analysis. Data were analyzed with the SPSS/PC Win package 13.0.[29]

Table 1. Characteristics of the Patients Alive/Nondisabled and Dead or Disabled

	Total (n=1118)	Alive, Nondisabled (n=663)	Dead or Disabled (n=455)	Significance
Age (median)	76.00	72.00	79.00	0.0001
First-ever stroke	944 (84.4%)	581 (87.6%)	363 (79.8%)	0.001
Sex (male)	625 (55.9%)	399 (60.2%)	226 (49.7%)	0.001
Risk factors				
Hypertension	829 (74.1%)	460 (69.4%)	369 (81.1%)	0.0001
Diabetes	231 (20.7%)	119 (17.9%)	112 (24.6%)	0.008
Current smoking	218 (19.5%)	158 (23.8%)	60 (13.2%)	0.001
Past smoking	188 (16.8%)	113 (17.0%)	75 (16.5%)	0.80
Alcohol abuse	35 (3.1%)	26 (3.9%)	9 (2.0%)	0.08
Hyperlipidemia	402 (35.9%)	259 (36.1%)	143 (31.4%)	0.009
Obesity	79 (7.1%)	40 (6.0%)	39 (8.6%)	0.12
Previous TIA	62 (5.5%)	34 (5.1%)	28 (6.1%)	0.50
Family history VD	247 (22.1%)	157 (23.7%)	90 (19.8%)	0.14
Symptomatic PAD	30 (2.7%)	13 (2.0%)	17 (3.7%)	0.08
Symptomatic IHD	150 (13.4%)	87 (13.1%)	63 (13.8%)	0.70
Atrial fibrillation	218 (19.5%)	106 (16.0%)	112 (24.6%)	0.0001
Leucoaraiosis	298 (26.6%)	129 (19.4%)	169 (37.1%)	0.0001
Side				
Right	517 (46.2%)	312 (47.0%)	205 (45.0%)	0.50
Left	567 (50.7%)	338 (51.0%)	229 (50.3%)	0.80
Bilateral	34 (3.1%)	13 (2.0%)	21 (4.6%)	0.01
Size and severity				
Small lesion	468 (41.9%)	353 (53.2%)	115 (25.3%)	0.0001
Medium	424 (37.9%)	235 (35.4%)	189 (41.5%)	0.045
Cortical	243 (21.7%)	135 (20.1%)	108 (23.7%)	0.18
Deep	181 (16.2%)	100 (15.1%)	81 (17.8%)	0.20
Large anterior	183 (16.4%)	44 (6.6%)	139 (30.5%)	0.0001
Large posterior	43 (3.8%)	31 (4.7%)	12 (2.6%)	0.16
NHISS (median)	6.0	4.0	13.0	0.0001
Cause				
Atherosclerosis	187 (16.7%)	76 (11.5%)	111 (24.4%)	0.0001
Small vessel disease	323 (28.9%)	243 (36.6%)	80 (17.6%)	0.0001
Cardioembolism	398 (26.6%)	137 (20.7%)	161 (35.4%)	0.0001
Unknown	213 (19.0%)	154 (23.2%)	59 (13.0%)	0.0001
Other cause	54 (4.8%)	36 (5.4%)	18 (3.9%)	0.30
Multiple possible causes	43 (3.8%)	17 (2.6%)	26 (5.7%)	0.01
Treatment before admission				
Antihypertensives	637 (57.0%)	348 (52.5%)	289 (63.5%)	0.0001
Antidiabetics	191 (17.1%)	99 (14.9%)	92 (20.2%)	0.02
Statins	94 (8.4%)	62 (9.3%)	32 (7.0%)	0.18
AC prophylaxis	12 (1.1%)	0	12 (2.6%)	0.0001
AC therapy	49 (4.4%)	22 (3.3%)	27 (5.9%)	0.03
Antiplatelets	325 (29.1%)	174 (26.2%)	151 (33.2%)	0.01
Treatment in hospital				
Antiplatelets	986 (88.2%)	588 (88.7%)	398 (87.5%)	0.50
AC prophylaxis	148 (13.2%)	44 (6.6%)	104 (22.8%)	0.0001
AC therapy	120 (10.7%)	72 (10.8%)	48 (10.5%)	0.90
Antiplatelets+AC prophylaxis	134 (12.0%)	34 (5.1%)	100 (22.0%)	0.0001
Thrombolysis (63 IV, 2 IA)	65 (5.8%)	33 (5.0%)	32 (7.0%)	0.15

(*Continued*)

Table 1. Continued

	Total (n=1118)	Alive, Nondisabled (n=663)	Dead or Disabled (n=455)	Significance
Hematological parameters (means)				
Platelets	229 980±72	227 730±69	233 250±76	0.20
INR	1.17±0.7	1.18±0.8	1.16±0.5	0.12
PTT sec.	30.2±5.2	30.3±5.3	30.1±5.1	0.40
Total cholesterol	188.43±42.8	190.24±43.3	185.61±42.0	0.08
LDL cholesterol	114.97±35.1	116.60±35.3	113.41±34.8	0.2
HDL cholesterol	51.92±14.1	52.01±15.1	51.80±14.1	0.8
Glicemia	118.72±49.4	115.00±50.0	123.91±48.1	0.003
Systolic blood pressure (median)	150.00	150.00	155.00	0.16
Diastolic blood pressure (median)	85.00	85.00	85.00	0.4
Hemorrhagic transformation				
Total	97 (8.7%)	29 (4.4%)	68 (14.9%)	0.0001
HI 1 and 2	61* (5.4%)	26 (3.9%)	35 (7.7%)	0.007
PH 1 and 2	36 (3.2%)	3 (0.4%)	33 (7.2%)	0.0001
Symptomatic	15 (1.3%)	2 (0.3%)	13 (2.8%)	0.0001

HI indicates hemorrhagic infarction; PH, parenchymal hemorrhage; VD, vascular disease; IHD, ischemic heart disease; TIA, transient ischemic attack; PAD, peripheral arterial disease; AC, anticoagulants. *1 patient lost at follow-up.

Results

Incidence and Type of Hemorrhagic Transformation

1136 patients were included in the study. Eleven were excluded from the analysis because they did not have a repeated CT examination according to the study protocol. Among 1125 consecutive patients (age: median 76.00 years; 56% males) included in the analysis, 98 (8.7%; age: median 78.00 years; 49% males) had HT: 62 (5.5%) had hemorrhagic infarction, and 36 (3.2%) parenchymal hematoma. Sixteen patients had a symptomatic HT (6 in the patients with hemorrhagic infarction and 10 in the patients with parenchymal hematoma).

Of 65 patients who received thrombolysis, 8 (12.3%) had HT. Two of these patients (3.2%) had symptomatic HT. Two of the 8 patients has hemorrhagic infarction and 3 parenchymal hematoma.

Influence of HT on Adverse Outcome

At 3 months, 7 patients were lost to follow-up, 326 patients (29.2%) were disabled, and 129 died (11.5%). The causes of death were neurological in 58 patients, cardiovascular in 24 patients, attributable to other causes in 20, and unknown in 27 patients. In Table 1 the characteristics of the patients alive/nondisabled and dead or disabled are summarized.

Death or disability were seen in 33 patients with parenchymal hematoma (91.7%), in 35 of the patients with hemorrhagic infarction (57.4%) as compared with 387 of the 1021 patients without HT (37.9%). Regression logistic analysis found that age (OR 1.07; 95% CI 1.05 to 1.09), history of hypertension (OR 1.72; 95% CI 1.11 to 2.65), history of diabetes (OR 2.10; 95% CI 1.38 to 3.19), high NIHSS score on admission (OR 1.35; 95% CI 1.30 to 1.41), and stroke attributable to atherosclerosis (OR 1.84; 95% CI 1.15 to 2.93) were associated with adverse outcome. First-ever stroke (OR 0.50; 95% CI 0.31 to 0.79) was associated with better outcome.

Parenchymal hematoma was associated with an increased risk for death or disability (OR 15.29; 95% CI 2.35 to 99.35). This was not the case for HT overall, hemorrhagic infarction, and symptomatic HT.

Independent Predictors of HT

The characteristics of patients with and without HT are summarized in Table 2.

At univariate analysis, HT (overall) was associated with the presence of atrial fibrillation (29/98, 29.6% versus 189/1027, 18.4%; $P=0.01$), large anterior stroke (53/98, 54.1% versus 131/1027, 12.7%; $P<0.0001$), stroke attributable to cardioembolism (51/98, 52.0% versus 249/1027, 24.2%; $P<0.0001$), high NIHSS score on admission (median 14.0 versus 6.0; $P<0.0001$), low LDL-cholesterol levels on admission (median 107.20±30.3 mg/dL versus 115.60±35.4 mg/dL; $P=0.02$), and in-hospital prophylaxis for deep venous thrombosis with anticoagulants associated with antiplatelet agents (26/98, 26.5% versus 110/1027, 10.7%; $P<0.0001$) or not (28/98, 28.5% versus 122/1027, 11.9%; $P<0.0001$) during hospitalization. HT (overall) was inversely associated with lesions of less than 1.5 cm (3/98, 3.0% versus 475/1027, 46.2%; $P<0.0001$). At logistic regression analysis, HT (overall) was independently predicted by large lesions (OR 4.57, 95 CI 2.83 to 7.39), stroke attributable to cardioembolism (OR 2.36; 95% CI 1.44 to 3.68), or low platelet count on admission (OR 1.01; 95% CI 1.01 to 1.08).

At univariate analysis, parenchymal hematomas were associated with the presence of atrial fibrillation (13/36, 36.1% versus 205/1089, 12.8%; $P=0.016$), leukoaraiosis (15/36, 41.7% versus 284/1089, 26.1%; $P=0.05$), large anterior stroke (25/36, 69.4% versus 159/1089, 14.6%; $P<0.0001$), stroke attributable to cardioembolism (21/36, 58.3% versus 279/1089, 25.6%; $P<0.0001$), high NIHSS score on admis-

Table 2. Characteristics of the Patients With and Without HT

	Total (n=1125)	Without HT (n=1027)	With HI (n=62)	Significance	With PH (n=36)	Significance
Age (median)	76.00	75.00	77.50	0.65	76.00	0.27
First-ever stroke	959 (84.4%)	866 (84.3%)	52 (83.9%)	0.85	32 (88.9%)	0.63
Sex (male)	631 (56.0%)	583 (56.8%)	30 (48.4%)	0.23	18 (50.0%)	0.49
Risk factors						
Hypertension	833 (74.0%)	765 (74.5%)	44 (71.0%)	0.55	24 (66.7%)	0.33
Diabetes	233 (20.7%)	217 (21.1%)	5 (8.1%)	0.01	11 (30.5%)	0.21
Current smoking	222 (19.7%)	200 (19.5%)	15 (24.2%)	0.41	7 (19.4%)	1.0
Past smoking	189 (16.8%)	174 (16.9%)	7 (11.3%)	0.29	8 (22.2%)	0.37
Alcohol abuse	35 (3.1%)	34 (3.3%)	0	0.25	1 (2.8%)	1.0
Hyperlipidemia	404 (35.9%)	375 (36.5%)	22 (35.5%)	1.00	7 (19.4%)	0.035
Obesity	81 (7.2%)	71 (6.9%)	5 (8.1%)	0.61	5 (13.9%)	0.17
Previous TIA	63 (5.6%)	55 (5.3%)	6 (9.7%)	0.15	2 (5.5%)	1.0
Family history VD	249 (22.3%)	230 (22.4%)	13 (21.0%)	0.87	6 (16.7%)	0.54
Symptomatic PAD	30 (2.7%)	29 (2.8%)	0	0.40	1 (2.8%)	1.0
Symptomatic IHD	150 (13.3%)	136 (13.2%)	11 (17.7%)	0.33	3 (8.3%)	0.61
Atrial fibrillation	218 (19.4%)	189 (18.4%)	16 (25.8%)	0.17	13 (36.1%)	0.01
Leucoaraiosis	299 (26.6%)	265 (25.8%)	19 (30.6%)	0.45	15 (41.7%)	0.05
Side						
Right	522 (46.4%)	475 (46.2%)	30 (48.4%)	0.79	17 (47.2%)	1.0
Left	569 (50.6%)	522 (50.8%)	29 (46.8%)	0.60	18 (50.0%)	1.0
Bilateral	34 (3.0%)	30 (2.9%)	3 (4.8%)	0.42	1 (2.8%)	1.0
Size and severity						
Small lesion	469 (41.7%)	466 (45.4%)	2 (3.2%)	0.0001	1 (2.8%)	0.0001
Medium	429 (38.1%)	390 (38.0%)	30 (48.4%)	0.10	9 (25.0%)	0.16
Cortical	246 (21.9%)	220 (21.4%)	20 (32.2%)	0.06	6 (16.7%)	0.67
Deep	183 (16.3%)	170 (16.5%)	10 (16.1%)	1.00	3 (8.3%)	0.25
Large anterior	184 (16.3%)	131 (12.7%)	28 (45.2%)	0.0001	25 (69.4%)	0.0001
Large posterior	43 (3.8%)	40 (3.9%)	2 (3.2%)	1.0	1 (2.8%)	1.0
NHISS (median)	6.0	6.0	14.0	0.0001	16.5	0.0001
Cause						
Atherosclerosis	191 (17.0%)	170 (16.5%)	15 (24.2%)	0.12	6 (16.7%)	1.0
Small vessel disease	323 (28.7%)	315 (30.7%)	7 (11.3%)	0.001	1 (2.8%)	0.0001
Cardioembolism	300 (26.7%)	249 (24.2%)	30 (48.4%)	0.0001	21 (58.3%)	0.0001
Unknown	213 (18.9%)	201 (19.6%)	8 (12.9%)	0.24	4 (11.1%)	0.28
Other cause	54 (4.8%)	48 (4.7%)	2 (3.2%)	1.00	4 (11.1%)	0.09
Multiple causes	44 (3.9%)	44 (4.3%)	0	0.17	0	0.39
Treatment before admission						
Antihypertensives	641 (57.0%)	589 (57.3%)	30 (48.4%)	0.18	22 (61.1)	0.73
Antidiabetics	193 (17.1%)	177 (17.2%)	5 (8.1%)	0.07	11 (30.5%)	0.04
Statins	94 (8.3%)	85 (8.3%)	7 (11.3%)	0.35	2 (5.5%)	0.76
AC prophylaxis	12 (1.0%)	10 (1.0%)	1 (1.6%)	0.47	1 (2.8%)	0.32
AC therapy	49 (4.3%)	41 (4.0%)	4 (6.4%)	0.31	4 (11.1%)	0.06
Antiplatelets	327 (29.1%)	296 (28.8%)	22 (35.5%)	0.25	9 (25.0%)	0.71
Treatment in hospital						
Antiplatelets	993 (88.3%)	910 (88.6%)	54 (87.1%)	0.68	29 (80.5%)	0.18
AC prophylaxis	150 (13.3%)	122 (11.9%)	17 (27.4%)	0.001	11 (30.5%)	0.003
AC therapy	120 (10.7%)	109 (10.6%)	7 (11.3%)	0.83	4 (11.1%)	0.78
Antiplatelets+AC prophylaxis	136 (12.1%)	110 (10.7%)	15 (24.2%)	0.003	11 (30.5%)	0.001
Thrombolysis (65 i.v., 2 i.a.)	67 (6.0%)	58 (5.6%)	5 (8.1%)	0.39	4 (11.1%)*	0.15

(*Continued*)

Table 2. Continued

	Total (n=1125)	Without HT (n=1027)	With HI (n=62)	Significance	With PH (n=36)	Significance
Hematological parameters (means)						
Platelets	221 000±72	224 000±72	217 550±61	0.15	220 810±86	0.41
INR	1.17±0.7	1.18±0.8	1.12±0.2	0.59	1.12±0.31	0.70
PTT sec.	30.2±5.2	30.2±4.9	31.2±9.3	0.15	29.7±2.9	0.60
Total cholesterol	188.43±42.8	188.88±43.1	179.76±40.2	0.10	191.17±36.7	0.75
LDL cholesterol	114.85±35.1	115.60±35.4	106.55±31.2	0.05	108.34±29.1	0.23
HDL cholesterol	51.90±14.6	51.81±14.7	53.97±14.2	0.26	50.89±14.1	0.71
Glicemia	118.72±49.4	118.50±49.0	109.34±39.9	0.15	141.71±67.6	0.007
Systolic blood pressure (median)	150.00	150.00	160.00	0.049	157.50	0.70
Diastolic blood pressure (median)	85.00	85.00	81.00	0.35	85.00	0.89

HT indicates hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hemorrhage; VD, vascular disease; IHD, ischemic heart disease; TIA, transient ischemic attack; PAD, peripheral arterial disease; AC, anticoagulants. *1 i.a. and 3 i.v. thrombolysis.

sion (median 16.5 versus 6.0; $P<0.0001$), high blood glucose levels on admission (mean 141.71±67.6 mg/dL versus 118.50±49.98 mg/dL; $P=0.007$), and in-hospital prophylaxis for deep venous thrombosis with anticoagulants associated with antiplatelet agents (11/36, 30.5% versus 125/1089, 11.5%; $P<0.002$) or not (11/36, 30.5% versus 139/1089, 12.8%; $P<0.005$). Parenchymal hematoma was inversely correlated with lesions less than 1.5 cm (1/36, 2.8% versus 468/1089, 43.0%; $P<0.0001$) or history of hyperlipidemia (7/36, 19.4% versus 397/1089, 36.5%; $P=0.05$). At logistic regression analysis, parenchymal hematoma was predicted by large lesions (OR 12.20, 95% CI 5.58 to 26.67), stroke attributable to cardioembolism (OR 5.25; 95% CI 2.27 to 12.14) or attributable to other causes (OR 6.77; 95% CI 1.75 to 26.18; 13 artery dissections, 9 during procedures for carotid revascularization, 7 paradoxical embolism, 6 tumors, 5 vasculitis, 3 during coronary angiography, 2 migrainous infarctions, 2 coagulopathies, and other 7 rare causes), high levels of blood glucose on admission (OR 1.01; 95% CI 1.00 to 1.01), or treatment with thrombolysis (OR 3.54, 95% CI 1.04 to 11.95).

The results of multivariate analysis are reported in Table 3.

Discussion

In this large cohort of consecutive patients with acute ischemic stroke, we observed an incidence of early HT of about 9%; parenchymal hematoma, seen in about 3% of the patients, was associated with an adverse outcome at 3 months. The size of the ischemic lesion and cardioembolism were independent predictors of early HT. High levels of fasting blood glucose on admission and thrombolytic treatment were independently associated with the development of parenchymal hematoma.

The incidence of HT observed in our study was lower than the rate reported from other authors. There are several explanations for this finding. First, in our study, the time interval between stroke onset and repeated CT examination was shorter than in other studies.[8,9] Second, the low rate of early HT could be explained by the inclusion in the study of a nonselected cohort of consecutive patients. Indeed, most of the previous trials included candidates to thrombolysis that presented with more severe stroke and with a larger lesion in the MCA territory. Our patients had lesions in different territories of variable severity. Furthermore, the definition of HT differed among studies. Indeed, severe HT, defined by the presence of parenchymal hematoma, was infrequent in our as well as in the previous studies.[1,9] The lower rate of HT reported could be also caused by false-negative findings at on site reading, a lack of standardized reading procedure, or a lack of central reading of negative cases. It can also be caused by better clinical management leading to less reperfusion damage.

In agreement with the literature, parenchymal hematoma was predicted by large lesions attributable to cardioembolism.[5,9] Hyperglycemia was found to be a risk factor for parenchymal hematoma consistently with what was previously observed in patients treated with rt-PA.[30]

No correlation was found between HT and any treatment on admission, except thrombolysis, which was independently associated with parenchymal hematoma, although this was

Table 3. Results of Multivariate Analysis

	OR	95% CI
Predictors of adverse outcome (dead or disability)		
Age	1.07	1.05 to 1.09
History of diabetes	2.10	1.38 to 3.19
High NIHSS	1.35	1.30 to 1.41
Atherosclerosis	1.84	1.15 to 2.93
First-ever stroke	0.50	0.31 to 0.79
Parenchymal hematoma	15.29	2.35 to 99.35
Predictors of HT		
Large lesion	4.57	2.83 to 7.39
Cardioembolism	2.36	1.44 to 3.68
Low platelet count	1.01	1.01 to 1.08
Predictors of PH		
Large lesion	12.20	5.58 to 26.67
Cardioembolism	5.25	2.27 to 12.14
Other cause	6.77	1.75 to 26.18
High levels of blood glucose	1.01	1.00 to 1.01
Treatment with thrombolysis	3.54	1.04 to 11.95

OR indicates odds ratio; CI, interval confidence.

present in only 4 of 67 patients treated with thrombolysis (6%). Of note, one of the patients with parenchymal hematoma had intraarterial thrombolysis within 6 hours from stroke onset. At the univariate analysis, prophylactic doses of either unfractionated or low molecular weight heparin administered to prevent deep venous thrombosis (DVT), with or without concomitant aspirin, were associated with HT, but the logistic regression analysis did not confirm this finding. This result was probably attributable to the fact that prophylaxis of DVT is performed in more severe patients with large ischemic lesions.

About 7% of the patients with a stroke attributable to a rare cause had parenchymal hematoma, and at logistic regression analysis this subgroup was associated with an increased risk of having parenchymal hematoma.

High levels of arterial blood pressure at admission are usually considered to be a risk factor for HT.[16,31] In our study, median systolic blood pressure was higher in patients with parenchymal hematoma than in patients without any HT (157.50 mm Hg versus 150.00 mm Hg). However, at regression logistic analysis, high systolic blood pressure was no longer associated with severe HT. Probably, blood pressure is an important risk factor in patients treated with rt-PA, in whom reperfusion could determine HT.[32]

In our study, leukoaraiosis was not correlated with HT. Our observation is in contrast with the findings of previous studies in which severe leukoaraiosis was found to be an independent predictor of HT.[33,34] The difference is probably attributable to the fact that we dichotomized leukoaraiois in present/absent without a quantification of severity.

Although rarely, HT was also observed in patients with small lesions (<1.5 cm). Three of 469 patients with small lesions (0.6%) had HT, and one of these had a parenchymal hematoma.

In our study, only 16/98 had symptomatic HT, but the distinction in symptomatic and asymptomatic HT is not precise. Clinical deterioration may have a variety of causes, such as another ischemic stroke, decrease in cerebral perfusion pressure, and mass effect of ischemic edema. Depiction of blood by neuroimaging per se does not mean that it is responsible for clinical deterioration, because intracranial blood may have been present before clinical deterioration was assessed.[35]

This study has some limitations. We have no information on 11 patients who died, before repeating CT scan according to the study protocol. This missed information could have led to an underestimation of HT, although it is unlikely that all the 11 patients had HT. Seven patients were lost at follow-up, and one of these had HT.

Conclusions

The incidence of early HT in an unselected population of consecutive patients with acute ischemic stroke is about 9%. Parenchymal hematoma, but not hemorrhagic infarction, resulted to be associated with an adverse outcome at 3 months. Parenchymal hematoma was predicted by large lesions attributable to cardioembolism or to rare causes, high blood glucose levels on admission, and treatment with thrombolysis.

Acknowledgments

We are grateful to Alessandra De Leo and Elisa Manfredi for their contribution to collect data and follow patients in the research center of Varese.

Disclosures

None.

References

1. Moulin T, Crapin-Leblond T, Chopard JL, Bogousslavsky J. Hemorrhagic infarcts. *Eur Neurol*. 1994;34:64–77.
2. Lodder J. CT-detected hemorrhagic infarction; relation with the size of the infarct, and the presence of midline shift. *Acta Neurol Scand*. 1984; 70:329–335.
3. Ott BR, Zamani A, Kleefield J, Funkenstein HH. The clinical spectrum of hemorrhagic infarction. *Stroke*. 1986;17:630–637.
4. Hornig CR, Dorndorf W, Agnoli AL. Hemorrhagic cerebral infarction – a prospective study. *Stroke*. 1986;17:179–185.
5. Hornig CR, Bauer T, Simon C, Trittmacher S, Dorndorf W. Hemorrhagic transformation in cardioembolic cerebral infarction. *Stroke*. 1993;24: 465–468.
6. Beghi E, Bogliun G, Cavaletti G, Sanguineti I, Tagliabue M, Agostoni F, Macchi I. Hemorrhagic infarction: risk factors, clinical and tomographic features, and outcome. A case-control study. *Acta Neurol Scand*. 1989; 80:226–231.
7. Okada Y, Yamaguchi T, Minematsu K, Miyashita T, Sawada T, Sadoshima S, Fujishima M, Omae T. Hemorrhagic transformation in cerebral embolism. *Stroke*. 1989;20:598–603.
8. Lyden PD, Zivin JA. Hemorrhagic transformation after cerebral ischemia: mechanisms and incidence. *Cerebrovasc Brain Metab Rev*. 1993;5:1–16.
9. Toni D, Fiorelli M, Bastianello S, Sacchetti ML, Sette G, Argentino C, Montinaro E, Bozzao L. Hemorrhagic transformation of brain infarct: predictability in the first 5 hours from stroke onset and influence on clinical outcome. *Neurology*. 1996;46:341–345.
10. Alexandrov AV, Black SE, Ehrlich LE, Caldwell CB, Norris JW. Predictors of hemarrhagic transformation occurring spontaneously and on anticoagulation in patients with acute ischemic stroke. *Stroke*. 1997;28: 1198–1202.
11. Kerenyi L, Kardos L, Szasz J, Szatmari S, Bereczki D, Hegedus K, Csiba L. Factors influencing hemorrhagic transformation in ischemic stroke: a clinicopathological comparison. *Eur J Neurol*. 2006;13:1251–1255.
12. Motto C, Ciccone A, Aritzu E, Boccardi E, De Grandi C, Piana A, Candelise L. Hemorrhage after an acute ischemic stroke. *Stroke*. 1999; 30:761–764.
13. Jaillard A, Cornu C, Durieux A, Moulin T, Boutitie F, Lees KR, Hommel M. Hemorrhagic transformation in acute ischemic stroke: the MAST-E Study. *Stroke*. 1999;30:1326–1332.
14. Berger C, Fiorelli M, Steiner T, Schabitz WR, Bozzao L, Bluhmki E, Hacke W, Von Kummer R. Hemorrhagic trasnformation of ischemic brain tissue. *Asymptomatic or symptomatic? Stroke*. 2001;32:1330–1335.
15. Saver JL. Hemorrhage after thrombolytic therapy for stroke: the clinically relevant number needed to harm. *Stroke*. 2007;38:2279–2283.
16. Lansberg MG, Thijs VN, Bammer R, Kemp S, Wiyman CAC, Marks MP, Albers GW. Risk factors of symptomatic intracerebral hemorrhage after tPA therapy for acute stroke. *Stroke*. 2007;38:2275–2278.
17. Fiorelli M, Bastianello S, von Kummer R, del Zoppo G, Larrue V, Lesaffre E, Ringleb AP, Lorenzano S, Manelfe C, Bozzao L. Hemorrhagic transformation within 36 hours of a cerebral infarct. *Stroke*. 1999; 30:2280–2284.
18. Dzialowski I, Pexman W, Barber PA, Demchuk AM, Buchan AM, Hill MD. Asymptomatic hemorrhage after thrombolysis may not be benign. *Stroke*. 2007;38:75–79.
19. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke: definition for use in a multicenter clinical trial. *Stroke*. 1993;241:35–41.
20. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischemic stroke in the Safe Implementation of Thrombolysis in Stroke. Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007; 369:275–282.
21. Pessin MS, Del Zoppo GJ, Estol CJ. Thrombolytic agents in the treatment of stroke. *Clin Neuropharmacol*. 1990;13:271–289.

22. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, Del Zoppo GJ, for the rtPA Acute Stroke Study Group. Neuroradiologic evaluation of patients with acute stroke treated with rtPA. *AJNR*. 1993; 14:3–13.
23. National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study Group. TPA for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
24. Tatu L, Moulin T, Bogousslavsky J, Duvemoy H. Arterial territories of the human brain: cerebral hemispheres. *Neurology*. 1998;50:1699–1708.
25. Tatu L, Moulin T, Bogousslavsky J, Duvemoy H. Arterial territories of the human brain: brainstem and cerebellum. *Neurology*. 1996;47: 1125–1135.
26. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin A, Sjogren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322.
27. De Haan R, Limburg M, Bossuyt P, van der Meulen J, Aaronson N. The clinical meaning of Rankin "handicap" grades after stroke. *Stroke*. 1995; 26:2027–2030.
28. SPSS Regression Models 13.0. Chicago: SPSS Inc. 2004.
29. SPSS for Windows 13.0. Chicago: SPSS Inc.; 2004.
30. Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rtPA Stroke Trial. *Neurology*. 2002;59: 669–674.
31. Gilligan AK, Markus R, Read S, Srikanth V, Hirano T, Fitt G, Arends M, Chambers BR, Davis SM, Donnan GA. Baseline blood pressure but not early computed tomography changes predicts major hemorrhage after streptokinase in acute ischemic stroke. *Stroke*. 2002;33:2236–2242.
32. Larrue V, von Kummer RR, Muller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with rtPA: a secondary analysis of the ECASS II. *Stroke*. 2001;32:438–441.
33. Palumbo V, Boulanger JM, Hill MD, Inzitari D, Bucham AM. Leukoaraiosis and cerebral hemorrhage after thrombolysis in acute stroke. *Neurology*. 2007;68:1020–1024.
34. Neumann-Haefelin T, Hoelig S, Berkefeld J, Fiehler J, Gass A, Humpich M, Kastrup A, Kucinski T, Lecei O, Liebeskind DS, Rother J, Rosso C, Samson Y, Saver JL, Yan B. Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. *Stroke*. 2006;37:2463–2466.
35. Trouillas P, von Kummer R. Classification and pathogenesis of cerebral hemorrhages after thrombolysis in ischemic stroke. *Stroke*. 2006;37: 556–561.

Stroke
Journal of the American Heart Association

Early Hemorrhagic Transformation of Brain Infarction: Rate, Predictive Factors, and Influence on Clinical Outcome: Results of a Prospective Multicenter Study

Maurizio Paciaroni, Giancarlo Agnelli, Francesco Corea, Walter Ageno, Andrea Alberti, Alessia Lanari, Valeria Caso, Sara Micheli, Luca Bertolani, Michele Venti, Francesco Palmerini, Sergio Biagini, Giancarlo Comi, Paolo Previdi and Giorgio Silvestrelli

Stroke. 2008;39:2249-2256; originally published online June 5, 2008;
doi: 10.1161/STROKEAHA.107.510321
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628