Stroke

CLINICAL AND POPULATION SCIENCES

Characteristics and Outcomes of Thrombolysis-Treated Stroke Patients With and Without Saccular Intracranial Aneurysms

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BACKGROUND: Intravenous thrombolysis seems safe in acute ischemic stroke patients with saccular, unruptured intracranial aneurysms (UIAs), but little is known about the differences in cardiovascular risk factors and outcomes between intravenous thrombolysis-treated stroke patients with and without UIAs. We hypothesized that UIA patients would have a higher burden of cardiovascular risk factors and, therefore, a higher risk of an unfavorable outcome.

METHODS: In this prospective cohort study conducted in Helsinki University Hospital, we identified intravenous thrombolysis-treated patients with concurrent saccular UIAs admitted to a comprehensive stroke center between 2005 and 2019 using 2 overlapping methods. For each UIA patient, a control patient was identified and matched (1:1) for age, sex, admission year, and stroke severity. The primary outcome was an unfavorable outcome at 3 months, defined as a modified Rankin Scale (mRS) score 3 to 6. The secondary outcomes were an excellent outcome (mRS score 0–1) at 3 months and mRS difference in shift analysis.

RESULTS: In total, 118 UIA patients and 118 matched control patients were identified. The UIA patients were more often current smokers, and their admission systolic blood pressure was higher. The rate of hemorrhagic complications did not differ between the groups. UIAs were not associated with an unfavorable outcome in the conditional logistic regression analysis (odds ratio, 1.41 [95% CI, 0.79–2.54]; P=0.25). However, the UIA patients were less likely to have excellent outcomes (odds ratio for non-excellent outcome, 2.09 [95% CI, 1.13–3.85]; P=0.02). In shift analysis, UIAs were associated with higher mRS (odds ratio, 1.61 [95% CI, 1.03–2.49]; P=0.04).

CONCLUSIONS: The intravenous thrombolysis-treated stroke patients with UIAs were more often current smokers and had higher systolic blood pressure than the matched patients without UIAs. They were as likely to have unfavorable outcomes at 3 months but seemed less likely to achieve excellent outcomes and were more likely to have higher mRS in shift analysis.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiovascular disease ■ hospital ■ intracranial aneurysm ■ ischemic stroke ■ risk factors

Recent data suggest that intravenous thrombolysis (IVT) is safe in patients with acute stroke with saccular unruptured intracranial aneurysms (UIAs).[1] Ischemic stroke and aneurysmal subarachnoid hemorrhage have similar risk factors, except for diabetes, which has not been associated with subarachnoid hemorrhage. However, little is known about the possible differences in cardiovascular risk factors or outcomes between IVT-treated patients with ischemic stroke with and without UIAs. We therefore aimed to compare IVT-treated patients with stroke with UIAs with matched stroke patients without UIAs. We hypothesized that the patients

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Nonstandard Abbreviations and Acronyms

ICH	intracranial hemorrhage
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
UIA	unruptured intracranial aneurysm

with UIAs would have a higher burden of cardiovascular risk factors and that those would be associated with a higher risk of an unfavorable outcome following IVT.

METHODS

Research Materials Transparency

Anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Cohort

We have previously described our cohort of UIA patients treated with IVT for ischemic stroke.[1] We used the prospectively collected Helsinki Stroke Thrombolysis Registry[2] to identify IVT-treated patients at Helsinki University Hospital between 2005 and 2019. We employed 2 overlapping methods to retrospectively identify patients with UIAs from the registry. First, we screened the radiology reports of all the patients in the registry for mentions of UIAs. The reports were limited to studies performed 1 day before or within 7 days of the IVT. Second, for all the patients in the thrombolysis registry, we searched the nationwide Finnish Care Register for Health Care for a UIA diagnosis made any time before or within 1 year after the IVT or for a diagnosis of subarachnoid hemorrhage dated within 1 year after the IVT. We then scrutinized the imaging studies of all patients identified through either method to confirm the presence of UIAs. A flowchart of the study is shown in Figure S1.

Only patients with saccular UIAs were included in the study, as we previously found that 6 of 14 (43%) patients with fusiform UIAs died due to aneurysm rupture between 1 day and 5 months after IVT.[1]

In the current study, each UIA patient was matched with a control patient without a UIA. The UIA patients and controls were matched on age (±3 years), sex, admission year (±1 year), and the National Institutes of Health Stroke Scale (NIHSS)[3] category reflecting symptom severity (0–4, mild; 5–15, moderate; 16–20, severe; >20, extremely severe) on admission. Regarding the selection of the matching parameters, older age and severe symptoms are associated with worse outcomes after IVT. The admission year was included as a matching parameter because acute stroke treatment has evolved during the cohort's collection period (eg, thrombectomy has become the standard treatment in large vessel occlusions). The matching based on the aforementioned parameters was performed randomly.

The local institutional research committee approved the study and waived the requirement for patient consent (HUS/203/2020 §14). The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The study was conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement.

Data Collection

The following variables were available from the Helsinki Stroke Thrombolysis Registry: date and time of the IVT, age, NIHSS score, systolic and diastolic blood pressure, weight on admission, and modified Rankin Scale (mRS)[4] at 3 months after the IVT. Weight was based on the patients' reports, except for the patients with aphasia, severe dysarthria, or lowered level of consciousness, for whom a treating physician estimated their weight. Blood tests on admission were available for plasma glucose and plasma lipids.

We also retrospectively collected data from the hospital's electronic records on the use of antithrombotic medication at the time of the stroke (antiplatelet or anticoagulant), history of smoking (never, ex-smoker, or current), and history of hypertension or diabetes (preexisting diagnosis of hypertension/diabetes or use of antihypertensive/antidiabetic medication at the time of the stroke).

We analyzed all the post-IVT computed tomography and magnetic resonance images taken during hospitalization to identify hemorrhagic complications following IVT. All the patients underwent routine control imaging at least once ≈24 hours after IVT.

Outcomes

Our primary outcome was favorable (mRS score 0–2) versus unfavorable (mRS score 3–6) outcome at 3 months after IVT. The secondary outcomes were excellent (mRS score 0–1) versus non-excellent (mRS score 2–6) outcome at 3 months after IVT, mRS difference in shift analysis (described below), in-hospital symptomatic intracranial hemorrhage (ICH) following IVT, according to the European–Australian Cooperative Acute Stroke Study 2 criteria[5] (an NIHSS score increase of ≥4 points and any ICH), and any in-hospital ICH following IVT.

Statistical Analyses

For the categorical variables, we report frequencies and proportions. For the continuous variables, we report means with SDs and medians with interquartile ranges.

For the 1:1 matched case-control comparisons, we used the paired *t* test for the continuous variables and McNemar test for the categorical variables.[6] To test whether the matched variables (age, sex, admission year, and NIHSS score at admission) were associated with an unfavorable outcome, we used a logistic regression model that included age, sex, admission year, and admission NIHSS score. Moreover, we used conditional logistic regression analysis to test if UIAs were associated with an unfavorable outcome. Systolic blood pressure, plasma glucose, and weight on admission have been associated with outcome after IVT in previous studies.[7–11] Therefore, in addition to the univariate model, we tested a multivariate conditional regression model that included these variables as covariates.

Table 1. Characteristics of the 118 Patients With Aneurysms and 118 Matched Patients Without Aneurysms Included in the Analysis

Variable	N	Matched patients without aneurysms	Aneurysm patients	*P* value
Age, y	236			0.90
Mean±SD		68.8±11.8	68.8±12.0	
Median (IQR)		69 (61–77)	69 (61–78)	
Male sex, n (%)	236	46 (39%)	46 (39 %)	1.00
Admission year	236			<0.01
Mean±SD		2013.0±4.2	2013.8±4.2	
Median (IQR)		2014 (2010–2017)	2015 (2011–2017)	
Baseline NIHSS	236			0.55
Mean±SD		9.4±7.5	9.6±8.2	
Median (IQR)		7 (4–14)	7 (4–15)	
History of hypertension, n (%)	235	71 (60 %)	67 (57 %)	0.68
History of diabetes, n (%)	236	18 (15 %)	22 (19 %)	0.60
Smoking status, n (%)	212			0.02*
Never smoked		47 (46%)	48 (43%)	
Ex-smoker		32 (32%)	23 (21%)	
Current smoker		22 (22%)	40 (36%)	
Anticoagulation, n (%)	230			0.09†
None		61 (53%)	73 (63%)	
Antiplatelet		45 (39%)	39 (34%)	
Anticoagulant		9 (8%)	3 (3%)	
Body weight, kg	236			0.90
Mean±SD		76±15	76±15	
Median (IQR)		75 (65–85)	75 (65–85)	
Admission systolic BP, mmHg	233			0.047
Mean±SD		153±29	160±24	
Median (IQR)		155 (135–172)	157 (144–177)	
Admission diastolic BP, mmHg	233			0.15
Mean±SD		84±17	87±16	
Median (IQR)		83 (73–95)	87 (78–98)	
Admission glucose, mmol/l	236			0.46
Mean±SD		7.5±2.4	7.3±2.2	
Median (IQR)		6.8 (6.0–8.4)	6.7 (5.8–8.0)	
Total cholesterol, mmol/l	228			0.69
Mean±SD		4.5±1.2	4.5±1.1	
Median (IQR)		4.4 (3.8–5.2)	4.5 (3.7–5.2)	
HDL, mmol/l	228			0.97
Mean±SD		1.4±0.4	1.4±0.5	
Median (IQR)		1.3 (1.1–1.7)	1.3 (1.1–1.5)	
LDL, mmol/l	228			0.62
Mean±SD		2.8±1.1	2.7±1.1	
Median (IQR)		2.6 (2.0–3.2)	2.6 (1.8–3.4)	
Triglycerides, mmol/l, median (IQR)	228			0.54
Mean±SD		1.2±0.6	1.2±0.6	
Median (IQR)		1.0 (0.8–1.4)	1.1 (0.9–1.5)	
Thrombectomy, n (%)	236	17 (14%)	13 (11%)	0.37
Hemorrhagic complications, n (%)	236			
Symptomatic ICH		5 (4%)	8 (7%)	0.37

(*Continued*)

Table 1. Continued

Variable	N	Matched patients without aneurysms	Aneurysm patients	*P* value
Any ICH		20 (17%)	22 (19%)	0.74
3-mo outcome, n (%)	236			
Favorable (mRS score 0–2)		77 (65%)	68 (58%)	0.20
Excellent (mRS score 0–1)		58 (49%)	41 (35%)	0.02
Mean mRS±SD		1.9±1.8	2.4±1.9	0.03

BP indicates blood pressure; HDL, high-density lipoprotein; ICH, intracranial hemorrhage; IQR, interquartile range; LDL, low-density lipoprotein; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*McNemars test *P* value for never or ex-smoker vs current smoker.

†McNemars test *P* value for none vs antiplatelet or anticoagulant.

For an additional shift analysis, we conducted an ordinal logistic regression analysis using 3-month mRS as an ordinal variable. Both univariate and multivariate models were tested, and we used robust estimators of variance and clustering to account for the matched structure of the study population.[12]

Since the UIA patients were less likely to have excellent outcomes (see results) and they were more often current smokers, we conducted a post hoc conditional regression analysis to test whether smoking status was associated with outcome.

There were few missing values, so we excluded subjects with missing values from the regression analyses and analyses comparing the groups. We report odds ratios (ORs) with 95% CIs for all regression analyses. A $P<0.05$ was considered statistically significant. We used Stata 17.0 (StataCorp, TX) for the statistical analyses.

RESULTS

Patient Characteristics

Of 3953 patients treated with IVT between 2005 and 2019, we identified 118 patients with saccular UIAs (Figure S1). As stated above, an additional 14 patients with fusiform UIAs were excluded from the study. Compared with the 3821 patients without UIAs, the UIA patients were more often female (42.8% versus 57.6%, respectively; $P=0.001$) but did not differ in age (68.0±13.8 years versus 69.7±12.0 years [mean±SD]; $P=0.10$) or NIHSS score (9.3±6.8 versus 9.5±8.2; $P=0.76$).

Our final cohort consisted of 118 patients with saccular UIAs and 118 matched control patients without UIAs. The mean age of the cohort was 68.7±11.9 years, the mean NIHSS score was 9.5±7.8, and 144 (61%) were female. The mean admission year of the matched patients was slightly earlier (2013.0±4.2 and 2013.8±4.2; $P<0.01$). Otherwise, the UIA patients and matched patients did not differ in any matched variable (Table 1).

The 118 UIA patients had a total of 137 saccular UIAs. The mean aneurysm diameter was 3.9±2.7 mm and 5 (4 %) were at least 10 mm in diameter. Eighteen (15%) UIA patients eventually underwent aneurysm treatment (surgical treatment in 7 patients and endovascular treatment in 11 patients), but none was treated during the 3-month follow-up period. Fourteen UIA patients died within 3 months after IVT. The cause of death was available for 13 of these patients, and none of them died due to a subarachnoid hemorrhage.

Vascular Risk Factors and Outcome

Table 1 shows the characteristics of the 118 UIA patients and the 118 matched patients. The UIA patients were more often current smokers and had slightly higher systolic blood pressure on admission. Otherwise, the groups did not differ in their vascular risk factor profiles. Five (4%) of the matched patients and 8 (7%) of the UIA patients had symptomatic ICH following IVT ($P=0.37$). Likewise, 20 (17%) of the matched patients and 22 (19%) of the UIA patients had any ICH following IVT ($P=0.74$).

Overall, 91 (39%) patients had unfavorable outcomes at 3 months. Older age, an earlier admission year, and a higher admission NIHSS score were associated with an unfavorable outcome (Table S1).

The Figure shows the 3-month mRS values for the UIA and the matched patients. Sixty-eight (58%) and 77 (65%) of the UIA and matched patients, respectively, had a favorable outcome (mRS score 0–2) at 3 months. In the univariate conditional logistic regression analysis, the presence of a UIA was not associated with an unfavorable (mRS score 3–6) outcome (OR, 1.45 [95% CI, 0.82–2.56]; $P=0.20$; Table 2). Similarly, UIA status was not associated with an unfavorable outcome in the multivariate conditional logistic regression analysis (Table 2). However, the UIA patients were less likely to have an excellent outcome (mRS score 0–1) at 3 months (35% versus 49%), with an OR of 2.06 ([95% CI, 1.14–3.75]; $P=0.02$) for a non-excellent (mRS score 2–6) outcome (Table S2).

In the shift analysis, UIA status increased the odds of higher 3-months mRS in both univariate (OR, 1.56 [95% CI, 1.03–2.35]; $P=0.04$) and multivariate models (OR, 1.61 [95% CI, 1.03–2.49]; $P=0.04$).

In a post-hoc analysis, the current smokers were not likelier to have unfavorable outcomes at 3 months compared with never smokers (OR, 1.33 [95% CI, 0.42–4.26]; $P=0.63$). However, the current smokers had suggestive evidence for higher odds of non-excellent outcomes at 3

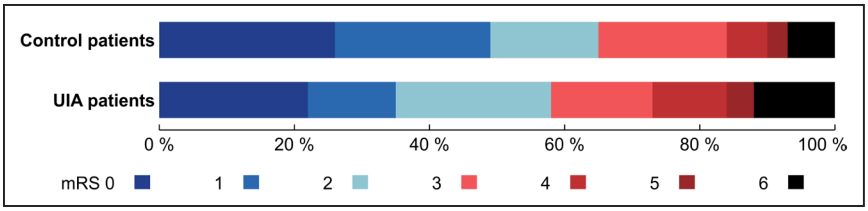

Figure. Three-month outcomes following intravenous thrombolysis for patients with unruptured intracranial aneurysms (UIA) and matched control patients.
mRS indicates modified Rankin Scale.

months compared with never smokers (OR, 3.61 [95% CI, 0.97–13.38]; *P*=0.06).

As the control patients had their strokes slightly earlier (by a few months) than the UIA patients, we also performed the analyses controlling for admission year, which did not affect the findings (results not shown).

DISCUSSION

Although the patients with ischemic stroke with and without UIAs in this study were as likely to have favorable (mRS score 0–2) outcomes at 3 months, the patients with UIAs did not achieve excellent outcomes (mRS score 0–1) as often. UIA patients also had an increased odds of higher mRS in shift analysis. The IVT-treated patients with stroke with saccular UIAs did not differ significantly in their cardiovascular risk factor profile, including in terms of diabetes, from the patients without UIAs matched for age, sex, and stroke severity. However, they were more often current smokers, and their admission systolic blood pressure was slightly higher. We found no differences in hemorrhagic complications following IVT in the patients with and without UIAs.

Our finding that smoking and hypertension are more common in UIA patients—even among patients with ischemic stroke, who are considered to have more cardiovascular risk factors compared with the general population—is in accordance with the known fact that these 2 modifiable risk factors contribute strongly to UIA formation, as, for example, a recent Mendelian randomization study has suggested.[13] Few studies have compared the outcomes[14–18] and/or characteristics[15–20] of patients with stroke with and without UIAs. Most studies have included a small number of UIA patients and, hence, have been limited to unadjusted analyses. These studies mostly found no differences in sex, age, or vascular risk factors between patients with and without UIAs; however, in some studies, UIA patients were older,[15,16] more often female,[15,16] or likelier to have hypertension.[19] Studies analyzing IVT complications[15,17,18,21,22] or outcomes[14,15,17,19] have not found any differences between patients with and without UIAs. The only study that was large enough to conduct multivariate analyses included 95 patients with minor stroke or transient ischemic attack and UIAs and found that the patients with UIAs were more often female, smokers, and likelier to have hypertension than the patients without UIAs.[20] These results are in accordance with our results.

To the best of our knowledge, our study is the first to report that IVT-treated stroke patients with UIAs were less likely to have excellent outcomes after their stroke than patients without UIAs. UIA patients are more often hypertensive and smokers, both of which are associated with reduced white matter integrity.[23,24] It is plausible that UIA patients therefore have reduced cerebral plasticity, rendering them less likely to make an excellent recovery.

Our study included a large cohort of patients with ischemic stroke with UIAs, and we conducted a matched comparison of patients with stroke with and without UIAs. The strengths of our study also include its prospective nature and that we were able to reliably record post-IVT complications, as all patients had at least 1 follow-up brain imaging scan. The major limitations of our study are that smoking status, diabetes, and hypertension were retrospectively recorded based on medical records. Moreover, weight was based on self-reports or clinical estimates. Our results are applicable only to stroke patients eligible for IVT, as the cohort did not represent all patients with ischemic stroke. We included patients who were treated with IVT but did not use any other criteria for stroke (eg, symptom duration or post-IVT imaging studies). Hence, it is possible that our cohort included a few stroke mimic patients, but this number is presumably rather small, and the proportion of such patients should not differ significantly between the 2

Table 2. Results of the Univariate and Multivariate Conditional Logistic Regression Analyses

	Univariate model (n=236)			Multivariate model (n=233)		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Saccular aneurysm	1.45	0.82–2.56	0.20	1.41	0.79–2.54	0.25
Systolic blood pressure, 10 mmHg increase*	1.14	0.97–1.33	0.10	1.13	0.96–1.33	0.14
Weight, 10 kg increase	1.05	0.71–1.55	0.80	1.02	0.66–1.56	0.94
Blood glucose, mmol/l	1.05	0.89–1.24	0.59	1.04	0.87–1.25	0.67

The multivariate model includes aneurysm status, admission systolic blood pressure, weight, and admission blood glucose. ORs with 95% CIs for unfavorable outcome (mRS score 3–6) are shown. OR indicates odds ratio.
*Missing for 3 patients, n=233.

groups (UIA patients and matched controls). As we limited the imaging studies to the day before and 7 days post-IVT, it is possible that we excluded a small number of patients who were admitted and imaged due to transient ischemic attack a few days before IVT. We did not have data on prestroke functional status (eg, mRS scale) and, therefore, we could not assess changes in the patients' functional status following stroke.

The findings of this study suggest that even among patients with ischemic stroke, smoking and hypertension are more common in patients with UIAs. In contrast, this association was not seen for diabetes or hypercholesterolemia. Also, IVT-treated ischemic stroke patients with UIAs may reach excellent outcomes less frequently than matched patients without UIAs. This finding needs to be confirmed in further studies.

ARTICLE INFORMATION

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Supplemental Material

Figure S1
Tables S1–S2

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