ORIGINAL RESEARCH

Hemorrhagic Transformation in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Time to Initiation of Oral Anticoagulant Therapy and Outcomes

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***Background*—**In patients with acute ischemic stroke and atrial fibrillation, early anticoagulation prevents ischemic recurrence but with the risk of hemorrhagic transformation (HT). The aims of this study were to evaluate in consecutive patients with acute stroke and atrial fibrillation (1) the incidence of early HT, (2) the time to initiation of anticoagulation in patients with HT, (3) the association of HT with ischemic recurrences, and (4) the association of HT with clinical outcome at 90 days.

***Methods and Results*—**HT was diagnosed by a second brain computed tomographic scan performed 24 to 72 hours after stroke onset. The incidence of ischemic recurrences as well as mortality or disability (modified Rankin Scale scores >2) were evaluated at 90 days. Ischemic recurrences were the composite of ischemic stroke, transient ischemic attack, or systemic embolism. Among the 2183 patients included in the study, 241 (11.0%) had HT. Patients with and without HT initiated anticoagulant therapy after a mean 23.3 and 11.6 days, respectively, from index stroke. At 90 days, 4.6% (95% confidence interval, 2.3–8.0) of the patients with HT had ischemic recurrences compared with 4.9% (95% confidence interval, 4.0–6.0) of those without HT; 53.1% of patients with HT were deceased or disabled compared with 35.8% of those without HT. On multivariable analysis, HT was associated with mortality or disability (odds ratio, 1.71; 95% confidence interval, 1.24–2.35).

***Conclusions*—**In patients with HT, anticoagulation was initiated about 12 days later than patients without HT. This delay was not associated with increased detection of ischemic recurrence. HT was associated with increased mortality or disability. **(*J Am Heart Assoc*. 2018;7:e010133. DOI: 10.1161/JAHA.118.010133.)**

Key Words: atrial fibrillation • hemorrhagic transformation • stroke

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Clinical Perspective

What Is New?

- Hemorrhagic transformation (HT) patients with acute stroke and atrial fibrillation received anticoagulation about 12 days later than patients without HT.
- This delay was not associated with a significant increase in ischemic recurrences (recurrent ischemic stroke, transient ischemic attack, and systemic embolism).
- HT was associated with increased mortality and disability.

What Are the Clinical Implications?

- Early initiation of anticoagulation does not appear necessary to prevent recurrent embolic events in HT patients.
- It may be beneficial to avoid therapies that can cause early HT.
- In addition to lesion size, reliable clinical and radiologic predictors are needed to identify those patients at highest risk for HT and worse outcomes.

Patients with acute ischemic stroke and nonvalvular atrial fibrillation (AF) are at a high risk of early recurrence.[1,2] In these patients, anticoagulant therapy (vitamin K antagonists or non–vitamin K antagonists [NOACs]) reduces the risk of recurrent ischemic stroke, but carries the risk of hemorrhagic transformation (HT). The possible intracerebral hemorrhagic complications in patients with acute stroke and AF are (1) intracranial hemorrhage occurring during anticoagulation therapy; (2) HT, ranging from hemorrhagic infarction (HI) to parenchymal hemorrhage (PH) in the area of an acutely infarcted brain after ischemic stroke; and (3) worsening of HT due to anticoagulation therapy initiated after the index stroke. In patients with acute stroke, early HT was reported in about 9% within 5 to 7 days from the index event. Of the observed HTs, 33% were PH and were associated with an adverse 3-month outcome.[3] In patients with acute stroke and AF, the rate of HT is higher. On neuroimaging performed 24 to 72 hours after stroke onset, HT was observed in 13.0%: 8.8% HI and 4.2% PH.[1] In patients with acute stroke and AF, the presence of HT is associated with a less favorable clinical outcome, and a potential delay in the initiation of oral anticoagulant therapy that could lead to an increase in the risk of early recurrence.

The aims of this multicenter, prospective, international study in consecutive patients with acute ischemic stroke and AF were (1) to evaluate the incidence of early HT, (2) to evaluate the time to initiation of oral anticoagulant therapy in patients with HT, (3) to correlate the presence of HT with ischemic recurrence, and (4) to assess the influence of HT on clinical outcome at 90 days.

Methods

The authors declare that all supporting data are available within the article.

We combined the databases of the RAF study and the RAF-NOAC study,[1,4] which were prospective observational studies that were carried out between January 2012 and March 2014, and between April 2014 and June 2016, respectively. Both studies enrolled consecutive patients with acute ischemic stroke and known or newly diagnosed AF without permanent contraindications to anticoagulation. The study was approved by the local institutional review boards, if required. Informed consent was provided by study participants in countries where this was required by law.

On admission, stroke severity was assessed in all patients using the National Institutes of Health Stroke Scale (NIHSS); noncontrast cerebral computed tomography (CT) or cerebral magnetic resonance imaging (MRI) scan was performed to exclude intracranial hemorrhage. Acute reperfusion therapies and carotid revascularization procedures were delivered as per standard local protocol, when appropriate. Standard stroke unit care, monitoring, and treatment were provided according to current international recommendations for acute ischemic stroke. Attending physicians made decisions regarding the type of anticoagulant to be prescribed for secondary stroke prevention, as well as the day of initiation of anticoagulant treatment. The RAF study included patients treated with either vitamin K antagonists or NOACs, and the RAF-NOAC study only patients who received NOACs.

A second brain CT scan or MRI was scheduled to be performed 24 to 72 hours from stroke onset in all included patients.

HT was defined as any degree of hyperdensity within the area of low attenuation and was classified as either HI or PH.[3] HI 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). PH 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. For analysis purpose, we considered 2 groups of HT: HI-1 and HI-2 together (HI), and PH-1 and PH-2 together (PH). HT was considered symptomatic if it was not seen on the admission CT and there was, subsequently, either a suspicion of hemorrhage (eg, sudden headache) or a decline in neurological status (an increase of ≥4 points in NIHSS).[5]

The site and size of the qualifying infarct were determined based on standard templates and classified as (1) *small*, when a lesion was <1.5 cm in the anterior or posterior circulations; (2) *medium*, when a lesion was in a cortical superficial branch

of the middle cerebral artery, in the middle cerebral artery deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, or in a cortical superficial branch of the anterior cerebral artery; (3) *large anterior*, when a lesion involved the complete territory of middle, posterior, or anterior cerebral artery; in 2 cortical superficial branches of the middle cerebral artery; in a cortical superficial branch of the middle cerebral artery plus the middle cerebral artery deep branch; or in more than 1 artery territory; (4) *large posterior*, when a lesion was >1.5 cm in the brain stem or cerebellum.[3]

Risk Factors

Data on known stroke risk factors were collected as follows: age, sex, history of hypertension (blood pressure >140/90 mm Hg at least twice before acute stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting glucose level >126 mg/dL preprandial on 2 examinations, glucose level >200 mg/dL postprandial, or HbA_{1c} >6.5% or under antidiabetic treatment), current cigarette smoking, past smoking (cessation <5 years prior), hyperlipidemia (total cholesterol >200 mg/dL or triglyceride >140 mg/dL or already under lipid-lowering therapy), history of symptomatic ischemic heart disease (myocardial infarction, history of angina, or previous diagnosis of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; or ankle/arm systolic blood pressure ratio <0.85 in either leg at rest, or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), alcohol abuse (>300 g per week), obesity (body mass index >30 kg/m^2), or previous stroke/transient ischemic attack. White matter changes (leukoaraiosis defined on the first CT [or MR] examination as ill-defined and moderately hypodense [or hyperintensity on T2-weighted MRI] areas >5 mm according to published criteria) were investigated. Leukoaraiosis in the deep white matter was dichotomized into absent versus present.[6] Other baseline variables obtained on admission for all patients included fasting serum glucose, fasting serum cholesterol (total, high-density lipoprotein, and low-density lipoprotein), platelet count, international normalized ratios, activated partial thromboplastin time, and systolic and diastolic blood pressure.

The prescription of any antiplatelet or anticoagulant before admission and the use of these agents on admission and during the follow-up period was recorded.

The CHA_2DS_2VASc score (2 points for history of stroke or age older than 75 years and 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age between 65 and 74 years, and female sex) was calculated before and after the index event.

Evaluation of Outcome

Patients were followed up prospectively by face-to-face or telephone interviews and review of medical charts. Three-month ischemic recurrence was defined as the composite of recurrent ischemic cerebrovascular events (stroke or transient ischemic attack) and symptomatic systemic embolism. Stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. Transient ischemic attack was defined as a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy.

Symptomatic cerebral bleedings over 90-day follow-up were also reported. Cerebral bleeding was considered symptomatic if associated with a decline in neurological status (an increase of ≥4 points in NIHSS score or leading to death).

Should an outcome event occur, patients were requested to hand in the related full documentation in a face-to-face visit.

Disability and mortality at 90 days were also assessed using the modified Rankin Scale. Functional outcome was defined as either nondisabling (modified Rankin Scale score, 0–2) or disabling (modified Rankin Scale score, 3–5).

Statistical Analyses

Patient characteristics were summarized as mean and SD for continuous variables and as absolute numbers and percentages for categorical variables.

Differences in the baseline characteristics of patients with or without HT were tested using the χ^2 test for nominal variables or ANOVA for quantitative variables. In these patients, univariate tests were used to compare both clinical characteristics on admission and preexisting risk factors for HT. A multivariable analysis was performed using logistic regression to determine independent predictors of HT.

Differences in the characteristics of patients with or without ischemic recurrence at 90 days were tested using the χ^2 test for categorical variables or ANOVA for continuous variables. In these patients, univariate tests were used to compare both clinical characteristics on admission and preexisting risk factors for ischemic events.

A multivariable analysis was performed using logistic regression to determine independent predictors of ischemic events. Furthermore, a multivariable analysis was performed

using logistic regression to determine independent predictors of mortality and disability at 90 days. Because it deals with only one outcome at a time, a multivariable analysis was used with logistic regression because the outcomes were binary.[7] The independent variables included in the multivariable models were selected from the univariate analysis with a 0.1 level as a screening criterion for selection of candidate variables.

Survival function and empirical cumulative hazards function for ischemic recurrence were estimated via the Kaplan-Meier estimator for patients with and without HT; the differences between survival functions were tested using the log-rank statistic (or Mantel-Haenszel test) that in the case of large samples has an asymptotic χ^2 distribution.[8] Patients were censored at the time of an outcome event or death. A two-sided $P<0.05$ was considered significant.

All statistical analyses were performed using the IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY).

Results

A total of 2196 patients were enrolled in the study and 2183 were included in the analysis (13 patients were lost during follow-up). On admission, 538 patients (24.5%) were on oral anticoagulants. After the index acute stroke, 1218 patients (55.8%) received NOACs, 567 (26.0%) vitamin K antagonists, and 383 (17.3%) did not receive any anticoagulant therapy. For the remaining 15 patients, no data were available concerning the type of anticoagulant therapy. Patients treated with NOACs initiated therapy after a mean of 13.2 days from index stroke compared with a mean of 11.4 days for those treated with vitamin K antagonists ($P=0.06$). More specifically, 166 patients treated with NOACs and 108 treated with vitamin K antagonists initiated therapy within 24 hours from acute index stroke.

Incidence and Predictors of HT

Among the 2183 patients included in the analysis, 241 (11.0%) had HT, of which 69 (3.1%) were PH; 13 of the 241 patients with HT were symptomatic (5.4%). All of these symptomatic patients with HT had PH. Thirteen patients had an HT that was observed on the first neuroimaging examination at admission. The baseline characteristics of patients with or without HT are summarized in Table 1. Patients with HT were more likely to have congestive heart failure, higher NIHSS score at presentation, treatment with acute reperfusion therapies, and large lesions ($P<0.05$).

Table 1. Characteristics of the Patients With or Without HT

	With HT (n=241)	Without HT (n=1942)	*P* Value
Age, y (mean SD)	75.6±9.9	76.4±9.8	0.19
Male sex	103 (42.7%)	900 (46.3%)	0.30
NIHSS on admission (median IQR)	11 (IQR, 12)	6 (IQR, 9)	0.0001
Diabetes mellitus	64 (26.6%)	424 (21.8%)	0.10
Hypertension	198 (82.0%)	1511 (77.8%)	0.07
Hyperlipidemia	83 (34.4%)	655 (33.7%)	0.82
AF paroxysmal	95 (39.4%)	829 (42.7%)	0.29
History stroke/TIA	52 (21.6%)	516 (26.6%)	0.19
Current smoker	29 (12.0%)	176 (9.1%)	0.16
Alcohol	20 (8.2%)	120 (6.1%)	0.21
History of congestive heart failure	54 (22.4%)	319 (16.4%)	0.02
History of myocardial infarction	37 (15.4%)	262 (13.5%)	0.43
Small lesion	23 (9.7%)	806 (41.5%)	0.0001
Large lesion	95 (39.4%)	305 (15.7%)	0.0001
Leukoaraiosis	110 (45.6%)	993 (51.1%)	0.09
Therapy with rtPA and/or IA	42 (17.4%)	238 (12.3%)	0.03
Bridging therapy with LMWH	40 (16.6%)	332 (17.1%)	0.92
Bridging therapy with antiplatelets	155 (64.3%)	1250 (64.4%)	0.90

AF indicates atrial fibrillation; HT, hemorrhagic transformation; IA, intra-arterial procedure; IQR, interquartile range; LMWH, low-molecular-weight heparin; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; TIA, transient ischemic attack.

Table 2. Results of Multivariable Model: Predictive Factors for HT

Variable	OR	95% CI	*P* Value
Large lesion	1.92	1.37–2.70	0.0001
NIHSS at admission	1.00	0.98–1.03	0.8
Diabetes mellitus	1.13	0.81–1.57	0.4
Hypertension	1.33	0.91–1.95	0.1
CHF	1.49	1.05–2.10	0.02
Leukoaraiosis	0.90	0.70–1.10	0.1
Reperfusion therapy	0.90	0.60–1.14	0.3

CHF indicates congestive heart failure; CI, confidence interval; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Of the 538 patients who were on oral anticoagulant treatment on admission, 55 (10.2%; 95% confidence interval [CI], 7.8–13.1) had HT at second brain CT scan compared with 183 of the 1645 (11.1%; 95% CI, 9.6–13.7) of the patients who were not on anticoagulant treatment (*P*=0.2).

The result of the multivariable analysis (Table 2) showed that the presence of a large lesion and history of congestive heart failure were significantly associated with HT (odds ratio [OR], 1.92; 95% CI, 1.37–2.70; *P*=0.0001; and OR, 1.49; 95% CI, 1.05–2.20; *P*=0.02, respectively). Tables 3 and 4 report the results of multivariable analyses for HI and PH separately.

Time of Initiation of Oral Anticoagulants in Patients With HT

Of the 241 with HT, 174 (72.2%) initiated oral anticoagulants: 63 (36.2%) with vitamin K antagonists and 111 (63.8%) NOACs. Of the 1942 patients without HT, 1626 initiated oral anticoagulants (83.7%), 491 (30.2%) with vitamin K antagonists, and 1135 (69.8%) NOACs.

Patients with HT initiated anticoagulant therapy after a mean of 23.3 days (median, 17; interquartile range [IQR], 24) from index stroke compared with a mean of 11.6 days (median, 7; IQR, 10) for those without HT (*P*=0.0001). In patients with HT, those with HI initiated anticoagulant therapy after a mean of 21.9 days (median, 15; IQR, 19) and patients with PH after a mean of 28.2 days (median, 26; IQR, 27) (*P*=0.0001). In Figure 1, the timing of initiating oral anticoagulant therapy in patients with and without HT is reported. Sixty-seven of the 241 (27.8%) patients with HT never initiated anticoagulant therapy compared with 316 of 1942 (16.3%) of those without HT.

Nine of the 166 patients (5.4%) treated with NOACs and one of the 108 patients (0.9%) treated with vitamin K antagonists, who initiated therapy within 24 hours from acute index stroke, had early HT.

Table 3. Results of Multivariable Model: Predictive Factors for HI

Variable	OR	95% CI	*P* Value
Large lesion	1.49	1.00–2.22	0.05
NIHSS at admission	1.00	0.97–1.03	0.9
Diabetes mellitus	1.06	0.73–1.56	0.7
Hypertension	1.35	0.87–2.10	0.2
CHF	1.44	0.97–2.14	0.07
Leukoaraiosis	0.90	0.60–1.10	0.1
Reperfusion therapy	0.90	0.50–1.19	0.2

CHF indicates congestive heart failure; CI, confidence interval; HI, hemorrhagic infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Of the 10 patients treated with oral anticoagulants within 24 hours from index stroke and early HT, 2 had large lesions, 5 had medium lesions, and 3 had small lesions.

Regarding patients treated with acute reperfusion therapy, patients treated with intravenous recombinant tissue plasminogen activator with or without intra-arterial thrombectomy, initiated anticoagulant therapy after a mean of 13.6 days (median, 7; IQR, 11) from index stroke compared with a mean of 12.3 days (median, 8; IQR, 10) for those not treated with recombinant tissue plasminogen activator (*P*=0.2).

Influence of HT on Outcome

Over the 90-day follow-up, 111 ischemic recurrences were recorded in 107 patients (82 ischemic strokes, 18 transient ischemic attacks and 11 systemic embolisms) (Table 5). Eleven of the 241 patients (4.6%; 95% CI, 2.3–8.0) with HT had an ischemic recurrence compared with 96 of the 1942 (4.9%; 95% CI, 4.0–6.0) without HT. The 90-day risk of ischemic recurrence was 2.9% (35 of 1218) for patients

Table 4. Results of Multivariable Model: Predictive Factors for PH

Variable	OR	95% CI	*P* Value
Large lesion	3.16	1.76–5.67	0.0001
NIHSS at admission	0.99	0.95–1.04	0.8
Diabetes mellitus	1.58	0.90–2.73	0.1
Hypertension	1.20	0.60–2.39	0.6
CHF	1.68	0.94–3.02	0.08
Leukoaraiosis	0.89	0.53–1.47	0.7
Reperfusion therapy	1.33	0.77 to 2.31	0.3

CHF indicates congestive heart failure; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hematoma.

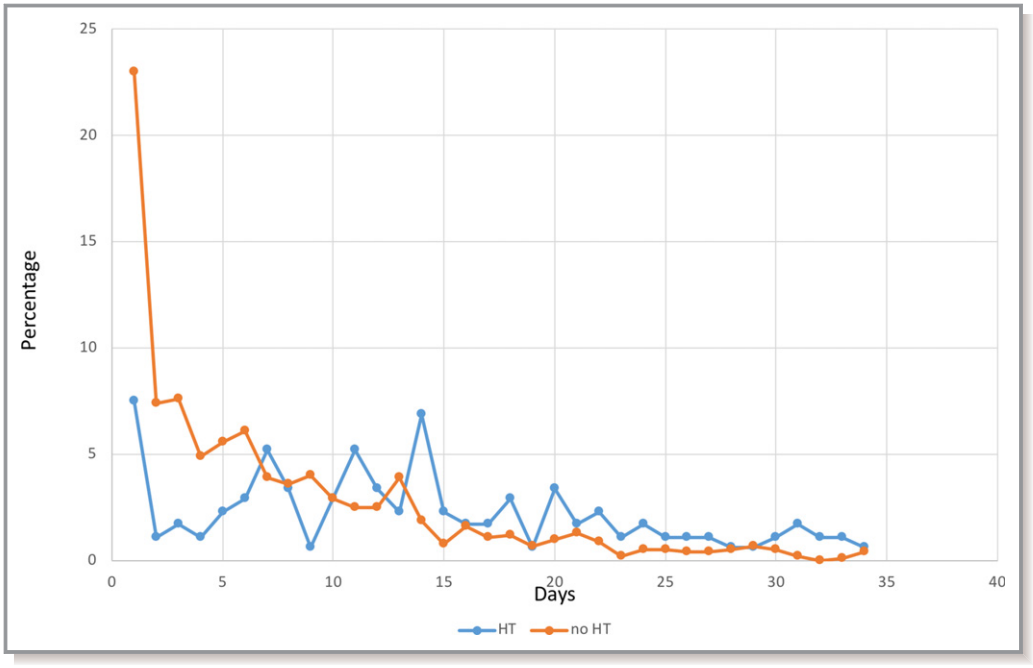

Figure 1. Timing of initiating oral anticoagulant therapy in patients with and without HT. HT indicates hemorrhagic transformation.

treated with NOACs, 6.7% (38 of 567) for those treated with a vitamin-K antagonist, and 8.9% (34 of 383) for those not receiving any antithrombotic treatment. On multivariable analysis (Table 6), the presence of HT was not associated with ischemic recurrence (OR, 0.50; 95% CI, 0.15–1.30; *P*=0.1). Vitamin K antagonists were associated with ischemic

Table 5. Characteristics of the Patients With or Without Ischemic Recurrence

	With Recurrence (n=107)	Without Recurrence (n=2076)	*P* Value
Age, y (median IQR)	10 (IQR, 12)	6 (IQR, 9)	0.03
Male sex	47 (43.9%)	945 (45.5%)	0.69
NIHSS on admission (mean±SD)	10.4±8.0	8.3±6.7	0.001
Diabetes mellitus	38 (35.5%)	443 (21.3%)	0.002
Hypertension	92 (86.0%)	1597 (76.9%)	0.07
Hyperlipidemia	37 (34.6%)	697 (33.6%)	0.91
AF paroxysmal	31 (29.0%)	886 (42.7%)	0.003
History stroke/TIA	35 (32.7%)	528 (25.4%)	0.11
Current smoker	8 (7.5%)	196 (9.4%)	0.61
Alcohol	9 (8.4%)	131 (6.3%)	0.41
History of congestive heart failure	29 (27.1%)	340 (16.4%)	0.008
History of myocardial infarction	17 (15.9%)	275 (13.2%)	0.46
Small lesion	31 (29.0%)	796 (38.3%)	0.05
Large lesion	27 (25.2%)	368 (17.7%)	0.07
Leukoaraiosis	61 (57.0%)	1013 (48.8%)	0.10
Pacemaker	13 (12.1%)	133 (6.4%)	0.03
CHA_2DS_2-VASc score >4 after index stroke	94 (87.9%)	1573 (75.8%)	0.03

AF indicates atrial fibrillation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.

recurrence when compared with NOACs (OR, 2.89; 95% CI, 1.66–4.80; *P*=0.0001) as was CHA_2DS_2-VASc as a continuous variable (OR, 1.24 for 1-point increase, 95% CI, 1.01–1.52; *P*=0.04).

Kaplan-Meier survival curve (Figure 2) suggested that patients with HT had an apparent nonsignificant earlier ischemic recurrence compared with those without HT (*P*=0.5). Mean latencies from the index stroke and ischemic recurrence were 36.2 days (±32.4) in patients without HT compared with 30.0 days (±20.9) in patients with HT (hazard ratio, 0.8; 95% CI, 0.4–1.6; *P*=0.6).

Over the 90-day follow-up, 55 symptomatic cerebral bleedings were recorded (2.5%; 95% CI, 1.9–3.0), and 13 of these were seen in the 241 patients with HT. Indeed, these 13 events were reported as symptomatic within 72 hours from stroke onset. Seven additional patients of the 241 with HT (2.8%; 95% CI, 1.4–5.8) had a second symptomatic cerebral bleed during follow-up, compared with 35 of 1942 patients (1.8%; 95% CI, 1.3–2.5) without HT. In patients with HT, 6 of 7 had the second symptomatic cerebral bleed after the initiation of anticoagulant therapy. The mean time between the initiation of anticoagulants and the second cerebral bleed was 8.5 days.

At 90-day follow-up, 128 (53.1%) of the 241 patients with HT were deceased or disabled (91 of 172 [52%] with HI and 37 of 69 [54%] with PH) compared with 695 of the 1942 patients (35.8%) without HT, *P*=0.001. Figure 3 shows the distribution of scores on the modified Rankin Scale at 3 months in patients with and without HT. On multivariable analysis, all types of HT were associated with mortality or disability at 90 days (HT [OR, 1.71; 95% CI, 1.24–2.35]; *P*=0.001; HI [OR, 1.75; 95% CI, 1.21–2.53]; *P*=0.003; PH [OR, 1.79; 95% CI, 1.00–3.27]; *P*=0.05). Other study variables associated with mortality and disability were age (OR, 1.05 for 1-year increase, 95% CI, 1.03–1.06; *P*=0.0001), diabetes mellitus (OR, 1.40; 95% CI, 1.10–1.79; *P*=0.007), and NIHSS on admission (OR, 1.18 for 1-point increase; 95% CI, 1.16–1.20; *P*=0.0001). Acute reperfusion therapies were inversely associated with mortality or disability (OR, 0.70; 95% CI, 0.51–0.96; *P*=0.027) (Table 7).

Regarding the 67 patients with HT who were not prescribed anticoagulant therapy, 6 (9.0%) had an ischemic recurrence, compared with 28 of the 316 (8.9%) without HT (OR, 0.98; 95% CI, 0.39–2.49; *P*=0.1). Overall, 55 of the 67 patients (82.1%) with HT were deceased or disabled at 90 days compared with 219 of the 316 patients (69.3%) without HT (OR, 2.3; 95% CI, 1.4–3.96; *P*=0.03). In these groups without anticoagulant therapy, 18 of the 67 patients (26.9%) with HT were deceased at 90 days compared with 68 of the 316 patients (21.5%) without HT (OR, 1.33; 95% CI, 0.73–2.44; *P*=0.34).

Table 6. Results of Multivariable Model: Predictive Factors for Ischemic Outcome Events (Stroke–TIA–Systemic Embolism)

Variable	OR	95% CI	*P* Value
Vitamin K antagonist vs NOACs	2.89	1.66 to 4.80	0.0001
CHA_2DS_2-VASc (as a continuous variable)	1.24	1.01 to 1.52	0.04
Paroxysmal AF	0.70	0.40 to 1.20	0.2
Small vs large lesion	0.66	0.37 to 1.19	0.2
NIHSS at admission	1.00	0.96 to 1.04	0.9
Pacemaker	1.89	0.80 to 4.31	0.2
Days from index stroke to anticoagulation	1.00	0.99 to 1.01	0.3
Hemorrhagic transformation	0.50	0.15 to 1.30	0.1

AF indicates atrial fibrillation; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; NOACs, non–vitamin K antagonists; TIA, transient ischemic attack.

Discussion

In our cohort of consecutive patients with acute ischemic stroke and AF, we observed an 11% incidence of early HT. Patients with HT initiated secondary prevention with oral anticoagulants on average 12 days later than those without HT, but this difference was not associated with any detected increase in 90-day stroke recurrence. HT was shown to be associated with worse 3-month functional outcome. This association did not appear to be influenced by stroke recurrence due to a recorded delay in the initiation of anticoagulation, but more likely due to a worsening of stroke provoked by the presence of HT itself. About one third of HT patients did not initiate anticoagulant therapy after the hemorrhagic complication, compared with about 16% of those

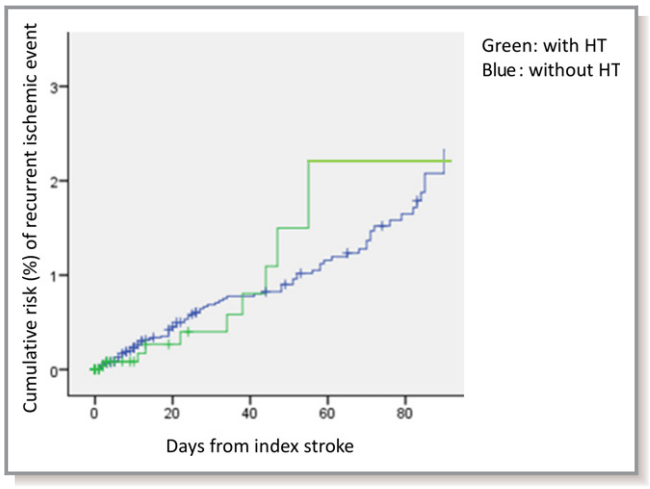

Figure 2. Cumulative risks (Kaplan-Meier survival curve) of ischemic recurrence for patients with and without HT. HT indicates hemorrhagic transformation.

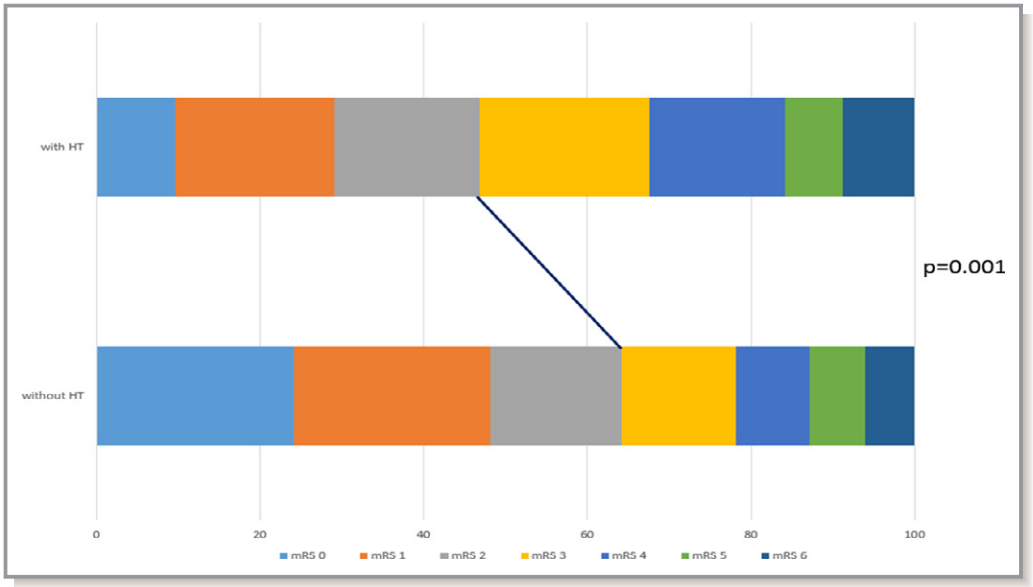

Figure 3. Distribution of scores on the mRS at 3 months in patients with and without HT. HT indicates hemorrhagic transformation; mRS, modified Rankin Score.

without HT. Patients with HT had more severe stroke and were more likely to be deceased at 90 days, which plausibly limited the subsequent number of ischemic recurrences that we could detect. By 90 days, about 53% of HT patients were deceased or disabled compared with about 36% of the patients without HT. The Kaplan-Meier survival curve results suggest that patients with HT perhaps had an earlier ischemic recurrence, even if not significant, compared with those without HT, despite the same total number of ischemic outcome events at 90 days. If so, the message for clinical practice might be to avoid early HT by refraining from using anticoagulants in the very early phases of acute stroke (24–48 hours), as this analysis observed that about 5% of the patients who had initiated NOACs within 24 hours from index acute stroke suffered from HT. Moreover, a thorough evaluation for glycemia and an appropriate selection of patients who need reperfusion therapy should be carried out. Finally, a CT scan 2 to 3 days after the index acute stroke should be performed before any anticoagulation strategy decision is made. Reliable clinical and radiologic predictors are needed to identify those patients at highest risk for HT. Our study supports the hypothesis that the larger the lesion size, the greater its predictive factor in HT and worse outcome.

Table 7. Results of Multivariable Model: Predictive Factors for Mortality or Disability

Variable	OR	95% CI	*P* Value
Age	1.05	1.03–1.06	0.0001
Sex, male	0.86	0.70–1.07	0.2
NIHSS at admission	1.18	1.16–1.20	0.0001
Diabetes mellitus	1.40	1.10–1.79	0.007
Hypertension	0.97	0.74–1.28	0.9
Hyperlipidemia	0.89	0.72–1.12	0.3
Reperfusion therapy	0.70	0.51–0.96	0.02
HT	1.71	1.24–2.35	0.001
HI	1.75	1.21–2.53	0.003
PH	1.79	1.00–3.27	0.05

CI indicates confidence interval; HI, hemorrhagic infarction; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hematoma.

Only 9% of the patients with HT were symptomatic. For this reason, we suggest performing a second brain CT scan 2 to 3 days from stroke onset or before initiating anticoagulant therapy to reduce the risk of worsening an asymptomatic HT. This follow-up CT examination could also provide prognostic indications for HT, even if asymptomatic, as HT generally worsens outcome. In fact, it was reported that even "asymptomatic" intracranial hemorrhage can be associated with poorer long-term neurologic outcomes.[9]

Our study has several limitations. First, the reported associations in our nonrandomized study were likely influenced by numerous potential confounders, even if adjusted statistical models were used to reduce their effects. Second, central adjudication of the outcome events and central reading of vascular imaging for the measurement of ischemic lesions were not performed. Specifically, the detection of recurrent ischemic stroke might have differed in patients with severe disability (especially for bedridden) compared with those with minor disability. This is because, for bedridden patients, the follow-up was more likely conducted by

telephone rather than face-to-face. Third, the neuroimaging follow-up examination could have differed among the centers, even regarding type. In fact, at a few centers, brain MRI was performed instead of CT scan with different sensitivity in detecting hemorrhagic transformation. Finally, the study might not have the power to detect a significant difference in ischemic recurrence in patients with and without HT.

The strengths of our study include the sample size and the prospective design. Moreover, our findings reflect real-life experiences and, in view of the presence of a single inadequately powered randomized trial,[10] may provide information that could assist stroke physicians in the management of patients with acute cerebral ischemia with AF.

In conclusion, early HT in patients with acute stroke and AF was observed in 11% of our patients. The presence of HT delayed the initiation of anticoagulant therapy. This delay was not associated with any detected excess of ischemic recurrence. HT was independently associated with both mortality and disability excess at 90 days.

Disclosures

Dr Paciaroni received honoraria as a member of the speaker bureau of Aspen, Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Daiiki Sankyo, and Pfizer. Dr Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. Dr Becattini received honoraria as a member of the speaker bureau of Bristol-Myers Squibb and Bayer. Dr Caso received honoraria as a member of the speaker bureau and as consultant or advisory board of Boehringer Ingelheim. Dr Putaala received honoraria for lectures related to atrial fibrillation and anticoagulants for Orion Pharma, Bristol-Myers Squibb, Pfizer, Bayer, and Boehringer Ingelheim. Dr Tatlisumak received honoraria as consultant or advisory relationship by Lundbeck and Boehringer Ingelheim. Dr Lees reports fees and expenses for data monitoring committee work and lectures from Boehringer Ingelheim. Dr Ageno has received speaker's honoraria from, and participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and has received research support from Bayer and Boehringer Ingelheim. Dr Toni received honoraria as a member of speaker bureau and as advisory board of Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb and Bayer. The other authors have nothing to disclose.

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