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Jussi-Pekka Pouru BM , Samuli Jaakkola MD, PhD , Juha Lund MD, PhD , Fausto Biancari MD, PhD , Antti Saraste MD, PhD , K. E. Juhani Airaksinen MD, PhD

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Running head: Single Antiplatelet Therapy After LAAC

Authors: Jussi-Pekka Pouru, BM[a], Samuli Jaakkola, MD, PhD[a], Juha Lund, MD, PhD[a], Fausto Biancari, MD, PhD[a,b,c], Antti Saraste, MD, PhD[a], K. E. Juhani Airaksinen, MD, PhD[a]

[a]Heart Center, Turku University Hospital and University of Turku, Turku, Finland
[b]Department of Surgery, University of Turku, Finland
[c]Department of Surgery, University of Oulu, Finland

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Corresponding author
Prof. K.E. Juhani Airaksinen, MD, PhD
Heart Center, Turku University Hospital, Turku, Finland
Hämeentie 11, PO Box 52, 20521, Turku, Finland
Email: juhani.airaksinen@tyks.fi
Phone: +358 2 313 1079 (executive secretary)
Fax: +358 2 313 8651

Abstract

Percutaneous left atrial appendage closure (LAAC) offers a feasible option for stroke prevention in patients with atrial fibrillation (AF), but the optimal antithrombotic treatment strategy for patients with strict contraindications to oral anticoagulation (OAC) remains uncertain. We sought to evaluate short- and long-term outcome after percutaneous LAAC in these very patients discharged on single antiplatelet therapy (SAPT) alone. All consenting AF patients who underwent LAAC from February 2009 to August 2018 in Turku University Hospital, Finland, were enrolled into a prospectively maintained registry. Only patients discharged on SAPT alone were considered for the present analysis. Patients were prospectively followed up to 5 years. The primary endpoints were thromboembolic event (stroke, transient ischemic attack, or systemic embolism) and intracranial bleeding. Of the 165 LAAC patients, 81 patients (mean age 75 ± 7 years; 44% women; CHA_2DS_2-VASc 4.8 ± 1.4; HAS-BLED 3.2 ± 0.8) were discharged on SAPT only (77 with aspirin 100 mg) following successful LAAC using Amplatzer devices. The duration of SAPT was ≤6 months in 61 (75%) patients. The most common contraindication to OAC was prior intracranial bleeding in 48 (59%) patients. During a mean follow-up of 2.9 years, there were 6 thromboembolic events (2.7/100 patient-years; 73% lower-than-predicted rate of thromboembolism). Eight patients (3.6/100 patient-years) suffered a major bleeding event after discharge, and 4 patients had intracerebral bleeding (1.7/100 patient-years). At 6-month landmark analysis, freedom from thromboembolism and intracranial bleeding at 3-year follow-up was similar in those with discontinued and life-long SAPT (95.1% vs 88.9% and 97.6% vs 91.7%, respectively). In conclusion, long-term outcome is satisfactory after LAAC in selected AF patients with strict contraindications to OAC receiving short-term SAPT. However, adverse events are not infrequent during early postoperative months.

Key Words: Atrial fibrillation; left atrial appendage closure; stroke; bleeding.

Atrial fibrillation (AF) is a major risk factor for stroke. Oral anticoagulation (OAC) reduces the risk of stroke in patients with AF by almost two-thirds and is recommended for most AF patients.[1] However, 1–4% of anticoagulated AF patients suffer from stroke and approximately 2–4% experience a major bleeding event per year.[2–4] Reducing this residual burden of adverse events is of clinical importance especially in patients with high risk of thromboembolic and bleeding events. Approximately 90% of cardioembolic strokes in AF originate from thrombus formation in the left atrial appendage.[5] Randomized studies have shown that percutaneous left atrial appendage closure (LAAC) prevents strokes with efficacy comparable to warfarin therapy without increasing the risk of major bleedings, particularly hemorrhagic strokes.[6] In current clinical practice, LAAC is mainly used as an alternative to OAC in AF patients with evident contraindications to OAC therapy, such as major bleeding events during adequate OAC therapy. However, there is limited data on long-term outcome in these high-risk patients, and the optimal antithrombotic treatment strategy of this fragile patient group remains to be established. The aim of the present study is to evaluate the long-term outcome of these high-risk patients with AF treated with single antiplatelet therapy (SAPT) after LAAC device implantation.

Methods

This observational cohort study is a part of wider protocol in progress to assess thromboembolic and bleeding complications of cardiac procedures in Western Finland.[7–10] All consecutive patients (>18 years) with AF who underwent percutaneous LAAC in Turku University Hospital were requested to participate in a prospectively maintained registry. Clinical follow-up visit was scheduled 1–3 months post-implantation including fluoroscopy and transesophageal or transthoracic echocardiography. Thereafter, patients were followed through annual phone calls or clinical visits up to 5 years. Data collection included detailed patient

characteristics, procedural data, antithrombotic medication, and prospective recording of outcomes and compliance to antithrombotic treatment regimen. CHA_2DS_2-VASc score and modified HAS-BLED score (no points for labile international normalized ratio and alcohol abuse) were employed to stratify the thromboembolic and bleeding risks. The primary outcomes were thromboembolism (ischemic stroke, transient ischemic attack [TIA], and systemic embolism) and intracranial bleeding. Secondary outcomes included major bleeding, all-cause mortality and other relevant adverse events (e.g. device embolization). All reports of adverse events were reviewed retrospectively. Thromboembolic events were defined according to Munich consensus document.[11] Major bleeding was defined according to the International Society on Thrombosis classification as overt bleeding with a decrease in hemoglobin of 2 g/dL or more, requiring the transfusion of 2 or more units of blood, occurring in a critical site, or contributing to death.[12] After the prospective follow-up period, the long-term outcome was further evaluated by reviewing comprehensive electronic patient records (last retrospective follow-up date April 26, 2019). Data on the causes of death were obtained from Statistics Finland and from electronic patient records.

Between February 2009 and August 2018, a total of 172 patients were enrolled in the registry and 165 (95.9%) of them were discharged following successful LAAC. The type and duration of antithrombotic treatment was individually chosen based on risk factors for bleeding and thromboembolic complications and comorbidities at operator's discretion. For the present analysis, we included patients who underwent successful LAAC and were discharged on SAPT (aspirin 100 mg or clopidogrel 75 mg daily) and without any anticoagulation therapy. According to the duration of chosen therapy, patients were grouped into short-term (≤ 6 months) and long-term (life-long) cohorts. Amplatzer Cardiac Plug and Amulet devices (Abbott Vascular, Santa

Clara, CA, USA) were used for LAAC as previously described.[13] To verify the correct device positioning with no significant residual leak, fluoroscopic and transesophageal echocardiographic guidance was used. Adequate device position was confirmed with fluoroscopy and pericardial effusion was excluded before discharge. The predicted annual rates of thromboembolic and major bleeding events were based on the CHA_2DS_2-VASc and HAS-BLED scores and incidence rates in historical controls.[14,15] The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, and the study was performed in accordance with the Declaration of Helsinki as revised in 2002. All patients provided written informed consent for the prospective follow-up.

Categorical variables are presented as counts and percentage. Continuous variables are presented as mean (standard deviation) if normally distributed, or median and interquartile range if skewed. A chi-square test and Fisher's exact test were used to compare dichotomized variables as appropriate. Independent sample t-test and Mann-Whitney U-test were used to assess differences in continuous variables between groups. Event rates were calculated as number of events per 100 patient-years. The Kaplan-Meier method was used for graphical assessment of outcomes. A landmark analysis was performed at the 6-month landmark, and patients with any primary or secondary outcome during the first 6 months were excluded. The log rank test was used to compare the Kaplan-Meier estimated survival between the groups. The sample size was not large enough for multivariable survival analysis. A p value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA).

Results

A total of 81 (49%) patients were discharged on SAPT following LAAC and included in the present analysis (Supplementary Table 1). The Amplatzer Cardiac Plug was implanted in 18 (22%) patients and the Amplatzer Amulet in 63 (78%) patients. The primary contraindication to OAC therapy was a prior major bleeding, which was intracranial in 48 (59%) patients and other major bleeding events in 16 (10%) patients. The baseline characteristics of the study population are presented in Table 1. Of these patients, 6 (7%) experienced non-fatal in-hospital complications: 1 cardiac tamponade, 4 access site bleedings, and 1 device embolization with a new device implanted without complications a few months later. No in-hospital cerebrovascular or thromboembolic complications occurred in this series.

At discharge, 77 (95%) patients were on aspirin and 4 (5%) patients on clopidogrel therapy. Long-term SAPT was initially prescribed in 20 patients (25%) while the majority (75%) received antiplatelet therapy ≤ 6 months (range, 3 weeks – 6 months) including 29 patients with ≤ 3 months therapy (36%). During follow-up, one patient had a deep vein thrombosis, which was treated with OAC for 6 months, in one patient SAPT was switched to dual antiplatelet therapy (DAPT) after an ischemic stroke, and another patient was admitted to chronic hemodialysis therapy with low-molecular-weight heparin. The mean CHA_2DS_2-VASc score was higher in patients assigned for long-term SAPT (5.5 ± 1.4) compared with patients assigned for short-term SAPT (4.5 ± 1.3, p=0.006) mostly driven by higher prevalence of heart failure (35 % vs. 11%, p=0.016) and peripheral vascular disease (70% vs. 16%, p<0.001).

Clinical follow-up data was complete in all patients. The mean follow-up time was 2.9 years (median, 2.5; interquartile range, 1.2–4.1 years). The early and long-term outcomes of the patients are presented in Table 2, and Figure 1 shows the effectiveness of LAAC with short

SAPT in reducing the risk of thromboembolic complications and major bleeding according to the predicted risk. Overall, there were 4 ischemic strokes (1.7/100 patient-years) and 2 TIAs (0.9/100 patient-years). Three out of the 4 ischemic strokes occurred within the first postoperative 6 months while on aspirin therapy (Table 3). The annual rate of major bleeding after index hospitalization was 3.6/100 patient-years. There were 4 intracranial bleedings (1.7/100 patient-years), which were all intracerebral and fatal within 30 days. All patients except one were on aspirin at the time of the intracranial bleeding. Moreover, 2 out of the 4 intracranial bleedings occurred within the first 6 months, 1 of which was a hemorrhagic transformation of ischemic stroke. The individual characteristics of the patients experiencing thromboembolic and intracranial bleeding events during the follow-up period are summarized in Table 3.

One patient had an asymptomatic device embolization to the descending aorta detected at routine 3-month follow-up visit. No attempts to retrieve the device was performed because of severe atherosclerosis of the aorta and iliac arteries. The patient has been asymptomatic during the follow-up of 66 months. A total of 15 deaths occurred during the follow-up period (6.4/100 patient-years) including 5 deaths at 6 months (12.8/100 patient-year, Table 2). Figure 2 shows the cumulative incidence of thromboembolic events, intracranial bleeding, and all-cause mortality.

At the 6-month landmark, 72 patients (89%) were free of any primary or secondary outcomes. In univariate Kaplan-Meier analysis, the 1-, 3- and 5-year survival rates were 100%, 98%, and 89% for the short-term SAPT group and 94%, 63%, and 63% for the long-term SAPT group (p=0.012). There was no statistically significant difference in freedom from thromboembolism, intracranial bleeding, and major bleeding between the two groups (Supplementary Table 2 and Supplementary Table 3).

Discussion

Our study demonstrated that a strategy of percutaneous LAAC followed by short individually planned SAPT was associated with a relatively low rate of thromboembolic and major bleeding events. During long-term follow-up (up to 8 years), use of SAPT (in half of all patients with LAAC) was associated with a lower-than-predicted rate of thromboembolic events (relative risk reduction of 73%), but the rate of bleeding events was comparable to that of patients treated with anticoagulation (Figure 1).[14,15] These findings suggest that this treatment strategy is a safe and feasible option for AF patients at very high risk of severe bleeding complications. On the other hand, a residual burden of thromboembolic complications and bleeding events still exists especially during the first 6 months after implantation. Pursuing to identify the optimal treatment strategy in these patients is of crucial importance to balance out such risk.

In the randomized PROTECT-AF and PREVAIL trials studying Watchman device for LAAC, warfarin therapy was continued for 45 days post-implantation, followed by DAPT up to 6 months and lifelong aspirin.[6,16] Obviously, this treatment protocol is not applicable in this clinically challenging patient population with contraindications to OAC. Currently, DAPT strategy is often recommended for high bleeding risk patients during the first post-operative months, although this regimen remains empirical.[17]

As expected, the first months following device implantation presented the highest risk for thromboembolic complications as most (3 out of 4) ischemic strokes occurred within the first 6 months after LAAC (Table 2). Thus, our results support the hypothesis that during these vulnerable first postoperative months, aspirin monotherapy may not be adequate to prevent thromboembolic complications, and OAC or DAPT might prove more effective in stroke

prevention. Unfortunately, the margins for more effective antithrombotic therapy seem to be limited in this setting, since also 5 out of 8 major bleeding events occurred within the first 6 months including 2 fatal intracerebral bleeding events (Table 3). It is well-established that DAPT almost doubles the bleeding risk compared to SAPT with aspirin, therefore a reduction in thromboembolic events with DAPT could be associated with an increase in bleeding events.[18]

As the long-term treatment regimen, SAPT may deliver sufficient antithrombotic efficacy without the bleeding risks of DAPT. In the present study, SAPT was discontinued within 6 months in most patients with no history of coronary artery disease as patients were deemed to be at very high risk of future bleedings. In spite of this conservative approach, one patient with no antithrombotic therapy suffered a fatal intracerebral bleeding almost 2 years post-procedure. On the other hand, late cerebrovascular ischemic events were rare in patients with no antithrombotic treatment, but it is noteworthy that carotid disease was a common finding in the patients with late events (Table 3). The optimal treatment strategy of patients with concomitant carotid disease might include long-term SAPT, but this requires future studies.[19]

Rodriquez-Gabella and colleagues were the first to report their experience with lifelong SAPT after LAAC. They observed no thromboembolic events in 31 patients followed for 19 months.[20] In another study of 76 patients with lifelong SAPT, the incidence of stroke was 4.0% over a mean follow-up of 13 months.[21] In a Danish study, the annual stroke rate was 2.3% in a patient group mainly treated with SAPT.[22] Of note, the annual stroke rate has ranged from 1.6 to 2.9% in the largest observational studies with Amplatzer devices using primarily DAPT strategy.[23–25] In the latest observational study with Watchman device, the stroke rate was also similar to our cohort (2.2% per year) in patients treated mostly without OAC.[26]

The main limitation of the present study was that the annual stroke and major bleeding rates were compared to estimated event rates extrapolated from historical controls based on the CHA_2DS_2-VASc and HAS-BLED scores, respectively. Secondly, our modified HAS-BLED score did not include points for labile international normalized ratio and alcohol use as we were not confident that they were adequately reported. The sample size of our study was limited, and the prospective follow-up data were collected only up to 5 years. In addition, our simplified protocol did not include routine transesophageal echocardiography during the first clinical visit to assess device-related thrombosis and modify the early antithrombotic treatment accordingly.

In conclusion, percutaneous LAAC with Amplatzer LAAC devices followed by short SAPT seems to be a reasonable treatment option for selected patients with strict contraindications to oral anticoagulation and no other indication for antiplatelet therapy.

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Figure titles and legends

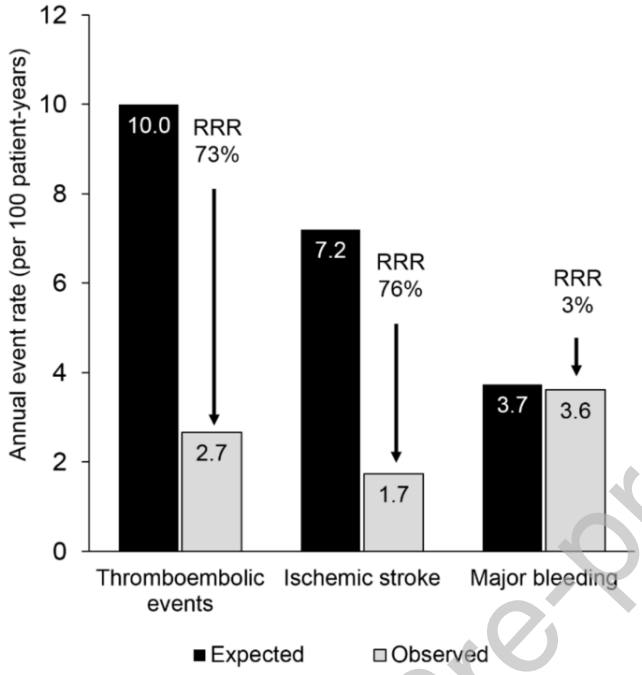

Figure 1. Effectiveness of single antiplatelet therapy after left atrial appendage closure in patients with atrial fibrillation and contraindications to oral anticoagulation. Legend: Predicted and observed rates of thromboembolic and major bleeding events are presented.[14,15] Abbreviations: RRR = relative risk reduction

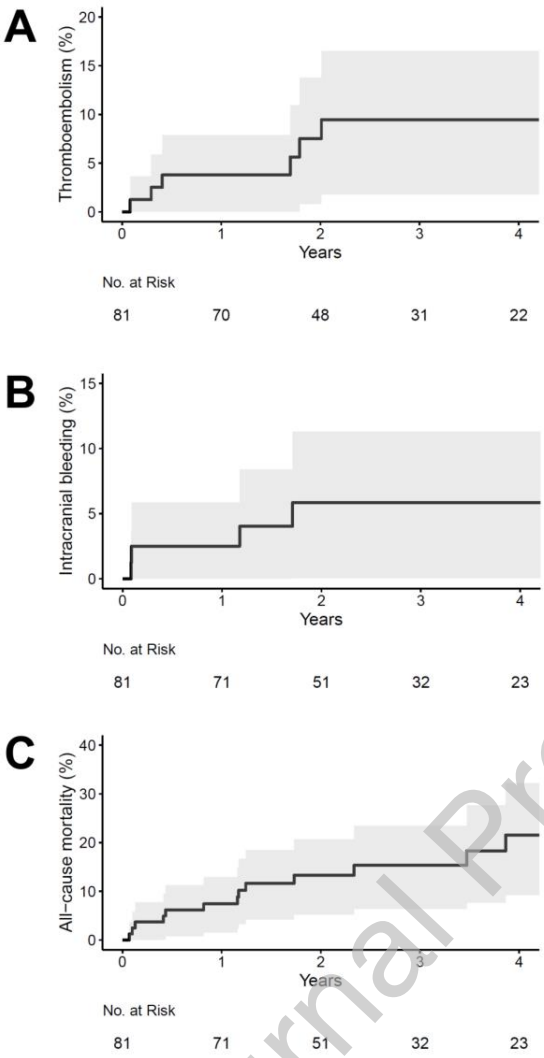

Figure 2. Kaplan-Meier curves of cumulative incidence. Legend: Kaplan-Meier curves showing cumulative incidence of thromboembolic events (A), intracranial bleeding (B), and all-cause mortality (C). The 95% confidence intervals are indicated by the shaded grey regions.

Table 1. Baseline characteristics of the study population (n = 81)*

Variable	Short-term (≤ 6 months; n = 61)	Long-term (Life-long; n = 20)	p value
Age (years)	74 ± 7	75 ± 8	0.932
Women	28 (46%)	8 (40%)	0.645
Chronic atrial fibrillation	28 (46%)	9 (45%)	0.944
CHA_2DS_2-VASc score	4.5 ± 1.3	5.5 ± 1.4	0.006
Heart failure	**7 (**11%)	7 (35%)	0.016
Hypertension	44 (72%)	14 (70%)	0.854
Diabetes mellitus	12 (20%)	9 (45%)	0.025
Stroke/transient ischemic attack/thromboembolism	44 (72%)	14 (70%)	0.854
Intracranial bleeding	40 (65%)	8 (40%)	0.043
Peripheral vascular disease	10 (16%)	14 (70%)	<0.001
HAS-BLED score†	3.1 ± 0.8	3.5 ± 1.0	0.142
Liver disease	1 (2%)	2 (10%)	0.149
Estimated glomerular filtration rate‡ (ml/min/1.73 m^2)	65 ± 18	56 ± 23	0.080
< 30	3 (5%)	3 (15%)	0.135
Prior drug usage predisposing to bleeding	18 (30%)	9 (45%)	0.202
Anemia§	13 (21%)	11 (55%)	0.004
Device			0.538
Amplatzer Amulet	46 (75%)	17 (85%)	
Amplatzer Cardiac Plug	15 (25%)	3 (15%)	
Device size (mm)	25 (22–28)	26 (25–28)	0.060
≥ 26	22 (36%)	11 (55%)	0.135

Values are number (%), mean ± standard deviation, or median (interquartile range).

*Baseline characteristics are grouped according to short-term (≤ 6 months) and long-term (life-long) single antiplatelet therapy strategies.

†Modified HAS-BLED score was calculated with no points for labile international normalized ratio and alcohol abuse.

‡Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

§Anemia was defined as hemoglobin concentration of <13 g/dL for men and <12 g/dL for women.

Table 2. Early and overall follow-up outcome after index hospitalization (n = 81)

Variable	≤ 6 months		During whole follow-up	
Endpoints	Number of events (%)	Rate per 100 patient-years (95% CI)	Number of events	Rate per 100 patient-years (95% CI)
Death	5 (6%)	12.8 (5.6–29.0)	15 (19%)	6.4 (3.9–10.5)
Cardiovascular	4 (5%)	10.2 (4.0–25.9)	9 (11%)	3.8 (2.0–7.3)
Thromboembolic events	3 (4%)	7.7 (2.6–22.9)	6 (7%)	2.7 (1.2–5.9)
Ischemic stroke	3 (4%)	7.7 (2.6–22.9)	4 (5%)	1.7 (0.7–4.6)
Transient ischemic attack	0	-	2 (2%)	0.9 (0.2–3.5)
Systemic embolism	0	-	0	-
Major bleeding events	5 (6%)	13.1 (5.8–29.7)	8 (10%)	3.6 (1.8–7.1)
Intracerebral bleeding*	2 (2%)	5.1 (1.3–19.7)	4 (5%)	1.7 (0.6–4.5)

Incidence rates are expressed as number of events per 100 patient-years of follow-up

Abbreviation: CI = confidence interval

*One patient had a hemorrhagic transformation of an ischemic stroke.

Table 3. Individual characteristics of patients with thromboembolic and intracranial bleeding events during follow-up (n = 9).

Age (years) and sex	Type of atrial fibrillation	Contraindication to oral anticoagulation	CHA_2DS_2-VASc	HAS-BLED	Device (size, mm)	Event	Fatal event* (+/0)	Antithrombotic therapy at the time of the event (+/0)	Timing post-procedure (days)	Carotid plaque (+/0)
55M	Paroxysmal	Major bleeding	4	3	Amulet (25)	Transient ischemic attack	0	+ (Aspirin, 100 mg)	654	–
62M	Permanent	Intracranial bleeding	2	3	ACP (18)	Intracerebral bleeding	+	0	624	–
68M	Paroxysmal	Intracranial bleeding	2	3	Amulet (25)	Intracerebral bleeding	+	+ (Aspirin, 100 mg)	33	+
70M	Persistent	Intracranial bleeding	4	3	Amulet (31)	Ischemic stroke	+	+ (Aspirin, 100 mg)	148	+
72F	Paroxysmal	Intracranial bleeding	3	3	Amulet (22)	Ischemic stroke†	+	+ (Aspirin, 100 mg)	30	–
78M	Permanent	Intracranial bleeding	2	3	Amulet (31)	Ischemic stroke	0	0	619	–
80F	Paroxysmal	Intracranial bleeding	6	4	ACP (30)	Transient ischemic attack	0	0	734	+
80M	Paroxysmal	High bleeding risk	4	4	Amulet (28)	Ischemic stroke	0	+ (Aspirin, 100 mg)	107	+
86F	Paroxysmal	Major bleeding	6	4	ACP (26)	Intracerebral bleeding	+	+ (Aspirin, 100 mg)	430	–

Abbreviations: ACP = Amplatzer Cardiac Plug; F = female; M = male

*Fatal within 30 days.

†Patient had a subsequent hemorrhagic transformation of an ischemic stroke.