

Acute treatment of stroke (except thrombectomy)

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Word count: 3486

References: 82

Abstract

Purpose of Review

The management of patients with acute stroke has been revolutionized in recent years with the advent of new effective treatments. In this rapidly evolving field, we provide an update on the management of acute stroke excluding thrombectomy, looking to recent, ongoing and future trials.

Recent Findings

Large definitive trials have provided insight into acute stroke care including broadening the therapeutic window for thrombolysis, alternatives to standard dose alteplase, the use of dual antiplatelet therapy early after minor ischemic stroke, and treating elevated blood pressure in intracerebral hemorrhage. Further ongoing and future trials are eagerly awaited in this ever-expanding area.

Summary

Although definitive trials have led to improvements in acute stroke care, there remains a need for further research to improve our understanding of pathophysiological mechanisms underlying different stroke types with the potential for treatments to be tailored to the individual.

(143/150 words)

Keywords

Acute ischemic stroke; intracerebral hemorrhage; thrombolysis; antiplatelets; blood pressure; stroke unit.

Introduction

Stroke is a common and devastating condition with a global incidence of 15 million people per year.¹ Although one of the most exciting developments in acute ischemic stroke (AIS) in recent years is the proven effectiveness of thrombectomy in large vessel occlusion, for the remaining 85% of acute stroke patients not eligible for thrombectomy there have been several important developments. Here we provide an evidence-based update of treatments of acute stroke outwith thrombectomy, using data from recently published trials, and look to ongoing and future research for improvements in acute stroke care.

Broadening the therapeutic window for use of intravenous thrombolysis in acute ischemic stroke patients with an unknown time of onset

Reperfusion therapy with the intravenous (iv) thrombolytic agent, recombinant tissue plasminogen activator (rtPA, or alteplase), is the standard, regulatory approved, medical treatment for patients with AIS who present within 4.5 hours from symptom onset.²⁻⁴ The safety and efficacy of this treatment is now well supported by combined data from multiple randomized controlled trials, and confirmed by clinical registry experience in real life settings.⁵ More recently, mechanical thrombectomy has been shown to be effective in patients meeting certain clinical characteristics and up to 24 hours from being last known to be well.⁶

However, making treatment decisions has been particularly challenging in the nearly 1 in 4 AIS patients who present with an unknown time of symptom onset.⁷ Several brain imaging modalities can help recognize potentially viable cerebral ischemia in those who present after awakening or without any history of ictus, indicating that they

may be candidates for iv thrombolysis with an acceptable risk.⁸ These include (i) computed tomography (CT) perfusion, (ii) mismatch between magnetic resonance imaging (MRI) using perfusion- weighted imaging (PWI) and diffusion- weighted imaging (DWI), or (iii) the visual or semi-quantitative fluid-attenuated inversion recovery (FLAIR)-DWI mismatch on MRI. In the case of CT perfusion, diverse hemodynamic parameters, such as cerebral blood volume (CBV), cerebral blood flow (CBF), delay time (Tmax), and mean transit time (MTT), have been proposed as identifying areas of critical hypoperfusion, while the ischemic core can be defined as a region with markedly reduced CBV or CBF in combination with prolonged MTT or Tmax. However, there is no definitive consensus on which parameters and thresholds best represent critical hypoperfusion and ischemic core.⁹⁻¹¹ While PWI-DWI mismatch is the most valid method of measuring 'tissue at risk', the clear disadvantage is the longer imaging time requirement and limited availability of MRI compared to CT. In addition, there are similar difficulties with CT in determining the optimal thresholds for differentiating ischemic core from salvageable brain tissue.¹² New software that provide automatic quantification of ischemic core and penumbra - both with CT or MRI - have been developed to help physicians in clinical decision-making with faster and easier interpretation of results, and were used in recent trials to broaden thrombectomy time window.¹³ Finally, the presence of a visible ischemic lesion on DWI on MRI, combined with the absence of a clearly visible hyperintense signal in the same region on FLAIR - the DWI/FLAIR mismatch - shows sensitivity of 62%, specificity of 78%, and positive likelihood ratio of 3.6, for detection of thrombolysis-eligible AIS patients within 4.5 h of stroke onset.⁸ This DWI/FLAIR mismatch is promising in centers with MRI availability with no need of quantification,

to detect patients with unknown time of stroke onset who could derive benefit from iv thrombolysis.

The WAKE-UP trial (The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) aimed to determine whether alteplase would improve functional outcome in AIS patients with an unknown time of stroke onset, using DWI / FLAIR mismatch on MRI as an eligibility criteria.¹⁴ Although the trial was stopped prematurely after 503 patients were enrolled on anticipation of cessation of funding from the European Union, the study showed a significantly more favorable functional outcome at 90 days in those who received iv alteplase compared to those who received placebo. Of note, most participants had mild baseline neurological severity (median [IQR] National Institute of Health stroke scale [NIHSS] score 6 [4–9]), over two thirds had no large vessel occlusion, and those eligible for thrombectomy were excluded. In regards to safety outcomes, there were numerically more deaths and significantly more patients with type 2 parenchymal hemorrhage in the alteplase than placebo group. In summary, this trial supports the benefit of thrombolysis reperfusion treatment in patients with minor or moderate AIS who have previously been denied such treatment. Nevertheless, it may be that the higher serious adverse events seen in the alteplase group would have become significant in a larger trial.

Alternatives to standard dose intravenous alteplase thrombolysis

Standard recommended iv dose for alteplase in AIS is 0.9 mg/kg, with an initial 10% of dose given as bolus over 1 minute followed by the remainder to a maximum of 90 mg over 60 minutes.⁵ Lower doses of iv alteplase (most typically, 0.6 mg/kg) have been used as an alternative to the standard regimen primarily on the basis of a perceived higher risk of intracranial hemorrhage (but also treatment affordability) in

Asia.¹⁵ The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) was undertaken to directly compare low-dose with standard-dose iv alteplase but failed to clearly show non-inferiority in the primary outcome of death or disability, defined by scores of 2 to 6 on the modified Rankin scale (mRS).¹⁶

Conversely, major symptomatic intracerebral hemorrhage (sICH) was halved, and mortality at 7 days was also lower in the low-dose group.¹⁶ A post hoc analysis suggested that patients receiving either aspirin or another antiplatelet agent prior to thrombolysis might derive benefit from the lower dose; however, no new recommendations over alteplase dose have been made in recent guidelines.¹⁷

Results from the more intensive blood pressure (BP) lowering arm of ENCHANTED are awaited, as they may provide new evidence to enhance the efficacy and safety of alteplase in AIS.

Alternatives to alteplase in AIS have been tested although neither streptokinase within 6 hours nor desmoteplase within 3 to 9 hours after symptom onset showed benefit in randomized placebo controlled trials.¹⁸⁻²⁰ Tenecteplase (TNK) is the most promising alternative as it has the convenience of being administered as a single iv bolus and shows comparable efficacy and safety to iv alteplase.²¹ On the basis of a small number of carefully selected AIS patients with CT perfusion-identified cerebral ischemia, TNK was shown to have significantly better reperfusion and clinical outcomes than alteplase,²² while the much larger Norwegian phase III trial did not show that TNK was clearly superior (or a priori statistically non-inferior) to alteplase in 1,100 AIS subjects with predominantly mild deficits.²³ Most recently, the EXTEND-IA TNK trial randomly assigned AIS patients with an occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible for thrombectomy to receive TNK (at a dose of 0.25 mg per kilogram of body weight; maximum 25 mg) or

standard dose alteplase within 4.5 hours after symptom onset.²⁴ Reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment were more than double in patients treated with TNK compared to alteplase. Moreover, TNK resulted in a better 90-day functional outcome than alteplase, and without any difference in sICH between the groups. TNK is not yet an approved treatment for AIS and results of ongoing trials are awaited.

Another emerging AIS treatment strategy is use of an iv antiplatelet agent. A Cochrane review of iv glycoprotein IIb/IIIa receptor antagonists for AIS found these agents to be associated with a significant risk of ICH without any measurable improvement in death or disability.²⁵ However, a majority of the trial data involved the use of abciximab.²⁶ Regarding other IV glycoprotein IIb/IIIa receptor antagonists, single-arm and phase II studies of eptifibatide as adjunctive therapy to iv alteplase support ongoing trials to establish safety and efficacy,^{27, 28} where the rate of sICH does not appear to be increased when used in combination with standard dose alteplase.²⁸ Results demonstrating comparable safety of this new regime with historical rates of sICH with tPA alone may prompt new trials evaluating alteplase combined with eptifibatide to improve outcomes after AIS.

Improving stroke systems of care

Well organized stroke care has demonstrated improved patient outcomes.^{29, 30} Having organized local stroke care protocols, established goals and quality improvement strategies, all have an important role in stroke care.³¹ Unfortunately, considerable regional differences remain in optimal stroke care, including access to stroke units,³² particularly in low resource settings. Such disparities require further urgent attention to reduce the burden of stroke, in particular in low and middle-

income countries where fewer resources are available and stroke rates are increasing.

Key elements for effective stroke treatment are: (a) early symptom recognition and prompt health system access; and (b) organized system response, triage and management, once stroke is detected. In less resourced areas, early recognition, rapid transport and ready access to thrombolysis are major barriers, whereas in more mature systems, attention has shifted to bypass algorithms to offer patients the most appropriate and efficient treatment approach, reduce treatment times, and extend stroke care to facilities to where thrombolysis has been absent.

A regional system of stroke care, with operationalized bypass algorithms according to local resources, is a critical aspect comprising healthcare facilities where initial emergency care, including administration of iv alteplase can be provided; and centers capable of performing endovascular stroke treatment with comprehensive periprocedural care to which rapid transport can be arranged. Patients with a positive stroke screen (i.e. the face, arm, speech, time [FAST] algorithm) and/or a strong suspicion of stroke should be transported rapidly to the closest healthcare facility available for administration of iv alteplase, since recovery is strongly dependent on the time to treatment.³³ When several iv alteplase–capable hospital options exist within a defined geographic region, the benefit of bypassing the closest to bring the patient to one that offers a higher level of stroke care is still uncertain. A number of stroke severity scales targeted at recognition of large vessel occlusion (LVO) in the prehospital setting are available, but their prediction is uncertain for recommending wider use for direct patient transfer to thrombectomy-capable centers.³⁴

Door-to-needle time (DNT) is a key performance indicator for efficient use of iv thrombolysis in AIS. Thus, quality improvement strategies have been developed to reduce treatment delays to thrombolysis.³⁵ One of them, the Helsinki stroke model, consists of 12 interventions involving patient pre-notification, rapid clinical assessment, image acquisition, and treatment administration in a chain of responses requiring parallel processing by on-site radiology and stroke/neurology personnel.³⁶ When applied in hospitals lacking a dedicated neurological emergency department or electronic patient records, it has led to an 18-minute reduction in in-hours DNT.³⁷ A key success factor is the close cooperation of ambulance, emergency, and stroke teams. The transferability and impact on DNT of the Helsinki stroke thrombolysis model has been tested in hospitals with 'real-world' resources, showing a striking reduction in median in-hours DNT from 87 to 34 min.³⁸

Another barrier to appropriate stroke treatment is the lack of specialized stroke care in the emergency department, which can be critical in less resourced areas. The use of telemedicine (or telestroke) seeks to overcome this gap by providing centralized stroke care to a network of emergency departments through video consultation and examination of patients.³⁹ Telestroke iv thrombolysis for patients with AIS has been shown to be safe and effective within a 3-hour time window, with similar rates of sICH and no difference in mortality or functional independence at 3 months when compared to iv alteplase provided at established stroke centers.⁴⁰ As shown in other health problems, it is expected that the use of new technologies, such as telemedicine, will provide greater reach and improved stroke treatment in an economical manner.

Antiplatelets

The risk of recurrent vascular events after an AIS or transient ischaemic attack (TIA)

is highest soon after the event and declines over subsequent weeks.⁴¹ Although aspirin has been shown to clearly reduce the risk of early and long-term recurrence,^{42, 43} there has been interest in examining the efficacy and safety of short-term use of dual antiplatelet therapy with aspirin and clopidogrel following minor stroke or high-risk TIA. The Chinese Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial found that combined aspirin and clopidogrel, commenced within 24 hours of onset and continued for 21 days, was superior to aspirin alone in preventing recurrent vascular events within 90 days in 5170 patients with minor AIS or TIA, with no apparent increase in hemorrhagic complications.^{44, 45} Recently, the US-initiated Platelet-Oriented Inhibition in New TIA and minor ischaemic stroke (POINT) trial, assessed the combination of aspirin and clopidogrel versus aspirin alone for 90 days in 4881 patients within 12 hours of minor stroke or TIA. Dual antiplatelet therapy was associated with a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days and, on the advice of the trial's data safety monitoring committee, was stopped early.⁴⁶

A newer antiplatelet agent, ticagrelor, licensed for use in coronary artery disease, has also been assessed against aspirin within 24 hours of minor AIS or TIA in over 13,000 patients.⁴⁷ Compared with aspirin, ticagrelor was not superior at reducing the rate of combined or individual components of the endpoint of stroke, myocardial infarction or death at 90 days and was not approved for secondary stroke prevention. However, in a pre-specified exploratory analysis involving 3081 participants with ipsilateral atherosclerotic stenosis, ticagrelor was superior to aspirin at preventing the primary vascular outcome.⁴⁸

As it appears that short-term dual antiplatelet therapy offers some superiority over monotherapy, a question existed as to whether triple therapy would be even better?

The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial assessed the combination of aspirin, clopidogrel and dipyridamole compared with guideline-recommended therapy (clopidogrel or combination aspirin and dipyridamole) commenced within 48 hours of the onset of AIS or TIA in 3096 patients.⁴⁹ Triple therapy did not reduce stroke recurrence but did cause more, and more severe, bleeding than guideline antiplatelet therapy. In contrast to the previous trials, TARDIS included patients up to 48 hours after symptom onset and with more severe stroke, in whom 11% were thrombolysed.

In summary, recent trials highlight that early treatment with dual antiplatelet therapy in minor AIS or TIA is beneficial, whilst later intensive treatment increases bleeding without any additional benefits derived from reducing recurrent serious vascular events. The optimum treatment duration with dual antiplatelet therapy is unclear and further analyses to assess whether efficacy can be achieved without compromising safety are needed. Furthermore, a better understanding of underlying stroke mechanisms and etiologies may assist future research in refining approaches towards safe and efficacious treatments.

Physiological management

Head positioning

A survey of clinical practice shows considerable variation in the use of head positioning to benefit patients with acute stroke across different health care settings.⁵⁰ In part, this relates to the variable uptake and residual uncertainty over the evidence indicating that the lying flat head position may benefit AIS patients from enhancing cerebral blood flow.⁵¹⁻⁵³ However, a large pragmatic study that used an innovative cluster crossover design to apply lying flat versus elevated head

positioning as a standard of care failed to show any difference in 90-day functional outcomes between the randomized groups.⁵³⁻⁵⁵

Control of elevated blood pressure (BP)

High BP is present in the majority of patients with acute stroke⁵⁶ and predicts increased risks of recurrent AIS,⁵⁷ hematoma expansion in acute ICH,⁵⁸ and death and dependency in both stroke types.^{59, 60} Whether or not lowering elevated BP in acute stroke provides any benefit over the plausible risks of cerebral ischemia has been hotly debated, and despite several large trials being conducted, the evidence remains uncertain albeit with less margin.⁶¹

Two trials have focussed on acute ICH – the main Intensive blood pressure reduction in acute cerebral hemorrhage trial (INTERACT2, n=2794)⁶² and the main Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II, n=1000)⁶³ – and have led to changes in clinical practice. In the former, intensive BP lowering (systolic target <140 mmHg) within 6 hours of symptom onset in INTERACT2 was associated with a positive shift in favorable functional outcome and improved quality of life but was neutral on primary dichotomized analysis of the mRS, compared to conventional recommended BP lowering (systolic target <180 mmHg). Conversely, the latter trial showed that more intensive (achieved systolic 110-139 mmHg) versus ‘standard’ (range 140-179 mmHg, most around 140 mmHg) BP lowering using predominantly a single agent, nicardipine, within 4.5 hours of stroke onset was neutral. Following publication of INTERACT-2, many guidelines were updated in recommending early and intensive BP lowering to a systolic 140mmHg⁶⁴⁻⁶⁶ but publication of ATACH-II has caused some guidelines to caution intensive BP lowering in ICH.^{67, 68} However, it is important to note that INTERACT-2 and ATACH-II have crucial differences in the way in which BP was managed. Firstly, the BP

lowering effect of nicardipine in attenuating hematoma growth (and clinical outcome) may have been negated by its mild antiplatelet action. Second, systolic BP eligibility for inclusion differed between the trials (INTERACT2: 150-220 mmHg; ATACH-II ≥ 180 mmHg) with many ATACH-II participants receiving BP lowering prior to randomization. Third, the more aggressive approach to BP lowering in both arms of ATACH-II resulted in the guideline group having a similar on-treatment BP profile to the intensive group in INTERACT2. As such, a lower systolic target of 110-139 mmHg maybe too low and aggressive than the <140 mmHg within 1 hour used in INTERACT2.⁶¹

Current guidelines recommend lowering elevated BP to $<185/110$ mmHg in the setting of thrombolysis for AIS.⁶⁶⁻⁶⁸ The results of the ENCHANTED-BP trial, which is assessing whether more intensive BP lowering (systolic <140 mmHg) improves outcome in patients undergoing thrombolysis are awaited in 2019.⁶⁹ Several large trials have assessed BP lowering in AIS and found it to be safe and feasible but without influencing overall clinical outcome.⁷⁰ Early treatment (<6 hours) with transdermal glyceryl trinitrate (GTN) was associated with improved clinical outcomes in a subgroup of the Efficacy of Nitric Oxide in Stroke (ENOS) trial,⁷¹ in line with a small, single-center, ambulance-based study assessing the same medication.⁷² The larger (n~1000) Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) is assessing transdermal GTN within 4 hours of symptom onset in a relatively unselected pre-hospital stroke population.⁷³

Oxygen

Hypoxia is common, affecting two thirds of people with acute hemiparetic stroke,⁷⁴ and most often intermittent and undetected, yet associated with higher rates of poor outcomes including neurological deterioration,⁷⁵ death, and death and

institutionalisation.⁷⁶ The Stroke Oxygen Study (SOS) trial assessed the effectiveness of prophylactic low-dose oxygen therapy for three days in 8003 non-hypoxic individuals with acute stroke and found no difference in 90 day death or disability between treatment groups.⁷⁷ However, participants mainly had mild strokes (NIHSS score median 5) and were recruited an average of 20 hours after symptom onset. Thus, whether oxygen therapy is beneficial in the first few hours of acute stroke remains unclear. High-flow oxygen therapy is currently being tested in AIS patients with the rationale that oxygenation of ischemic and surrounding tissues may be protective in those patients with more severe strokes mediated by large vessel occlusion.⁷⁸ In the meantime, oxygen supplementation should be limited to those with reduced saturations (<95%) and without any contraindications.⁶⁶

Glucose

High glucose within the first 24 hours of onset has been associated with poor outcome following both AIS and acute ICH. However, glycemic control has not been shown to improve outcome after AIS.⁷⁹ Therefore, guidelines recommend a medium level range of target blood glucose levels in AIS: 7.8-10 mmol/L¹⁷ versus. 5-15 mmol/L.⁶⁶ The third in the series, INTERACT-3, is currently assessing more early and intensive glucose management as part of a bundle of care, for improving outcome in acute ICH (NCT03209258).

Oedema

In the setting of malignant middle cerebral artery infarction with associated cerebral edema, decompressive hemicraniectomy is a proven life-saving treatment in those aged >60 years – with a similar survival benefit to younger patients – within 48 hours of symptom onset.^{17, 66} Therefore, prompt referral for neurosurgery in suspected cases is required for a shared decision-making approach to ensure agreement over

the potential for surviving with residual disability. Medical therapies for cerebral oedema are commonly used in clinical practice, but have limited proven benefit. Mannitol, an intravascular osmotic agent, reduces cerebral oedema and lowers intracranial pressure but there is no trial evidence of efficacy in either AIS or ICH.⁸⁰ In INTERACT-2, mannitol use was common (two thirds) but safe and without any influence on outcome in a post-hoc analysis.⁸¹ The sulfonylurea receptor 1 inhibitor glibenclamide given initiated within 10 hours and continued for 3 days after large anterior circulation AIS has been shown to improve markers of cerebral oedema, but not surprisingly, no effect on clinical outcome was shown in a small (n=86) phase II trial.⁸² Future trials of medical therapies in cerebral oedema in both AIS and ICH are needed.

Treatment failures

Neuroprotection

Despite numerous trials of pharmacological and non-pharmacological therapies with putative neuroprotective mechanisms, none have proved efficacious in acute stroke, and are therefore not recommended.¹⁷ Whether neuroprotective therapies have a role in patients eligible for recanalization in AIS is unclear, and requires further study.

Early anticoagulation

A Cochrane review found that early anticoagulation within 14 days of AIS was not associated with any net short- or long-term benefit in 24 trials totalling 23,748 patients.⁸³ Anticoagulation increased bleeding risk despite reducing rates of stroke recurrence, deep vein thrombosis and pulmonary embolus. Thus, the benefits of

anticoagulation are offset by increased bleeding and are not recommended routinely early after AIS.¹⁷

Conclusion

In summary, there have been significant improvements in our understanding of, and potential ability to treat, acute stroke. Recent large trial results need to be adopted by national and international guidelines to aid implementation into clinical practice.

There remains a need for further research to improve our understanding of the pathophysiological mechanisms underlying different stroke types so that, in future, treatments can be tailored to the individual stroke patient.

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Table 1: Summary of recent major acute stroke trial results

	Trial	Population	Intervention	Outcome	Comment
<i>Thrombolysis for AIS</i> Broadening the thrombolysis time window Lower dose alteplase (0.6 mg/kg) Tenecteplase (TNK)	WAKE-UP	503 AIS patients with unknown time of onset	MRI DWI/FLAIR mismatch: alteplase vs. placebo	More favorable functional outcome at 90 days in alteplase vs. placebo groups	Alteplase is safe and efficacious when using MRI DWI/FLAIR mismatch eligibility
	ENCHANTED	3310 AIS patients within 4.5 hours of onset	Alteplase 0.6 mg/kg vs. 0.9 mg/kg	Failed to show non-inferiority	Post-hoc analysis: those on antiplatelet agents may benefit from lower dose
	NOR-TEST	1100 AIS patients within 4.5 hours of onset	TNK 0.4 mg/kg vs. alteplase 0.9 mg/kg	No difference in functional independence by day 90	Predominantly mild strokes and a high proportion of mimics recruited
	EXTEND-IA	202 AIS within 4.5hrs with large vessel occlusion eligible for thrombectomy	TNK 0.25 mg/kg vs. alteplase pre-thrombectomy	TNK resulted in increased recanalization rates at angiography and improved 90 day functional outcome	No difference in symptomatic ICH rates
<i>Antiplatelets</i> Dual antiplatelet therapy (DAPT) in minor stroke and TIA Ticagrelor	CHANCE	5170 minor stroke or TIA patients within 24 hours of onset	Clopidogrel + Aspirin vs. aspirin alone for 21 days	DAPT reduced recurrent vascular events without increasing hemorrhage rates at 90 days	Chinese population
	POINT	4881 minor stroke or TIA patients within 12 hours of onset	Clopidogrel + Aspirin vs. aspirin alone for 90 days	DAPT reduced major ischemic events but increased major hemorrhage rates at 90 days	Trial stopped early
	SOCRATES	13000 minor stroke or TIA within 24 hours of onset	Ticagrelor vs. Aspirin	Ticagrelor not superior to aspirin	In a secondary analysis, Ticagrelor was superior to aspirin in those with ipsilateral carotid stenosis

Triple antiplatelets in stroke and TIA	TARDIS	3096 stroke or TIA patients within 48 hours of onset	Aspirin + Dipyridamole + Clopidogrel vs. guideline therapy (Aspirin + Dipyridamole or Clopidogrel only) for 28 days	Triple therapy did not reduce stroke recurrence but did increase bleeding	Trial stopped early due to futility 11% thrombolysed
<i>Head positioning</i>	HEADPOST	11093 acute stroke patients	Lying flat vs. elevated head positioning for 24 hours	No difference in 90-day functional outcome	Mild strokes Position initiated an average of 14 hours after symptom onset
<i>Control of elevated BP</i>	INTERACT2	2794 ICH patients within 6 hours of onset	Intensive (systolic target <140 mmHg) vs. guideline (<180 mmHg)	Intensive: favorable shift in functional outcome, improved quality of life	Mixture of agents used
	ATACH-II	1000 ICH patients within 4.5 hours of onset	Intensive (110-139 mmHg) vs. 'standard' (140-179 mmHg)	No difference in 90-day functional outcome	Predominantly nicardipine
<i>Oxygen</i>	SOS	8003 non-hypoxic acute stroke patients	Prophylactic low-dose oxygen therapy vs. none for 3 days	No difference in 90-day functional outcome	Mild strokes, recruited an average of 20 hours after symptom onset