REVIEW ARTICLE

What's new in stroke? The top 10 studies of 2009–2011

Part I

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KEY WORDS

cerebral aneurysm, patent foramen ovale, stroke, tissue plasminogen activator, venous thromboembolism

ABSTRACT

Five important studies from 2009–2011 that influence the clinical management of stroke and threatened stroke are summarized. Pooled analysis of individual patient data from 8 randomized trials testing intravenous tissue plasminogen activator confirmed important benefits for patients treated 3 to 4.5 hours after stroke onset, but treatment after 4.5 hours was associated with a higher mortality. Blood pressure lowering with candesartan in the first few days after stroke was of no benefit and was possibly harmful (SCAST trial). Thigh-length graduated compression stockings did not reduce venous thromboembolism after acute stroke and were associated with skin complications (CLOTS Trial 1). Long-term follow-up showed that endovascular coiling was as good as neurosurgical clipping for patients with small, ruptured intracranial aneurysms (ISAT trial). Percutaneous closure of a patent foramen ovale offered no apparent benefit to young patients with cryptogenic ischemic stroke based on the first randomized trial testing this intervention, but the number of stroke events was insufficient to draw definitive conclusions (CLOSURE I trial).

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Introduction Stroke remains a major public health burden throughout the world.[1] Important advances in the prevention and treatment of stroke published between 2006 and 2008 were previously summarized in this journal.[2,3] Here, we update our "top 10" for 2009 to 2011. The main selection criterion was that the study influenced our day-to-day management of patients with stroke and threatened stroke.

All are randomized clinical trials, reflecting this research design as providing the best evidence on which to base treatment decisions (**TABLE 1**).[4-14] The number of participants per study ranged widely, from 909[8] to over 18,000.[9] Half of the trials were sponsored by pharmaceutical companies or medical device manufacturers.[5,8-11] Five of the selected articles tested surgical procedures and/or devices,[6-8,12,13] reflecting the high quality of data available in recent years to assess nonmedical interventions for stroke treatment and prevention. Several are "negative" trials in which the experimental intervention was not shown to be better than the control.[5,6,8] Nevertheless, "usefully negative" trials that are well designed and well executed, with adequate statistical power to exclude a clinically important benefit, allow ineffective interventions to be avoided.

Part I of this review summarizes 4 studies concerning management of patients with acute stroke and 1 trial assessing the value of closure of patent foramen ovale (PFO) for secondary stroke prevention. Part II discusses 3 trials testing antithrombotic drugs for stroke prevention in patients with atrial fibrillation and 2 trials comparing carotid artery stenting with endarterectomy. By way of disclosure, one of us (RGH) participated as a site investigator in the CLOSURE I trial.[8]

1. Pooled analysis of 8 randomized trials showed substantial benefit of intravenous tissue plasminogen activator given 3 to 4.5 hours after stroke onset

In the wake of the positive results of the ECASS III

TABLE 1 The top 10 stroke studies of 2009–2011

1. Pooled analysis of 8 randomized trials shows substantial benefit of i.v. tPA given 3 to 4.5 hours after stroke onset.[4]
2. Blood pressure lowering with candesartan may be harmful within the first days after acute stroke (SCAST).[5]
3. Thigh-length graduated compression stockings do not reduce venous thromboembolism in patients with acute stroke (CLOTS 1).[6]
4. Endovascular coiling is as good as neurosurgical clipping in the long-term for small, ruptured intracranial aneurysms (ISAT).[7]
5. Percutaneous occlusion of a PFO does not add to medical therapy in young cryptogenic stroke patients (CLOSURE I).[8]
6. Novel oral direct thrombin inhibitor dabigatran is as good or better than warfarin for stroke prevention in patients with AF (RE-LY).[9]
7. Clopidogrel plus aspirin is superior to aspirin alone for preventing stroke, but with increased bleeding, in AF patients deemed unsuitable for warfarin (ACTIVE A).[10]
8. Novel oral direct factor Xa inhibitor apixaban is superior to aspirin for AF patients deemed unsuitable for warfarin (AVERROES).[11]
9. Complication rates of carotid stenting and carotid endarterectomy are equal (CREST).[12]
10. Carotid stenting has a higher complication rate than carotid endarterectomy (ICSS and pooled analysis of 3 European trials).[13,14]

Abbreviations: AF – atrial fibrillation, i.v. tPA – intravenous tissue plasminogen activator, PFO – patent foramen ovale

trial (European Cooperative Acute Stroke Study) testing intravenous tissue plasminogen activator (i.v. tPA) in the 3 to 4.5 hour window,[15] pooled analysis of individual patient-level data from all 8 double-blind randomized trials testing i.v. tPA for acute ischemic stroke was recently undertaken.[4] Among 3670 participants, 75% were treated >3 hours from stroke onset, permitting reliable estimates of treatment effects when thrombolysis is undertaken after 3 hours. The pooled analysis confirmed that for patients treated with i.v. tPA in the 3 to 4.5 hour window, the odds ratio for a good outcome (i.e., modified Rankin score of 0–1) at 90 days was 1.3 (P = 0.01) (TABLE 2, FIGURE 1).[16] Mortality was significantly increased for patients treated with i.v. tPA after 4.5 hours from stroke onset (odds ratio 1.5, P = 0.05).

The investigators concluded that "patients with ischemic stroke selected by clinical symptoms and CT [computed tomography] benefit from intravenous alteplase when treated up to 4.5 hours. To increase the benefit to a maximum, every effort should be taken to shorten delay in initiation of treatment. Beyond 4.5 hours, risk might outweigh benefit."[4] The restricted eligibility criteria used in the ECASS III trial should be applied when treating patients beyond 3 hours from stroke onset: excluding those over 80 years old, those whose National Institutes of Health Stroke Scale score >25, those with >⅓ middle cerebral artery territory hypodensity on computed tomography, those with recent oral anticoagulant use, and those with diabetes and prior history of stroke. Based on analysis of the ECASS III results, the magnitude of benefit of i.v. tPA given in the 3 to 4.5 hour window has been characterized as follows: for an additional improvement of ≥1 Rankin grade, 6 patients would need to be treated. For worsening of ≥1 Rankin grade, 35 patients would need to be treated. In short, patients are 6 times as likely to be helped as harmed by i.v. tPA given 3 to 4.5 hours after ischemic stroke onset.[17] The large, ongoing International Stroke Trial III is randomizing patients to i.v. tPA vs. control treated 0 to 6 hours from stroke onset, with results anticipated in 2012.

Treatment with i.v. tPA in the 3 to 4.5 hour time window has been endorsed by the European Stroke Organisation, the Canadian Best Practice Guidelines, and the American Heart Association. While not yet considered by the European Medicines Agency, treatment up to 4.5 hours after stroke onset is currently widely applied in Europe. However, the longer time window should *not* be an excuse to delay treatment: time is brain, and minutes count when treating acute stroke patients.

2. Blood pressure lowering may be harmful within the first days after acute stroke Elevated blood pressure is frequent in patients presenting with acute stroke, and optimal management has not

TABLE 2 Pooled analysis of 8 randomized trials testing intravenous tissue plasminogen activator in acute ischemic stroke: time to treatment vs. functional outcome[4]

Time to treatment, min	Randomized treatment, %		Odds ratio for good outcome[a]	P
	i.v. tPA	placebo		
0–90	42	29	2.6	0.001
91–180	42	29	1.6	0.01
181–270	45	38[b]	1.3	0.01
271–360	37	36	1.2	NS

a good outcome is defined as a modified Rankin score of 0–1 at 90 days, implying no disability
b patients with less severe stroke were included after 180 minutes per the ECASS III inclusion criteria, accounting for better outcomes among the placebo-treated patients

Abbreviations: NS – nonsignificant, others – see TABLE 1

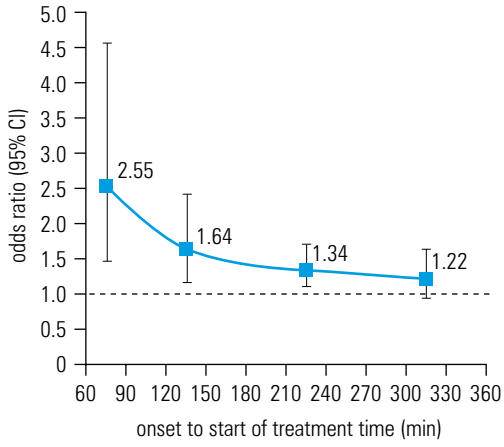

FIGURE 1 Relationship between time-to--treatment from stroke onset and good functional outcome Adjusted odds ratio with 95% CI (vertical bars) for achieving a Rankin score of 0–1 at 90 days.[16] Abbreviations: CI – confidence interval

been defined by randomized trials. In the double--blind SCAST trial (Scandinavian Candesartan Acute Stroke Trial), 2029 patients with acute stroke within 30 hours of symptom onset and a systolic blood pressure of ≥140 mmHg were randomized between 2005 and 2010 at 146 centers in Northern Europe to receive candesartan (initial dose 4 mg daily, increasing to 16 mg on day 7) vs. placebo for 7 days.[5] The mean patient age was 71 years, blood pressure at entry averaged 171/90 mmHg, 14% were hemorrhagic strokes, and the mean time to randomization was 18 hours from stroke onset.

Blood pressures diverged on day 2, and by day 7 the mean systolic blood pressure was 5 mmHg lower in those assigned candesartan (P <0.0001; TABLE 3). However, there were no significant effects on the primary outcome composite of stroke, myocardial infarct or vascular death at 6 months, and there was no interaction of treatment effects with the type of stroke (ischemic vs. hemorrhagic) (TABLE 3). Unexpectedly, the prespecified adjusted ordinal regression analysis of Rankin scores favored placebo (P = 0.05), as did a secondary analysis of early stroke progression (TABLE 3). The investigators concluded that "there was no evidence that careful blood pressure lowering ... [with] candesartan is beneficial in patients with acute stroke and raised blood pressure. If anything, the evidence suggested a harmful effect."[5]

Limitations of the SCAST include the relatively small achieved difference in blood pressure, explained in part by clinicians adding additional antihypertensive drugs based on their clinical judgment. Other limitations include the inclusion of heterogeneous types of vascular disease and the relatively mild average stroke severity. Two other recent randomized trials also did not find clinical benefits of blood pressure lowering in acute stroke patients.[18,19] The SCAST results support the recommendation of the European Stroke Organisation (2008) that "after ischemic stroke, routine blood pressure lowering is not recommended," but cautious blood pressure lowering should be undertaken in patients with extremely high blood pressure (>220/120 mmHg) on repeated measurements.[20] The American Stroke Association recommends a target systolic blood pressure of <220 mmHg for most patients presenting with ischemic stroke and of <185 mmHg for those eligible for tPA.[21]

3. Thigh-length graduated compression stockings do not reduce venous thromboembolism after acute stroke Venous thromboembolism poses a substantial threat to immobile patients with acute stroke. Subcutaneous heparin can reduce the risk; however, it is associated with a small increased risk of intracranial hemorrhage.[22] Studies in patients undergoing surgery have shown that graduated compression stockings are effective for prevention of venous thromboembolism.[23] Most patients do not like wearing graduated compression stockings: they are uncomfortable, difficult to put on, and generally cumbersome. Nurses have found stockings difficult to keep clean and to keep on patients with acute stroke.

The CLOTS Trial 1 (Clots in Legs Or sTockings after Stroke) tested whether the use of thigh-length graduated compression stockings reduced venous thrombosis in patients with acute stroke.[6] At 64 sites in the United Kingdom, Italy, and Australia between 2001 and 2008, 2518 patients with acute stroke who were unable to walk without help were randomized within 10 days (most within 2 days) of stroke onset to graduated compression stockings or their avoidance until the patient was independently mobile or until hospital discharge. The mean age of participants was 76 years, 49% were men, 85% had an ischemic

TABLE 3 Main results of the SCAST: candesartan in patients with acute stroke[5]

	Candesartan n = 1017	Placebo n = 1012	P
blood pressure at 7 days, mmHg	147/82	152/84	<0.001
stroke, myocardial infarct, or vascular death at 6 months[a], %	12	11	NS
good functional outcome at 6 months[a]: Rankin score of 0–2[b], %	65	67	NS
stroke progression[c], %	6	4	0.04

a coprimary outcome
b a prespecified adjusted ordinal regression analysis of Rankin scores favored placebo (P = 0.05)
c neurological deterioration of –2 points on the Scandanavian Stroke Scale within 72 hours of stroke onset, not attributable to systemic causes

Abbreviations: see TABLE 2

TABLE 4 Main results of CLOTS Trial 1: thigh-length graduated compression stockings vs. their avoidance in immobile patients with acute stroke[6]

	Compression stockings n = 1256	No compression stockings n = 1262	Odds ratio
proximal deep vein thrombosis, %	10.0	10.5	NS
symptomatic proximal deep vein thrombosis, %	2.9	3.4	NS
any proximal or distal deep vein thrombosis, %	16.3	17.7	NS
pulmonary embolism, %	1.0	1.6	NS
death by 30 days, %	9.7	8.7	NS
skin complications (skin breaks, blisters, ulcers, or necrosis), %	5.1	1.3	4.2 (P <0.001)

Abbreviations: see TABLE 2

TABLE 5 Long-term results of the ISAT: clipping vs. coiling of ruptured intracranial aneurysms[7]

	Clipping n = 1046	Coiling n = 1041	P
dead or dependent[a] at 5 years, %	29	26	NS
dead at 5 years, %	14	11	0.03
re-ruptures			
– during the first year, n (%)	39 (4)	45 (4)	NS
– after 1 year (mean follow-up 9 years), n (%)	7 (1)	17 (2)	–
from the index aneurysm, n	3	10[b]	0.06
from another known aneurysm, n	1	3	–
from a new or unknown aneurysm, n	3	4	–

a Rankin score of 3–6
b absolute rate of re-rupture of the originally treated aneurysm was 0.1%/y

Abbreviations: see TABLE 2

stroke, most (>92%) did not receive subcutaneous heparin. A technician who was blinded to treatment performed compression Doppler ultrasound to detect deep vein thrombosis after 7–10 days, repeated after 25–30 days in one-third of participants. The use of thigh-length graduated compression stockings did not reduce symptomatic or asymptomatic proximal deep vein thrombosis and was associated with an increased risk of skin complications (TABLE 4). The investigators concluded that "these data do not lend support to the use of thigh-length graduated compression stockings in patient admitted to hospital with acute stroke."[6]

The unexpected results of the companion CLOTS Trial 2[24] comparing thigh-length vs. below-knee graduated compression stockings clouded the interpretation of CLOTS Trial 1. Involving 3114 acute stroke patients who were immobile, the observed rate of proximal deep vein thrombosis was 6.3% with thigh-length stockings vs. 8.8% with below-knee stockings (P = 0.01).[24] The CLOTS Trial 2 results suggest that either thigh-length stockings reduce proximal deep vein thrombosis (conflicting with the CLOTS Trial 1 results) or that below-knee stockings increase deep vein thrombosis! The investigators concluded that "the results of the two completed CLOTS trials suggest that thigh-length stockings are unlikely to have clinically important benefits for patients with stroke."[24] For prevention of venous thromboembolism in acute ischemic stroke patients, the European Stroke Organisation (2008) recommends early rehydration and early mobilization and that low-dose subcutaneous heparin or low-molecular-weight heparins are indicated for patients at high risk (e.g., immobilization, obesity, diabetes, previous stroke).[20]

4. Endovascular coiling is as good as neurosurgical clipping in the long-term for small, ruptured intracranial aneurysms Between 1994 and 2002, the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group randomized 2143 patients with ruptured intracranial aneurysms to neurosurgical clipping vs. endovascular repair ("coiling").[7] European and Canadian centers that treat large numbers of patients with subarachnoid hemorrhage randomized about 20% of patients with ruptured aneurysms seen during the recruitment interval; eligibility required that the patient be a good candidate for both procedures. Average patient age was 52 years, and most patients were good grade at randomization and had small (90% <1 cm) anterior circulation aneurysms. Patients were randomized a median of 2 days after rupture

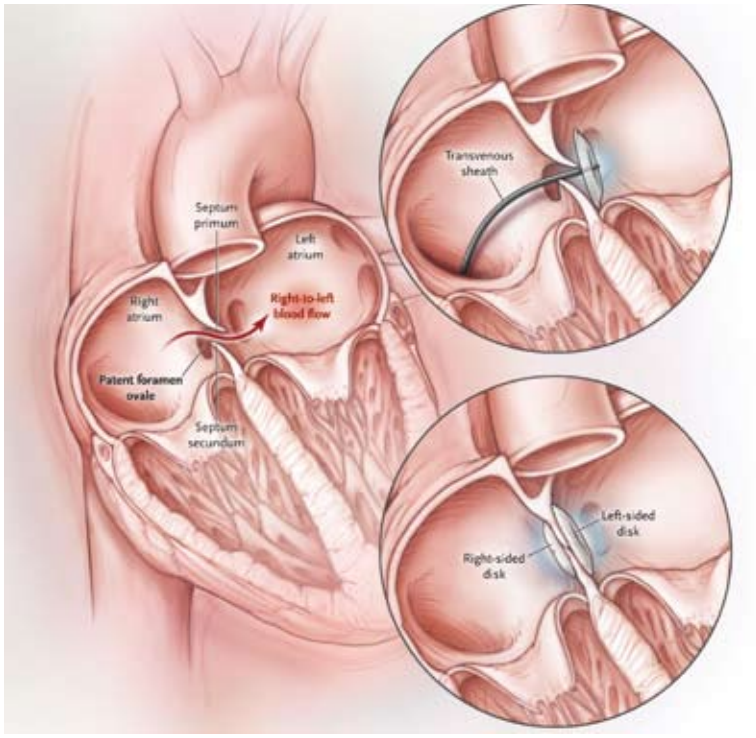

FIGURE 2 Percutaneous closure of a patent foramen ovale. Through a femoral approach, a transvenous sheath is advanced across the foramen ovale into the left atrium, where a folded disk is deployed and retracted, apposing the primum and secundum septa. This is followed by placement of a right-sided disk, and finally the two-disk device is released. (Kizer JR, Devereux RB. N Engl J Med. 2005: 353: 2361-2372; reproduced with permission from the Massachusetts Medical Society).

and were treated an average of 1 to 2 days later. The durability of coiling has been a long-standing concern, and in this third report from the ISAT provided outcomes for 2087 (97%) participants followed for a mean of 9 years.

The primary outcome of death or dependency (modified Rankin scores of 3–6) were about equal during long-term follow-up, but 5-year survival favored coiling (TABLE 5). Late re-rupture (after 1 year) of the originally-treated aneurysm was infrequent with either treatment (≤1%) during the mean 9-year follow-up. The investigators concluded that "there was an increased risk of recurrent bleeding from a coiled aneurysm compared with a clipped aneurysm, but the risks were small. The risk of death at 5 years was significantly lower in the coiled group."[7]

Commentaries appearing in the neurosurgical journals emphasized the selected study population: that ISAT results "should not necessarily be generalized beyond ... patients with ruptured aneurysms who were classified in a relatively good grade ... and who had primarily small anterior circulation aneurysms."[25] Some have speculated that specialized neurovascular surgeons using intraoperative angiography would have better results with clipping than those reported from the ISAT, while others have suggested that technical advances in coiling since the ISAT was initiated in 1994 would likely improve coiling results. To our knowledge, the European Stroke Organisation has not made recommendations, while American Heart Association guidelines (that did not consider these recent ISAT follow-up data) recommend that "for patients with ruptured aneurysms judged ... to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling can be beneficial ... it is reasonable to consider individual characteristics of the patient and the aneurysm ... and management in centers offering both techniques is probably indicated."[26]

5. Percutaneous occlusion of a patent foramen ovale does not add to medical therapy in young cryptogenic stroke patients The value of percutaneous device occlusion of a PFO in patients with cryptogenic ischemic stroke has been a long-standing conundrum (FIGURE 2)[27] The CLOSURE I trial (2003–2010) enrolled patients aged ≤60 years who had cryptogenic stroke or transient ischemic attack (TIA) within 6 months and a PFO detected by transesophageal echocardiography.[8] Among 909 participants recruited from 87 North American sites, the mean age was 46 years, 52% were men, 72% had a stroke (rather than a TIA) as the qualifying event, and 36% had an associated atrial septal aneurysm. Patients were randomized open-label to closure with the "double-umbrella" STARFlex device (NMT Medical, Boston, United States) followed by clopidogrel plus aspirin for 6 months followed by aspirin alone vs. antithrombotic therapy per the choice of the local investigator (warfarin, aspirin, or their combination; 30% received warfarin alone, 53% received aspirin alone). In those undergoing percutaneous occlusion, repeat echocardiography after 6 months showed persistent PFO occlusion in 86%.

TABLE 6 Main results of the CLOSURE I trial: patent foramen ovale closure in young adults with cryptogenic stroke[8]

Outcome	PFO closure n = 447	Antithrombotic therapy alone n = 462	*P*
primary outcome[a], n (%)	25 (5.9)	30 (7.7)	NS
stroke in 2 years, n (%)	12 (3.1)	13 (3.4)	NS
AF, n	23[b]	3	<0.001

a two-year incidence of stroke or transient ischemic attack, all-cause mortality for the first 30 days after randomization, and neurologic mortality >31 days to 2 years; for the participant subgroup with atrial septal aneurysms, the primary outcome was 7/142 with closure vs. 9/139 with antithrombotic therapy
b 14 were periprocedural and of unclear duration

Abbreviations: see TABLES 1 and 2

During the 2-year follow-up period, no significant benefits of PFO closure were evident (TABLE 6). Stroke rates were low (<2% per year) and nearly equal in both treatment arms. Atrial fibrillation was more frequently identified in those undergoing PFO closure.

The CLOSURE I trial results do not support the routine addition of PFO closure to antithrombotic medications for secondary prevention of stroke in young patients with cryptogenic brain ischemia. However, recurrent strokes (25 in total) were few, the confidence intervals around the treatment effects are wide, and consequently there is inadequate statistical power to convincingly exclude an important benefit (i.e., the trial does not fully meet the criteria for "usefully negative" as defined above). The CLOSURE I trial is the first of 5 randomized trials to report testing percutaneous device closure of PFO in patients with cryptogenic brain ischemia.[28] The European Stroke Organisation guidelines (2008) recommend that endovascular closure be considered for selected patients with cryptogenic stroke and PFO.[20]

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ARTYKUŁ POGLĄDOWY

Co nowego w udarze mózgu? Dziesięć najważniejszych badań dotyczących udaru w latach 2009–2011

Część I

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SŁOWA KLUCZOWE

przetrwały otwór owalny, tętniak mózgowy, tkankowy aktywator plazminogenu, udar mózgu, żylna choroba zakrzepowo-zatorowa

STRESZCZENIE

Podsumowano 5 ważnych badań klinicznych opublikowanych w latach 2009–2011, które wpłynęły na postępowanie kliniczne w przypadku udaru mózgu i zagrażającego udaru mózgu. W łącznej analizie danych poszczególnych chorych uczestniczących w 8 badaniach z randomizacją nad dożylnym stosowaniem tkankowego aktywatora plazminogenu potwierdzono korzyści dla chorych otrzymujących lek 3–4,5 h od początku udaru, ale leczenie po upływie 4,5 h wiązało się z większą śmiertelnością. Obniżanie ciśnienia tętniczego za pomocą kandesartanu w ciągu pierwszych kilku dni po udarze nie dało korzyści, a być może było szkodliwe (badanie SCAST). Pończochy o stopniowanym ucisku zakładane na całą kończynę dolną nie zmniejszyły częstości żylnej choroby zakrzepowo-zatorowej po świeżym udarze mózgu, a wiązały się z powikłaniami skórnymi (badanie CLOTS 1). Długoterminowa obserwacja wykazała, że embolizacja małych pękniętych tętniaków wewnątrzczaszkowych za pomocą sprężyn wewnątrznaczyniowych jest równie skuteczna, jak ich klipsowanie neurochirurgiczne (badanie ISAT). Przezskórne zamknięcie przetrwałego otworu owalnego nie dało wyraźnych korzyści u młodych chorych po kryptogennym niedokrwiennym udarze mózgu w pierwszym badaniu z randomizacją dotyczącym tej metody, ale liczba przypadków udaru była za mała, aby wyciągnąć ostateczne wnioski (badanie CLOSURE I).

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