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CLINICAL REVIEW

Diagnosis and management of transient ischaemic attack and ischaemic stroke in the acute phase

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The care of people with acute ischaemic stroke has improved dramatically in recent years. Both stroke and transient ischaemic attack (TIA) are now recognised as medical emergencies that must be treated with the same urgency as myocardial infarction. Treatments such as thrombolysis are now widely adopted and underpinned by a robust evidence base. Rapid and accurate recognition of cerebral ischaemia, prompt treatment, and referral to specialist services can reduce the risk of further events.

Although cautious optimism has replaced therapeutic nihilism, stroke remains an important cause of death and disability and improvements in stroke services are still sorely needed. There are an estimated 900 000 stroke survivors in England, half of whom are dependent on others for care at an estimated cost of £8bn per year (about €9bn or \$13bn).¹ This burden will increase as population demographics change. We review the diagnosis and acute management of cerebral ischaemia drawing on evidence from original research (particularly multicentre randomised clinical trials), registry data, and systematic review and meta-analysis, and with particular attention to national and international clinical guidelines. Further discussion of the epidemiology and economical aspects of contemporary stroke care are available elsewhere^{1 2w1}; the management of intracerebral haemorrhage was reviewed in a previous *BMJ* article (2009;339:b2586) and is not discussed here. We will review care in hospital, rehabilitation, and secondary prevention of stroke in a second paper.

What is an acute cerebrovascular event?

The World Health Organization defines stroke as the sudden onset of focal neurological signs, of presumed vascular origin, lasting longer than 24 hours or causing death. It can be further classified as ischaemic, due to interruption of blood supply, or haemorrhagic, due to rupture of a cerebral artery. The term cerebrovascular accident is now discouraged, because there is nothing “accidental” about cerebrovascular disease. In recognition of stroke as a medical emergency the term “brain attack” has been used and seems appropriate. Symptoms of a

TIA are similar to those of stroke but last less than 24 hours. Indeed, a truly “transient” ischaemic event, with no cerebral infarction, will usually manifest as a symptom complex lasting only minutes. Longer events are typically associated with infarction and should be considered “stroke”; definitions are likely to change to reflect this.³

Various clinical, radiological, and pathological classification systems have been proposed to further classify stroke. The Oxford clinical classification is often used because it is simple to apply and is of prognostic use.⁴ It describes four subtypes of stroke; total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke (LACS), and posterior circulation stroke (POCS) (box 1).

Once an ischaemic cause is confirmed, the nomenclature can be altered to convey greater specificity for example, a partial anterior circulation infarct (PACI). The underlying cause in most cerebral ischaemic events is cardioembolic or atherosclerotic arterial disease, which can cause either in situ thrombosis or distal embolism. Other causes are much rarer. Common sources of cardiac emboli are atrial fibrillation, mural thrombus, and valvular heart disease and these typically involve the territory of the large intracerebral arteries, particularly the middle cerebral artery. Atherosclerotic disease typically affects the extracranial internal carotid artery but also the vertebral and basilar arteries. Lacunar infarction results from occlusion of deep perforating arteries, which arise from both the anterior and posterior circulation, and supply the white matter of the cerebral hemispheres and brainstem.

Is it an acute cerebrovascular event?

Clinical diagnosis

It is important to rapidly distinguish stroke from one of the numerous conditions that resemble it (“stroke mimics”, box 2). In a UK observational study of 350 consecutive suspected stroke presentations to a teaching hospital at least 30% of referrals resulted in a non-stroke diagnosis.⁵ This distinction is important

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Summary points

Education of patients and their relatives to recognise signs of stroke and transient ischaemic attack (TIA) is crucial to promote early presentation to medical services

TIA and stroke are medical emergencies; refer for urgent specialist opinion

The risk of further cerebrovascular event following TIA is substantial, immediate, quantifiable, and preventable; do not be reassured by resolution of symptoms

Effective treatments for selected stroke patients include: aspirin within first 48 hours; intravenous thrombolysis; surgical decompression of cerebral oedema

Admission to a dedicated stroke unit offers mortality and functional benefits to all patients with stroke

Deranged physiology is common in acute stroke and associated with poor prognosis

Sources and selection criteria

The review is based on the authors' clinical and research experience and informed by a search of published literature. Electronic databases (Medline and Embase) were searched from inception to December 2010 inclusive, using truncated keywords: "transient ischaemic attack"; "thrombolytic"; "stroke or cerebrovascular". In addition, key reference works; national and international guidelines; and key journals were searched for relevant papers. Particular attention was given to large randomised controlled trials, systematic reviews, and meta-analyses. The intention was not to offer a comprehensive systematic review, rather to give a narrative overview and critique of published literature.

Box 1: Oxford system of stroke classification⁴

Total anterior circulation stroke (TACS)

All three of:

- Contralateral motor or sensory deficit
- Homonymous hemianopia
- Higher cortical dysfunction*

Partial anterior circulation stroke (PACS)

Two of:

- Contralateral motor or sensory deficit
- Homonymous hemianopia
- Higher cortical dysfunction

Posterior circulation stroke (POCS)

Any one of:

- Isolated homonymous hemianopia
- Brain stem signs
- Cerebellar ataxia

Lacunar stroke (LACS)

Any one of:

- Pure motor deficit
- Pure sensory deficit
- Sensorimotor deficit

*Higher cortical dysfunction includes dysphasia/visiospatial disturbance.

to allow evidence based treatment to be started early and to refer alternative conditions to the appropriate team. It may be useful to consider the definition of stroke "sudden onset, focal neurology, of presumed vascular cause". Thus, for patients with gradual onset of symptoms, who have no focal symptoms (such as those who have lost consciousness), or who give a history that suggests a non-vascular basis for the episode (seizure, migraine), stroke can probably be excluded, albeit with a few exceptions.

Formal assessment tools are available to facilitate diagnosis and are based on these simple principles. Box 3 outlines two tools commonly used in routine practice. The Face Arm Speech Test (FAST) is suitable for use by the general public and has a

positive predictive value of 78% (95% confidence interval 72 to 84) for stroke⁶ while the ROSIER scale, designed for emergency department use, functions similarly well and includes a screen for common stroke mimics (but can still be administered in less than five minutes⁷). Similar tools are available for the diagnosis of TIA but have yet to be widely adopted.⁸

Imaging

Brain imaging is indicated to help confirm the diagnosis, identify the causes, and help initiation of evidence based treatment. The usual imaging modality is non-contrast computed tomography (CT) and this remains useful particularly in excluding

Box 2 Frequency of common conditions that mimic stroke⁵

Seizure	21%
Sepsis	13%
Toxic/metabolic	11%
Space occupying lesion	9%
Syncope	9%
Delirium	7%
Vestibular	7%
Mononeuropathy	6%
Functional	6%
Dementia	4%
Migraine	3%
Spinal cord lesion	3%
Other	3%

Box 3: Clinometric properties of tools to aid recognition and diagnosis of a cerebrovascular event³⁴*Recognition of Stroke in Emergency Room (ROSIER) scale*

- Loss of consciousness or syncope? Yes: -1 point
- Seizure activity? Yes: -1 point
- New acute onset:
 - Asymmetric facial weakness? Yes: +1 point
 - Asymmetric arm weakness? Yes: +1 point
 - Asymmetric leg weakness? Yes: +1 point
 - Speech disturbance? Yes: +1 point
 - Visual field defect? Yes: +1 point
- Total -2 to +5
- Stroke likely if score >0 in the absence of hypoglycaemia
- Sensitivity for stroke diagnosis 82%
- Specificity for stroke diagnosis 42%

The Fast Arm Speech Test (FAST) scale

- Facial asymmetry? Yes: +1 point
- Arm (or leg) weakness? Yes: +1 point
- Speech disturbance? Yes: +1 point
- Total 0 to 3
- Suspect stroke if score >0
- Sensitivity for stroke diagnosis 82%
- Specificity for stroke diagnosis 37%

For comparison, diagnosis of stroke by clinical staff's first impression had sensitivity 77% and specificity 58%.

intracerebral haemorrhage and important mimics such as brain metastasis. However, sensitivity for detection of ischaemia is low in the very early stages of stroke and differentiating ischaemic from haemorrhagic strokes can be difficult on CT after a period of several days. More advanced CT imaging techniques such as CT perfusion and angiography are available and are likely to be used in the future to help better select patients for some of the acute treatments discussed below. At present, however, magnetic resonance imaging (MRI) is the modality of choice. In a study of 217 sequential acute stroke patients who underwent imaging using both non-contrast CT and MRI, CT demonstrated sensitivity of 26% (95% CI 20% to 32%) compared with 83% (78% to 88%) for MRI in the detection of early ischaemia. Further, concerns that MRI may

not detect intracerebral haemorrhage or proves impractical for "emergency" imaging were not supported.^{w2}

Imaging of the extracranial carotid arteries is required for patients with anterior circulation stroke. Carotid endarterectomy is of proved benefit for those with at least moderate carotid stenosis ipsilateral to an ischaemic stroke in the carotid artery (?).^{9 10} This procedure should be performed early; further details on patient selection will be discussed in a future review. Carotid duplex ultrasonography is well tolerated and non-invasive but substantial interobserver variability limits its accuracy.^{w3} Most surgical teams will require corroborative imaging, often with CT or MR angiography, before surgical intervention and many specialist centres use these as modalities of choice.

Other investigations

Electrocardiogram abnormalities may suggest a cardiac origin for thrombus. Where brain imaging and clinical presentation fit with embolic stroke, or where clinical findings suggest cardiac disease, cardiac imaging and more detailed telemetry are indicated. Routine screening for vasculitides or thrombophilia is not justified.

How should I approach suspected TIA?

Remember that all patients who have ongoing symptoms, however mild, are considered to have had stroke and urgent transfer to hospital should be arranged. Where symptoms have resolved before presentation urgent hospital transfer may not be required but rapid assessment and treatment if TIA has occurred is mandatory.

A substantial risk of stroke exists in the early period after TIA. The magnitude of risk is greater and the time to event shorter than previously recognised. A recent systematic review reported an overall 7 day stroke risk of 5.2% after TIA.¹¹

Simple stratification scores can be used to better estimate a patient's individual risk. The most commonly used (and best validated) tool is the ABCD² score¹² (table 1). ABCD² estimates risk of recurrence at two days from 1% for patients with "low risk" to 8.1% for those patients with "high risk". ABCD² scoring is recommended in UK national guidelines and many centres offer same day assessment of patients at highest risk of stroke. ABCD² may also be useful in diagnosis. Single centre registry data (3646 patients) showed that few referrals with an ABCD² score of 0 were subsequently found to have a cerebrovascular diagnosis.¹³

The fact that the increased risk occurs so soon after TIA tells us that same day assessment should be the aim for patients with TIA, although the practicalities of referral and investigation of stroke will vary according to the local facilities available. UK guidelines (National Institute for Health and Clinical Excellence and Scottish Intercollegiate Guidelines Network)^{14 15} suggest starting all patients on antiplatelet treatment (aspirin 300 mg) and referring them for urgent specialist assessment. NICE recommends that patients with ABCD² scores greater than 4 be assessed within 24 hours. Delivery of these targets on a nationwide and fully inclusive basis will require substantial investment in services.

The landmark EXPRESS study compared stroke events in Oxford, UK, before and after a move from their standard to an immediate access, comprehensive, TIA assessment service.¹⁶ An 80% reduction in recurrent stroke at 90 days was demonstrated with no increase in adverse events (fig 1). Although we extrapolate these results from a single centre with caution, it is worth noting that if outcomes were replicated across all UK stroke centres 10 000 stroke events could be prevented annually.

How will specialist services manage the patient with suspected stroke or TIA?

The aim of specialist stroke assessment is confirmation of stroke diagnosis, identification of the causes, and timely initiation of evidence based treatment.

Brain imaging should be performed with minimal delay to distinguish ischaemic from haemorrhagic stroke. Even when the patient is not eligible for thrombolysis, imaging within 24 hours (although ideally as soon as possible) is the most cost effective strategy. The need for imaging in transient ischaemic

attack is more contentious. In our unit we routinely scan anyone with symptoms lasting more than one hour before starting secondary prevention.

Patients with TIA

Treatments are aimed at preventing a further event, similar to the secondary treatments given to patients following acute stroke. In those with confirmed atrial fibrillation or mural thrombus anticoagulants are warranted. Antiplatelet or anticoagulant drugs may be considered in all patients, as may lipid lowering therapy, antihypertensive therapy, carotid surgery, treatment of diabetes, and advice about diet, lifestyle, and smoking cessation. A recent focus of research has been the potential benefits of early antiplatelets, statins, and antihypertensives. The marked reduction in stroke rate seen in EXPRESS may have been caused by immediate delivery of these therapies (patients were given medication at clinic review). We await results of ongoing trials, although emergent stroke data suggest that "acute" prescription of antihypertensives may have no clinical benefit.¹⁷

Patients with acute ischaemic stroke

Within the first hours to days, proved treatments for acute ischaemic stroke include admission to a dedicated stroke unit; administration of intravenous tissue plasminogen activator (rt-PA); antiplatelet agents; and surgical decompression of massive cerebral oedema (table 2).

Aspirin

A systematic review of antiplatelets after ischaemic stroke (n=43 041) demonstrated that for every 1000 patients treated acutely with aspirin (160-300 mg) 13 fewer deaths occurred by the end of follow-up, which is a modest but important effect at a population level.¹⁸ UK guidelines recommend that patients with acute ischaemic stroke are prescribed aspirin 300 mg daily for two weeks, followed by a long term secondary preventative antiplatelet strategy.^{14 15} Aspirin should be withheld for 24 hours after thrombolysis. Where a patient's swallowing is impaired to a degree that precludes oral administration, rectal preparations may be used. In patients unable to take aspirin, alternatives such as clopidogrel may be used. There is no evidence to support the use of early anticoagulation as a treatment for acute ischaemic stroke.¹⁹

Thrombolysis

Intravenous tissue plasminogen activator (rt-PA) alteplase is beneficial if given within 4.5 hours of acute ischaemic stroke in selected patients. In Europe, rt-PA is licensed for the treatment of acute ischaemic stroke provided it is administered within three hours of symptom onset, but many centres will administer it up to 4.5 hours based on evidence.²⁰ The benefits of rt-PA are in reducing longer term disability and not in improved survival or in immediate improvement in neurological impairment (although anecdotally this has been observed). Two recent pooled meta-analyses of the major thrombolysis trials (n=2775²¹ and n=3670²²) have demonstrated clear benefit of thrombolysis with significantly better outcomes seen with early treatment (table 3) In the larger analysis the odds ratios of a favourable outcome with rt-PA were 2.55 (95% CI 1.44 to 4.52) for 0-90 minutes, 1.64 (1.12 to 2.4) for 91-180 minutes, 1.34 (1.06 to 1.68) for 181-270 minutes, and 1.22 (0.92 to 1.61) for 271-360 minutes in favour of the rt-PA group.²² Trials have reported that mortality rates at three months are equivalent to placebo.

The limited time window for delivery of thrombolytic therapy is a major barrier to its delivery. The risk:benefit ratio beyond 4.5 hours has not been fully established and ongoing clinical trials aim to provide further evidence. Patients older than 80 years were excluded from most of the clinical trials. Non-randomised observational data suggest that their risk:benefit ratio is similar to that of other patients²³ (fig 2) and many centres will give thrombolysis to selected older patients. However, data from randomised studies are lacking and we await results of the third international stroke trial.^{w4}

Many clinicians fear the potential for iatrogenic intracerebral haemorrhage after thrombolysis and patient selection guidance is designed to minimise this risk. A list of contraindications to thrombolysis is shown in table 4. For many of these, as we have gained more experience with thrombolysis, conditions that were previously “absolute” contraindications to rt-PA are now deemed “relative” contraindications. Because this is an evolving landscape, we advise referral of all hyperacute suspected strokes to a specialist team unless there is substantial pre-morbid disability. As the benefits of rt-PA are in reducing disability, this approach is not routinely used in patients who are already functionally impaired.

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) registry of clinical practice was conducted in accordance with the terms of the restricted European licence for alteplase use and has helped to assuage some concerns about the potential for iatrogenic intracerebral haemorrhage.²⁴ Across 285 European centres (and 6483 patients), rates of “good” outcome (independence) were comparable or improved compared to those seen in clinical trials and likewise for rates of haemorrhagic transformation. Importantly, outcomes were similar regardless of levels of experience of the centre.

Provision of a comprehensive thrombolysis service demands substantial economic investment and infrastructural change. Despite endorsement by guideline and national targets, geographical disparity in availability and use of rt-PA are apparent within the UK and internationally. In an era of increasing financial scrutiny it is reassuring that the (limited) economic data on use of rt-PA suggest overall cost benefit, driven by prevention of longer term disability.²⁵

Surgical intervention

“Malignant” swelling of an infarcted cerebral hemisphere can arise in the days following occlusion of the carotid or middle cerebral artery, and although uncommon it is associated with a very high mortality.²⁶ However, surgical intervention saves lives and reduces disability in selected patients younger than 60. In this group, meta-analysis of three randomised controlled trials showed superiority of surgical craniotomy compared to standard medical care with a number needed to treat of two to reduce disability.²⁶ Reducing mortality at the expense of substantial disability remains a possibility and improved data on selecting patients for surgery are urgently needed.

Physiological monitoring and other treatments

Failure of homeostatic mechanisms during the acute phase of stroke is common and supportive care delivered through a specialist stroke unit is crucial. However, evidence to support taking measures to “correct” deranged physiology is lacking; even simple interventions such as supplementary hydration and oxygen therapy are of unproved benefit and are currently being investigated. Regular observation of level of consciousness is useful as change in Glasgow coma scale can herald potentially

treatable complications such as development of cerebral oedema or haemorrhage.

The role of blood pressure control in the immediate phase after stroke is unclear. Arterial hypertension is found in 80% of patients following acute stroke and is associated with a poor outcome.²⁷ The ACCESS study suggested that early use of angiotensin receptor blockade was safe in acute ischaemic stroke;²⁸ however, recent publication of a larger phase III efficacy trial (SCAST) has demonstrated no benefit and a suggestion of increased harm.²⁹ Routine lowering of blood pressure is not recommended in UK or international guidelines. Treatment may be appropriate in specific circumstances such as hypertensive encephalopathy or aortic dissection; however, guidance on agent to use and target blood pressure varies across guidelines.

A meta-analysis of observational studies showed that the acute phase of stroke carries a high risk of infection and pyrexia is associated with a poor outcome, possibly because of adverse effects on free radical production or intracerebral metabolism.³⁰ Limited data support the use of anti-pyretic medication and cooling³¹ but no adequately powered randomised trial has investigated their benefits. Standard treatment of pyrexia is recommended and should prompt an assessment for a possible underlying source of sepsis.

Raised blood glucose is also common in the acute phase after ischaemic stroke, often in the absence of pre-existing diabetes, which may represent a stress response. Despite its association with increased mortality and poor functional outcome,³² the largest randomised controlled trial of blood glucose reduction in stroke reported no benefit of insulin infusion compared with placebo;³³ although some have argued that the study was underpowered to detect a true effect. Lowering of abnormally high blood glucose (>11 mmol/L) with titrated insulin remains common practice to maintain normoglycaemia. Aggressive treatment of hyperglycaemia in critically ill patients was found to increase mortality in the NICE SUGAR study.^{w5} Although this study was not specific to stroke patients, we must be cautious in the use of intravenous insulin in any severely unwell group of patients.

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Provenance and peer review: Commissioned, externally peer reviewed.

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Additional educational resources*Resources for healthcare professionals*

Stroke Association Professional Training (www.stroke.org.uk/professionals/training_and_development/index.html)—A selection of training and education programmes offered by the stroke association, suitable for all healthcare professionals

European Stroke Organisation (www.eso-stroke.org)—Comprehensive access to European stroke guidelines and educational resources for health professionals and lay people

UK Stroke Research Network (www.uksrn.ac.uk)—Provides an infrastructure to facilitate stroke research and improve communication between academics, stroke clinicians, stroke service users, and research funders

Stroke Training and Awareness Resources (STARS) project (www.stroketraining.org)—Commissioned by the Scottish Government to provide an e-learning resource for all healthcare professionals and social care staff working with patients affected by stroke

Resources for patients

The Stroke Association (www.stroke.org.uk)—Produces a number of publications to help educate and inform and increase awareness of stroke, including patient leaflets, and *Stroke News* (a quarterly magazine)

Act FAST campaign (www.nhs.uk/actfast/Pages/stroke.aspx)—Public awareness campaign to improve community recognition of stroke symptoms and encourage those affected to seek urgent medical help

Connect (www.ukconnect.org/index.aspx)—communication disability charity for patients and carers affected by aphasia

Carers UK (www.carersuk.org)—charity providing support for home carers

Tips for non-specialists

- Sudden onset focal neurological symptoms represent a medical emergency and should be treated as such
- Eligibility for acute treatments is constantly evolving, discuss any patient with possible acute stroke with the local stroke team
- A sudden change in consciousness of an acute stroke patient may indicate a treatable complication and warrants urgent investigation.

Questions for future research

What factors influence a patient's decision to seek medical help following stroke or TIA, and how can we use this to improve rates of early presentation?

Should secondary prevention be initiated by the referring clinician before assessment in TIA clinic?

Is routine screening for cardioembolic disease cost effective?

How can we improve access to thrombolysis in remote or rural areas?

How safe and effective is thrombolysis in elderly patients or those with a previous stroke?

Is intervention to correct deranged physiology of clinical benefit in acute stroke patients?

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Tables

Table 1 | ABCD² score and risk of stroke¹²

Characteristic	ABCD ² score	Risk of stroke	
		2 days	7 days
Age ≥60 years	1 point	–	–
Blood pressure ≥140/90 mm Hg	1 point	–	–
Clinical features			
Focal weakness	2 points	–	–
Speech disturbance without weakness	1 point	–	–
Duration			
≥60 minutes	2 points	–	–
1-59 minutes	1 point	–	–
Diabetes	1 point	–	–
Total ABCD² score			
Low risk	<4 points	1%	1.2%
Moderate risk	4-5 points	4.1%	5.9%
High risk	>5 points	8.1%	11.7%

Table 2| Effective treatments for stroke

	Aspirin	Stroke unit	rt-PA	Surgery
Number needed to treat	100	20	10	2
Proportion eligible	70-80%	100%	10%*	5%†

*Based on UK data; some European centres have achieved far higher rates of thrombolysis within licence.

†Based on European data; values vary depending on demographics (particularly age) of population served.

Table 3| Benefit of rt-PA treatment at 90 days²²

Time between event and treatment	Odds ratio in favour of favourable outcome (95% CI)	Estimated number needed to treat for favourable outcome
0-90 minutes	2.55 (1.44 to 4.52)	4.5
91-180 minutes	1.64 (1.12 to 2.40)	9.0
181-270 minutes	1.34 (1.06 to 1.68)	14.1
271-360 minutes	1.22 (0.92 to 1.61)	21.4

Favourable outcome defined as modified Rankin score of 0-1 at 90 days.

Table 4| Contraindications to use of rt-PA in acute ischaemic stroke

General contraindications to any use of rt-PA	Specific contraindications to use in ischaemic stroke
Severe bleeding within past six months	Evidence of intracranial haemorrhage
Known bleeding diathesis	Onset of symptoms >4.5 hours
Oral anticoagulant use (INR >1.4)	Unclear time of onset
History of intracranial haemorrhage	Age <18 or >80 years
Recent (<10 days) cardiopulmonary resuscitation	Mild stroke (NIHSS <5) or rapid improvement
Bacterial endocarditis or pericarditis	Severe stroke (NIHSS >25 or imaging)
Acute pancreatitis	Seizure at onset of stroke
Recent (<3 months) peptic ulcer disease	Symptoms indicating subarachnoid haemorrhage
Neoplasm with bleeding risk	Platelet count < 100 ×10 ⁶ /L
Recent puncture of non-compressible vessel	Heparin within last 48 hours with raised PTT
Major surgery or trauma (<3 months)	Previous stroke within past three months
Severe liver disease	Previous stroke and concomitant diabetes
Recent obstetric delivery	Systolic BP >185 mm Hg or diastolic BP >110 mm Hg

INR=international normalised ratio, NIHSS=National Institute of Health Stroke Scale, PTT: prothrombin time, BP=blood pressure.

Figures

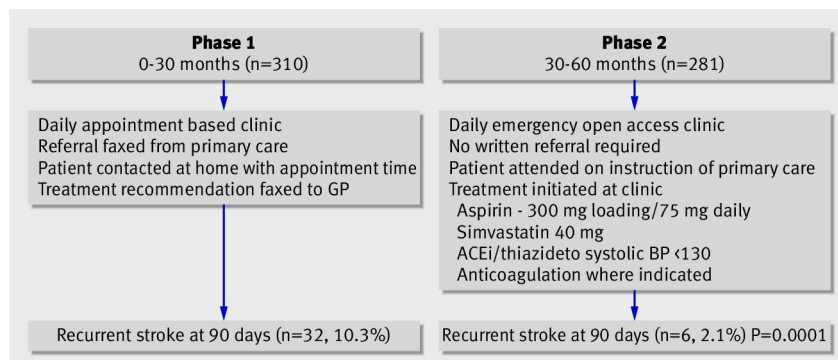
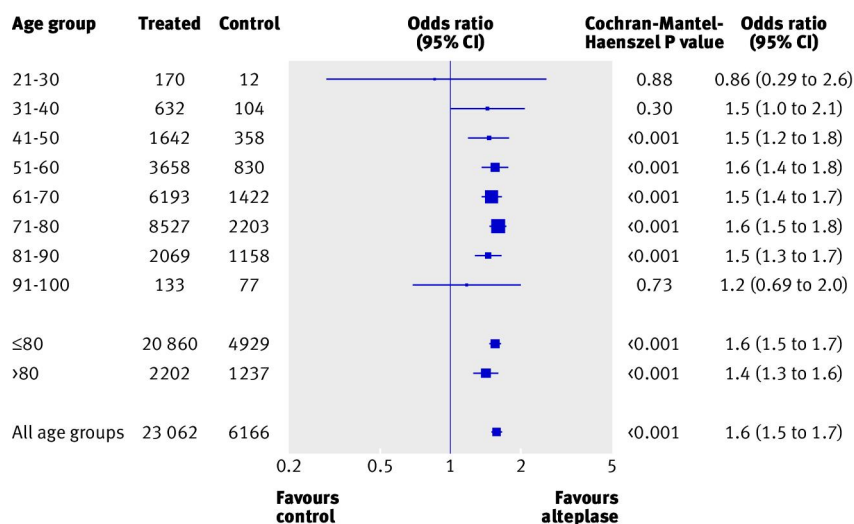


Fig1 EXPRESS study protocol¹⁶



Shift towards better outcomes on modified Rankin scale at three months adjusted for age and baseline severity (defined by National Institutes of Stroke scale)²³