Outcomes after acute Intracerebral Haemorrhage

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Abstract

Primary Intracerebral haemorrhage is a severe form of stroke with poor prognosis attributed to haematoma characteristics. High blood pressure is present during the acute phase of intracerebral haemorrhage and associated with poor outcome in part through expansion of haematoma.

Data from the 'Efficacy of Nitric Oxide in Stroke trial' (ENOS) was used to analyse the performance characteristics of qualitative and quantitative descriptors of intracerebral haematoma. The results showed that formal measurement of haemorrhage characteristics and visual estimates are reproducible. Intracerebral haemorrhage volumes measured using the modified ABC/2 formula were significantly lower compared to standard ABC/2 and computer assisted semi-automatic segmentation.

In 629 patients with intracerebral haemorrhage presenting within 48 hours, the effect of blood pressure lowering with transdermal glyceryl trinitrate was assessed. Glyceryl trinitrate lowered blood pressure, was safe but did not improve functional outcome. In a small group of patients treated within 6 hours, glyceryl trinitrate improved functional outcome.

Analysis of 246 patients with acute intracerebral haemorrhage from ENOS was undertaken to assess whether there were any differences in functional outcome among those who continued prior antihypertensive drugs during the immediate stroke period compared to those assigned to stop temporarily for 7 days. The results were neutral indicating that there was no benefit in those who continued treatment.

Data of 1,011 patients with intracerebral haemorrhage in hyperacute trials from the VISTA collaboration showed differences in baseline characteristics and functional outcomes among patients from various ethnic backgrounds.

A systematic review was updated to assess the effect of 26 randomised controlled trials that aimed to alter blood pressure within one week of acute stroke. The results showed that blood pressure reduction did not improve functional outcome irrespective of stroke type. When examined by time, treatment within 6 hours appeared to benefit but the number of patients were small and more studies are needed. The analysis also showed that continuing prestroke antihypertensive drugs in the immediate period after stroke did not benefit and might be harmful.

In summary, this thesis provides new information on parameters used to estimate intracerebral haematoma, relationship between management of blood pressure and outcomes after haemorrhagic stroke. The work supports testing of whether very early blood pressure lowering after ictus is beneficial as is being undertaken in ongoing randomised controlled trials. Adjusting for ethnic differences may further identify patients in whom treatment may confer measurable advantage.

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List of abbreviations

3-D	Three dimensional
ACA	anterior cerebral artery
ACE-I	angiotensin converting enzyme inhibitor
ADP	adenosine diphosphate
AF	Atrial fibrillation
ARA	angiotensin receptor antagonist
ARR	absolute risk reduction
BI	Barthel Index
BP	blood pressure
CA	cerebral autoregulation
CBF	cerebral blood flow
CCB	calcium channel blocker
CEA	carotid endarterectomy
CI	confidence interval
CPP	cerebral perfusion pressure
CT	computed tomography
CTA	computed tomography angiography
CVP	central venous pressure
DBP	diastolic blood pressure
DICOM	Digital Imaging and Communications in Medicine
DVT	deep vein thrombosis
ENOS	Efficacy of Nitric Oxide in Stroke trial
EQ-5D	European quality of Life-5 Dimensions questionnaire
EQ-VAS	European quality of life-visual analogue scale
FFP	fresh frozen plasma
GCS	Glasgow Coma Scale
GTN	glyceryl trinitrate
HR	heart rate
HE	haematoma expansion
HUS	health utility status
ICC	intraclass correlation coefficient
INR	International Normalised Ratio
ICH	intracerebral haemorrhage
ICP	intracranial pressure
IVH	intraventricular haemorrhage
LACS	lacunar syndrome

LDL	low density lipoprotein
mRS	modified Rankin scale
MAP	mean arterial pressure
MCA	middle cerebral artery
MD	mean difference
MIS	minimally invasive surgery
MMSE	Mini mental state examination
MRI	magnetic resonance imaging
NO	nitric oxide
NIHSS	National Institutes of Health Stroke Scale
OCSP	Oxfordshire Community Stroke Project
OEF	oxygen extraction fraction
OR	odds ratio
PACS	Partial Anterior Circulation Syndrome
PCA	posterior cerebral artery
PCC	prothrombin cell concentrate
PET	positron emission tomography
POCS	Posterior circulation stroke syndrome
r-FVIIa	recombinant Factor VIIa
ROI	Region of Interest
RCT	Randomised controlled trial
RR	relative risk
r-tPA	recombinant tissue plasminogen activator
SAE	serious adverse event
SAS	semi-automatic segmentation
SBP	systolic blood pressure
SD	standard deviation
SPSS	Statistical software for social science
SSS	Scandinavian Stroke Scale
TACS	Total anterior circulation stroke syndrome
TICS	Telephone interview for cognitive status
TIA	Transient Ischaemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UK	United Kingdom
ZDS	Zung Depression score

Chapter 1 - Background

1.1 Introduction

'Stroke' as a condition includes a range of clinical and etiological syndromes. It is defined as a ' rapidly developed clinical sign of focal or global disturbance in cerebral function, lasting more than 24 hours or until death with no apparent cause other than of vascular origin'.[1] This includes cerebral infarction, intracerebral and subarachnoid haemorrhage but excludes transient ischaemic attack, subdural and extradural haemorrhage and infarction or haemorrhage due to infection or malignancy. If the symptoms resolve in less than 24 hours, for epidemiological purposes the syndrome is defined as a transient ischaemic attack (TIA). Most TIA's resolve within 60 minutes.[2] The cut-off point of 24 hours is useful and valid when there is no permanent damage to brain tissue or retina.[3]

Stroke is a worldwide condition and is the third most cause of death after heart disease and cancer.[4] In the UK, stroke accounts for 11% of all deaths.[5] Nearly 150,000 patients are affected in the UK every year. Stroke costs the UK around £8.2 billion a year and the estimated cost for treating each patient is around £30,000 in the first five years.[6] Survivors

can be severely disabled and heavily reliant for self-care. [5] In a population based study, two-fifth of stroke survivors after five years were more disabled than they were few months after stroke.[7]

1.2 Incidence and prevalence

Incidence is defined as the number of first strokes occurring in a population per unit time. The incidence of stroke and TIA combined exceeds incidence of acute coronary syndrome.[8] Stroke can occur at any age. In developed countries, one in every 20 adults (>14 years) is affected by stroke.[9]

The risk of stroke increases with age with most patients aged above 65 years. With increase in each year, the risk of fatal and non-fatal stroke increases by around 10% in men and women.[10] This is due to effects of ageing on the vascular system. Men are at a higher risk of compared to women. One in every four men and one in five women aged 45 can expect to have a stroke if they lived upto their eighties.[11]

The risk of dying from stroke is higher in women.[12] This is due to the higher age of onset of stroke in women and longevity.[13] The incidence and prevalence vary according to geography

and ethnicity.[14, 15] A higher incidence of stroke in blacks is probably due to poor control of hypertension and small vessel disease.[15-17]

Prevalence of stroke is the number of all individuals affected by stroke at a particular time and can be derived from stroke registers.[18] With developments in stroke prevention such as antiplatelets, antihypertensive agents and lipid lowering agents, the number of survivors has increased in the last few years. One year after a stroke, 30% of patients will have died, 30% are independent and 40% will be dependent for self-care.[19] One in six people who survive a first-stroke will have a recurrent stroke over the next five years, so strategies for secondary prevention should be initiated soon after the index event.[20]

1.3 Stroke subtypes and classification

Eighty-five percent of acute stroke is ischaemic, ten-fifteen percent is haemorrhagic and five percent includes sub-arachnoid haemorrhage. In blacks, the incidence of primary intracerebral haemorrhage (ICH) is higher.[16]

The only reliable method used to differentiate between ischaemic and haemorrhagic stroke is by scanning the brain using computerised tomography (CT) or magnetic resonance imaging (MRI). Further subclassification is useful and has implications with regards to prevent recurrent stroke. In addition, very early identification of different subtypes is useful when therapy such as thrombolysis in large vessel occlusion is guided by the classification.

1.3.1 Oxford Community Stroke Project (OCSP) Classification

The Oxford Community Stroke Project (OCSP) classification defines four subtypes according to clinical presentation.[21, 22] It is based on characteristic pattern of symptoms attributed to a vascular territory and has prognostic significance. This approach has the advantage that it is performed by the bedside and classifies patients even when brain imaging is normal.[23]

1.3.1.1 Total Anterior Circulation Syndrome (TACS)

This is defined by a combination of higher cerebral dysfunction, homonymous visual field defect and ipsilateral motor and or sensory deficit. These are consistent with middle

cerebral or anterior cerebral artery (ACA) infarction or haematoma in the lobes. Prognosis is poor with 39% dead in a month and 60% at one year.[21]

1.3.1.2 Partial Anterior Circulation Syndrome (PACS)

A PACS is caused by occlusion of one of the branches of the middle cerebral or anterior cerebral artery or a lobar haemorrhage.[22]

PACS consists of one of the following:

- 2 out 3 of TACS syndrome
- Higher cerebral dysfunction
- Monoparesis

Risk of recurrence is very high but prognosis is better than TACS; 15% are dead and 30% independent at one year.[21]

1.3.1.3 Lacunar stroke (LACS)

LACS is usually due to an infarct in upto 90% of cases.[24, 25]

Each of the five classical lacunar syndromes has a distinct sympton complex. Symptoms may be suddenly, progressively or in a fluctuant manner. If severe hemiplegia alternates repeatedly with normal function, the phenomenon is called

'capsular warning syndrome'.[25] Occasionally, cortical infarction or haemorrhage can mimic lacunar infarcts, but true cortical signs (dysphasia or inattention) are always absent.

- Pure motor stroke or hemiparesis; most common lacunar syndrome; 33-50% of cases (affecting the face, arm or leg on one side). The lesion usually occurs in the posterior limb of the internal capsule, pons and corona radiata.
- Ataxic hemiparesis; second most frequent lacunar syndrome; usually affects the leg more than arm. Hence it is also known as homolateral ataxia or crural paresis. The lesion is in one of the posterior limb of the internal capsule, pons, corona radiata, red nucleus and lentiform nucleus.[25]
- Dysarthria/clumsy hand; the main symptons are dysarthria and weakness of the hand in particular when writing. The lesion may occur in the pons, anterior limb or genu of internal capsule, corona radiata, basal ganglia, thalamus or cerebral peduncle.
- Pure sensory stroke marked by persistent or transient numbness, tingling, pain, burning or unpleasant sensation on one side of the body. The location of the

lesion may be in the contralateral thalamus, internal capsule, corona radiata or midbrain.

- Mixed sensorimotor stroke; this syndrome involves hemiparesis or hemiplegia with ipsilateral sensory loss. The lesion occurs is the thalamus and adjacent posterior internal capsule or lateral pons.

Thirty percent of patients affected by lacunar stroke are dependent at one year.[21]

1.3.1.4 Posterior circulation stroke (POCS)

This is defined by any of

- Ipsilateral cranial nerve palsy with contralateral motor deficit
- Bilateral sensory or motor deficit
- Disorder of conjugate eye movement
- Cerebellar dysfunction
- Isolated hemianopia[22]

The lesion may be an infarct or haemorrhage including the occipital lobe, brain stem or thalamus. Risk of stroke recurrence is high with 19% dead at one year.[21]

Following brain imaging, patients are further classified as infarction (TACI, PACI, LACI and POCI) or haemorrhage (TACH, PACH, LACH and POCH).

1.3.2 Trial of Org 10172 (TOAST) classification

The Trial of Org 10172 (TOAST) system is used to categorise ischaemic stroke based on clinical features and results of investigations.[26] This is as follows:

1.3.2.1 Large-artery atherosclerosis

Large-artery atherosclerosis accounts for 50% of ischemic stroke. Atherosclerosis is a chronic inflammatory disease of large and medium size arteries. Atherosclerotic plaques consist of cholesterol rich necrotic core surrounded by smooth muscle cells and fibrous tissue. Atherosclerosis can cause problems through two mechanisms. The atheromatous plaque may rupture, exposing its centre to platelets and the coagulation pathway is activated. This may cause arterial blockage at the site of thrombus or cause emboli to travel distally. Secondly, the large plaque may cause narrowing of the artery, which may result in ischaemia of distal tissue. This causes conditions such as stroke, myocardial infarction or an ischaemic limb.

Advancing age, male sex, lipid abnormalities, cigarette smoking, hypertension, diabetes mellitus, heavy alcohol consumption and obesity increase the risk of atherosclerosis. Other factors that are also associated include increased serum homocysteine levels, hormone replacement therapy, haemostatic factors and family history.

1.3.2.2 Cardio-embolism

Cardio-embolism accounts for about 30% of ischaemic stroke. This includes patients when arterial occlusions occur either due to vegetation, fibrin debris or platelet aggregates that originate from the heart. Cardiac arrhythmia, in particular atrial fibrillation (AF) is the commonest cause of cardio-embolism. In patients with non-valvular AF, the absolute risk of stroke increases is 5% per year.[27, 28] Also, thrombo-embolism can occur in the presence of damaged myocardium, after myocardial infarction. Less common causes of stroke in this category include patients with prosthetic heart valves, mitral regurgitation, mitral valve prolapse and tumours in the heart.

1.3.2.3 Small vessel disease

Small vessel disease accounts for 20% of all stroke. The precise mechanism in small vessel disease that causes stroke is not clear.[24] It is thought that stroke is due to microatheroma and thrombosis of a single, deep perforating vessel in the internal capsule, basal ganglia or thalamus.[24] The risk factors for lacunar stroke may be different from large vessel stroke with diabetes and hypertension most common; cigarette smoking, excess alcohol consumption are less common.[29]

1.3.2.4 Stroke of other determined etiology

The majority of ischaemic strokes can be classified in one of the previous categories. Rarely, stroke can occur in patients who are young and have no obvious risk factors. Amongst these are causes including vasculopathies, inherited errors of metabolism and genetic disorders.

1.3.2.5 Stroke of undetermined etiology

In some patients, no clear cause for stroke can be determined despite extensive diagnostic evaluation. It is thought that stroke occurs from an unknown cardiac source, paradoxical

embolism or non-occlusive atherosclerotic plaque in the aortic arch, cervical or vertebral arteries.[30] These strokes are classified as stroke of undetermined etiology or cryptogenic stroke.

1.4 Diagnosis

Stroke is a clinical diagnosis and recognition in the acute stage is important for the following reasons:

- It enables to exclude 'stroke mimics' such as migraine, epilepsy, anxiety, hypoglycaemia, posterior reversible encephalopathy syndrome (PRES) and rare presentations such as cognitive behavioural disorders.
- Next, it helps to plan acute interventions such as thrombolysis or surgical evacuation of haematoma. Some subtypes of stroke caused by proximal intracranial artery occlusion may be appropriate for endovascular intervention.
- Localisation helps to direct further investigations and follow up. If a cardioembolic cause is suspected, tests such as echocardiogram or 24-hour holter monitoring will be performed. In contrast, cardiac investigations may be limited if a lacunar etiology is presumed.
- It allows the clinician to anticipate and treat complications related to a stroke subtype, such as brain

stem compression with hydrocephalus related to primary intracerebral haemorrhage.

- Last, making the correct diagnosis will lead to the appropriate secondary intervention.

All patients who have had a stroke or TIA should have full blood count, clotting screen, electrolytes, glucose, lipid profile and 12 lead electrocardiogram. Further tests depend on age, risk factors, and possibility of recovery. Younger patients are more likely to have an identifiable cause of stroke and may need serological, immunological, genetic and thrombophilia screening.

1.4.1 Diagnostic Imaging

Current guidelines recommend that brain imaging should be undertaken as soon as possible but immediately (within 1 hour) if any of the following apply:

- Indications for thrombolysis or early anticoagulation
- Decreased level of consciousness
- Unexplained progressive or fluctuant symptons
- On anticoagulants or known bleeding disorder
- Papilloedema, neck stiffness or fever
- Severe headache at onset of symptons[31, 32]

Even in those patients without these indications, immediate scanning improves outcomes and has shown to be cost-effective.[31]

In patients with TIA, brain imaging should be performed if the vascular territory or pathology is not clear.[33] Scanning, preferably diffusion-weighted MRI should be done urgently in 'high risk' patients with an $ABCD^2$ score of 4 or more, or with two or more TIA's in a week.[33]

Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) is vital to differentiate between ischaemic and haemorrhagic stroke since treatment differs for the two types.[31] The posterior fossa of the brain is better visualised on MRI scan and in such patients, the imaging of choice. [34] MRI identifies a broader range of acute and chronic cerebrovascular pathologies such as anatomy, cerebral blood flow, perfusion, old or new lesions and hence, may replace CT in the future to aid decisions about acute intervention and further management.[35]

A number of infarcts may not be detected with CT in the early phase, and as such a normal CT does not exclude the diagnosis of ischaemic stroke. [36] Diffusion weighted MRI

imaging is more sensitive than non-contrast CT to identify early ischaemic changes identified as bright lesions and is especially useful in patients with minor stroke symptons. Combined multimodal parenchymal, perfusion or angiography with CT or MRI is useful to identify tissues at risk of infarction that is salvageable (an estimate of the ischaemic penumbra) and may respond to recanalisation therapy even beyond three hours after onset of stroke.[34, 37]

Both CT and MR imaging can detect intracerebral haemorrhage accurately in the early stage.[38 39] CT scanning is used as first line because it is cheap, quicker to perform and readily available.[34] In comparison with MRI, claustrophobic patients or those with pacemakers in situ tolerate CT scans better. Upto a week, CT is reliable in detecting haemorrhage and after this the haemorrhage loses the white hyperdense appearance to a dark hypodense appearance. MRI has an advantage over CT scan in detecting micro bleeds, indicative of underlying vascular disease and a risk factor for recurrent lobar ICH.[38] After haemorrhage, haemosiderin, which is a breakdown product of haemoglobin is stored indefinitely in macrophages and can be detected months or years after the initial event by gradient-recalled echo MRI.[40]

The ‘hyperdense artery’ (MCA) sign and the ‘dot’ sign associated with acute embolic occlusion may be identified on CT scan as increased attenuation of the proximal portion of the MCA or its distal branches in the sylvian fissure.[41, 42] In acute intracerebral haemorrhage, the ‘swirl’ sign is sometimes seen on nonenhanced CT scans as a heterogenous collection of clotted blood (hyperattentuating) and a small ‘swirled’ configuration of non -clotted blood, which appears hypoattentuating.[43] Recent studies have indicated the presence of ‘spot sign’ as a predictor of haematoma enlargement in the acute phase.[44] [45, 46] It is visualised as small enhancing foci of ‘bright spots’ depicting active bleeding.[44, 47]

Both CT and MR angiography are useful in detecting arterial rare causes of stroke such as dissection or vasculitis. Catheter angiography may be considered in patients with subarachnoid haemorrhage, abnormal calcifications, blood in unusual locations such as sylvian fissure and isolated intraventricular haemorrhage (IVH) to investigate for underlying aneurysm or arteriovenous malformation.[48]

1.5 Primary and secondary stroke prevention

Prevention of stroke may be primary- in individuals with no previous history of stroke or transient ischaemic attack (TIA), and secondary prevention in those who have already had such an event. The key to stroke prevention is identification of risk factors both by a patient and the clinician treating the patient. Non-modifiable risk factors include age, sex, ethnicity and family history. Modifiable risk factors include hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, obesity and carotid disease. Each of these modifiable risk factors are discussed in the following sections.

1.5.1 Lifestyle

Considerable benefit in lowering risk is noted upon smoking cessation and should be recommended for all patients with stroke or TIA.[49] As compared with nonsmokers, cigarette smokers have a two to three time risk of both ischaemic and haemorrhagic stroke after control for age, blood pressure, coronary artery disease and other risk factors.[50] The proportional risk increases with the number of cigarettes smoked per day.[51] Passive smoking also increases the risk of ischaemic stroke.[50] Treatment options for smoking cessation

include counselling, nicotine replacement, antidepressants such as bupropion or nortriptyline and the partial nicotinic acetylcholine receptor agonist varenicicline.[52-54]

Daily alcohol consumption in small or moderate amounts is protective against total and ischaemic stroke whereas heavy consumption (more than 60 gm) is associated with increased risk of both ischaemic stroke (OR 1.64, 95%CI 1.39-1.93) and intracranial haemorrhage (OR 2.18, 95% CI 1.48-3.20).[55] A diet with increased content of fruits and vegetables, reduced intake of sodium, increased intake of potassium and low content of saturated fat lower blood pressure and therefore may benefit reducing risk of stroke.[56] Vascular risk factors such as hypertension, diabetes, hypercholesterolemia are more in common in obese individuals effecting a three fold increased risk of ischaemic stroke.[57] Weight reduction targeting a body mass index 18.5 to 24.9 kg/m2 results in better control of these factors and lower the risk of stroke.[57]

1.5.2 Antihypertensive therapy

Although few treatments have created ethical dilemmas as profound as managing blood pressure in acute stroke, hypertension treatment in the context of primary and secondary prevention is robust and has most impact amongst

all modifiable risk factors.[51] In primary prevention, antihypertensive treatment lowers systolic and diastolic blood pressure and reduces the risk of stroke.[58] In comparison to the older antihypertensive agents (βblockers, diuretics), treatment initiated with newer blood pressure lowering drugs (CCB's, ARB's) lower the incidence of stroke.[58]

In two large trials enrolling patients with a history of cerebrovascular disease, the use of Indapamide both alone or in combination with Perindopril was effective in lowering blood pressure and significantly reduced recurrent stroke.[59, 60] The HOPE study showed that in patients, particularly at high risk of fatal or nonfatal cardiovascular events, lowering blood pressure with Ramipril was safe and effective in reducing the risk of stroke (32%), myocardial infarction (20%) and cardiovascular death (26%).[61] A systematic review of all trials (excluding one study) revealed that blood pressure lowering reduced the odds of recurrent stroke by nearly 25%.[58] Current guidance recommends lowering and maintaining blood pressure below 130/80, except in those patients with bilateral carotid stenosis for whom a systolic target in the range 130-150 is appropriate.[33] After a stroke or TIA, treatment should be initiated before hospital discharge or at 2 weeks whichever is earlier. The algorithm to treat is based on classifying

patients with essential hypertension into low and high renin subgroups.[62] More than a single drug is usually required to achieve good quality control.[63]

For patients, younger than 55 years and not of African or Afro-Caribbean origin, the first choice initial therapy is with an ACE inhibitor or an ARB blocker.[32] In those aged 55 years and over, or of Afro-Caribbean ethnicity of any age, treatment should begin with a long acting calcium channel blocker or thiazide class diuretic.[63]

1.5.3 Antiplatelet therapy

Antiplatelet therapy decreases stroke incidence in patients at high risk of atherosclerosis and in those with known symptomatic cerebrovascular disease. In primary prevention without previous disease, aspirin is of uncertain value whereas in secondary prevention, aspirin given within 48 hours of onset of presumed ischaemic stroke reduces the risk of recurrent ischaemic stroke and increases the odds of making a complete recovery (OR 1.06, 95% CI 1.01 to 1.11).[64, 65] Two randomised controlled trials comparing the efficacy of combination therapy using aspirin and dipyridamole than aspirin alone showed sufficient evidence to prefer the combination regimen over aspirin alone for the primary

composite end point of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction or major bleeding complication.[66, 67]

In preventing stroke recurrence, combined therapy of aspirin and dipyridamole does not differ in effect when compared to another antiplatelet agent, clopidogrel (ADP receptor binder).[68] When clopidogrel is added to aspirin, the short-term benefits of lower vascular events were offset by a higher risk of bleeding in three trials but not seen in a recent trial performed in China.[69-72] Current guidelines in the UK recommend clopidogrel at a dose of 75 mg daily for patients with ischaemic non- cardioembolic stroke or TIA and in those intolerant to clopidogrel, aspirin 75 mg daily and dipyridamole 200 mg twice a day.[33]

If two antiplatelet agents are superior to one, then intensive triple antiplatelet treatment may be better still in the acute phase; this concept was recently tested in a large trial and the results showed increased risk of bleeding with triple therapy.[73]

1.5.4 Anticoagulation

Atrial Fibrillation (AF) increases with age, causes ~15% of all strokes and is associated with strokes with higher morbidity and mortality when compared with non-AF related ischaemic stroke.[51, 74]

Evidence shows that in patients with nonvalvular AF comparing adjusted-dose warfarin and no treatment, the absolute reduction in annual stroke decreases from 4.5% in control patients to 1.4% in patients randomised to warfarin.[57] Also, the efficacy of aspirin is substantially weaker than that for warfarin.[75] Warfarin is known to be relatively safe, with an annual rate of major bleeding of 1.3% compared to 1% for patients taking aspirin or no treatment.[51]

Experts recommend commencing anticoagulation with warfarin immediately following a TIA once haemorrhage is excluded whilst treatment should be deferred for atleast 7 days after minor stroke.[76] Once initiated, INR should be maintained between 2.0-3.0 for optimal effect.[77] For patients where treatment with warfarin is proven impractical or poorly controlled, or results in an allergy or intolerance, a direct

thrombin inhibitor (such as dabigatran) or factor Xa inhibitor (such as rivaroxaban or apixaban) should be used.[33]

There is no evidence supporting stroke prevention using treatment with anticoagulation in those patients with ischaemic non-cardioembolic stroke.[78]

1.5.5 Carotid endarterectomy

Carotid endarterectomy (CEA) reduces the risk of stroke in patients with recent symptomatic stenosis.[79] Analysis of data from three trials involving 6092 patients shows that CEA is highly beneficial in those patients with 70-99% stenosis (ARR 16.0%) without near-occlusion and of some benefit in those with 50-69% symptomatic stenosis (ARR 4.6%).[80] The results do not recommend surgery in patients with near-occlusions. Benefit from surgery is greatest when performed within two weeks after the last symptomatic event.[80] By comparison, meta-analysis has shown that carotid stenting is no more effective than CEA in symptomatic patients and therefore not recommended.[81, 82]

1.5.6 Lipid lowering therapy

Although observational studies have not shown an association between cholesterol levels and stroke incidence, trials using

statins have found reduction in risk of stroke associated with lowered lipid levels.[83-85] In one of these studies involving patients with a previous stroke or TIA, Atorvastatin used at a dose of 80 mg demonstrated an absolute risk reduction of 2.2% and significantly lowered LDL cholesterol of 53% from baseline.[86] There were more incidence of haemorrhagic strokes in those treated with Atorvastatin and suggests a possible association between low cholesterol levels and brain haemorrhage.[87] Therefore, careful consideration should be given when administering statins to those patients who may have had a haemorrhagic stroke. In comparison, for patients with ischaemic stroke or TIA unless contraindicated, treatment should be initiated with Simvastatin at a dosage of 40 mg daily.[33]

1.6 The role of hypertension in the pathophysiology of acute stroke

Hypertension is the commonest risk factor in the development of ischaemic and haemorrhagic stroke.[88] The relationship between BP and stroke risk is linear, continuous and independent, with the risk increasing continuously above a BP of 115/75 mm Hg.[89] Patients with hypertension are 3 to 4 times more likely to have a stroke than normotensives.[90] In

particular, a 2 mm Hg rise in systolic BP in middle age is associated with a 10% increased risk of stroke.[90]

Increase in both systolic and diastolic components of BP are associated with stroke and treatment reduces the risk of first and recurrent stroke.[58] In addition, high pulse pressure, an indicator of arterial stiffness and defined as the difference between systolic and diastolic blood BP is associated with reduction in cerebral blood flow and a 20% increase in risk of stroke.[90, 91]

Of recent, variability in blood pressure has been recognised as a risk factor for stroke.[92] In patients with TIA, visit-to-visit variation in systolic BP is more predictive of stroke risk than mean systolic BP.[92] Also, within drug- class effects on variation in blood pressure may account for differences in preventing risk of stroke;[93] calcium-channel blockers, non-loop diuretics are effective in lowering BP variability whereas, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers and beta blockers increase BP variability.[93]

Several mechanisms have explained the contribution of hypertension in acute ischaemic stroke. High intraluminal pressures lead to extensive alteration in the endothelium and

smooth muscle function in the cerebral vasculature.[94] As a result, increase in permeability of the blood brain barrier causes local or widespread cerebral oedema. With endothelial damage, blood cell- endothelial interaction is altered, promoting leucocyte adhesion and thrombus formation. In addition, longstanding hypertension accelerates atherosclerosis, which causes cerebral infarction related to stenosis and embolism from intra and extracranial blood vessels, the aorta and the heart. The causal mechanisms of hypertension in lacunar stroke are unclear because of methodological inconsistencies and lack of pathological studies.[95, 96] Perivascular oedema and thickening, arteriolar wall inflammation and disintegration is common, whereas vessel occlusion is rare.[96, 97]

1.7 Cerebral blood flow and cerebral autoregulation

1.7.1 Cerebral blood flow

The brain is vulnerable to any vascular insult, as it requires a constant supply of oxygen and glucose to meet its high-energy demand.

Cerebral blood flow (CBF) depends on the cerebral perfusion pressure (CPP)- which is the difference between the mean

arterial pressure (MAP) and intracranial or central venous pressure (CVP) whichever is the highest.

The absolute level of CBF is the same in healthy normotensive individuals and in patients with uncomplicated essential hypertension i.e. around 50 ml/100 g/min. This varies from 20 ml/100g/min in white matter to 70 ml/100g/min in grey matter and decreases by approximately 0.5% every year.[98]

1.7.2 Cerebral autoregulation

1.7.2.1 Mechanisms

Cerebral Autoregulation (CA) can be defined in terms of arteriolar calibre changes as blood pressure or perfusion pressure varies.[99, 100] Under normal circumstances, these changes regulate cerebral blood flow between mean arterial pressure of 60 to 150 mmHg.[101]

CA is regulated by several mechanisms including intrinsic myogenic vasomotor responses, arterial oxygen and carbon dioxide levels, metabolites such as adenosine, nitric oxide, endothelin and neurogenic control, in particular the sympathetic system related to extrinsic innervation of parenchymal arteries and intrinsic innervation of intra-parenchymal arterioles.[102, 103]

Chronic hypertension stimulates the growth of smooth muscle within the intracranial vessels. The altered thickness enables the vessels to tolerate a higher intraluminal pressure protecting the blood brain barrier and shifting the cerebral autoregulation curve to the right. The increased resistance can compromise collateral blood flow in the 'border zone' regions or to an area distal to an occlusion thereby increasing the risk of ischaemic events.[104]

1.7.3 Cerebral blood flow and metabolism in acute stroke

As an initial response to focal ischaemia, intracranial resistance vessels dilate to increase CBF. After maximum threshold of vasodilatation is achieved, further decrease in CPP results in a fall in CBF. In the initial period, oxygen delivery to the brain is maintained by increasing the extraction fraction from the blood.[105] As CBF falls, oxygen extraction is increased and functional consequences of reduced CBF occur when oxygen extraction fraction (OEF) is maximal.[106, 107] When CBF falls below a critical level (approximately 10-12ml/100 gm/min) irreversible neuronal injury occurs.[108]

In the acute phase just after infarction, CBF is extremely low or even absent in the centre of the lesion.[109] In the periphery, exists a 'penumbra' region, trying to maintain perfusion by

extracting more oxygen from the blood. It implies that if blood flow is restored to this region within a specific duration, tissue recovery is possible.[105] Therefore treatment such as thrombolysis will be most effective when given early.[110, 111] Once the clot material is lysed, ischaemia is followed by hyperaemia but invariably the tissue involved is irreversibly lost.[106] In the days following infarction, CBF again decreases, and adapts itself to the lower or even absent oxygen consumption of the lesion.[106]

A cerebral haemorrhage forms a haematoma and in its surroundings, areas of ischaemia and hyperaemia similar to infarction.[109, 112] Three phases of perihaematoma blood flow and metabolism are known to occur after ICH.[102, 113] The acute hibernation phase occurs within the first two days.[102] In this phase, there is decrease in CBF and metabolism mainly in the ipsilateral perihaematoma region and contralateral hemisphere. During the subacute reperfusion phase, areas of normal, low and hyper-cerebral perfusion occur in the peri-haematoma region. The normalisation phase is observed after 14 days when normal blood flow is restored except in necrotic tissue.[114]

1.8 Hypertensive response after acute stroke

For the use in estimating its prevalence, the acute hypertensive response is defined as 'systolic BP>=140 mm Hg or diastolic BP of >=90 mm Hg demonstrated on 2 recordings taken 5 minutes apart within 24 hours of sympton onset'.[115] It is observed in upto>80% of patients in the immediate period after both ischaemic and haemorrhagic stroke.[115] In a large portion or atleast in some of these patients, the acute hypertensive response is a reflection of poorly controlled or undetected long-standing high BP; however, in most cases, BP falls to pre-stroke levels over the first week.[116, 117] The prognostic effect is shown in a systematic review which revealed that patients with stroke and high initial BP suffered a 1.5 to 5 fold increased risk of death or dependency.[118]

Although the strength of the relationship between acute stroke and high BP is well established, the precise mechanism that causes elevated BP is not known. In acute stroke, elevated intracranial pressure, decreased parasympathetic activity, direct injury to the prefrontal and insular cortices and pathways to the nucleus solitarius in the medulla and effects of neurotransmitters can cause hypertension.[119-123] In addition, stress from hospitalisation, headache, urinary retention and concomitant infection may increase sympathetic

drive and circulating inflammatory cytokines and contribute to increase in BP. [123, 124]

1.9 Blood pressure and outcome in acute stroke

Analysis of data from 10,892 patients revealed that both high SBP and DBP were associated with combined death or dependency in both ischaemic stroke and ICH.[125] Among patients with acute stroke, a U- shaped relationship was found between baseline SBP and both early death, late death and poor outcome.[126] In multivariable analysis, high systolic BP 2 to 24 hours after thrombolysis was significantly associated with worse outcome and as a categorical variable showed a linear association with symptomatic haemorrhage and a U-shaped association with mortality and independence with systolic BP 141 to 150 mm Hg associated with most favourable outcomes.[127] It is not clear why high BP is associated with poor outcome in acute ischaemic stroke; explanations include severe cerebral oedema and early recurrence of stroke.[128] In patients with ICH, worse outcomes with high BP is probably due to a single or combination effects of the following: excessive perfusion pressure, worsening cerebral oedema, haemorrhage expansion, increased ICP and aggravated ischaemia in the penumbra region.[103, 129]

When considering the available evidence, low blood pressure in the immediate stroke period is also associated with poor outcome.

Concomitant presence of sepsis, cardiac failure or factors directly relating to the stroke such as low blood pressure in those with larger strokes causing worsening of ischaemia in the penumbra may explain why low BP is associated with poor outcome.[115, 130]

1.10 Lowering blood pressure in acute stroke

Hypertension is associated with poor outcome and is present in approximately 80% of patients with acute stroke.[125] Cerebral autoregulation is dysfunctional in acute stroke and therefore cerebral perfusion may be fully dependent on blood pressure.[99] The dilemma whether to treat blood pressure in acute stroke is balanced between epidemiological data which suggests that blood pressure lowering is likely to be beneficial and countered by pathophysiological evidence that lowering BP may reduce cerebral blood flow (CBF). In addition, deciding which antihypertensive agent to use is not clear as different antihypertensive medications have been tested in acute stroke, with different effects on blood pressure and clinical outcomes.

A systematic review of thirteen trials (1325 participants) using different antihypertensive drugs was performed to assess whether blood pressure should be altered actively during the active phase in both acute ischaemic and haemorrhagic stroke.[131] The results showed that angiotensin converting inhibitors, angiotensin receptor antagonists, β-receptor antagonists, calcium channel blockers, and glyceryl trinitrate lowered both systolic and diastolic blood pressure while phenylephrine, increased it.[131] Functional outcome and death were not significantly altered by any of the drug classes used to alter blood pressure.

A meta-regression of 13 drug classes analysing the relationship between the change in BP and functional outcome revealed no positive association.[132] No significant effects of any single antihypertensive class were seen in the study. Lowering SBP in order of 8-14 mm Hg reduced the combined odds of early death or dependency, although the CI's were wide and compatible with an overall benefit or harm.[132] The results support the rationale for ongoing clinical trials lowering BP in acute stroke[133, 134] and in the meanwhile the approach is to treat each patient on an individual basis. Guidelines usually

recommend more active intervention in ICH in comparison to ischaemic stroke.[135]

Lowering blood pressure in patients with acute stroke is recommended only if there is a hypertensive emergency with one or more of the following complications:

- Hypertensive encephalopathy
- Hypertensive nephropathy
- Hypertensive cardiac failure or myocardial infarction
- Aortic dissection
- Pre-eclampsia/ eclampsia
- Intracerebral haemorrhage with systolic blood pressure above 150 mm Hg within 6 hours of onset[33]

Approximately 50% of all patients with acute stroke are taking blood pressure lowering medications, and it is unclear whether pre-existing antihypertensive therapy should be continued or discontinued temporarily during the acute phase, this is the subject of two RCT's one stopped and the other recently completed.[136, 137]

1.11 Acute treatment of stroke

Acute stroke care begins in the community with patient recognition of 'stroke warning signs' of sudden weakness; sudden speech difficulty; sudden visual loss; sudden dizziness and sudden, severe headache.[138] Early management performed by paramedics includes urgent triage, stabilisation and transfer to a stroke-ready hospital. A useful tool to enhance recognition of stroke by the paramedics is the FAST test (Face, arm, speech) which shows good agreement with physician assessment even allowing time for evolution of deficits.[139]

1.11.1 Stroke Unit care

All patients with stroke should be treated in a designated specialist stroke unit.[33] Patients with acute stroke who received specialist inpatient stroke unit care have significant reduction in death after one year (OR 0.86, CI 0.76- 0.98) and the combined outcome of death or dependency (OR 0.82, 95% CI 0.73-0.92).[32] Care should be provided by a coordinated multidisciplinary team offering rehabilitation in a discrete ward setting.[140]

1.11.1.1 General Measures

All patients with acute stroke regardless of etiology should receive supportive care with maintaining oxygen saturation, fluids, antibiotics and ensure that temperature remains within normal limits. Maintaining physiological homeostasis may improve outcome in stroke patients, which suggests the need for close monitoring and treatment of any dysequilibrium.[141] Management of hyperglycemia may be important with poor outcome seen in those patients with high glucose levels. No evidence at present exists to support aggressive glucose lowering [142] and guidelines suggest maintaining blood glucose between 4 and 11 mmol/l.[33]

Measures should be undertaken to prevent complications after stroke such as pneumonia, pressure sores with proper assessment of swallowing, positioning and continence. There is a high risk of venous thromboembolism following stroke and is a major cause or morbidity and mortality. Analysis of nine trials involving 3137 patients suggests that treatment with low molecular weight heparin or heparinoid after acute ischaemic stroke lowers the occurrence of deep vein thrombosis compared with standard unfractionated heparin; more data is needed on the effects on critical outcomes, including death and haemorrhage.[143] Data from a large international trial (2518 patients) revealed that thigh- length graduated

compression stockings failed to prevent deep vein thrombosis and were associated with increase in skin ulcers and necrosis and therefore not recommended.[144]

The Clots in Legs or Thromboembolic diseases after Stroke 3' (CLOTS 3) trial tested routine care plus intermittent pneumatic compression with routine care versus avoidance of intermittent pneumatic compression in 2876 patients who were admitted within three days of stroke onset.[145] The study showed a significant reduction of symptomatic deep venous thrombosis (DVT) or DVT detected using duplex ultrasound in patients allocated to IPC than those allocated to avoid their use (OR 0.65, 95% CI 0.51-0.84).[145] The results therefore support the use of intermittent pneumatic compression in patients admitted with acute stroke and poor mobility.

1.12 Treatment of acute ischaemic stroke

1.12.1 Aspirin

Two large clinical trials have assessed the role of aspirin. The Chinese Acute Stroke trial (CAST) used 160 mg of aspirin within 48 hours of the onset of suspected stroke in 21,106 patients and the International stroke trial treated 19435 patients with unfractionated heparin 5000 units daily, aspirin

300 mg, both or neither. Taken together, the results showed that aspirin started early in hospital within 48 hours produces a definite benefit, with about 9 fewer deaths or non fatal strokes per 1000 patients in the first few weeks and 13 fewer dead or dependent per 1000 after some weeks or months of follow up. [146, 147] Aspirin therapy was associated with a small but definite excess of symptomatic intracranial haemorrhages, but this risk was offset by the reduction of recurrent ischaemic stroke.[65, 147] Current guidelines recommend that all acute ischaemic stroke patients, should as soon possible, but certainly within 24 hours, be given aspirin 300 mg orally if they are not dysphagic or aspirin 300 mg rectally or by nasogastric tube if not able to swallow.[32] Thereafter, aspirin 300 mg should be continued until 2 weeks, at which time definitive long-term antithrombotic treatment should be initiated.[32]

1.12.2 Intravenous Thrombolysis

Intravenous thrombolysis was the first proven effective medical intervention in acute ischaemic stroke.[148] Thrombolytic drugs help to re-establish blood flow to the brain by dissolving the clots, which block the flow. t-PA is an enzyme found naturally in the body that converts,

plasminogen into plasmin to dissolve a blood clot. Recombinant t-PA is licensed for treatment of acute ischaemic stroke in the early hours after symptom onset. Administration of intravenous r-tPA at 0.9 mg/kg may result in clot lysis and restore blood flow to the ischaemic penumbra and limit further neuronal death. Successful treatment could mean the patient is more likely to recover from their stroke. Meta-analysis of twelve trials involving 7012 patients (including the very elderly, diabetics with previous stroke) comparing r-tPA with no treatment revealed that r-tPA administered within 6 hours found significant increased odds of being alive and independent at six months (OR 1·17, 95% CI 1·06-1·29) and the benefit greatest in patients treated within 3 hours (OR 1·53, 95% CI 1·26-1·86).[111] This was in spite of significant increase in death within 7 days (OR 1.44, 95% CI 1.18-1.76) the main cause of which was symptomatic intracranial haemorrhage (OR 3.72, 95% CI 2.98-4.64).[111] The results strengthen the evidence to treat with r-tPA as early as possible after acute ischaemic stroke and patients older than 80 years achieve similar benefit to those aged 80 years or younger.[105, 149] Current guidelines recommend intravenous r-tPA in patients presenting within 4.5 hours of symptons.[33]

Treatment with 'standard dose' 0.9 mg/kg r-tPA is associated with risk of intracerebral haemorrhage particularly higher among Asians[150] and a lower dose of 0.6 mg/kg in a recent trial did not show non-inferiority in reducing death or dependency after acute ischaemic stroke.[151] The primary outcome defined by the modified Rankin scale of 2 (mild disability) to 6 (death), occurred in 53.2% of patients who received the low dose and 51.1% in those who received the standard dose (OR 1.09, 95% CI 0.95-1.25).[151] Although significantly few rates of intracerebral haemorrhage were observed in those treated with low-dose alteplase compared to those in the standard-dose group,[151] the study did not report on vessel occlusion or rates of recanalisation.

1.12.3 Endovascular therapy

Of recent, studies have been performed testing alternative methods of restoring blood flow with intra-arterial thrombolysis with r-tPA, mechanical clot disruption or retrieval in acute ischaemic stroke.[152-155] The concepts were driven by the need to find treatment options in patients who present beyond 4.5 hours or with contraindications to intravenous t-PA (e.g. recent major surgery or active bleeding). Moreover, evidence suggests that the rates of recanalisation can be

incomplete in proximal anterior circulation artery occlusions after treatment with r-tPA alone allowing the risk of permanent infarction and significant neurological deficit.[156-158] As a result, multiple randomised trials were launched to identify patients based on CTA confirmed proximal occlusions, presence of collateral circulation and salvageable penumbra based on imaging criteria.[153-155, 159-163] Whether one approach is superior to another is unclear, but five recent trials (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT)[159-163] demonstrated efficacy of intra-arterial therapy in patients with persistent ICA or M1 occlusions treated within 6 hours (except REVASCAT <8 hours). In all studies, there were no significant differences in 90-day mortality or symptomatic intracranial haemorrhage. Although the odds ratio (favouring good outcome range from 1.8 to 3.8) may be exaggerated given the total number of patients included in the trials, the results along with recent meta-analysis[164, 165] demonstrate that endovascular therapy is beneficial in patients with large vessel ischaemic stroke.

1.12.4 Decompressive surgery in ischaemic stroke

Malignant MCA infarctions constitute between 1% and 10% of all supratentorial ischaemic strokes and those patients show a

progressive deterioration of consciousness due to severe brain swelling over the first 24-48 after stroke onset, reduced ventilatory drive and may require intubation.[166]

The aetiology is mostly caused by thrombosis or embolic occlusion of the internal carotid artery or proximal middle cerebral artery.[167] Anatomical variances that predispose an individual to a malignant MCA infarction include an atresia or hypoplasia of parts of the ipsilateral circle of Willis and insufficient number of vessels available to maintain collateral circulation.[168]

In selected group of patients aged<60 years with space-occupying unilateral malignant middle cerebral artery infarctions, trials have shown that decompressive surgery by hemicraniectomy (DHC) can improve outcome and survival.[166, 169] Clinical tools that may be useful to identify such patients include those with severe neurological deficit National Institutes of Health Stroke Scale (NIHSS) score>20 if dominant hemisphere is involved and between 15-18 in infarction of the non-dominant hemisphere, thrombus at terminal internal carotid artery, symptoms of nausea and vomiting, elevation of white blood cell count, early involvement of >50% of the MCA territory on CT, infarct

volume of greater than 145 ml on diffusion weighted MR scanning and concomitant involvement of both anterior and posterior cerebral artery territories.[170-172]

It is recommended that surgery should be undertaken early within 48 hours; the procedure involves opening of the skull and removal of a bone flap (of atleast 12 cm) to allow the oedematous brain to swell outward, thereby preventing midline shift and herniation.[169, 173]

A systematic review of 16 trials (382 patients) in quality of life in survivors after hemicraniectomy revealed that most patients and caregivers (77%) were satisfied and would again consent again for the procedure.[173] This was in spite of moderately severe disability (47% had mRS Score 4) and moderate to severe depression in patients at one year follow up.[173]

1.13 Neuroprotection

The theory of neuroprotection supports benefit using pharmacological intervention in the pathophysiological cascade between the occlusion or bleeding of a cerebral artery and irreversible neuronal death.[174]

Neuroprotective drugs appear to be effective in animals, at present not successful in humans. This may have occurred for a number of reasons: inadequate studies, benefits were smaller than predicted from the animal studies and unexpected toxicity.[175] Some agents are relatively simple to administer, whereas others may require infusions to be maintained over several days.[110]

Preliminary evidence suggests that treatment with cooling therapy, ancrod, pro-urokinase, thiazolidinediones, edaravone (free radical scavenger) and citicoline may be effective in patients with acute ischaemic stroke. [110, 176-179] Other agents e.g. aptiganel, nimodipine, tirilazad, lubeluzole, corticosteroids, ifenprodil, magnesium, piracetam, pentoxifylline, vinpocetine, selfotel have shown to be toxic or ineffective.[180] Although considerable research has been undertaken in this area, [110, 181-184] no neuroprotective drug as yet been found to have sufficient favourable benefit to be licensed for clinical use.[110]

1.14 Primary Intracerebral Haemorrhage

Intracerebral Haemorrhage (ICH) occurs when a blood vessel within the brain parenchyma ruptures and causes accumulation of blood in the brain tissue. ICH causes 10-15% of all strokes in Caucasians with incidence rising sharply with age.[185] A higher risk of ICH is observed in Blacks and tends to affect younger men compared to women.[16]

ICH may be due to two main arteriopathies: hypertension and cerebral amyloid angiopathy.[186, 187] Other causes include the use of antiplatelet agents, thrombolytics, anticoagulants particularly when the levels are above therapeutic levels, excess alcohol consumption, tumours, vascular malformation, drugs abuse (cocaine, heroin, amphetamines and cannabis)[188] and inherited bleeding disorders. In addition, cerebral reperfusion syndrome is a rare cause of ICH and can occur upto several weeks after revascularisation procedures including carotid endartrectomy and angioplasty or stenting.[189]

Hypertensive bleeds tend to occur in the deeper areas of the brain including the basal ganglia, pons, thalamus and cerebellum whereas cerebral amyloidosis tends to occur in the lobar regions.[186]

In chronic hypertension, degenerative changes from

hypertrophy to hyalinisation occur in the vascular wall. Excess or lack of collagen leads to arteriolar occlusion, dilatation or both.[187] Eventually breakdown of the vascular wall occurs with bleeding as collagen has no contractile capability and unable to withstanding stress from high blood pressure.

Pathophysiologically, cerebral amyloid results from impaired removal of beta-amyloid protein from the brain interstitial fluid and Virchow-Robin spaces resulting in its accumulation between the media and adventitial layers. As a result, the walls of blood vessels become weaker, form microaneurysms and in combination with chronic perivascular inflammation leads to vessel breakdown and haemorrhage.[190]

ICH is a devastating stroke, with a fatality of approximately 40% in the first month.[191] Significant determinants of mortality at 30 days include age>80 years, ICH volume, infratentorial location of haematoma, hydrocephalus, Glasgow coma scale, and intraventricular haemorrhage (IVH).[192]

A simple ICH score derived using clinical and radiological parameters may be used and relates to poor outcome.[193] The ICH score calculates the sum of individual points assigned as follows: GCS score 3 to 4 (=2 points), 5 to 12 (=1), 13 to 15 (=0); age ≥80 years yes (=1), no (=0); infratentorial origin

yes (=1), no (=0); ICH volume ≥30 cm^3 (=1), <30 cm^3 (=0); and intraventricular hemorrhage yes (=1), no (=0).[193] Higher scores suggest worse prognosis.

1.15 Antithrombotic and anticoagulant-related intracerebral haemorrhage

The evidence that ICH expansion and poor outcome relate to antiplatelets is countered by no increase in haematoma volume or worsening outcome in human and animal studies.[194] The reasons for these differences may be attributed to the following: inclusion or exclusion of posterior fossa bleeds which may undergo limited expansion from anatomical restrictions, choosing different haematoma measurement techniques, defining haematoma expansion, the variety of antiplatelet agents used at different doses, reliability of antiplatelet use and differences in anti-aggregant activity and resistance.[195] Although tested in small studies, platelet dysfunction related to aspirin may be associated with haematoma expansion, intraventricular haemorrhage and poor outcome.[196-198]

Anticoagulant use has been mostly studied in relation to warfarin use and studies are awaited with the newer anticoagulants. The risk factors associated with warfarin-

related ICH include the following: age, hypertension, concomitant use of antiplatelets, intensity of anticoagulation, leukoaraiosis and amyloid angiopathy.[199-201] Most warfarin related ICH occurs with INR in the therapeutic range [202] with a 2-fold increased risk of ICH observed in each 0.5 increase in INR above 4.5.[192] In addition, elevated INR caused by warfarin increases haematoma growth (OR 6.2), with enlargement continuing longer than in patients not taking warfarin.[203] When compared to spontaneous ICH, haematomas related to warfarin tend to have larger initial volumes, less oedema, impair thrombus formation and associated with greater mortality.[204, 205]

1.16 Haematoma expansion in acute intracerebral haemorrhage

Haematoma expansion or growth is thought to occur from a single vessel that ruptures and continues to bleed.[102, 189] This is easy to conceptualise when explaining haemorrhage expansion from a single vessel in the first few hours after rupture. However, it is difficult to relate to this model in cases where haematoma expansion occurs several hours afterwards.[190]

Based on a neuropathological study, it is postulated that haematoma expansion may occur several hours later facilitated by secondary mechanical shearing of neighbouring blood vessels caused by the spreading initial haemorrhage.[206] Three findings add support to this theory. First, haemorrhage volumes tend to occur in a bimodal distribution either as 'micro bleeds' or large 'macro bleeds' which may represent two separate haemorrhagic events.[207] Second, genetic data has shown that possession of the apolipoprotein E allele predisposes to increased break down of capillary walls and haematoma expansion in lobar ICH.[208] Therefore, it may be derived that this allele increases the tendency of the vessel to rupture and cause bleeding. Finally, multiple 'spot signs' have been observed within a single haematoma[209] suggesting simultaneous bleeding from shearing of the surrounding vasculature rather than a persistently bleeding vessel.[190]

ICH haematoma can enlarge up to 24 hours, with maximal expansion occurring within the first 6 hours.[210, 211] Determinants of haematoma expansion include anticoagulant use, larger size, irregular shape, heterogeneous density, reduced platelet activity, vascular injury with systemic inflammation (increase in serum interleukin 6, tumour necrosis factor-alpha, matrix metalloproteinase-9 and cellular

fibronectin levels), possession of apolipoprotein E ε2 (APOE ε2) allele and extravasation of contrast into the haematoma.[212-214]

Elevated SBP is associated with haematoma expansion and poor outcomes; however the cause -and -effect relationship is not known.[215] Lowering blood pressure may not be harmful with studies showing reduced metabolism ('tissue hibernation') and preserved autoregulation in the perihaematoma region during the acute phase.[216-218]

Only ICH size and IVH are potential targets to intervention as intracerebral expansion of the haematoma and intraventricular extension may occur as a result of the dynamic properties of the haematoma.[195] However, based on a study that showed that IVH is a consequence of haemorrhage enlargement and size,[219] it may be derived that the single most modifiable target becomes limitation of haematoma expansion. Several large trials testing therapies aimed at preventing haematoma expansion are in progress, including blood pressure reduction, haemostatic agents and surgical intervention.[133, 220, 221] The search for factors that attenuate haematoma expansion continue as it is identified as the principal cause of neurological deterioration during the acute phase and associated with poor outcome.[211]

1.17 Defining Haematoma Expansion (HE)

At present, there is no clear consensus defining haematoma growth.[214]

The majority of studies assessing haematoma expansion have used CT as imaging modality, mainly because of its widespread use and easy availability.[31, 222] Varied definitions used for expansion are based on thresholds when expansion is visible on CT scans including 40% relative volume increase or an absolute volume increase of 12.6 ml, 33% relative increase, combination of 50% relative increase and 2 ml absolute increase, 20 ml absolute increase and a combined cut off 33% relative and 12.5 ml absolute increase.[212, 223] An absolute increase of 6 ml was used in CT angiography studies examining haematoma enlargement.[194, 224]

A cohort study of 531 patients with ICH was performed to test how different definitions of HE compare in their ability to predict poor outcome and assess if relationships between HE and poor outcome were dependent on the definition of poor outcome used.[223] The results revealed that all definitions independently predicted outcome; positive predictive values (ranged from 68 to 78%) increased with higher growth cut-off

but were offset by lower sensitivity (<50%). Absolute growth cutoff of 12 mls or more were more predictive than relative when mRS 5-6 or 6 was defined as poor outcome.[223] The results suggest the following: absolute growth may be more clinically relevant than relative growth; HE appears more predictive of severe than moderate outcomes and therefore an outcome based on death or severe disability may be more sensitive to detect intervention in trials involving haemostatic treatment.[211, 222, 225]

1.18 Perihaematoma oedema and metabolism

As the haematoma spreads, brain oedema occurs in the immediate vicinity of the clot with maximal expansion within the first day as a result of both blood brain barrier disruption and the local generation of osmotically active substances.[226, 227] The exact nature of oedema is not clear -serum from haematoma contraction, vasogenic substances from disruption of capillary membranes or cytotoxic components resulting from compromised microvascular perfusion or structural damage. It is suggested that brain damage is from the enlarging haematoma compressing and causing ischaemia of the perihaematoma regions.[228] On the other hand, studies have disputed this. A positron emission tomography (PET)

study analysing perihaematoma ischaemia in 19 patients within 22 hours after haemorrhage onset, revealed that cerebral metabolic rate of oxygenation (CMR02) and oxygen extraction fraction (OEF) was reduced to a greater degree than cerebral blood flow (CBF).[229] Similar results were confirmed with diffusion-weighted (DWI) and proton magnetic resonance spectroscopic imaging.[230] A histological study evaluating brain metabolism in patients with ICH and control patients, revealed that mitochondrial dysfunction suggesting tissue hibernation and not ischaemia was the cause for reduced oxygen utilisation.[231]

The prognostic value of relative perihaematoma oedema volume which is the ratio of absolute oedema volume and haematoma volume is unclear with studies reporting contrasting results in relation to outcomes.[232, 233]

1.19 Intraventricular haemorrhage

Intraventricular haemorrhage (IVH) can be primary arising from within the ventricle or a lesion close to the ventricles. Such causes include trauma, aneurysm, arteriovenous malformation and tumours involving the choroid plexus.[234] Factors promoting IVH growth include older age, location of lesion, larger baseline ICH volume, mean arterial pressure

greater than 120 mm Hg and presence of IVH at baseline.[234, 235] Bleeding sites in the deeper areas of the brain near the ventricles including the putamen, thalamus, caudate and cerebellum extend early into the ventricles, whilst bleeding sites further from the ventricles cumulate blood before mechanical pressure and size of the haemorrhage forces extension of blood into the ventricles.[236]

The rupture into the ventricles causes damage to the reticular activating system resulting in decreased level of consciousness that is prolonged by a larger volume of blood and longer duration of exposure.[237] Ventricular blood causes blockage in flow of cerebrospinal fluid causing life threatening acute obstructive hydrocephalus which in turn contributes to mass effect and further reduces cerebral perfusion.[238]

Determinants of poor outcome in patients with IVH include increasing age, baseline lower level of consciousness, initial larger baseline ICH volume, IVH volume more than 20 ml, IVH growth and presence of IVH at baseline or 24 hours.[235-237, 239]

1.19.1 Scoring systems of Intraventricular Haemorrhage

Three scoring systems have been developed to estimate severity of IVH on CT scans.[240-242] The Graeb score adds a maximum score of 4 for each lateral ventricle and a score of 2 for the third and fourth ventricle when filled with blood and fully expanded to produce a total score of 12.[240] By comparison, the modified Graeb score allocates scores for separate ventricular compartments to reflect selective regional accumulation of blood and extra points for expansion of each ventricle.[241] The maximum score is 32. The IVH score assumes that in comparison to the lateral ventricles, the third and fourth ventricles contribute less to the ventricular volume and in the presence of hydrocephalus, the ventricular volume increases through expansion.[243] The score ranges from 0 to 23 and grades each lateral ventricle with a maximum score of 3 when mostly or completely filled with blood and the third and fourth ventricles receive a score of 1 each when partially or wholly filled with blood.[243] Hydrocephalus is coded 1 when present. IVH volume in ml is calculated from the IVH score using logarithmic transformation [IVH volume = eIVHS/5].[195, 243] Amongst these scales, the Graeb score is the only system which has been validated in relation to clinical outcome.[244]

1.20 Methods for estimating haematoma volume

Whilst there is no standard method for measuring all ICH volumes, literature considers computer-assisted volumetry to be reliable for parenchymal haemorrhages.[245, 246] Although observers can be trained to use software, accuracy in measurement depends on software type and slice thickness.[247-249] Moreover, studies have shown that volume calculation using computer-assisted methods are also time-consuming and reliant on radiological expertise.[249, 250]

The ABC/2 formula is the most widely used bedside method for estimating ICH volume and values can be obtained in less than a minute.[251] However researchers have questioned the reliability as it was shown in small studies to underestimate or overestimate volumes in regular and irregular shaped haemorrhages.[250, 252-254] In a small study involving haemorrhages related to anticoagulation, haemorrhage volume using ABC/2 overestimated volumes by nearly 15% in irregular and >32% in separated haemorrhages.[250] However, in this study CT images obtained were of large slice thickness and this is likely to have introduced measurement errors.[250] In the same study, increasing the denominator to 3 (i.e. ABC/3) revealed better correlation with computer assisted volumetry.[250] These findings are important as haematoma volume has been identified as a predictor of haematoma

growth, which in turn is an indicator of acute neurological deterioration. Although the formula ABC/3 has not been validated since,[253] the impact of error using the ABC/2 formula needs further investigation as every millilitre of haematoma volume counts in relation to clinical outcome.[255]

1.21 Management of intracerebral haemorrhage

ICH is a medical emergency and delays in treatment can result in worse outcome. Rapid diagnosis and intensive monitoring is important, as early deterioration is common in the first few hours.[256] More than 20% of patients suffer a decrease in GCS of more than >=2 points between paramedic evaluation and assessment in the emergency department.[256] Within the first hour of presentation to a hospital, 15% of patients have a further decrease in GCS of >=2 points.[256]

To-date, definite treatment for ICH is lacking.[135] Potential treatment options include stopping or slowing the initial bleeding, removing haematoma from the parenchyma or ventricles and managing complications such as raised intracranial pressure and lowered cerebral perfusion. Endotracheal intubation and mechanical ventilation may be indicated in the unconscious patient or in those with deterioration of consciousness.[257, 258] Further brain supportive

therapy may involve intra-arterial lines to monitor administration of vasoactive drugs, assessing intracranial pressure with catheters inserted into the brain parenchyma, treating acute hydrocephalus with drains and managing seizures with antiepileptics.[135, 257]

1.21.1 Medical management

It is recommended that patients with any of the following are unlikely to require surgical intervention and be treated medically initially:

- Small deep haemorrhages
- Lobar haemorrhage with no evidence of hydrocephalus or rapid deterioration in neurological state
- Large haemorrhages in those with significant co-morbidity before stroke onset
- Supratentorial haemorrhage with Glasgow coma scale less than 8 unless this is attributed to hydrocephalus[32]

1.21.1.1 Blood pressure management in intracerebral haemorrhage

Two theories have caused uncertainty in managing BP in acute ICH; first, the perihaematoma region might suffer ischaemia if the blood pressure is lowered precipitously and on the other hand, acute elevation in blood pressure may promote haematoma growth.[124] A complicating factor when deciding if and when to treat is that evidence that is available does not show definite benefit to lowering BP and the risks and benefits may vary with the type of agent used. This is reflected in the number of drugs that have been assessed including labetalol, nicardipine, candesartan, esmolol, enalapril, hydralazine, nitroprusside and nitroglycerin.

Based on epidemiological data suggesting poor outcome with high BP in ICH[118] and the results of experimental studies that failed to demonstrate the presence of ischaemic penumbra,[216, 259] two trials tested the feasibility in lowering BP in acute ICH.

INTERACT (Intensive blood pressure reduction in acute cerebral haemorrhage trial), was an open labelled trial in 404 patients, with no definite indication or contraindication to treatment randomised to early intensive lowering of BP (target systolic BP 140 mm Hg; n=203) or standard guideline-based

management of BP (target systolic BP 180 mm Hg; n=201).[260] Participants with lower levels of consciousness (GCS 3-5) were excluded and enrolled patients had mean volumes of 12 ml (guideline) and 14 ml (intensive). The primary efficacy endpoint was proportional change in haematoma volume at 24 h; secondary efficacy outcomes included other measurements of haematoma volume.[260] From randomisation to 1 h, mean systolic BP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13.3 mm Hg, 95% CI 8.9-17.6 mm Hg; p<0.0001); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10.8 mm Hg, 95% CI 7.7-13.9 mm Hg; p<0.0001).[260] A significant reduction was observed in the proportional haematoma growth between the intensive group (13.7%) and the guideline group (36.3%) at 24 h.[260]

The Antihypertensive Treatment of Acute Cerebral Haemorrhage trial (ATACH) tested the feasibility of three levels of systolic blood pressure reduction with intravenous nicardipine-170 to 200 mm Hg (n=18), 140 to 170 mm Hg (n=20) and 110 to 140 mm Hg (n=22) in patients with supratentorial intracerebral hemorrhage treated within 6 hours after symptom onset.[215] Other important outcomes included neurologic deterioration within 24 hours and serious adverse

events within 72 hours. The results demonstrated that it was feasible to intensively lower blood pressure and importantly no significant adverse events were observed.[215]

INTERACT-2 was a natural follow on and tested intensive with guideline lowering of blood pressure in 2839 patients predominantly from China with various antihypertensive agents (such as diuretic, calcium channel blocker, ACE inhibitor, Beta-blocker, Angiotensin II receptor antagonist) admitted within 6 hours of stroke onset.[261] The mean difference in systolic blood pressure at 1 hour after treatment initiation was 14 mm Hg (150 mm Hg vs 164 mm Hg). At 90 days, the trial was neutral in its primary outcome of modified Rankin scale (mRS)>2; however key secondary outcomes were positive including shift analysis of mRS and quality of life after stroke.[261]

Although INTERACT 2 provided optimism for lowering blood pressure in treatment of intracerebral haemorrhage, it equally generated more questions: What next? Are the results applicable to a population non-Chinese? Do single agents work? Will earlier treatment targeting haematoma expansion further improve outcomes? Although no clear answers can be given to these questions yet, four recent studies

heterogeneous in their design, patient population, time of treatment initiation and testing various agents provide important information.[137, 262-264]

In the Controlling hypertension and hypotension post-stroke trial (CHHIPS), hypertensive patients with ICH were randomised to lisinopril, the mixed alpha/beta-receptor antagonist labetalol or placebo within 36 hours. The results showed that neither the primary outcome (death or dependency at 2 weeks) nor early neurological deterioration was significantly altered using either agent or route of administration.[262] SCAST (Scandinavian Candesartan Acute Stroke trial) tested a specific question whether oral candesartan given within 36 hours for 7 days was beneficial in acute stroke.[263] In 274 patients with ICH, blood pressure was lowered to a modest level at 5 mm Hg but associated with a non-significant higher risk of vascular events (hazard ratio 1.36, 95% CI 0.65-2.83, p=0.41) and significantly worsening in functional outcome at 6 months (common odds ratio 1.61, 95%CI 1.03-2.50, p=0.04).[265] ENOS was larger than SCAST and in a partial-factorial design tested BP lowering in 4,011 patients with glyceryl trinitrate (GTN) within 48 hours of symptom onset with SBP thresholds at 140 mm Hg and 220 mm Hg.[137]

Two trials tested the agents GTN and lisinopril in earlier time-windows (pre-hospital/ultra-acute setting).[264, 266] In both studies, paramedics were able to identify suspected stroke patients, obtain consent and administer BP lowering treatment. It is difficult to draw any definite conclusions as the trials were performed in a small number of patients. [264, 266]

1.21.1.2 Haemostasis

The concepts of haemostatic intervention were based on observations that substantial ongoing bleeding occurred in patients with ICH in particular during the first few hours after onset and directly linked to poor outcome.[211, 267]

For patients with ICH related to anticoagulants, the recommendation is to reverse the INR as rapidly as possible.[268] A single agent, protamine sulphate reverses heparin anticoagulation.[268] Conversely, several alternative measures are available to counteract the effect of warfarin including vitamin K, fresh frozen plasma (FFP), prothrombin cell complex (PCC) and recombinant factor V11a (r-FVIIa).

Vitamin K is usually administered in combination with FFP or PCC as it takes several hours as a single agent to correct INR.[269] FFP acts quicker than Vitamin K. Nevertheless, its use is limited by the risk of allergy, transfusion reactions, long duration to administer (with the potential for continuing haematoma enlargement), incomplete haemostasis (factor 1X level may remain low) and risk of cardiac failure (large volume in constitution).[195, 270] In comparison, PCC's contain high concentration of coagulation factors II, VII, IX and X and can be rapidly administered in small volumes. The lower risk of thromboembolism with PCC's is offset by rapid correction of INR.[271]

A retrospective study of anticoagulant related ICH comparing PCC alone or in combination with FFP or Vitamin K showed those who received PCC had rapid correction in INR and reduced haematoma growth.[168] Despite lack of evidence on clinical outcomes in a recent trial comparing PCC versus FFP,[272] neurovascular society experts recommend PCC in rapid correction of INR in anticoagulation related ICH.[268]

r-FVIIa contains a single coagulation protein and therefore not effective in reversal of warfarin anticoagulation. r-FVIIa fails to reverse bleeding even if the INR is normal[273] and not able to

restore thrombin generation.[274] With the additional risk of systemic thrombosis and possible need for repeated dosage the use of this drug becomes limited. Hence, neurovascular society guidelines do not recommend use of r-FVIIa.[268]

In patients with ICH not taking anticoagulants, early therapy with r-FVIIa (40, 80 and 160 μgm) as a haemostatic agent was tested in the proof-of-concept dose escalation FAST trial.[275] r-FVIIa has been shown to induce haemostasis in patients with haemophilia, and profuse bleeding caused by surgery or trauma.[276] It acts by generating a tight haemostatic plug through increased thrombin generation. For the nearly 400 patients in FAST, mean treatment time was 167 minutes after symptom onset.[275] Proof -of -concept was achieved with a reduction in ICH haematoma volume by half in the r-FVIIa group whereas a 29% increase was seen in the placebo group.[275] In addition, secondary outcome of mortality was significantly lower at 18% in the pooled treated group.[277] The larger FAST III trial randomly assigned 841 patients with spontaneous intracerebral haemorrhage to r-FVIIa (20 and 80 μgm) or placebo.[278] In spite of reduction in ICH volume for the 80 μgm group (11% versus 26%), no significant differences in outcome were observed among the three groups those randomised to treatment and placebo (24% in the placebo

group, 26% in the group receiving 20 μgm of r-FVIIa and 29% in the group receiving 80 μgm).[278] In addition, there was a 5% increased in number of arterial occlusive events in those treated with r-FVIIa.[278] Possible explanations for the observed results include low mortality (19%) in the placebo group, increase in IVH in patients receiving r-FVIIa (38% versus 29%) and increased frequency of thrombotic complications in those receiving r-FVIIa (8% in comparison to 4%). A post hoc analysis identified a subgroup of patients who may benefit from r-FVIIa: patients aged <=70 years with baseline ICH volume <60 ml, IVH volume <5 ml and those treated within 2.5 hours after ictus.[279] Incorporating markers of ongoing bleeding might delineate further those who may benefit from r-FVIIa; this aspect is currently being assessed in two ongoing RCT's- STOP-IT and SPOTLIGHT.[280, 281]

The newer anticoagulants which act by direct inhibition of thrombin or factor Xa are likely to be seen more in the setting of ICH because of increasing use, greater efficacy over aspirin and safety profile than warfarin, advantage of not requiring regular monitoring and higher incidence of atrial fibrillation in the elderly.[282, 283] With the exception of dabigatran,[284] no antidote is available to completely neutralise the anticoagulant activity of other agents, [285] suggesting patients taking these

might be at greater risk of ongoing bleeding, haematoma expansion and mortality. However, partial control of haemorrhage may be achieved using greater concentration of factor X and thrombin in PCC's than FFP or r-FVIIa.[195]

The decision of reintroducing anticoagulation after warfarin related ICH in those taking warfarin for prevention of cardioembolic stroke associated with chronic AF or prosthetic heart valves is complex with the balance between the risk of ischaemic stroke and recurrence of ICH. At present, limited data is available assessing the recurrence rate of ICH in those patients taking warfarin. In such situations, the newer oral anticoagulants with lower risk for ICH than warfarin (0.2% compared to 1% per year) may be preferred, but the rate of recurrent ICH with these agents are yet to be determined.[199]

The risk of recurrence of either lobar and deep cerebral haemorrhage does not appear to increase with Aspirin and reinstitution following ICH may be considered based on the risk of ischaemia, underlying cause of ICH and on the added risk of haemorrhage from antithrombosis.[286, 287] In the absence of randomised evidence,[286] current management of antithrombotic and anticoagulant introduction is largely derived from expert opinion and suggest reintroduction of

antiplatelets after 2 weeks and approximately 4 weeks for anticoagulants.[288, 289]

Epsilon-aminocaproic acid (EACA) was tested in a small proof-of concept trial in patients recruited within 12 hours of ICH onset.[290] A total of 5 gm EACA was administered in 1 hour and then 1 gm/hour over 24 hours. EACA failed to prevent expansion as growth occurred in three patients of the five patients treated with EACA.[290]

The concept of administering Tranexamic acid (fibrinolytic agent) in spontaneous ICH gained optimism from a large landmark trial in more than 20,000 trauma patients that showed that a significant lowered risk of bleeding (OR 0.85 95%CI 0.76-0.96) and all cause death (OR 0.91 95%CI 0.85-0.97) in those patients randomised to receive the drug.[291]
A subgroup with traumatic intracranial bleeding allocated to Tranexamic acid 1 gm infused over 10 minutes followed by an infusion over 8 hours showed non-significant trend to lower haematoma growth and improved outcome.[292] Following this, a small phase study tested the safety and efficacy of Tranexamic acid in 24 patients diagnosed with ICH.[293] Median time from stroke onset to randomisation was 14 hours and time from randomisation to treatment was less than half

hour.[294] Although no significant differences were observed in relation to safety and functional outcome, the study showed that it is feasible to administer tranexamic acid in the setting of acute ICH.[294] In another small study involving 156 patients, rapid administration of a bolus of tranexamic acid within 24 hours of stroke was shown to reduce haematoma expansion (17.5% versus 4.3%).[295] At present, two large trials are assessing the efficacy and safety of this drug as potential treatment, one in all cases of spontaneous ICH and the other only in 'spot sign positive' patients.[220 296]

Other tested approaches include the use of platelet transfusions and whether desmopressin improves platelet activity in intracerebral haemorrhage patients who take aspirin or any other antiplatelet agent.[297, 298] Unlike measures of anticoagulant activity for example INR for warfarin, or partial thromboplastin time for heparin, there are no standardised methods for quantifying platelet activity.[299] In one recent trial, platelet transfusion was associated with harm.[300]

To-date, there have been five phase II RCTs and one phase III trial of any haemostatic drug therapy versus placebo or control with outcomes. Meta-analysis show that haemostatic therapy and rFVIIa do not lower death or disability in

spontaneous ICH but tend to increase the risk of thromboembolic events (RR 1.37, 95%CI 0.74 to 2.55).[301]

In summary, while off-license use of haemostatic agents such as PCC's in ICH is very tempting, more studies are necessary to confirm the safety and efficacy. In particular, it will be useful to assess treatment effects in patients with longer time windows.

1.21.2 Surgical management

Intracranial surgery may involve craniotomy, which involves opening the skull or less invasive methods such as endoscopy or stereotactic surgery using catheters to evacuate haematoma. The opinion that mechanical decompression of a growing haematoma and its toxic effects is countered by the surgical risks in a patient with ongoing bleeding and navigating through pivotal motor and sensory regions. Another problem exists in that is unclear when to surgically remove intracerebral haematoma clot with clinical studies reporting from within 4 hours to 96 hours from the onset of symptoms and this limits direct comparison and analysis of the impact of timing of surgery.[302, 303] To complicating matters, when deciding if and when to intervene the opinion

varies between neurosurgeons when considering haematoma size, location and premorbid dependency.[304]

1.21.2.1 Craniotomy

Current management of cerebellar ICH is largely derived from expert opinion and recommends surgery in those patients with >3 cm haematomas or cerebellar haemorrhages with brain stem compression or obstruction of the fourth ventricle causing hydrocephalus.[268, 305, 306]

Craniotomy is associated with poor outcome for thalamic and pontine haemorrhages and therefore not recommended.[307, 308]

The STICH trial (1033 patients) compared the role of supratentorial haematoma evacuation within 72 hours and initial medical management, although later evacuation was allowed because of neurological deterioration.[303] The type of surgical procedure was left to the discretion of the neurosurgeon. The results revealed that patients who underwent early surgery did not benefit when compared to those who received conservative treatment. Early surgery in patients with a GCS score<=8 was associated with poor outcome and probable harm.[303] The concept of a second

randomised trial by the same investigators was derived from a subgroup analysis of STICH, which indicated a possible advantage with early surgery <8 hours in patients not in a coma with lobar haemorrhage and those with haematomas extending to within 1 cm of the cortical surface.[303, 309] In STICH international trial undertaken in 78 centres in 27 countries, early surgical evacuation of haematoma within 12 hours of randomisation and initial medical treatment was compared with regular medical treatment alone.[310] Of 601 patients recruited, 307 were assigned to early surgery and 294 participants to conservative treatment. Nearly all patients taken to surgery were treated with craniotomy.[310] The primary outcome was computed from a postal questionnaire based on the Extended Glasgow Outcome Scale.[303 311] The intention-to-treat analysis showed a small but non-significant increase in favourable outcome in patients treated with early surgery.[311] Additionally, the investigators found trends to benefit from early surgery in a subgroup of patients with poorer prognosis (GCS between 9-12) and those who suffered rapid decline in neurological state.[303, 311, 312] Limitations to interpreting the results of the two trials are the lack of true randomisation with inclusion determined by clinical uncertainty (those with haematomas for whom it was uncertain whether surgery would be beneficial), variation between institutions in clinical

equipoise and the option for cross over between the treatments based on clinical condition.[195] Equally important, intracranial pressure was not measured in both trials and therefore its impact on surgical decision-making and outcome is unclear. In STICH II, mean time to surgery in those allocated to conservative treatment was 64.2 hours, raising a debate if these patients should have been taken to surgery earlier thereby preventing further neurological injury. Taking the two results together along with previous studies, an individual patient data meta-analysis indicated that surgery may have still have a role in patients with intracerebral haemorrhage but uncertainty remains about which patients benefits most.[311] Inspite of the current evidence, experts still favour craniotomy and clot removal in younger patients with neurological decline from an initially conscious state with a superficial lobar haematoma.[309, 313]

1.21.2.2 Minimally invasive surgery

The refinement of minimally invasive surgery (MIS) for clot evacuation is driven by the lack of effective outcomes by craniotomy. Of relevance, both Factor V11a and STITCH trials focussed only on a single prognostic factor, ICH size and no standard plan was made in the trial protocols to stabilise and

remove intraventricular clot that occurred in nearly half of all recruited patients. This is important when considering the modest treatment effect observed in these trials despite consistent evidence that all three factors- ICH size, IVH and early clinical deterioration independently affect outcome.[303, 314] In addition, evacuation of haematoma can be compromised by clot retraction, advocating the need for clot liquefaction prior to complete evacuation.[315] MIS offers potential advantages over conventional surgery with the possibility of local anaesthesia, minimal brain injury, reduced operating time, maintain intracranial pressure monitoring during procedure, deliver thrombolysis with or without clot aspiration or evacuate haematoma under direct vision with an endoscope.

Using this background, small studies assessed administration of recombinant tissue plasminogen activator (r-tPA) as a treatment option in ICH.[316, 317] The encouraging results led to the MISTIE II trial designed to test image-guided removal of blood in patients with ICH and performed in two stages: dose finding and safety phase.[318] In this multicentre trial, eighty-one patients were allocated to MIS and forty- two participants to medical care in accordance with guidelines from the American Heart Association. Most patients in the surgical arm received surgical aspiration and r-tPA whereas 10 patients had

surgical aspiration only. Following surgical aspiration, those patients allocated to r-tPA received doses of 0.3 ml or 1.0 ml administered through the catheter and the drainage system closed for an hour to allow drug -clot interaction. The dosage was repeated every 8 hours upto 9 doses until a reduction in clot to 20% of the original size or ≤10 cc was achieved.[318] Follow up CT scans were undertaken to assess drainage. Baseline ICH volumes were similar in both treatment arms (surgical-43.8±17.2 cc, medical-42.2±14.8 cc).[318, 319] The results revealed a mean reduction in clot size by nearly 50% in those treated with surgery and r-tPA whereas those treated as per guidelines had a 4% clot size reduction.[318] Significant adverse events and 30-day mortality were below prespecified limits.

Similar protocols were used when testing the role of r-tPA in IVH. With safety aspects of intraventricular r-tPA already addressed in a pilot study by Naff and colleagues, results from The Clot Lysis Evaluating Accelerated Resolution on Intraventricular Haemorrhage (CLEAR-IVH) provided more insight into the effectiveness of r-tPA.[320-322] In this trial, r-tPA in higher doses from 0.3 mg upto 3 mg twice a day increased resolution of IVH in all ventricles and quicker in the midline than in the posterolateral ventricles.[321] Furthermore, IVH

reduced faster with increasing r-tPA dose.[321] The investigators concluded that the differential treatment effect was probably due to the midline ventricles closer to the drug delivery system promoting greater drug-clot interaction and clot lysis and once the ventricular system was opened, r-tPA diverted away from regions further from the extraventricular drain.

A subgroup analysis of a systematic review assessing the effectiveness of effectiveness of MIS as compared to conservative medical treatment and conventional craniotomy in patients with supratentorial intracerebral hemorrhage revealed that likely candidates to benefit from MIS are conscious patients between 30 to 80 years of age with superficial haematoma, those with haematoma volume between 25 and 40 ml and treated within 72 hours after the onset of symptoms.[323] Although the methodological quality of included studies were not high, a review involving 1717 patients concluded that MIS was associated with a significant reduction in relative risk of death when compared to both craniotomy and medical management.[324] Examining the current data, no definite conclusions can be made about the role of MIS in spontaneous ICH but certainly provides impetus to further research in this subject.

1.21.2.3 Decompressive surgery

The recommendation of decompressive hemicraniectomy (DHC) to treat patients with hemispheric ICH is not robust as those with traumatic brain injury, high grade subarachnoid haemorrhage and malignant middle cerebral artery infarction.[325] Although mortality has been shown to be reduced, survivors are severely disabled.[313] DHC is attempted in patients with acute elevation in ICP, which can occur within few hours after haematoma evacuation.[325] In addition, the procedure might contribute to improvement in cerebral perfusion, oxygen supply and brain compliance.[326] In the absence of randomised evidence, experts suggest DHC with haematoma evacuation in patients with disturbed consciousness (GCS<8) and large haematomas volumes greater than 60 ml.[327] The application of DHC without haematoma evacuation is even more unclear.[328] For now, DHC remains a question of interest and does not form part of routine clinical care in ICH.[313, 326]

The various therapeutic approaches discussed in the above sections are aimed to lessen morbidity and mortality after primary brain injury. The following is a brief outline of work in limiting secondary brain injury after ICH, not used in this thesis, but included for the purposes of information as well as

to inform future work. The underlying mechanisms underlying secondary brain injury are unclear and compared with primary brain injury, fewer trials have been undertaken in this area.

1.21.3 Anti-inflammatory therapy

Because many patients continue to deteriorate clinically despite no signs of haematoma expansion or rebleeding, there is an increased interest in limiting secondary brain injury elicited by the physiological response to the haematoma (inflammation) in the perihaematoma tissues initiated by products of coagulation (thrombin) and clot breakdown (haemoglobin and iron).[329] Blood brain barrier breakdown in ICH as such could be linked to this inflammatory process through leucocyte infiltration,[330] but also could be a result caused by upregulation of leucocyte-derived reactive oxygen substances and pro-inflammatory cytokines such as TNF-α, interleukin -1β, chemokines and matrix metalloproteinases-MMP9 and MMP 3.[331, 332] The inflammatory process has been shown to start very soon after ictus, peaks in about a week and can persist for a month.[333] Activation of the resident microglia and astrocytes results in release of chemotactic factors and recruitment of haematogenous neutrophils, monocytes, macrophages and T cells which then engulf the deposited blood and repair damaged and dead tissue.

In a small study, the cyclo-oxygenase inhibitor celecoxib given for 14 days reduced peri-ICH oedema volume and lowered the expansion rate by half of that in the control group.[334] Another agent with anti-inflammatory properties, pioglitazone has been studied in a phase 11 study to determine the rate of haematoma resolution and the results are awaited.[335] A pilot trial of rosuvastatin also testing this hypothesis showed a positive effect,[336] but another involving simvastatin was stopped because of poor enrolment.[337]

Data from preclinical studies show that the thrombin inhibitor, argatroban reduces secondary brain injury after ICH.[338, 339] Antithrombin treatment seems paradoxical given its key role in haemostasis after ICH and neuroprotection in small concentrations. However, in large doses thrombin has been also shown to cause proliferation of mesenchymal cells, formation of scar tissue and brain oedema.[340] Although the majority of haematoma expansion occurs in the first few hours after ictus, thrombin release continues for upto 2 weeks.[341] Therefore, there may be a time window after the haematoma has stopped expanding when thrombin inhibitors could be administered and further research in this area is warranted.

1.21.4 Deferoxamine

The chelator, deferoxamine has been tested for its effects following growing evidence that excessive iron levels from haematoma breakdown mediate neuronal damage.[342, 343] In preclinical rodent studies, deferoxamine lowered brain oedema, neuronal death, cerebral atrophy and improved behavioural recovery.[342, 344] Based on safety data provided by a small study in patients with ICH,[345] a larger trial assessing the therapeutic efficacy of deferoxamine administration is ongoing.[346] Other approaches that are being investigated are whether inhibiting the enzyme haem oxygenase that releases iron from erythrocytes and removing free radicals generated by iron can reduce brain injury after ICH.[347]

1.21.5 Hypothermia

Hypothermia as a treatment approach in ICH is emerging, with preclinical studies suggesting the effects are mediated by preventing growth of peri-ICH oedema, reducing oxidative damage and blood-brain barrier disruption.[348, 349] However, the benefits depend on the type of cooling system, depth of cooling and duration of hypothermia.[350] A small study on 12 patients with large ICH treated with mild endovascular hypothermia (35 degrees) for 10 days, reported that

treatment was well tolerated and all patients survived upto final follow-up at 90 days.[351] Furthermore, there was no increase in peri-ICH oedema after rewarming. Although, no firm conclusion can be made, the results suggest further work in this area might be useful.[347]

Summary

Stroke, is a syndrome of vascular origin with diagnosis made at the bedside and confirmed on brain imaging. Management in a dedicated stroke unit with specialist staff is important and attention should be paid to avoid complications. Intracerebral haemorrhage is the most devastating stroke subtype and in comparison with ischaemic stroke in which acute treatments are proven to be beneficial, is more difficult to treat and associated with higher mortality in the acute phase. A substantial number of patients decline early from multiple factors including haemorrhage size, brain location, early haematoma expansion, raised intracranial pressure, intraventricular extension and hydrocephalus. The pathophysiological mechanisms are now being understood and provide a starting point for identification of treatment targets. In addition to primary brain injury, secondary brain damage occurs from blood and its toxic products released within hours and lasts upto several days. Haematoma expansion is

maximum in the first few hours and brain scan repetition showing surrogate markers of ongoing bleeding appear to be useful.

Medical management of intracerebral haemorrhage has shifted from one of passive care to specific measures aimed at stopping or reducing haematoma expansion, prevention of intraventricular extension, treating cerebral oedema and mass effect. Accurate, reproducible and validated measurement of haemorrhage size (also allowing measurement in change) is therefore critical to identify thresholds where treatment may benefit or modest at best. Cerebral autoregulation is disrupted in the acute phase and accumulating evidence suggests lowering elevated blood pressure may not cause ischaemia in the penumbra region surrounding the haematoma. A complicating factor when deciding if and when to treat post-stroke hypertension is that the potential risks and benefits vary with the type of agent, formulation and route of administration. To complicate matters, upto one-half of patients admitted with acute stroke are on blood pressure lowering medications and it is unclear whether they should be continued or stopped. Preclinical studies targeting secondary brain injury are promising, but limited clinical data is available and many questions remain unanswered.

1.22 Aims : The Current Investigation

The work to-date examining intracerebral haemorrhage is wide-ranging in its scope, from preclinical models, through observational data of clinical studies to clinical trials of intervention resulting in consistent and inconsistent evidence on several parameters. There appear to be gaps in current knowledge on clinical characteristics, radiological parameters (haematoma characteristics, markers of haematoma expansion) and treatment options (such as non-invasive blood pressure treatment, haemostasis and surgery). There is variation in both magnitude and rate of recovery with a large proportion of patients failing to survive in the first weeks.

The challenges and questions listed above are wide-ranging and too complex to be answered by a single study. However, if we are to make some progress in this field of acute stroke, each or some of these questions must be examined in turn.

This thesis will concentrate on few aspects outlined below:

1. To evaluate the methods for quantifying volume of intracerebral haemorrhage and to determine sources of error that effect variation using data from a large multinational trial, The Efficacy of Nitric Oxide in Stroke Trial (ENOS)
2. To assess the effects of blood pressure lowering with transdermal glyceryl trinitrate (GTN) in acute intracerebral haemorrhage and effects on functional outcome
3. To evaluate the effects of continuing versus stopping prior antihypertensive drugs in the hyperacute stages of intracerebral haemorrhage using data from ENOS
4. To compare the baseline characteristics and outcomes of patients with spontaneous intracerebral haemorrhage from different ethnic backgrounds
5. To update a systematic review assessing the effects of deliberately altering blood pressure in stroke.

Chapter 2 - Materials and Methods

Publications contributing to this chapter:

Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, Sprigg N, Berge E, Beridze M, Caso C, Chen C, Christensen H, Collins R, El Etribi A, Laska A, Lees KR, Ozturk S, Phillips S, Pocock S, Asita de Silva HA, Szatmari S, Utton S.

Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial

Lancet 2015; 385 (9968): 617-28

This chapter outlines the background and the methods applied to chapter 3,4,5 where the performance characteristics of the various methods used to measure ICH parameters (including volume, shape, density, bleeding into the ventricles) and the relationship between clinical characteristics and functional outcomes were assessed.

2.1 Background and purpose

The combination of ICH volume, an early increase in amount and initial level of consciousness relate to poor outcome[225] and therefore the ability to rapidly perform accurate measurements can be considered an important component in early clinical management. The first study to describe calculation of ICH volume was in the 1980's by Kwak et al and involved patients with thalamic haemorrhages.[352] Here, the maximum width (X), length (Y) and height (Z) of haemorrhage on a CT scan was estimated visually and the volume derived from multiplying X, Y and Z divided by 2.[352] With advances in scanning techniques, each parameter can be measured thereby allowing more accurate value incorporation into a formula adjusting for the slice thickness. It was debated whether approximating a haemorrhage as a sphere, ellipsoid or rectangulopiped figure produced accurate volume

measurements, but incorporating shape as an ellipsoid correlated well with volume values obtained from software aided measurements.[251, 353, 354]

2.1.1 Intracerebral haemorrhage volume measurement

Three methods are commonly used to measure haematoma volume- ABC/2, semi-automatic segmentation (SAS) and fully automatic 3-D volume rendering. The ABC/2 method can be performed by the bedside whilst SAS and 3-D volume rendering need the help of a computer and use of advanced software.[246, 251, 252, 353-355]

Calculating haematoma volume as an 'ideal' ellipsoid equates to 4/3 $\prod$*A/2*B/2*C/2 where 'A' constitutes the greatest measured length of the haemorrhage, 'B' is the largest diameter perpendicular to the greatest length and 'C' corresponds to the number of slices with haemorrhage visualised multiplied with the slice thickness.[251, 353] Approximating $\prod \sim 3$ simplifies the formula to ABC/2. This formula was modified in 1993, by Kothari and colleagues.[251] Here, the authors attempted to adjust for the height dimension (which assigned a value of 1 for each slice the haemorrhage was viewed) by introducing the modified 'C' rule.[251] If the scan slice showing haemorrhage was estimated

to be less than 25% of the slice with the largest surface area, then that slice was excluded. For a given slice area, a score of 0.5 was allocated if the measured area was between 25% of the largest haemorrhage area and a score of 1 was recorded if the measured area was greater than 75% of the largest area.[251] Next, the sum of each haemorrhage area slice was calculated to obtain C. Finally, A, B and C were multiplied together and the product divided by 2 to obtain the calculated haemorrhage volume in cubic centrimetres (cm^3). One variation, 2/3 SH where (S) is the largest surface area and the height (H) of the haematoma denoted by the scan slice thickness multiplied by the number of slices[356] has been proposed but the methodological reasons are not understood.

SAS method is based on an interactive region growing process using computer software to isolate haemorrhage from surrounding tissue via the intensity of different tissue types on a CT scan.[357-359] The user draws a curve through the region of interest (ROI) considered to be haemorrhage and the algorithm calculates the image features along the user-defined path and the computed features are used in the region-growing process.[245] On CT scans, blood appears 'whitish' (hyperintense between 40-80 Hounsfield units) compared to brain tissue and relevant parameters can be set to exclude

normal brain tissue and bone. The process can be repeated until the user is satisfied with the included segmented region. The area of each slice measured within these parameters is added together and multiplied with the slice thickness to obtain the haemorrhage volume.

3-D volume rendering utilises complex software algorithms and provides effective visualisation including rotated views of the haemorrhage.[359, 360] The user is required to specify the position of the ICH on the image and the program extracts the surrounding volume and performs the analysis. First, the ICH region is highlighted by a light source and the shading information is calculated by multiplying the 3-D gradient vector of the ICH region with the vector of the light source.[245] Further, distance shading is performed to obtain a realistic view of the image and then the scan slices are merged into lines.[359] Finally, the procedure is repeated for several rotated versions of the haematoma region to provide a set of rotated 3-D views.[245]

2.1.2 Assessment of Intracerebral haematoma shape and density

Variation in visual assessment of intracerebral haematoma shape and density attenuation as predictors of haemorrhage

growth was first suggested by Fujii et al[361] and further developed by Barras and colleagues.[212, 362] The theory underpinning this was a haemorrhage seen on a CT scan arising from a ruptured single blood vessel appears homogeneous whereas bleeding from multiple foci and ongoing bleeding presents with an irregular edge and heterogeneous attenuation.[212] In a small trial population of ICH patients scanned very early, a novel visual and density scale was introduced in an ascending order from 1 to 5 and each progressive category added an extra lesion edge irregularity suggestive of active bleeding on either scale.[212] For example, Category 1 was assigned to a regular shape and homogeneous haematoma whilst Category 5 was given to the most irregular shape and heterogeneous density.[212] Those patients with haemorrhages extending into the ventricles were excluded. The results revealed a strong relationship between shape irregularity and density heterogeneity.[212] On a continuous scale, the study also revealed that larger haematomas were irregular in shape, more heterogeneous at baseline and significantly more likely to expand.[212]

To quantitatively describe haemorrhage shape, it can be expressed as a variation from 'roundness' or deviation from isometry.[363] When considering the physical properties, the

assessment of a 'round' shape may not imply isometry as blood leakage and extension occur in any direction when a vessel wall ruptures and blood components such as platelets and smooth vessel fibres travel at various speeds.[363] Therefore, a concept combining circularity and isometry is suggested to describe haemorrhage shape: the formula $P^2/4\pi A$ where 'A' is the surface area of the largest haemorrhage slice and 'P' is the perimeter.[363] The value obtained is a number and $\leq$ 1 implies that the shape is circular and >1 as non-circular.

Quantitative assessment of haemorrhage density was performed in a pilot study of 90 patients with ICH and the measured parameters included mean attenuation of haemorrhage, standard deviation, coefficient of variation, skewness and kurtosis.[362] Of these, the coefficient of variation was the most significant individual predictor of haematoma growth.[362] However, patients were from a placebo arm of a trial[362] and scanned very early.

To conclude, haemorrhage parameters assessed using quantitative and qualitative approaches seem to be useful and each studied in part. The techniques are reliant on computer software, radiological interpretation and so far the information

is confined to small datasets. Hence, the objective was set to examine the accuracy and reliability of ICH volume calculation -formula ABC/2, its modified version, automated 3-D rendering in conjunction with estimating haematoma shape and density (both qualitative and quantitative) in a large population of ICH patients and those receiving treatment. Furthermore, examining their association with key clinical variables (such as baseline blood pressure, level of consciousness and time to scanning) and prognosis might aid rapid decision-making in acute clinical situations and selection of patients to future clinical trials. The hypothesis was tested in the setting of a large, randomised controlled trial, Efficacy of Nitric Oxide in Stroke (ENOS)[364] involving patients with ICH, presenting within 48 hours and treated in various health-care systems.

2.2 Materials and methods

2.2.1 The Efficacy of Nitric Oxide in Stroke (ENOS) trial

2.2.1.1 Methods

ENOS was an international, multicentre, single-blind, prospective randomised controlled trial investigating the management of blood pressure in acute stroke.[364] The trial ran for 13 years and was conducted in accordance with the Declaration of Helsinki and 'International Conference on Harmonisation of Good Clinical Practice'. Patient data management was according to the UK Data Protection Act 1998.

2.2.1.2 Subjects

Previously independent patients aged 18 years or older having motor weakness in arm/and or leg and systolic blood pressure of 140-220 mm Hg presenting within 48 hours of symptom onset were assigned to 7 days of transdermal GTN 5 mg patch or no GTN. Patients were blinded with placement of a gauze dressing over an area of skin out of view with or without the patch underneath. A subset of patients who were taking antihypertensive drugs prior to their stroke were allocated to

continue or stop medications in a partial-factorial design. Assent from a proxy carer or relative was allowed if the participant was confused, dysphasic or semi-conscious. Randomisation was performed centrally over a password protected, data encrypted website, with stratification by prior antihypertensive treatment and country; minimisation on key prognostic variables: sex, age, stroke severity, time to treatment and total anterior circulation syndrome. Patients were excluded if they had one or more of the following: Glasgow coma scale <8; definite need or contraindication to nitrates; clinical indication to continue or stop blood pressure lowering drugs; confounding neurological disorder or psychiatric disease; liver or renal dysfunction.

2.2.1.3 Haemodynamic measures

SBP, DBP and HR were recorded at baseline and daily 1-2 hours after administration or change in patch with the patient lying or sitting in bed. Day 1 measurement of BP was taken 1-2 hours after the patch was applied. Both BP and HR values were measured using validated automatic digital monitors (Omron HEM-705CP or HEM, 757, Illinois, USA).[365]

2.2.1.4 Clinical outcomes

The primary outcome was assessed using the mRS determined by a trained assessor masked to treatment allocation in each country at day 90 (+10 days). For participants not contacted through telephone, information was obtained using a follow up questionnaire sent through the post. Key outcomes assessed at the end of treatment included blood pressure and heart rate, proportion of patients with neurological deterioration (defined as reduction in SSS of >5 points or decrease in the consciousness domain of SSS of >2 points or both), recurrent stroke at day 7, episodes of hypo or hypertension requiring medical intervention and death. Other key outcomes included disability (Barthel Index), duration of hospital stay, discharge destination (patient's own home or other such as institution) and mood (short Zung depression score); these were determined centrally at day 90. An independent data monitoring committee assessed unblinded safety data in respect of safety and efficacy and in the context of other ongoing blood pressure trials in stroke.

2.2.1.5 Neuroimaging measures

The diagnosis of ischaemic or haemorrhagic stroke was confirmed using CT or MRI scans before or by 7 days after

enrolment according to standard imaging protocols in the local investigating centre. If possible, a repeat scan was performed at end of treatment (day 7+1). Scan interpretation by the local investigator was collected; the images were also adjudicated centrally over the Internet NeuroGrid[366] by an independent neuroradiology expert panel blinded to treatment allocation. Scans for adjudicated for the location of haemorrhage, estimate of its size and for the presence of other background findings (mass effect, leukoaraiosis, brain atrophy, old infarct or haemorrhage) using validated scoring systems.[367] The imaging administrator of ENOS transferred images to trained observers blinded to clinical data and treatment allocation. Haemorrhage parameters including volume, shape and density were measured using a software suitable Osirix, for viewing CT and MRI images.

2.2.2 Osirix software for Viewing CT/MRI scans

2.2.2.1 Introduction

Osirix (www.osirix-viewer.com) is an image processing interactive software available for free to download and view CT/MRI images.[368, 369] The application displays, reviews, interprets and helps in post-processing images optimally handed and stored in DICOM (Digital Imaging and

Communications in Medicine) format. The software can only be installed on a Mac running operating systems (OS).[369] For the purpose of assessing intracerebral haematoma characteristics of patients recruited into ENOS, Osirix version 3.3.2 was installed on an iMAC 7.1 model, Intel 4GB processor with monitor resolution of 1200 pixels.

The 2D viewer window consisting of the Toolbar, The Image view and the Preview list is the starting point. The thickness between each slice is displayed in the lower left hand viewing panel. The Growing Button displays the Region Growing Panel with Region of Interest (ROI) tools. In Osirix, ROI is used to describe a measurement, area or an annotation. ICH is indicated by a high density (white spot or region) in parenchymal tissues, according to the principles of a CT scan.

2.2.2.2 General Methods

Once the software is opened, each scan image of a patient with intracerebral haemorrhage was obtained using the 'Import' tab. By selecting the study name the image was seen. To draw a haemorrhage ROI, the corresponding tool from the Mouse Button Function in the 2D viewer bar was selected. The length ROI was used to draw simple lines and obtain linear

measurements. The starting point was clicked, mouse button pressed and dragged to the ending point and released. The underlying DICOM image with pixel size information and length in cm or μm was shown. If one parameter was incorrect or unavailable, the software displayed an error message. This was observed when some images were in different format other than DICOM, for instance: jpeg, png and gif. In such cases, the parameters were defined using the Calibrate Resolution tool.

To assign calibration parameters for an image, a centimetre scale was used to measure the distance across the scan image. With the length and measurement, the number of pixels to traverse the distance measured included in the image was noted. The value of each pixel length was calculated by dividing the measured length using the centimetre scale by the number of pixels over that distance. The Calibrate Resolution tool was selected, values entered and the OK button clicked to derive the ROI's.

The Brush ROI tool was used to click on the image and the desired shape of haemorrhage drawn while holding down the mouse button. The mouse button was released to finalise the ROI. Following this the 'compute' button was clicked and the

area (in cm2 or μm2), mean, standard deviation, sum, minimum and maximum value were obtained. The Brush ROI is the only ROI that cannot be moved; it is attached to its underlying pixels.

The Closed Polygon ROI was used to draw polygons to find specific areas of irregular shaped-haemorrhages or in presence of other structures. This application is available in the 'Mouse Button' function in Osirix. Here, clicking on as many corners around the haematoma is needed to isolate the area of interest and a double-click on the last focus region to complete the ROI. The first and the last corners are connected upon completion. The area of haemorrhage, perimeter length, mean and maximum density heterogeneity are then displayed. To measure another area of haemorrhage on the same scan slice, all selected ROI's were deselected by clicking anywhere on the first image with a ROI tool or choosing the Deselect All ROI's in the Series item in the ROI menu.

2.2.2.2.1 Calculating Intracerebral haemorrhage volume using Osirix

This section describes how haemorrhage volume was determined using Osirix.

2.2.2.2.1.1 ABC/2 formula

For the ABC/2 method, the scan slice with the largest area of haemorrhage was identified. 'A' was the measured largest diameter of the largest haemorrhage slice, 'B' the largest diameter perpendicular A on the same slice and C was calculated as the number of slices in which the haematoma was visualised multiplied by the slice thickness (Figure 2.1). For the modified ABC/2, a slice was considered as C depending on the size of the haemorrhage area on that particular size. The haemorrhage area was considered as '1' haemorrhage slice if that area was more than 75% of the largest haemorrhage area in that series. If that area was between 25-75% of the largest haemorrhage area then it was considered as 0.5 haemorrhage slice. If the haemorrhage area was less than 25% of the largest haemorrhage area, the slice was discarded.

2.2.2.2.1.2 Automatic volume calculator (3-D rendering)

The first step was to create a ROI as explained in the earlier general methods section. Upper and lower thresholds of density values for example, 40-80 Hounsfield units over an area of haemorrhage are displayed by clicking on the area

with the computer mouse and moving the cursor. In the segmentation parameter, upper and lower thresholds of density of haemorrhage were then recorded. In the same page, the '3D growing region (entire series)' and 'Neighbour' Algorithm (to exclude an area of similar density elsewhere in the brain for example choroid plexus) were selected. Finally, the 'Compute Volume' tab under ROI Volume in the ROI menu was clicked. A 3D image of the haemorrhage shaded in green with the computed volume appeared on the screen. (Figure 2.2)

2.2.2.2.1.3 Semi-automated Segmentation

The first step in segmentation involved isolating areas of haemorrhage based on higher densities indicated by moving the mouse cursor over the scan image. Once the areas of haemorrhage were identified, the segmentation parameters were created manually by drawing the ROI using the tools in Osirix (as described earlier). The area within each segmented region was displayed once the ROI was complete. The final step was to sum up each of the slice areas and multiplying the value with the slice thickness for each scan. Thus the semi-automated segmentation volume was obtained.

Figure 2.1 Osirix software image of a CT scan of patient recruited into the ENOS trial showing an area of hyperattenuation in the region of the left internal capsule suggesting rupture of the middle cerebral artery.

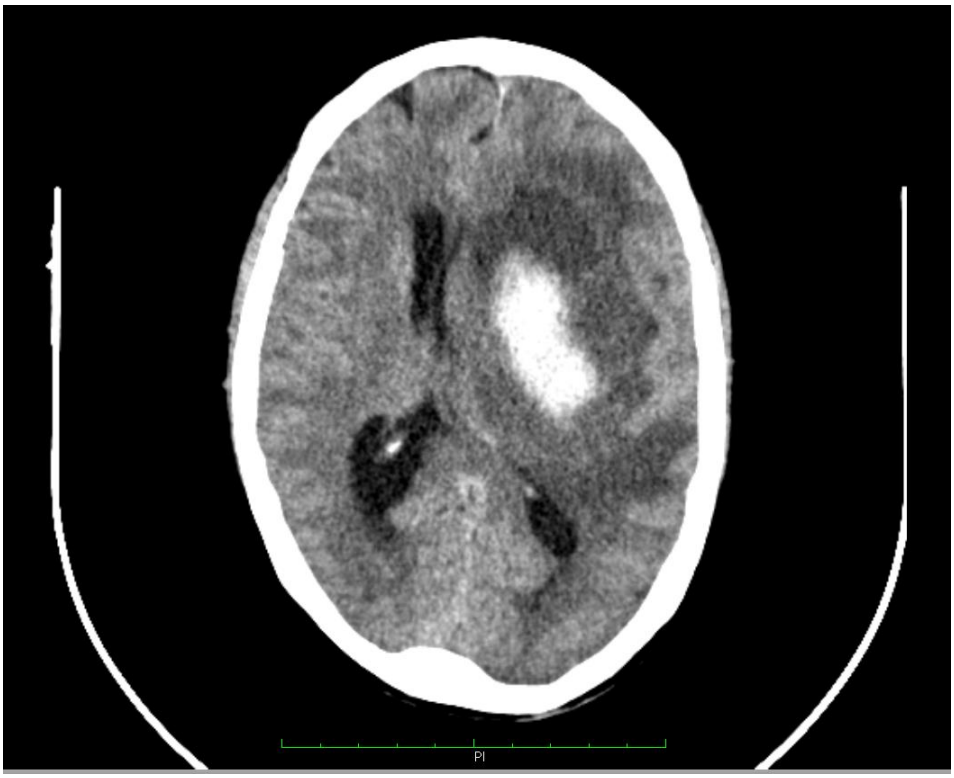


Figure 2.2 Example of using Brush ROI for estimating ICH volume. The arrow indicating the region of haemorrhage is highlighted in green once the pixel thresholds are determined. The panel on the left displays the segmentation parameters.

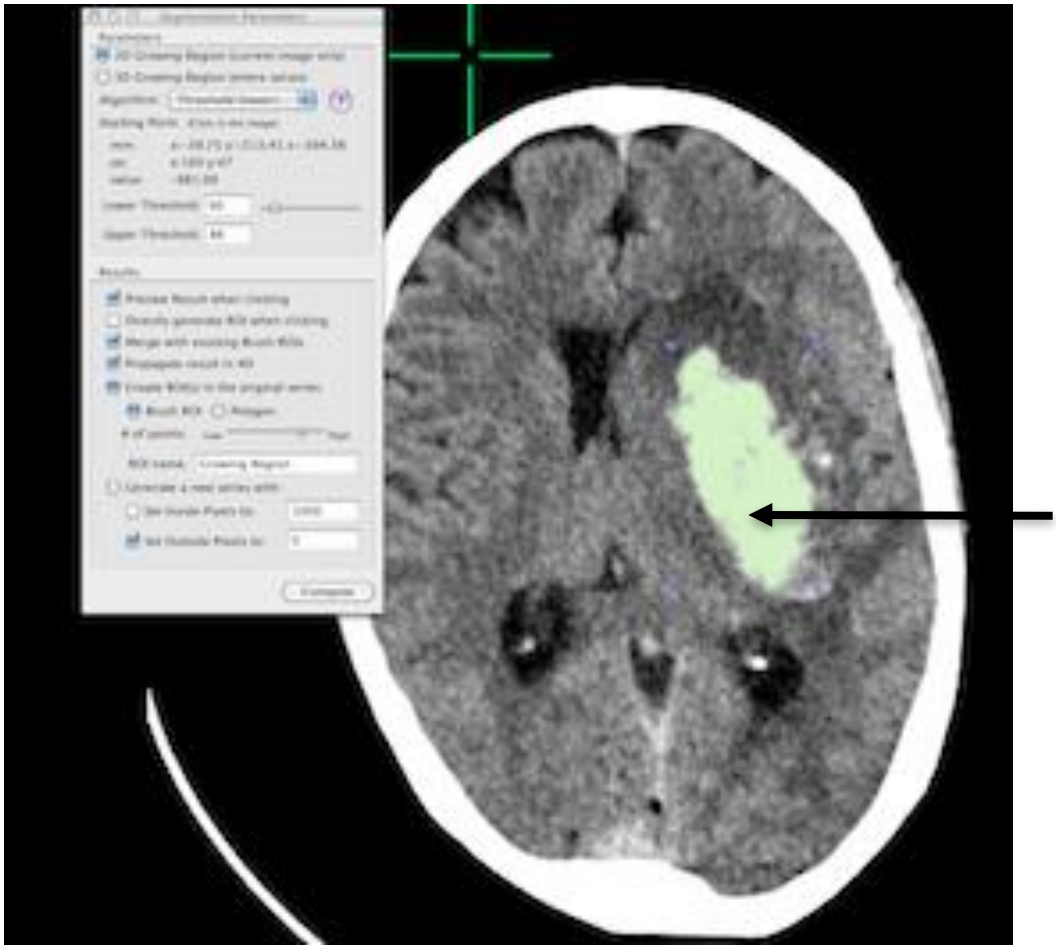


Figure 2.3 Example of closed polygon method using Osirix. The panel shows the surface area of haemorrhage, mean, standard deviation, min and maximum haematoma density attenuation and length (perimeter).

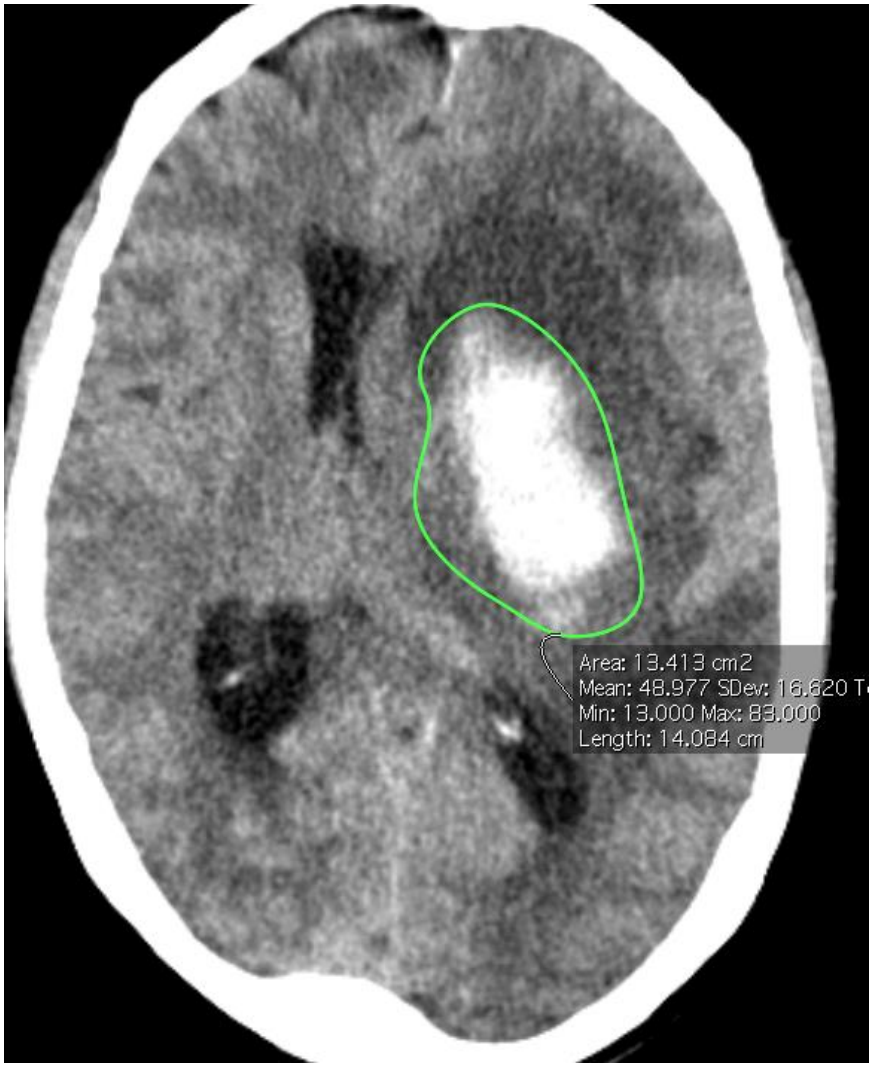


Figure 2.4 ABC/2 method using Osirix. The red lines are the measured largest haemorrhage diameter 'A' and the largest perpendicular diameter 'B'.

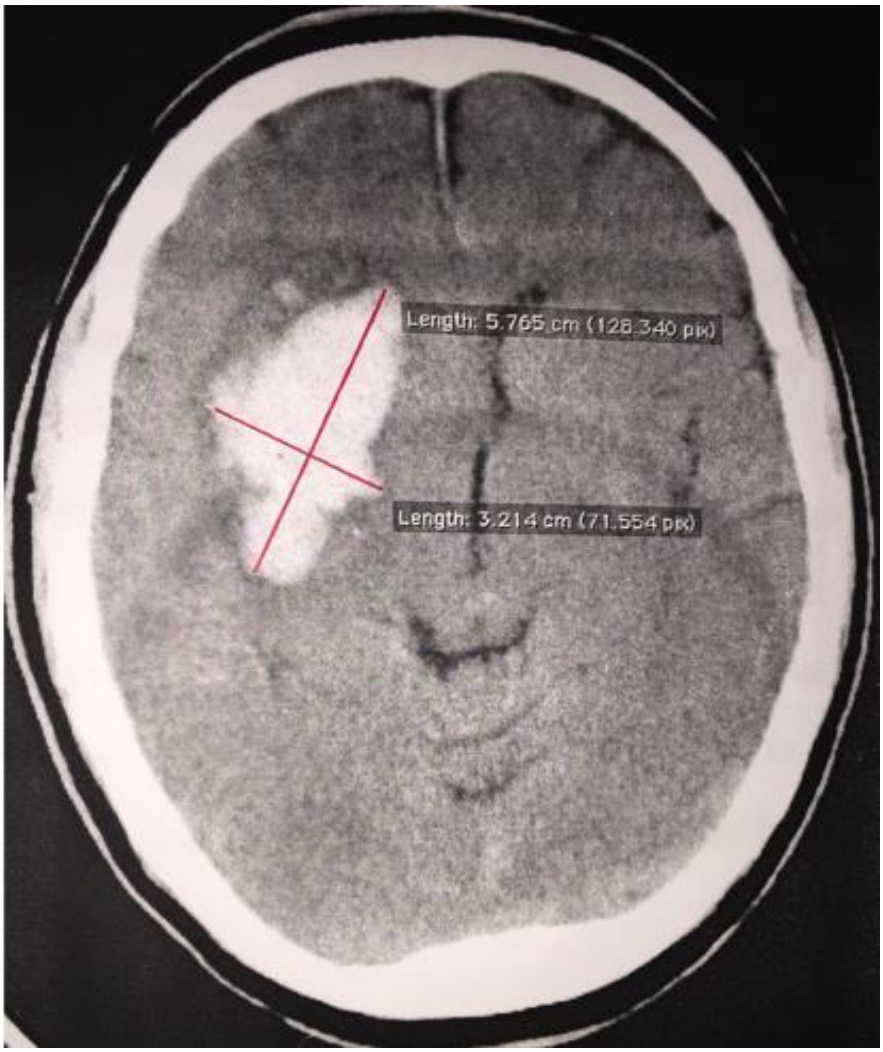


Figure 2.5 An example of the 3-D image from Osirix showing automatic computed haemorrhage volume.

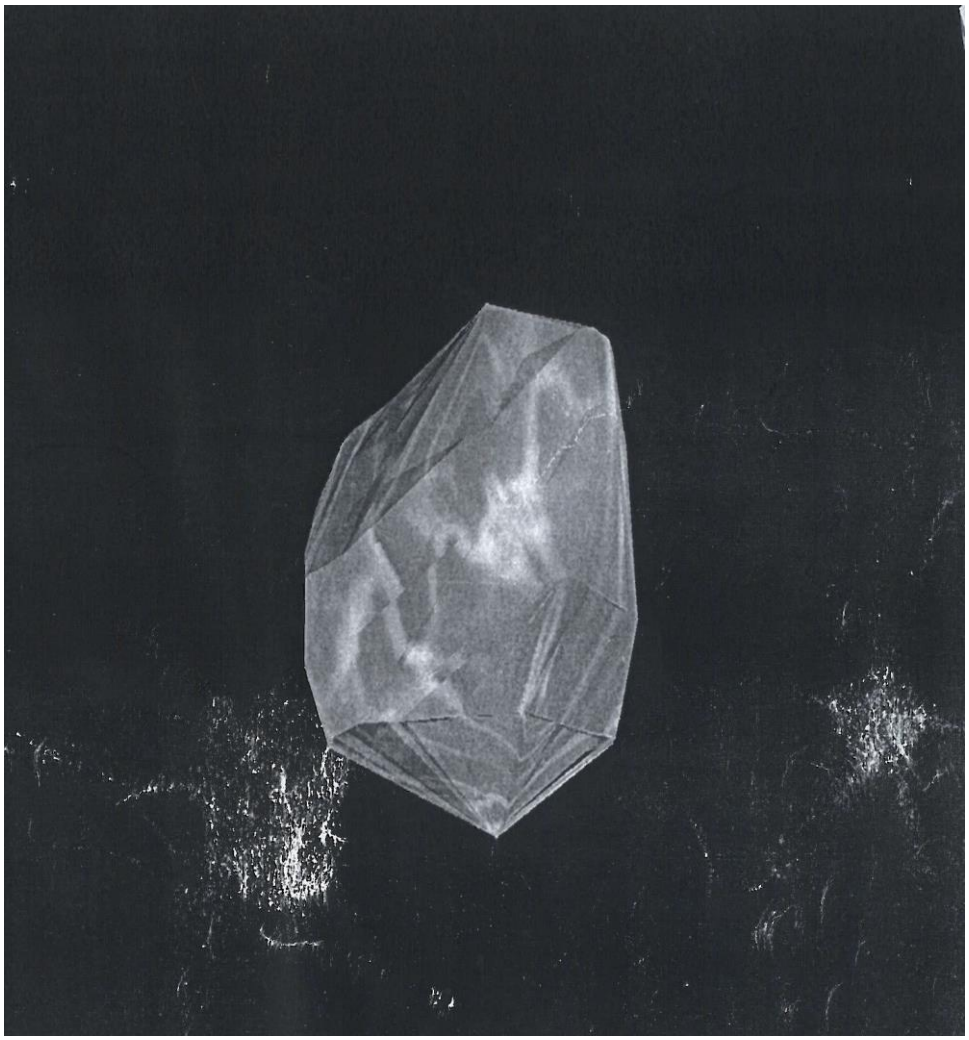
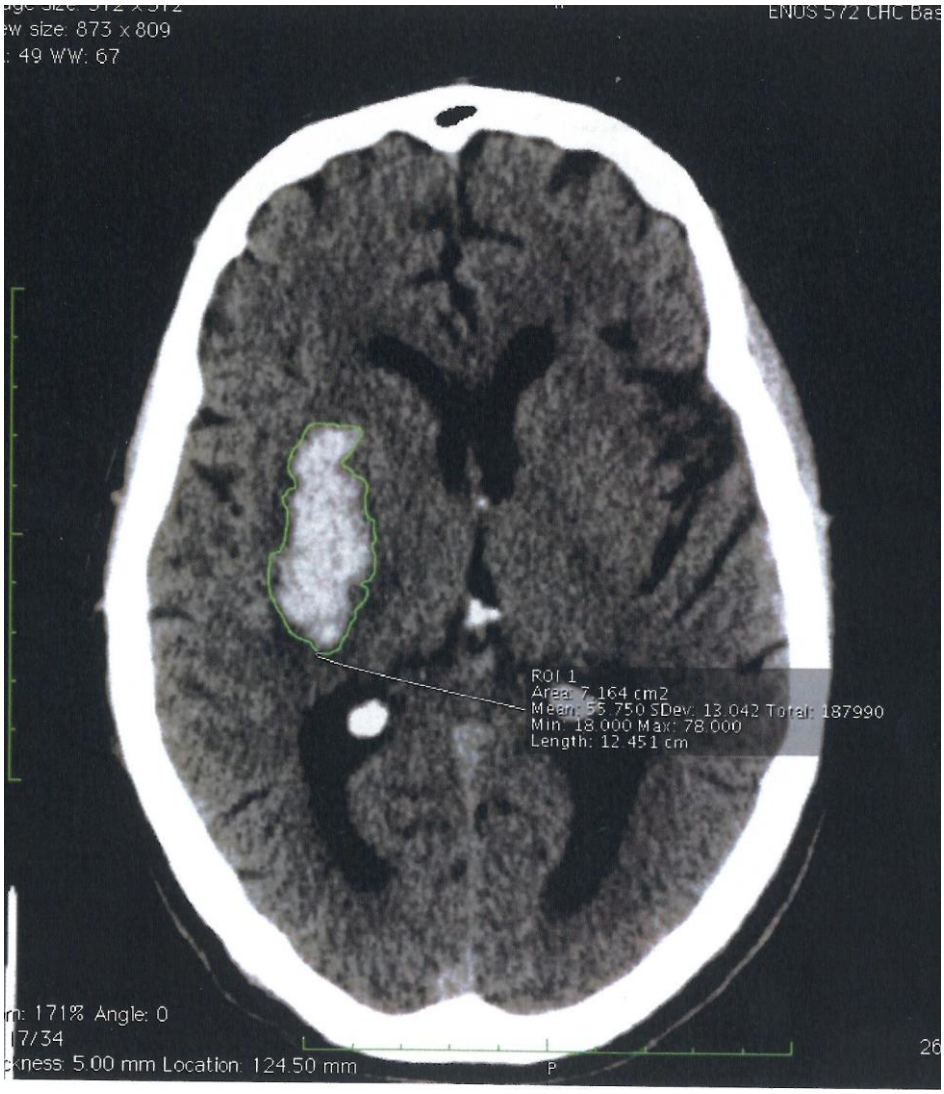


Figure 2.6 An example of semi-automated segmentation. The highlighted area is the ROI. The scan slice thickness is indicated in the bottom left hand corner.



Chapter 3 - Performance characteristics of the methods used to quantify spontaneous intracerebral haemorrhage

Publications contributing to this chapter:

Krishnan K, Siti F Mukhtar, Lingard J, Houlton A, Walker E, Jones T, Sprigg N, Cala LA, Becker JL, Dineen RA, Koumellis P, Adami A, Casado AM, Bath PMW, Wardlaw JM

Performance characteristics of methods for quantifying spontaneous intracerebral haemorrhage: data from the Efficacy of Nitric Oxide in Stroke (ENOS) trial (ISRCTN99414122).

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ABSTRACT

Background and Purpose

Poor prognosis after intracerebral haemorrhage (ICH) is related to haemorrhage characteristics. With developing therapeutic interventions, there is a pressing need to understand the performance of haemorrhage descriptors in large clinical trials.

Methods

Clinical and neuroimaging data were obtained for 548 participants with ICH from the Efficacy of Nitric Oxide in Stroke trial. Independent observers performed visual categorisation of largest diameter, measured volume using ABC/2, modified ABC/2, semi-automated segmentation, fully automatic measurement methods; shape, density and intraventricular haemorrhage were assessed. Intra-and inter-observer reliability were determined for these measures.

Results

ICH volume was significantly different between standard ABC/2, modified ABC/2 and SAS: (mean) 12.8 (s.d.16.3), 8.9 (9.2), 12.8 (13.1) cm^3 respectively ($p<0.0001$). There was excellent agreement for haemorrhage volume (n=193): ABC/2 intra-observer intraclass correlation coefficient (ICC) 0.96-

0.97, inter-observer ICC 0.88; modified ABC/2 intra-observer ICC 0.95-0.97, inter-observer ICC 0.91; SAS intra-observer ICC 0.95-0.99, inter-observer ICC 0.93; largest diameter: (visual) inter-adjudicator ICC 0.82, (visual vs. measured) adjudicator vs. observer ICC 0.71; shape intra-observer ICC 0.88 inter-observer ICC 0.75; density intra-observer ICC 0.86, inter-observer ICC 0.73. Graeb score (mean 3.53) and modified Graeb (5.22) scores were highly correlated. Larger ICH's were more irregular in shape (64%) ($p<0.0001$). Using modified ABC/2, ICH volume was underestimated in regular (by 2.2-2.5 cm3, $p<0.0001$) and irregular shaped haemorrhages (by 4.8-4.9cm3, $p<0.0001$). Fully automated measurement of haemorrhage volume was possible in 5% of cases.

Conclusions

Formal measurement of haemorrhage characteristics and visual estimates are reproducible. The standard ABC/2 is superior to the modified ABC/2 method for quantifying intracerebral haemorrhage volume.

3.1 Introduction

Spontaneous intracerebral haemorrhage (ICH) is usually a severe form of stroke with a high mortality rate (~ 50%) by the end of the first year.[225] As discussed in the chapter 1, the combination of ICH volume and initial Glasgow Coma scale is reported to be the strongest independent predictor of 30 day outcome.[225] Hence, reliable measurement of haemorrhage size is an important component of early clinical management and for stratification in clinical trials.

Although any effective intervention will ultimately need to show an effect on functional outcome (e.g. using the mRS [370]) in phase III trials, earlier developments will need to study the effect of treatment on a surrogate measure. Where the intervention aims to limit haemorrhage expansion, accurate, reproducible and validated measurement of haemorrhage size (thereby allowing measurement of the change in volume) will be critical. Hence, phase II trials of blood pressure lowering and haemostatic interventions have utilised measurement of haemorrhage expansion as a key primary outcome.[260, 371]

There are multiple methods for measuring haemorrhage volume on a CT scan, ranging from qualitative visual

estimation to computerised automatic measurement. Visual approaches (i.e. visual size categorisation based on the largest diameter) are quick and as detailed in chapter 2, ABC/2 method, modified version of ABC/2, semi-automatic or fully automatic computerised methods may also be used. The relative advantages and disadvantages of these approaches reflect the balance between measurement time, type of data required, accuracy and availability of computer workstations, and sample size, all studied in part.[249, 250, 252, 253] Assessment of additional properties of haemorrhage such as shape and density[212, 362], and extension into the ventricles or subarachnoid space as detailed in the introduction, may also be useful.[240, 241]

In this study, we assessed and compared methods for measuring haemorrhage size, shape and density, and IVH size. The data come from the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial,[364] which included patients with ICH.

3.2 Methods

3.2.1 Patients

The methodology of the ENOS trial is described in chapter 2. Participants had a baseline CT or MRI brain scan as part of clinical care, usually before randomisation. Where possible, a second (research) CT or MRI scan was performed at day 7±1 (end-of-treatment). DICOM, JPEG, PNG or GIF files are sent, to the coordinating centre. Any scans sent on film were digitised using a VICOM digitiser (VIDAR Diagnostic PRO™ Advantage, USA). The following study assesses only those patients with a CT scan. For each patient, images were received with the thinnest slices provided by CT scan machines using standardised protocols in the recruiting centres. However, during the course of the trial more volumetric images were made available because of advances in imaging technology.

3.2.2 Scan adjudication

Complete CT scan series were made available for assessment by a group of 7 adjudicators comprising accredited neuroradiologists or neurologists trained in CT brain imaging

assessment in stroke (www.neuroimage.co.uk/sirs, with coordination by JMW).[367] Images were viewed over the web, blind to all clinical and treatment information except for patient age, time since onset of stroke and side of brain symptoms. Responses were entered directly into the trial database via a web-based response form. Collected information included whether the patient had an ICH and, its location; an estimate of its size (sorted into ordered categories based on the longest diameter in any plane): <3, 3-4.9, 5-8, >8 cm; and the presence of other qualitative findings (mass effect,[367] atrophy,[367] white matter disease,[372] old infarct or haemorrhage) using validated scoring methods.

3.2.3 Scan haemorrhage quantification

Scans were visualised and analysed using OsiriX software for Mac (version 3, 32 bit, www.osirix-viewer.com)[368] and the details discussed in chapter 2. Two trained observers (K.K., S.M.) measured baseline ICH volumes of 193 patients using ABC/2, modified ABC/2, semi-automatic segmentation (SAS) and automatic volume calculation (AVC, using 3D rendering of a stack of 2D slices). Both observers assessed scans blinded to each other's data, and repeated a proportion of the scans (47 and 34 scans for KK and S.M. respectively) at a different time blinded to their original measurements. Thus, intra and

inter-observer variation could be estimated. For the remaining 355 patients, one observer (K.K.) calculated ICH volumes using all four methods. Appendix I shows a diagram with the number of scans used to assess intra and inter observation variation.

The methodology of haematoma volume measurement using ABC/2 method and the modified version, SAS and AVC is detailed in chapter 2.

For SAS and AVC, it was possible to use thresholds so that the haemorrhage Region of Interest (ROI) was measured within certain segmentation parameters. Upper and lower attenuation values (typically 40-80 Hounsfield units) of haemorrhage were established manually by sampling from the haemorrhage and normal brain. Where the threshold did not exclude non-haemorrhage areas (as with the pineal gland, calcified choroid plexus, bone) in close proximity with the haemorrhage, the haemorrhage boundary was manually edited. The area of each slice that was included within these parameters was measured, added together and multiplied by scan thickness to obtain the semi-automatic segmentation volume. AVC used an Osirix '3D growing region (entire series)' method after selecting a threshold part of the haemorrhage

near to its centre. With all methods, intraventricular haemorrhage blood was included in the final ICH volume.

Additionally, four haemorrhage characteristics (area, perimeter, mean attenuation, and standard deviation of attenuation) were recorded for the haemorrhage from the slice with the largest area of haemorrhage. Haemorrhage shape and density indices were then calculated as:

- Shape index [363] = perimeter ^{2} / 4∏ x area
- Density index[362] = standard deviation / mean (i.e. coefficient of variation)

The heterogeneity of haemorrhage shape and density were also assessed visually using an ordered categorical scale (1 to 5) where for an extra lesion edge irregularity an additional point was given on the shape and density scale.[212] Similarly, intraventricular blood volume was assessed visually using the Graeb score and modified Graeb ordered categorical scales.[240, 241]

Intra- and inter-observer reliability was determined for visual categorisation of shape and density. In addition, intraobserver reliability was assessed for measured shape, density index, Graeb, modified Graeb and intraventricular haemorrhage

volume over different reading sessions, separated by a minimum of fourteen-days. All adjudication and haemorrhage measurements were made blind to baseline and follow-up clinical information, other imaging and treatment assignment.

3.3 Statistical Analysis

Data are shown as number (%), median [interquartile range] or mean (standard deviation). Measurement of intra-observer and inter-observer variability was assessed using the intra-class correlation coefficient (ICC).[373] A probability value of <0.05 was considered statistically significant. Analyses were performed using SPSS (version 21) and checked with Medistat running on an Apple Mac.

3.4 Results

Altogether, 629 patients with ICH were enrolled into ENOS.[137, 374] Of these, 548 patients had CT-confirmed ICH and a baseline scan available for measurement; 81 other patients either had ICH diagnosed on MRI or had no CT scan available, and these were excluded. Patient demographic and clinical details are shown in table 3.1. The mean age of the 548 patients in the present analysis was 67 (standard deviation 12) years, 66% of patients were male, mean baseline blood

pressure was 171 (19)/92 (13) mmHg, and the median time from onset of ictus to performing neuroimaging was 4.5 [interquartile range 5.6] hours. When adjudicated visually by experts, 63% of haematomas were located in the middle cerebral artery territory (table 3.1); most haemorrhages caused mass effect (86%) and many patients had leukoaraiosis (66%) and/or previous stroke lesion (49%) present on their scans. The most frequent visually assessed haemorrhage length category was 3-5cm (224, 41.3%), closely followed by <3 cm (220, 40.6%) with much fewer larger haemorrhages. The mean measured haemorrhage length was 3.4 cm (longest diameter) (Table 3.1).

3.4.1 Intracerebral Haemorrhage (ICH) volume

ICH volume was significantly different between ABC/2, modified ABC/2 and SAS: 12.8 (mean) (s.d.16.3), 8.9 (9.2), 12.8 (13.1) cm^3 respectively ($p<0.0001$) (Table 3.2). The ICC was 'excellent' at 0.84-0.96 when comparing the observers' measurements for each of ABC/2, modified ABC/2 and semi-automatic segmentation (Table 3.2). The observers found haemorrhage volume to be larger, by an average of 2.7-4.0 cm^3 with standard ABC/2 as compared to modified ABC/2, and 1.4-4.0 cm^3 smaller with SAS as compared to modified ABC/2.

As the mean ICH value increased, the difference between ICH volume measured by modified ABC/2 versus the other two methods increased (Figures 3.1, 3.2) but no significant difference was observed between standard ABC/2 and SAS (Table 3.2, Figure 3.3). The slope of the best-fit regression line for the increasing difference between modified ABC/2 versus ABC/2 was -0.44, and -0.36 for modified ABC/2 versus SAS (both $p<0.0001$)(Figure 3.1, Figure 3.2).

We used the intraclass correlation coefficient (ICC) to assess intra and inter observer agreement and values between 0.75 and 1.00 were defined as excellent, 0.60 and 0.74 as good and 0.40 to 0.59 as fair. There was good intra-observer agreement for measurements assessed on 34-47 scans (5-10% of the total of 548). For ABC/2, modified ABC/2 and semi-automatic segmentation, the intra-observer ICC was 'excellent' ranging between 0.97-0.98, and 0.95-0.99 respectively (Table 3.3).

There was excellent inter-observer agreement (ICC) based on 193 scans at 0.88 for ABC/2, 0.91 for modified ABC/2, and 0.93 for SAS (Table 3.4). Both ABC/2 and modified ABC/2 showed excellent correlation with SAS ($p<0.0001$, Figures 3.4-3.6). Only 23 of 548 scans were amenable to analysis

using the fully automatic volume calculation method as the software was unable to handle scan image with varying slice thickness; this approach was therefore ignored in further analyses.

Across the ICH visual size categories, ICH volumes calculated by modified ABC/2 were significantly smaller compared to SAS (Figure 3.7). As the ICH size category increased, the difference between modified ABC/2 and SAS also increased. By comparison, there was no significant difference between ICH volumes measured by standard ABC/2 and SAS when compared by ICH visual size categorisation (Figure 3.7).

There was good agreement between the adjudicators across ICH visual size categories (n=47, ICC 0.82, $p<0.001$) (Table 3.5) using the ordered categorical scale (<3, 3-4.9, 5-8, >8 cm [367]) and strong agreement between visual size category and the observer's measured largest diameter in the axial plane 'A' (ICC 0.71, $p<0.001$) (Table 3.6).

3.4.2 Intracerebral haemorrhage (ICH) volume and shape

The most common shape was irregular (64%) followed by regular ICH. Small ICH's (5.5-8.06 cm^3) were more regularly

shaped than larger haemorrhages ($p<0.0001$) (Table 3.7). Using modified ABC/2, haemorrhage volume was significantly lower for regular shaped haemorrhages when compared with ABC/2 (by 2.5 cm3) and SAS (by 2.2 cm3) (Table 3.7) (Figure 3.8); the difference was greater with larger irregular shaped haemorrhages (between standard ABC/2 and modified ABC/2 by 4.8 cm3 and SAS and modified ABC/2 by 4.9 cm3). When compared by shape, ICH volume calculated by standard ABC/2 did not differ from those measured by SAS (Figure 3.8).

3.4.3 Intracerebral haemorrhage (ICH) shape and density in patients with no IVH

Intra- and inter-agreements were both 'good' for visual assessments of haemorrhage shape: intra-observer ICC 0.88 (Table 3.8), inter-observer ICC 0.75 (n=47) (Table 3.9); and density: intra-observer ICC 0.86, inter-observer ICC 0.73. Intra-observer ICC for calculated shape index was 0.53 and 0.86 for density index (Table 3.8).

3.4.4 Intraventricular haemorrhage (IVH) volume and severity

Intra-observer agreement for assessment of IVH volume on baseline scans from 49 patients was excellent (ICC 0.98-0.99) whether using the Graeb score, modified Graeb score or semi-

automatic segmentation (Table 3.8). The Graeb and modified Graeb scores were highly correlated with each other (rs=0.88, p<0.01). Both were also highly correlated with measured IVH volume using the SAS method: Graeb, (rs=0.73, p<0.01); modified Graeb (rs=0.72, p<0.01).

3.4.5 Comparison of ICH volume by ABC/2, modified ABC/2 to SAS

We performed a non-systematic review to compare our study with previously published work comparing ABC/2, modified ABC/2 and SAS volume measures in ICH.[249-254, 356, 375, 376] (Figures 3.9-3.12).

Some studies used the standard ABC/2 formula, others used variations of it;[249, 251] Gebel and colleagues used the central haemorrhage slice to measure largest diameter 'A' and found higher volumes computed by ABC/2 when compared to SAS.[249] With regards to shape, three studies studied errors in warfarin-related haemorrhage due to higher frequencies of irregular shape.[250, 252, 253] Huttner et al, showed that volume of regular shaped haematomas using ABC/2 were significantly increased in both regular and irregular shaped haemorrhages.[250] However, the large slice thickness used

during CT image acquisition in this study may have produced significant errors during calculation.[250]

This review comparing all three methods showed that ABC/2 formula tended to marginally overestimate ICH volume, but there was no absolute significant difference compared to SAS (Figure 3.9); when assessed by variability in haemorrhage shape, the results follow the same sequence (Figure 3.10). By comparison, ICH volumes computed using modified ABC/2 are significantly smaller when compared with SAS; the difference is greater as the haemorrhage sizes became larger and more irregular (Figure 3.11).

3.5 Discussion

This is the first study, to our knowledge, that compares several methods for assessing volume of spontaneous ICH and intraventricular haemorrhage volume on CT scanning and tests the effect of haematoma shape and regularity on these measures. The major findings are: (1) Agreement within and between observers was excellent for measures of haemorrhage volume (ABC/2, modified ABC/2, SAS) and other haemorrhage parameters (visual categorisation by maximum length, description of shape, density and intraventricular

haemorrhage); (2) Haemorrhage volumes measured by modified ABC/2 were significantly lower from those measured by ABC/2 and SAS planimetry; the discrepancy increased as haematoma size became larger; (3) Larger haemorrhages were significantly more irregular in shape; (4) Agreement was good between visual size categorisation and measured computerised measurement of maximum haemorrhage diameter; (5) Attempts to perform a fully automated volume measurement method failed in more than 95% of patients, as the software was unable to work with scans in which slice thicknesses varied.

The sources of error that effect variation between ABC/2 and SAS merit consideration. First, the largest diameter of haemorrhage was measured in the axial plane but this may not be the largest ICH diameter, which may also have contributed to differences between 'A' and the visual size categorisation. Sucu et al suggested using the maximum length and width not necessarily on the same slice and found better correlation between ABC/2 and SAS.[377] However, this adaptation applies only to chronic subdural haematomas which differ from spontaneous haemorrhages by extending to the cranial vault and being crescentic.[377] Second, when using the ABC/2, the scan plane is measured through AB/2, the formula

for the area of a triangle. However, a triangle is not necessarily the most appropriate description of a haematoma. Last, standard ABC/2 approximates haematoma volume as an ellipsoid with all three axes extending in three perpendicular directions;[352] to compensate for varying slice thickness, 'C' is derived by multiplying the number of slices of which the haematoma is seen by the slice thickness in centimetres. For the modified ABC/2, 'C' does not include slices if the area of the haemorrhage is less than 25% of the largest area,[251] an approach that has no theoretical justification. Hence, this method does not estimate all three Cartesian co-ordinates of the ellipsoid. Since the modified ABC/2 method underestimated ICH volume (by 2 to 4 cm^3), and small differences in volume equate to variation in outcome,[211] the modified ABC/2 method cannot be recommended. Further, modern CT scanners provide thin slices and the ability to directly measure 'C' thereby eliminating the need for approximating slice areas.[88, 248]

Although computer-assisted methods are considered the gold standard for volume measure,[225, 249, 250, 358] the SAS method was time consuming and at times technically challenging. For instance, it was difficult to set segmentation parameters to identify a haemorrhage that was adjacent to bone; and the

threshold may miss an area of haemorrhage. Additionally, the threshold method will not account for oedema associated with the ICH, which increases mass effect; thus the space occupying effect of the ICH may be much larger than its measured hyperattenuated area. As segmentation is semi-automatic, it is feasible to adjust manually for errors if they are apparent, although any adjustment may be subjective. All images require visual checking and manual correction; failure to do this would result in erroneous measurements. The problem is compounded by more irregular spontaneous haemorrhages e.g. due to amyloid, in anticoagulant-associated bleeds and in traumatic haematomas, where typically lesions are irregular, of varied attenuation and often next to bone.

In this series of patients with spontaneous intracerebral haemorrhage, a high proportion (64%) of irregular shaped haemorrhages were found. The effectiveness of the ABC/2 method has been validated in regular, oval shaped haemorrhages but researchers have doubted its accuracy in complex irregular haemorrhages (e.g. as seen with warfarin or in large or amyloid-related haemorrhage) and those with intra-ventricular extension.[250, 358] It has been suggested that adjusting the denominator from 2 to 3 in ABC/2 in irregularly

shaped haematomas may produce more accurate measures, but this concept is yet to be supported.[250, 253] Combining the present and published findings,[356] it may be postulated that as the haemorrhage became more irregular, the surface area and volume changes more than the largest diameter. Hence the area of the largest haemorrhage slice may be more representative of total haemorrhage size than its diameter. As a result, the true volume of an irregular haemorrhage may be better estimated using SAS. This finding is important since irregular shape haemorrhages are more likely to expand and affect morbidity and mortality.[378]

Our study is novel in design as it compares two commonly used methods ABC/2 and the modified formula (25%/75% distinction) with computer-assisted SAS and pragmatic visual scoring. Moreover, haemorrhage shape was incorporated in the analysis so that the source of error within each individual measurement method was assessed further. Our results show good compatibility between ABC/2 and computer-assisted SAS irrespective of haematoma shape and poor approximation using modified ABC/2.

There are several potential explanations for variation in inter-observer performance. Thinner slices may produce more

accurate volume measurement [88, 248] although the scans were identical for each observer. Alternatively, each additional slice to measure increases the potential for errors. Furthermore, observers may have chosen slightly different window settings; Additionally, although the observers were all trained in using OsiriX, accuracy in measurement does depend on operator experience.[88, 247]

When comparing haemorrhage size on the basis of its longest measured diameter ('A' in ABC/2) with an adjudicated visual categorisation, there was 'strong' agreement within the adjudicators and between the observers and adjudicators, with ICC 0.72. Hence it is unsurprising that the visual category versus largest measured axial diameter has slightly lower agreement than some of the other measured values. Note that the visual categorization assigns an ordinal value based on the largest size in any plane, not just the axial plane, and thus is not the same as a linear measure of largest axial diameter.

Our study also shows that qualitative descriptors of haemorrhage characteristics of haemorrhage shape, density, presence of intraventricular haemorrhage using the Graeb and modified Graeb scores can be reliably measured and are reproducible.

Of note, when measuring density heterogeneity, we used only the coefficient of variation (cv) whereas Barras used four additional measures (although these were apparently inferior to cv).[362] Calculation of shape index using parameters obtained from the windowed haemorrhage had a low ICC of 0.53. When this result is held in context with similar computed volumes, it could be interpreted that the observer chose different threshold settings which explains the source of variability.

This study has several strengths including the use of multiple assessors, multiple methods for assessing haemorrhage characteristics, and a large dataset. To minimise measurement error, observers were trained to use the OsiriX software for measuring brain CT scan parameters and in recognition of haemorrhages. Similarly, CT adjudicators were experienced neuroradiologists. Multiple observers were used to allow measurement of both intra-observer and inter-observer variation. The dataset involved patients from five continents and so the findings have excellent external validity.
Nevertheless, the study has three significant limitations. First, the data come from a randomised controlled trial in acute stroke. Trial exclusion criteria can limit the type of patients

(and therefore variation in haemorrhage) so that the dataset studied here did not include patients with normal/low blood pressure, GCS<8, or without motor signs. As a result, patients with very large haematoma were underrepresented. Second, the time from stroke onset to neuroimaging was relatively long (median 4.2 hours), reflecting that the ENOS protocol allowed enrolment up to 48 hours after stroke. Hence ICH on later scans may already have developed some peri-ICH oedema. Finally, just over 25% of the patients had measureable intraventricular haemorrhage and therefore the results do not represent a population where intraventricular haemorrhage is more frequent. The failure to get a fully automated volume measure in 95% of scans may be less of a problem with other software that can handle scans of variable slice thickness.

In conclusion, the modified ABC/2 formula significantly underestimates haemorrhage volume when compared to standard ABC/2 and computer assisted semiautomated segmentation; the difference increased as haematoma volume became larger and more irregular in shape. Most relevant for clinicians, our results show that the standard ABC/2 method offers more accurate quantification of intracerebral haemorrhage volume by the bedside. Although semi-

automated segmentation is consistent and reliable, the method is slow, reliant on manual correction, advanced software and likely to cause delay in clinical decision-making often in emergency situations. Further research is required to create a faster computerised volumetric model for accurate and reliable measurement of haematomas in the clinical setting. The visual categorisation has the strength of providing an 'instant' marker of haemorrhage size in the acute situation and can be applied in the absence of measurement tools and historical cut film data, and where very large study sizes or very moved images preclude computer based ABC/2 or SAS measurements. This study importantly shows that haemorrhage characteristics can be reliably measured as accuracy is pivotal to clinical trials in which ICH volume change may be a surrogate end-point.

Table 3.1 Baseline demographic, clinical and neuroradiological factors in 548 patients with primary intracerebral haemorrhage in the ENOS trial. Data are number (%), median [interquartile range], or mean (standard deviation).

Variable	Data
Demographics	
Age (years)	67.9 (12.1)
Sex, male (%)	360 (65.7)
Country, UK (%)	
Asia	117 (21.4)
Europe	67 (21.4)
Other (Africa, Australasia, North America)	42 (7.7)
UK	322 (58.8)
Clinical findings	
Pre-morbid modified Rankin Scale =0 (%)	418 (76.3)
Previous stroke (%)	69 (12.6)
Prior antihypertensive medication use (%)	227 (41.4)
Prior history of high BP (%)	341 (62.2)
Diabetes mellitus (%)	67 (12.2)
Ischaemic heart disease (%)	56 (10.2)
Atrial fibrillation (%)	30 (6.5)

Total anterior circulation syndrome (%)	195 (35.6)
Scandinavian Stroke Scale (/58)	30.1 (12.3)
National Institutes of Health Stroke Scale (/42)	12.8 (5.3)
Systolic blood pressure (mmHg)	171.6 (19.3)
Diastolic blood pressure (mmHg)	92.2 (13.3)
Heart rate (bpm)	77.7 (14.5)
Time, stroke to neuroimaging (hr)	4.5 [11.6]
Adjudicated CT scan findings	
Location of haemorrhage (%)	
Middle cerebral artery territory (MCA)	346 (63.1)
Anterior cerebral artery territory (ACA)	22 (4.0)
Posterior cerebral artery territory (PCA)	5 (0.9)
MCA + ACA	2 (0.4)
Borderzone	14 (2.6)
Lacunar (ie small subcortical) stroke	142 (25.9)
Brainstem and/or cerebellum	16 (2.9)
Leukoariosis	362 (66.1)
Lesion mass effect (minimal to extreme swelling)	470 (85.9)
Previous stroke lesion	270 (49.3)
Intraventricular haemorrhage	141 (25.7)
Intracerebral haematoma size category (%)	

<3 cm	220(40.6)
3 to <5cm	224 (41.3)
5 to 8 cm	87 (16.1)
>8 cm	11 (2.0)
Measured CT scan findings	
Volume, ABC/2 (cm^3)	12.77 (16.32)
Longest diameter (cm)	3.38 (1.4)
With IVH, n=141	
Graeb score (/12) [240]	3.52 (2.4)
Modified Graeb score (/32) [241]	5.19 (4.7)
Without IVH, n=407	
Shape (/5)[378]	3.00 (1.4)
Shape index[363]	1.22 (1.1)
Density (/5)[378]	2.54 (1.3)
Density index[362]	0.19 (0.1)

bpm: beats per minute; IVH: intraventricular haemorrhage; SAS: semi-automatic segmentation. NIHSS calculated from SSS[379]

Table 3.2 Comparison by two observers of different methods for measuring haemorrhage volume (cm^3) on CT scans: ABC/2 versus modified ABC/2 versus semi-automated segmentation (SAS). Data are mean (standard deviation), difference (Δ) in haemorrhage volume and intra-class correlation (lowest value is listed).

	Haematoma volume		Difference	p value	ICC
Observer1 n=548	ABC/2 12.77(16.32)	Modified ABC/2 8.90(9.21)	3.96	<0.0001	0.84
	ABC/2 12.77(16.32)	SAS 12.76(13.06)	-0.01	1.00	
	SAS 12.76(13.06)	Modified ABC/2 8.90(9.21)	3.97	<0.0001	

Observer 2 n=193	ABC/2 12.05(12.40)	Modified ABC/2 9.70(10.05)	2.67	<0.0001	
	ABC/2 12.05(12.40)	SAS 11.08(11.38)	0.05	0.89	0.96
	SAS 11.08 (11.38)	Modified ABC/2 9.70(10.05)	1.38	<0.0001	

Table 3.3 Intra-observer comparison for two observers (KK and SM) of haemorrhage size (n=47, 34 scans respectively) on baseline CT scans from patients with ICH. Data are mean (standard deviation), difference in means, and intra-class correlation (ICC). Both observers assessed scans blinded to each other's data, and repeated a proportion of the scans at a different time blinded to their original measurements.

			Diff (p)	ICC			Diff (p)	ICC
Observer	1				2			
Measurement	1	2			1	2		
Modified ABC/2 (cm^3)	8.67 (8.34)	9.10 (8.34)	0.43 (0.80)	0.97	16.88 (14.60)	16.90 (14.63)	0.016 (0.97)	0.95
ABC/2 (cm^3)	10.42 (10.28)	10.98 (10.79)	-0.55	0.97	20.97 (19.32)	20.15 (17.98)	0.82 (0.39)	0.96
SAS (cm^3)	11.11 (10.38)	11.69 (10.99)	0.58 (0.80)	0.98	19.41 (15.32)	19.42 (15.51)	-0.11 (0.87)	0.99
Diameter (A) (cm)	3.41 (1.28)	3.37 (1.31)	0.04 (0.89)	0.98	3.89 (1.48)	4.01 (1.45)	-0.12 (0.43)	0.96

SAS: semi-automatic segmentation volume

Table 3.4 Inter-observer comparison for two observers (n=193) of haemorrhage volume (cm^3) on CT scans from patients with ICH.

	Observer		Difference (Δ)	ICC
	1	2		
ABC/2	10.58 (10.20)	12.05 (12.40)	-1.40	0.88
Modified ABC/2	8.42 (8.53)	9.70 (10.05)	-1.3	0.91
SAS	12.02 (12.05)	11.08 (11.38)	0.95	0.93

Data are mean (standard deviation), difference (Δ) in haemorrhage volumes and intra-class correlation coefficient

Table 3.5 Inter-adjudicator comparison of visually estimated longest haemorrhage diameter across four size categories (<3 cm, 3-5 cm, 5-8 cm, >8 cm) in 47 patients; intra-class correlation (ICC)=0.82, p<0.001.

	Observer 2				
Observer 1	<3	3-5	5-8	>8	Total
<3	36	3	0	0	39
3-5	1	3	1	0	5
5-8	0	0	3	0	3
>8	0	0	0	0	0
Total	37	6	4	0	47

Table 3.6 Comparison of visually estimated maximum haemorrhage category versus computerised measurement (n=548). Data are number (%), mean (standard deviation) or median [interquartile range]; intra-class correlation (ICC) = 0.71 (p<0.001). Modal diameter 0.59 cm

Size category (cm)	Axial diameter 'A', minimum (cm)	Axial diameter 'A', mean (SD) (cm)	Axial diameter 'A', maximum (cm)
<3	0.66	2.22 (0.74)	5.10
3 to <5	0.59	3.76 (0.92)	7.29
5 to 8	2.12	5.07 (1.09)	7.53
>8	3.46	5.44 (1.27)	7.52
3 to <5 [<3]	0.59	3.38 (1.39)	7.53

Table 3.7 Comparison of volumes (cm^3) using ABC/2, modified ABC/2 and semi-automated segmentation (SAS) (n=548) by haematoma shape. Data are mean (standard deviation), difference (Δ) in volume and p value.

	Haematoma volume		Difference (Δ)	p value
Regular (1,2) n=198	ABC/2 8.06(10.43)	Modified ABC/2 5.56(6.31)	2.51	<0.0001
	ABC/2 8.06(10.43)	SAS 7.77(8.75)	0.29	0.20
	SAS 7.77(8.75)	Modified ABC/2 5.56(6.31)	2.21	<0.0001
Irregular (3,5) n=350	ABC/2 15.48(18.37)	Modified ABC/2 10.66(10.07)	4.81	<0.0001
	ABC/2 15.48(18.37)	SAS 15.62(14.22)	-0.14	0.82
	SAS 15.62(14.22)	Modified ABC/2 10.66(10.07)	4.96	<0.0001

Table 3.8 Intra-observer comparison of haemorrhage shape, Graeb and modified-Graeb scores, and intraventricular haemorrhage. Data are mean (standard deviation) and intra-class correlation coefficient (ICC).

	Measure 1	Measure 2	ICC
Without IVH, n=82			
Shape (/5)	3.68 (1.18)	3.74 (1.14)	0.88
Shape index	1.26 (0.37)	1.24 (0.34)	0.53
Density (/5)	2.94 (1.07)	2.87 (0.99)	0.86
Density index	0.22 (0.09)	0.21 (0.08)	0.86
With IVH, n=49			
Graeb score (/12)	4.10 (2.47)	4.04 (2.43)	0.99
Modified Graeb score (/32)	6.94 (4.94)	7.04 (4.96)	0.99
Volume (by SAS, cc^3)	5.36 (8.33)	5.69 (9.32)	0.98

Table 3.9 Inter-observer comparison of visually estimated haemorrhage shape and density. Data are mean (standard deviation) and intra-class correlation coefficient (ICC).

	Observer 1	Observer 2	ICC
N=48			
Shape (/5)	2.70 (1.23)	2.96 (1.28)	0.75, p<0.001
Density (/5)	1.62 (0.60)	1.92 (0.70)	0.73, p<0.001

An ascending scale of 1 to 5 was used and higher scores mean adding an extra lesion edge or irregularity on either scale.

Figure 3.1 Bland-Altman Plot for assessment of variation in estimating haematoma volume between modified ABC/2 and standard ABC/2 (n=548), r^2 = 0.64, p<0.0001. The continuous and dotted lines represent the regression lines. The slope of the best-fit regression line gradient was -0.44 (p<0.0001).

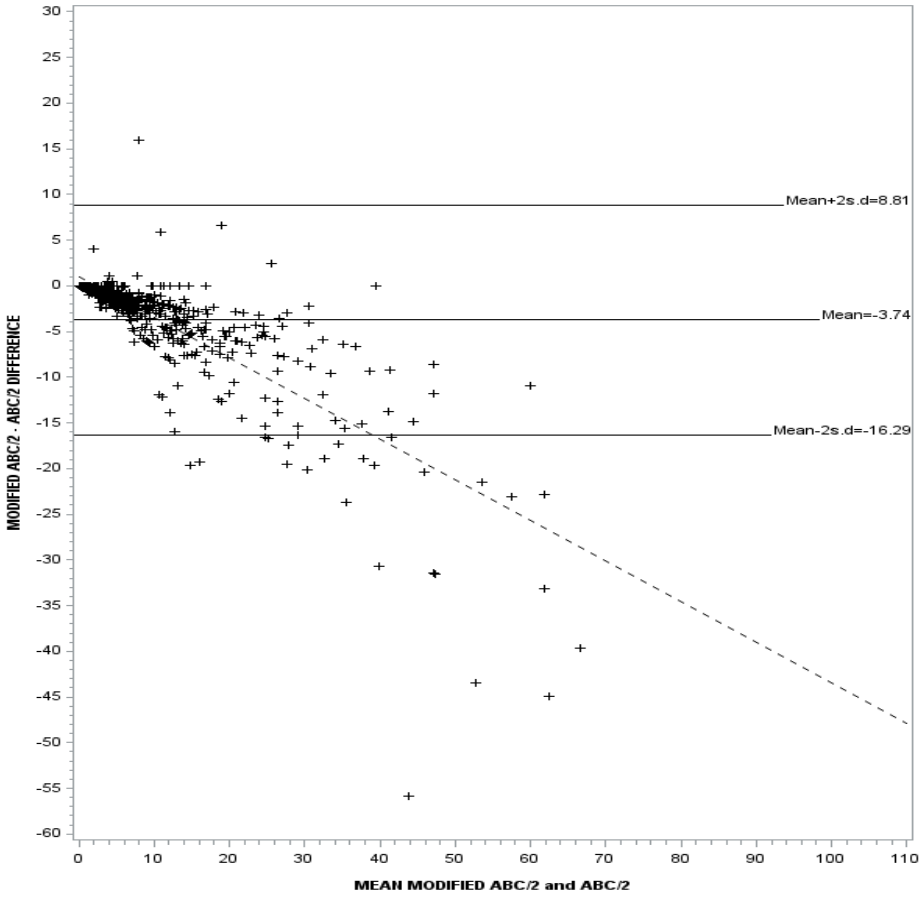


Figure 3.2 Bland Altman plot for assessment of variation in estimating haematoma volume between modified ABC/2 and semi-automatic segmentation (n=548), r^2 =0.45, p<0.0001. The continuous and the dotted lines represent the regression lines. The slope of the best-fit regression line was -0.36 (p<0.0001)

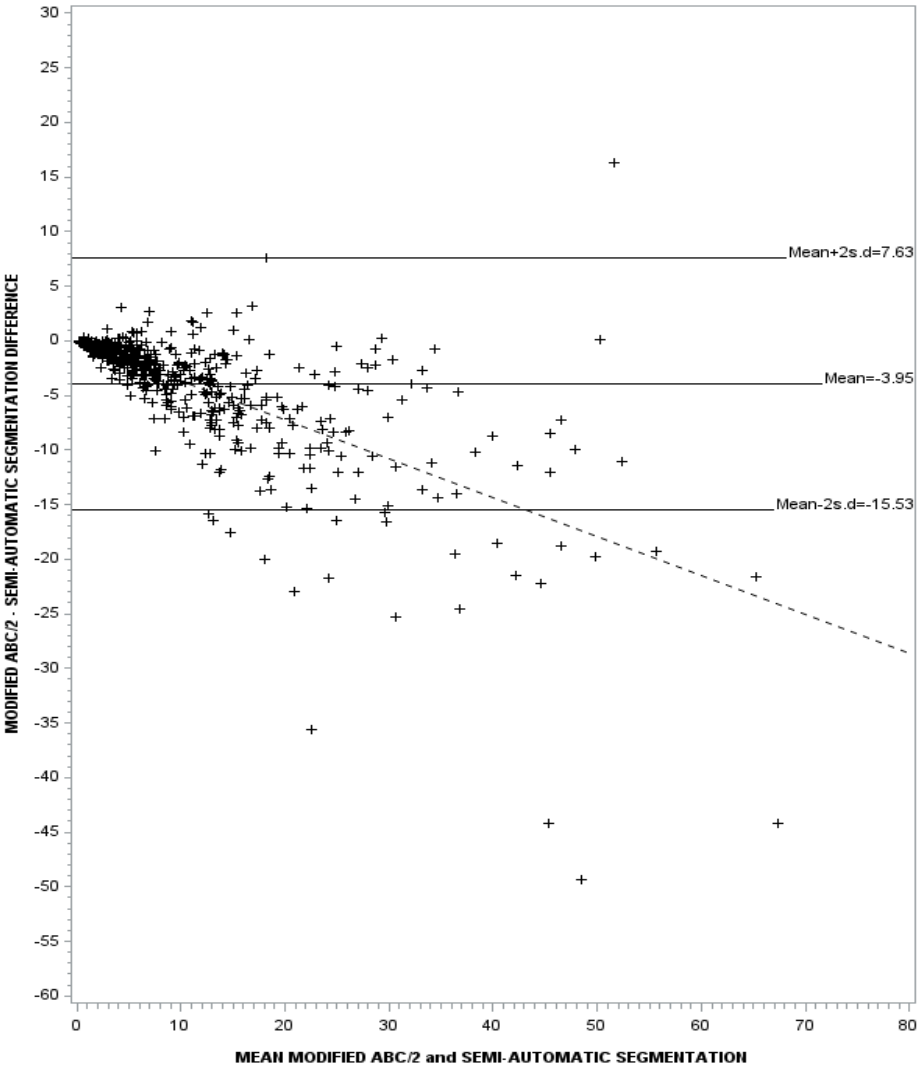


Figure 3.3 Bland Altman plot for assessment of variation in estimating haematoma volume (n=548) using ABC/2 and semi-automatic segmentation (n=548), r^2 =0.03, p<0.0001.

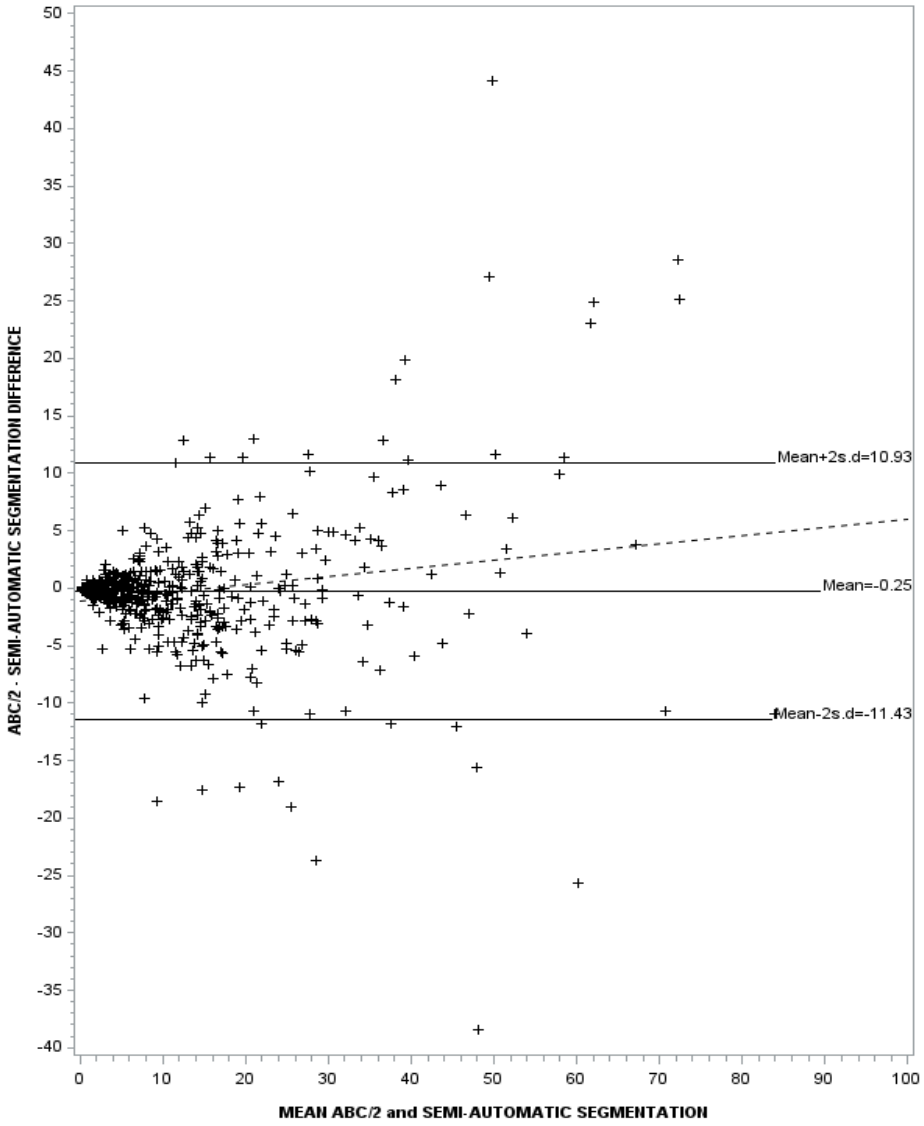


Figure 3.4 Graph for assessment of variation between two observers in estimating haematoma volume using ABC/2 and semi-automatic segmentation (n=193), r^2 =0.93, p<0.0001. The continuous and the dotted lines represent the regression lines. The slope of the best-fit regression line was 1.05 (p<0.0001).

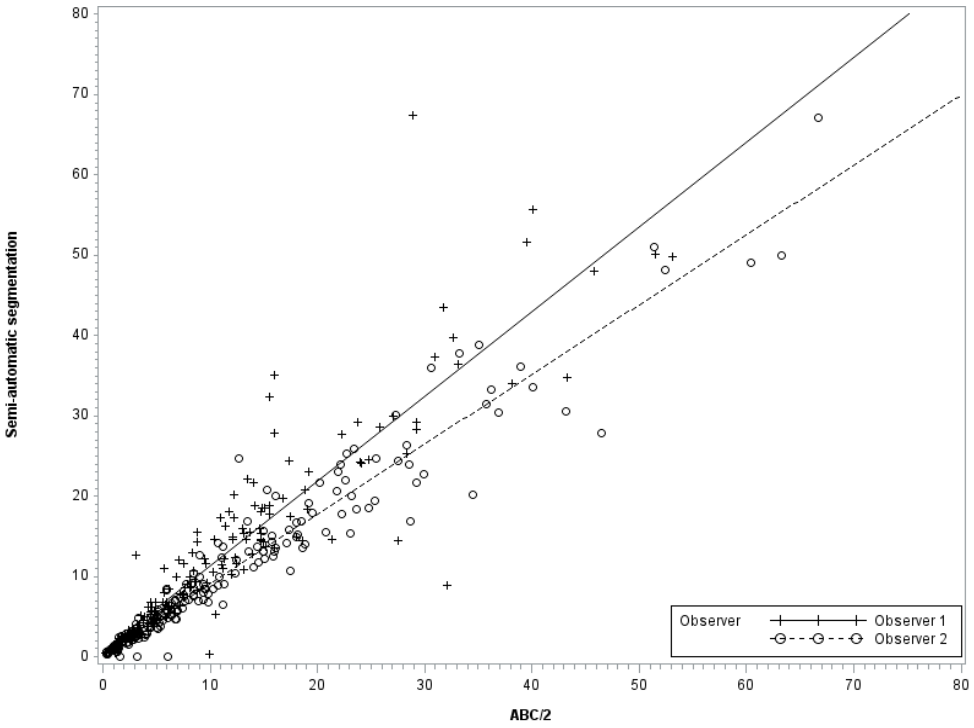


Figure 3.5 Graph for assessment of variation in estimating haematoma volume using ABC/2 and modified ABC/2 (n=193), r^2 =0.94, p<0.0001. The continuous and the dotted lines represent the regression lines. The slope of the best-fit regression line was 0.78 (p<0.0001)

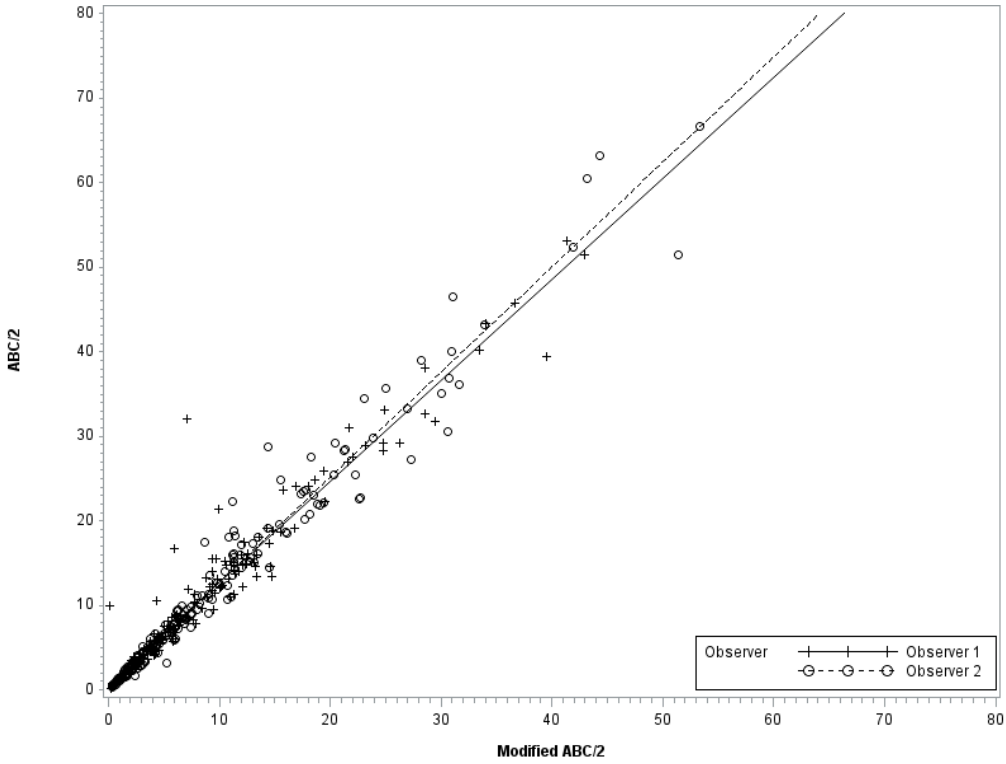


Figure 3.6 Graph for assessment of variation in estimating haematoma volume using modified ABC/2 and semi-automatic segmentation, r^2 =0.86, p<0.0001. The continuous and the dotted lines represent the regression lines. The slope of the best-fit regression line was 1.31 (p<0.0001)

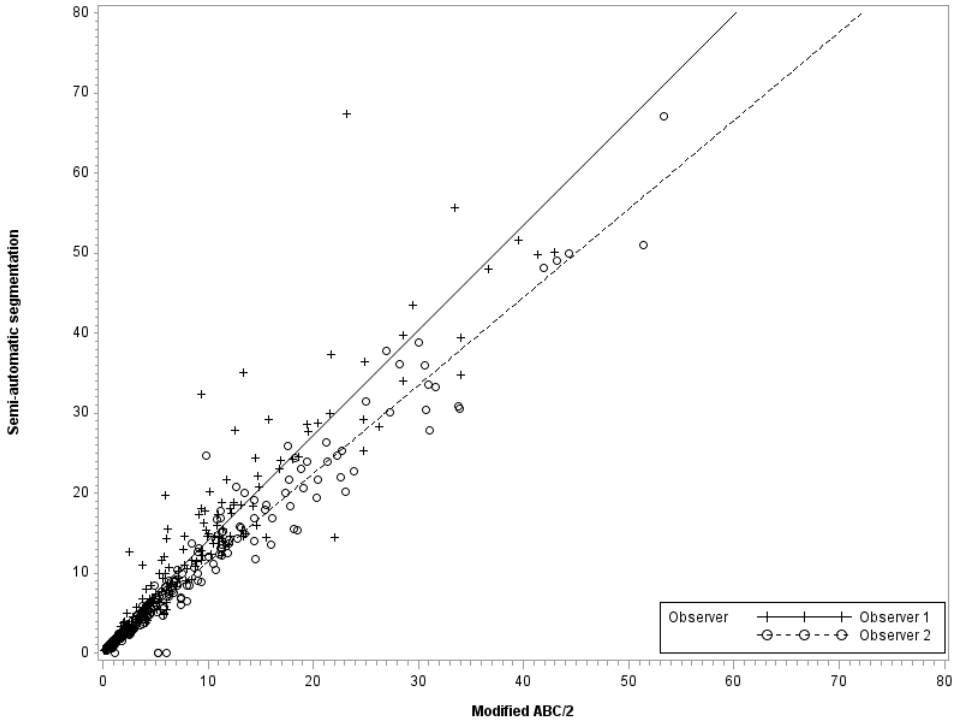


Figure 3.7 Box plots of ICH volumes (n=548) by visually estimated size and corresponding volume measured by ABC/2, modified ABC/2 and SAS. The difference between modified ABC/2 versus standard ABC/2 and modified ABC/2 versus SAS increases as the size category increases and is present in all four size categories [<3 (paired t-test p<0.0001), 3-5(p<0.001), 5-8(p<0.0001) and >8 (p<0.0001)]. There was no significant difference between standard ABC/2 and SAS in all four size categories.

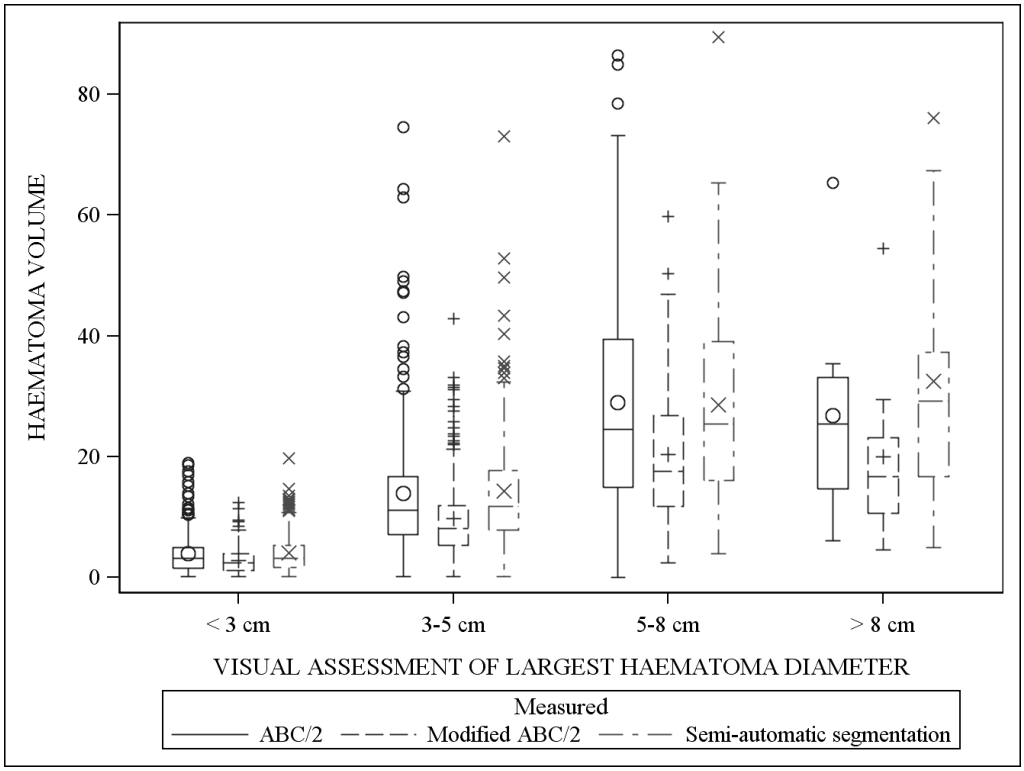


Figure 3.8 Box plots of ICH volumes (n=548) by visually assessed shape and corresponding volume assessed by ABC/2, modified ABC/2 and SAS show:(i) larger ICH's are irregular in shape ($p<0.0001$); (ii) the mean difference between modified ABC/2 versus standard ABC/2 and modified ABC/2 versus SAS increased as haematoma shape became more irregular (paired t-test $p<0.0001$). No significant difference was observed between standard ABC/2 and SAS.

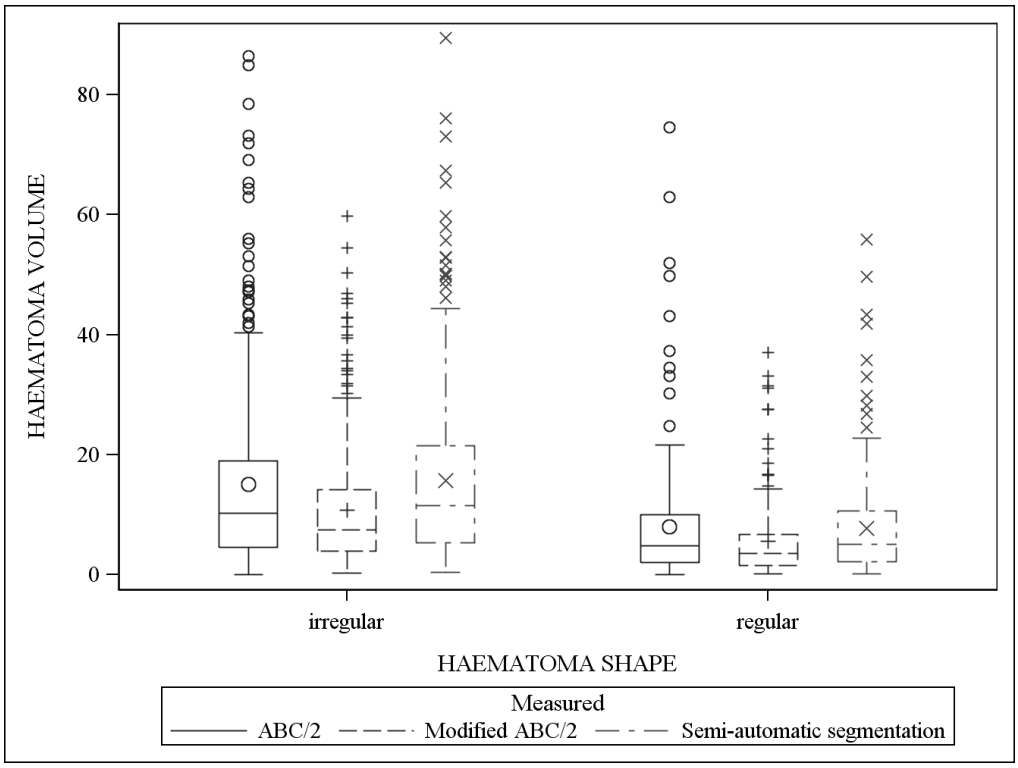


Figure 3.9 Forest plot of studies comparing ICH volume measurement by ABC/2 and computer- assisted planimetry in spontaneous and anticoagulant related ICH. The squares indicate the point estimates and the width of the horizontal lines is the 95% confidence interval of the estimate. The diamond at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within the categories.

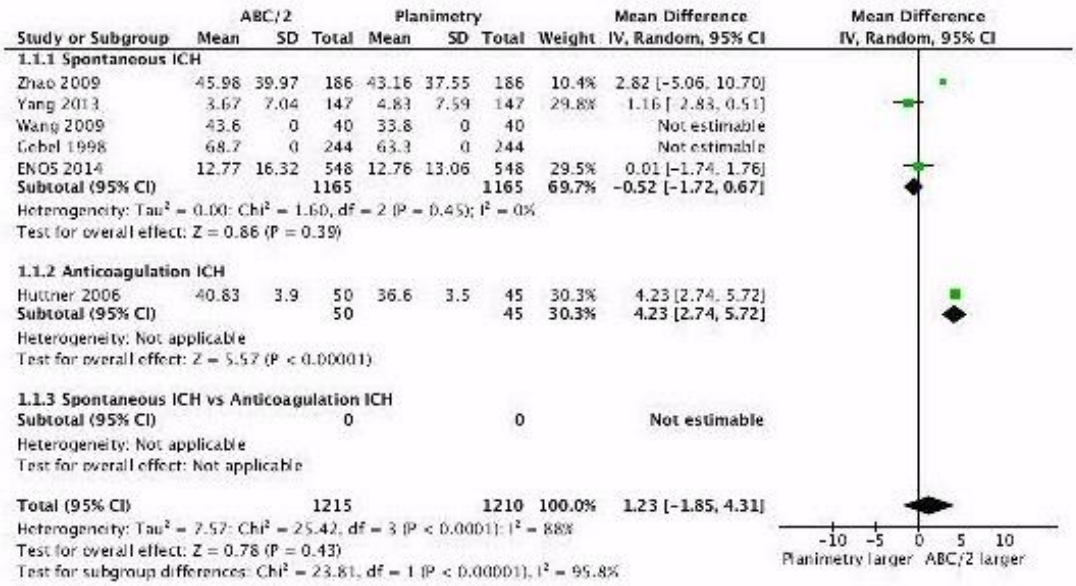


Figure 3.10 Forest plot of studies comparing variation between ABC/2 and computer- assisted planimetry measurements by haematoma shape. The squares indicate the point estimates and the width of the horizontal lines is the 95% confidence interval of the estimate. The diamond at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within the categories.

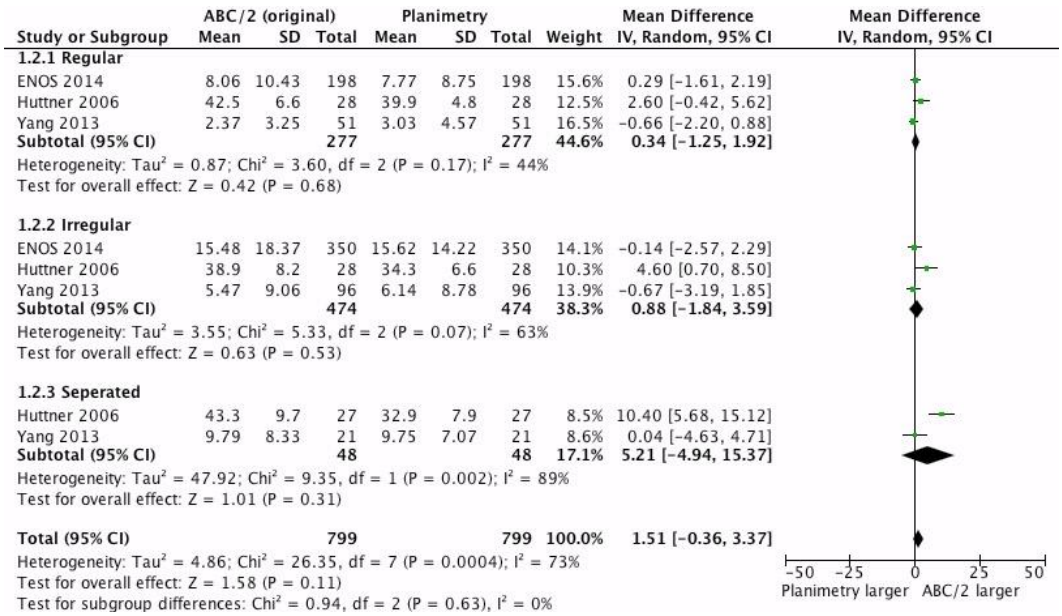
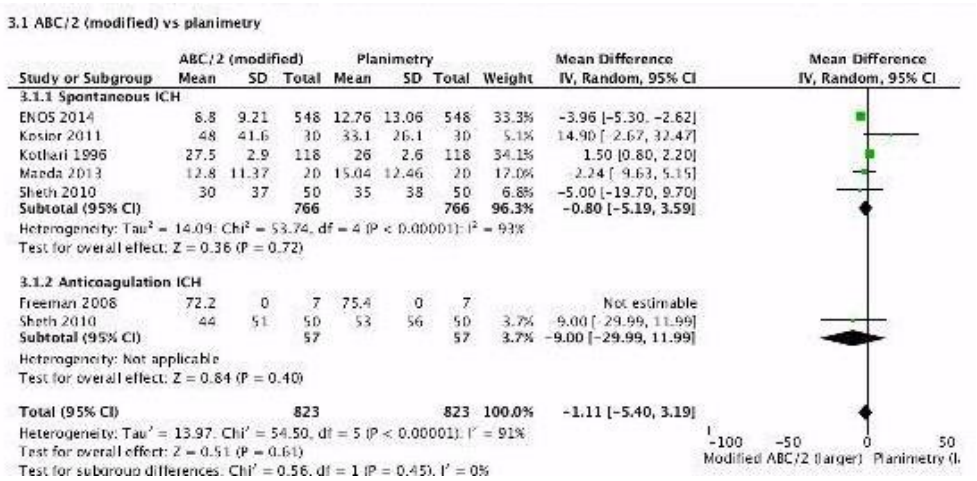


Figure 3.11 Forest plot of studies comparing ICH volume by modified ABC/2 and computer-assisted planimetry in spontaneous and anticoagulation related ICH. The squares indicate the point estimates and the width of the horizontal lines is the 95% confidence interval of the estimate. The diamond at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within the categories.



Chapter 4 - The effects of blood pressure lowering with transdermal glyceryl trinitrate in acute intracerebral haemorrhage

Publications contributing to this chapter:

Kailash Krishnan, Polly Scutt, Lisa Woodhouse, Alessandro Adami, Jennifer L Becker, Eivind Berge, Lesley A Cala, Ana M Casado, Valeria Caso, Christopher Chen, Hanna Christensen, D Ronan Collins, Anna Czlonkowska, Robert A Dineen, John Gommans, Panos Koumellis, Kennedy R Lees, George Ntaios, Serefnur Ozturk, Stephen J Phillips, Stuart J Pocock, Asita de Silva, Nikola Sprigg, Szabolcs Szatmari, Joanna M Wardlaw, Philip M Bath

Glyceryl trinitrate for acute intracerebral haemorrhage: results from the Efficacy of Nitric Oxide in Stroke (ENOS) trial, a subgroup analysis

Stroke 2016; 47(1): 44-52

Abstract

Background and purpose

The Efficacy of Nitric oxide in Stroke (ENOS) trial found that transdermal glyceryl trinitrate (GTN, a nitric oxide donor) lowered blood pressure but did not improve functional outcome in patients with acute stroke. However, GTN was associated with improved outcome if patients were randomised within 6 hours of stroke onset.

Methods

In this pre-specified subgroup analysis, the effect of GTN (5 mg/day for 7 days) versus no GTN was studied in 629 patients with intracerebral haemorrhage presenting within 48 hours and with systolic blood pressure $\geq$140 mm Hg. The primary outcome was the modified Rankin Scale at 90 days.

Results

Mean blood pressure at baseline was 172/93 mm Hg and significantly lower (difference -7.5/-4.2 mm Hg; both $p \leq 0.05$) on day 1 in 310 patients allocated to GTN as compared with 319 randomised to no GTN. No difference in the mRS was observed between those receiving GTN versus no GTN (adjusted odds ratio, OR for worse outcome with GTN 1.04,

95% confidence interval (CI) 0.78-1.37; p=0.84). In the subgroup of 61 patients randomised within 6 hours, GTN improved functional outcome with a shift in the modified Rankin Scale (OR 0.22, 95% CI 0.07-0.69, p=0.001). There was no significant difference in the rates of serious adverse events between GTN and no GTN.

Conclusions

In patients with intracerebral haemorrhage within 48 hours of onset, GTN lowered blood pressure, was safe but did not improve functional outcome. Very early treatment might be beneficial but needs assessment in further studies.

4.1 Introduction

As detailed in the chapter 1, spontaneous intracerebral haemorrhage (ICH) is a severe form of stroke with more than two-third of survivors disabled at three months and less than one-half surviving the first year.[380] High blood pressure (BP) is common in acute ICH and is associated independently with a worse outcome,[118] in part mediated through expansion of the haematoma.[381, 382] In the large INTERACT-2 trial, intensive BP lowering during the first 6 hours was associated with a trend to improved functional outcome in comparison with guideline BP lowering.[261] In contrast, in a subgroup analysis of patients with acute ICH enrolled into the Scandinavian Candesartan Acute Stroke Trial (SCAST), treatment with oral candesartan was associated with a worse functional outcome.[383] Hence, the management of high BP in acute ICH remains uncertain.

Transdermal glyceryl trinitrate (GTN), a nitric oxide donor is a candidate treatment for acute ICH because it can lower blood pressure without changing cerebral blood flow, has no negative effects on platelet function [384-386] and can be given to patients with dysphagia, a common clinical complication of stroke.[264] The Efficacy of Nitric Oxide in Stroke trial (ENOS) assessed the safety and efficacy of blood pressure lowering

with transdermal glyceryl trinitrate (GTN), a nitric oxide donor, in 4,011 patients with acute stroke;[137] nearly one-fifth of these presented with spontaneous ICH.[137] Although the main analysis showed that GTN did not improve death or dependency at 90 days after acute ischaemic stroke or ICH, apparent benefit was observed in patients randomised within 6 hours of stroke onset.[137] This result mirrored a result seen in the pre-hospital pilot Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) where GTN was administered by paramedics within 4 hours of onset.[264] In this pre-specified analysis,[387] we have further assessed the effect of GTN in the subgroup of patients randomised into the ENOS trial following ICH, both overall (here called ENOS-ICH) and within 6 hours; the time window of 6 hours matches that for recruitment into the INTERACT-2 trial,[261] and encompasses the time window studied in RIGHT.[264]

4.2 Methods

The ENOS trial protocol is detailed in chapter 2. The statistical analysis plan, baseline data and main results have been published.[137, 374, 387] During treatment, BP was measured daily using a validated automatic BP monitor (Omron 705CP)

supplied to each site.[388] In the present analysis, we included all patients enrolled into ENOS with ICH (ENOS-ICH).

4.3 Brain imaging

Participants had a baseline CT or MRI scan as part of clinical care, usually before randomisation. Where possible, a second research CT or MRI was performed at day 7+1 (end of treatment). All imaging assessments were performed by a single investigator (KK), masked to clinical data and treatment assignment.

4.4 Outcomes

As detailed in chapter 2, the primary outcome was functional outcome assessed using the modified Rankin Scale at 90 days after randomisation. Secondary outcomes studied at day 90 included activities of daily living (Barthel Index, BI [389]); cognition (modified telephone Mini-Mental State Examination, t-MMSE [390]); and Telephone Interview for Cognition Scale, (TICS-M [391]); health-related quality of life (European Quality of Life-5 dimensions-3 level, EQ-5D,[392] from which health utility status, HUS, was calculated [393]) and mood (short Zung Depression Score, ZDS [394]). Safety outcomes comprised all-cause mortality and case-specific fatality, early neurological

deterioration (defined as a decrease of at least 5 points or decrease in consciousness of more than 2 points from baseline to day 7 on the Scandinavian Stroke Scale, SSS), recurrent stroke by day 7, symptomatic hypotension, hypertension,[137] and serious adverse events. Outcomes at day 90 were assessed via telephone by trained investigators at national coordinating centres who were masked to treatment allocation.

4.5 Analyses

Statistical analysis was performed by intention-to-treat and followed the trial's statistical analysis plan and analysis approaches used in the primary publication.[137, 387] Analyses were performed for all patients with ICH in ENOS, and separately for those with ICH who were randomised within 6 hours of onset. Data are shown as number (%), median [interquartile range], or mean (standard deviation). Patients who died were allocated an extreme score: -5: Barthel Index; EQ-VAS -1: EQ-VAS, SSS 0, t-MMSE, TICS-M, verbal fluency; 0: health utility status (derived from EQ-5D); 6: mRS and 102.5: Zung Depression Scale.[137, 395] Comparisons between the treatment groups were performed with binary logistic regression, ordinal logistic regression, Cox proportional

regression, or multiple linear regression. Statistical models were adjusted for prognostic baseline covariates: age, systolic BP, SSS score, time from symptom onset to randomisation, haematoma volume and treatment assignment (GTN vs no GTN). Odds ratio, hazard ratio or mean difference, with 95% confidence intervals, are given and statistical significance was set at $p \leq 0.05$. Heterogeneity of treatment effect was assessed by including an interaction term in adjusted models. Analyses were performed using SPSS (version 21) on an Apple Mac.

4.6 Results

4.6.1 Baseline characteristics

Between July 2001 and October 2013, a total of 629 participants with ICH were enrolled in the trial; 310 participants were randomly assigned to receive GTN and 319 participants to no GTN (Table 4.1). Baseline characteristics were well matched between the two groups. The average age was 67 years; 66% of patients were male; 54% were enrolled from the UK; mean time from onset to recruitment 25 hours; and mean stroke severity 30.5 (s.d.12.4) on the SSS, equivalent to NIHSS 12.6 (5.3).

A majority (71%) of patients had their baseline scans performed within 12 hours of onset (Table 4.1). 87% of haemorrhages were deep-seated in the lacunar and striato-capsular brain regions, most haematomas caused mass effect (moderate or extreme swelling, 63%), and many patients had leukoaraiosis (67%). Evidence of a previous stroke was present in 50% of patients and brain atrophy was seen in 62% of the available scans. The mean haematoma volume was 13.3 cm^3, and 153 (26%) of patients had an intraventricular haemorrhage. More information on baseline neuroimaging is given in Table 4.2.

4.6.1.1 Blood pressure

Mean BP at baseline was 172.1/93.4 mmHg and fell in both treatment groups over the first week. Following the first dose of GTN versus no GTN, BP was significantly lower by 7.5/4.2 mmHg (p=0.02/0.05 respectively); BP did not differ thereafter (Figure 4.1).

4.6.1.2 Clinical outcomes

At day 90, the median mRS was 3 [IQR 2] in both the GTN and no GTN groups and did not differ in an adjusted analysis, common OR 1.04 (0.78-1.38) (Table 4.3, Figure 4.2) or

unadjusted analysis (data not shown). A test of 'goodness-of-fit' showed that the assumption of proportional odds was not violated (p=0.09). When assessed in subgroups defined by baseline clinical or neuroimaging factors, there were significant interactions between treatment and mRS for time to randomisation and stroke subtype (Figures 4.3 and 4.4).

The cumulative risk of all causes of death during follow up did not differ between GTN and no GTN (adjusted hazard ratio 1.02, 95% CI 0.67-1.56, p=0.92; Figure 4.5). There were no significant differences between the two groups in any of the secondary outcomes studied at days 7 or 90, including measures of disability, cognition, mood and quality of life (Table 4.3). The number of patients with a serious adverse event during follow-up did not differ between the treatment groups (24.2% vs. 21.9%, p=0.50) (Table 4.4).

4.6.2 Relationship between baseline neuroimaging and mRS at day 90

Table 4.5 shows the association between baseline neuroimaging characteristics and the primary outcome of mRS. Imaging measures that were significantly associated with outcome on both univariate and co-variate adjusted analyses comprised the presence of intraventricular

haemorrhage or atrophy, irregular haematoma shape and heterogeneous density.

4.6.3 Patients randomised within 6 hours

Of the 629 patients with ICH, 61 (9.7%) participants were randomised within 6 hours; the average time to treatment was 4.4 (1.2) hours (Table 4.1). Patients were less likely to be enrolled in Asia or other non-UK countries, had a larger initial haemorrhage volume (mean 16.9 cm3) and were more likely to have IVH.

Patients randomised to GTN (versus no GTN) had less impairment (higher SSS) at day 7, and were less likely to die in hospital (Table 4.3). At day 90, GTN was associated with an improved functional outcome assessed using the mRS, manifest as a shift to less dependency (Table 4.3, Figure 4.6). Similarly, participants randomised to GTN were less disabled and had significantly better quality of life, mood and cognition scores (Table 4.3). A trend to a reduction in death was seen in those patients randomised to GTN versus no GTN (adjusted hazard ratio 0.19, 95% CI 0.03-1.01, p=0.051).

4.6.4 Effect of GTN on haemorrhage measures at day 7

One hundred and eighty-one patients had repeat brain imaging at one week for an assessment of the effect on haemorrhage characteristics (Table 4.6). Of these, 93 patients received GTN and 88 to no GTN. When adjusted for baseline value, treatment with GTN was associated with a non-significant reduction in haematoma volume (mean difference -4.3 cm^3; p=0.06).

4.7 Discussion

In this subgroup of patients enrolled into the ENOS trial with ICH, functional outcome (assessed using the mRS) did not improve with GTN as compared to no GTN. This result mirrors that across the main study and is in spite of GTN reducing BP by 7.5/4.2 mm Hg. Further, no benefit was seen in key secondary outcomes, including activities of daily living, cognition, mood and quality of life. The absence of significant differences in the rates of deaths or serious adverse events between the two treatment groups suggests that treatment with GTN is safe. In a pre-specified analysis of the effect of treatment in patients randomised within 6 hours of ICH onset, GTN reduced early impairment; late dependency, disability,

and death; and improved late cognition, mood and quality of life.

These findings may have a number of explanations. First, patients could be randomised up to 48 hours after stroke onset. The large INTERACT-2 trial suggested that intensive BP lowering might be effective in patients enrolled within 6 hours [261] so the time window for recruitment into ENOS (mean 25.1 hours, maximum 48 hours) may have been too long. Supporting this is the observation that patients randomised within 6 hours of the onset of ICH into ENOS appeared to benefit with less dependency, disability, impairment and mood disturbance, and better cognition and quality of life. Very early BP lowering might help limit haematoma expansion.[260, 396] Second, the degree by which BP was lowered may have been too small; INTERACT-2 achieved a reduction of 14 mmHg by 6 hours and showed a near-significant effect on functional outcome.[261] Last, the length of BP control in ENOS-ICH was limited to 3 days as tachyphylaxis developed, a known feature of organic nitrate therapy. Nevertheless, these explanations are confounded by results from the subgroup of patients with ICH randomised into the large SCAST trial,[383] where oral candesartan was associated with a worse functional outcome.[383] Here, treatment could be started up to 30 hours

after stroke onset and the difference in BP between active and placebo groups was smaller than in ENOS-ICH at 6.3/3.3 mmHg.

The reduction in ICH volume in the GTN group (4 cm^3) was similar to the effect observed in trials of rFVIIa although the agent was tested in earlier time windows.[277, 278] Mechanisms by which nitric oxide donors might reduce haematoma volume, and improve functional outcome if given early, include lowering BP, neuroprotection, and improving collateral blood flow. The latter two effects have been seen in experimental models of brain ischaemia[397, 398] and may be of relevance after ICH.

This subgroup analysis of ENOS has a number of strengths including recruitment of patients with ICH from multiple ethnic groups across five continents over a wide time window representative of routine clinical practice. Baseline neuroimaging and clinical outcomes were assessed masked to treatment assignment,[399] follow-up was near complete,[137] and the analysis was pre-specified.[387] However, exclusion of patients with low or normal BP (systolic BP <140 mmHg) or very high (>220 mmHg), those with reduced consciousness (GCS<8), and those without motor signs, will have limited the

external validity of the findings and especially the number of patients with large haematoma.

In conclusion, this subgroup analysis of ENOS was neutral and did not identify any beneficial effect or harm in lowering BP with GTN in patients with acute ICH. Trasndermal GTN appears to be safe and modestly effective in lowering BP in acute ICH, which can be useful in patients who are unable to swallow. The results in those patients randomised within 6 hours of ICH onset support ongoing or planned trials of lowering BP in the ultra-acute and hyper-acute periods after stroke, including the ATACH-2 trial of intravenous nicardipine,[400] and RIGHT-2 trial of GTN administered in the pre-hospital phase of stroke (ISRCTN26986053).

Table 4.1 Baseline clinical and neuroimaging characteristics of all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), median [interquartile range], or mean (standard deviation). Comparison of patients randomised within 6 hours versus those randomised later by Fisher's exact test, Mann-Whitney U test or t test.

	All	GTN	No GTN	All ≤6 hours	GTN	No GTN	2p
Clinical characteristics							
Number of patients (N)	629	310	319	61	29	32	-
Age (years)	67.0 (12.4)	66.6 (12.0)	67.5 (12.7)	69.6 (12.5)	68.3 (11.4)	70.8 (13.5)	0.12
Sex, male (%)	415 (66.0)	217 (70.0)	198 (62.1)	38 (62.3)	16 (55.2)	22 (68.8)	0.56
Premorbid mRS>0 (%)	143 (22.7)	66 (21.3)	77 (24.1)	12 (19.7)	5 (17.2)	7 (21.9)	0.58
Country (%)							
UK	337 (53.6)	170 (54.8)	167 (52.4)	35 (57.4)	18 (62.1)	17 (53.1)	0.57

Asia	179 (28.5)	87 (28.1)	92 (28.8)	8 (13.1)	2 (6.9)	6 (18.8)	0.010
Other	113 (18.0)	53 (17.1)	60 (18.8)	18 (29.5)	9 (31.0)	9 (28.1)	0.028
Time to randomisation (hours)	25.1 (13.0)	25.2 (13.1)	25.1 (12.9)	4.4 (1.2)	4.5 (1.1)	4.4 (1.3)	-
<6 hours (%)	61 (9.7)	29 (9.4)	32 (10.0)	-	-	-	-
Smoking, current (%)	124 (20.4)	58 (19.3)	66 (21.4)	11 (18.0)	8 (27.6)	3 (9.4)	0.84
Treated hypertension (%)	253 (40.2)	121 (39.0)	132 (41.4)	17 (27.9)	8 (27.6)	9 (28.1)	0.06
Previous stroke (%)	79 (12.6)	41 (13.2)	38 (11.9)	10 (16.4)	6 (20.7)	4 (12.5)	0.39
Ischaemic heart disease (%)	58 (9.2)	29 (9.4)	29 (9.1)	5 (8.2)	3 (10.3)	2 (6.3)	0.86
Atrial fibrillation (%)	42 (6.7)	18 (5.8)	24 (7.5)	2 (3.3)	1 (3.4)	1 (3.1)	0.30
Diabetes mellitus (%)	81 (12.9)	44 (14.2)	37 (11.6)	9 (14.8)	3 (10.3)	6 (18.8)	0.68
TACS (%)	217 (34.5)	105 (33.9)	112 (35.1)	22 (36.1)	10 (34.5)	12 (37.5)	0.81

SSS (/58)	30.5 (12.4)	30.1 (12.7)	30.9 (12.1)	30.1 (11.1)	30.3 (11.4)	30.0 (10.9)	0.81
NIHSS (/42), calculated	12.6 (5.3)	12.7 (5.5)	12.4 (5.2)	12.7 (4.8)	12.7 (4.9)	12.8 (4.7)	0.81
Glasgow Coma Scale [/15]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	0.43
Blood pressure (mmHg)							
Systolic	172.1 (19.4)	172.3 (18.9)	171.8 (19.9)	172.4 (16.8)	174.4 (19.2)	170.6 (14.4)	0.90
Diastolic	93.4 (13.9)	94.0 (13.1)	92.7 (14.6)	95.7 (12.2)	96.9 (13.4)	94.7 (11.1)	0.19
Heart rate (bpm)	77.9 (14.5)	78.0 (14.6)	77.8 (14.4)	76.7 (13.6)	75.6 (15.5)	77.8 (11.8)	0.54
Neuroimaging characteristics							
Available scan	587 (93.3)	296 (95.5)	291 (91.2)	57 (93.4)	28 (96.6)	29 (90.6)	0.89
Time, onset-neuroimaging (%)							
≤12 hours	414 (70.5)	220 (74.3)	194 (66.7)	53 (93.0)	27 (96.4)	26 (89.7)	0.78
>12 hours	173 (29.5)	76 (25.7)	97 (33.3)	4 (7.0)	1 (3.6)	3 (10.3)	0.50

Adjudicated findings							
Haematoma location (%)							
Lobar or cerebellar †	79 (13.5)	42 (14.2)	37 (12.7)	12 (21.1)	7 (25.0)	5 (17.2)	0.76
Deep ‡	508 (86.5)	254 (85.8)	254 (87.3)	45 (78.9)	21 (75.0)	24 (82.8)	0.75
Mass effect (%)							
No swelling or mild swelling	218 (37.2)	107 (36.3)	111 (38.1)	22 (38.6)	11 (39.3)	11 (37.9)	1.00
Moderate to severe swelling	299 (50.9)	155 (52.4)	144 (49.5)	28 (49.1)	14 (50.0)	14 (48.3)	0.90
Extreme swelling	70 (11.9)	34 (11.5)	36 (12.4)	7 (12.3)	3 (10.7)	4 (13.8)	1.00
Leukoaraiosis (%)	391 (66.6)	199 (67.2)	192 (66.0)	38 (66.7)	19 (67.9)	19 (65.5)	1.00
Previous stroke lesion (%)	291 (49.6)	149 (50.3)	142 (48.8)	33 (57.9)	18 (64.3)	15 (51.7)	0.21
Atrophy (%)	366 (62.3)	186 (62.8)	180 (61.9)	40 (70.2)	19 (67.9)	21(72.4)	0.79

Measured CT scan findings							
Volume, ABC/2 (cm3)	13.3 (16.5)	13.2 (15.3)	13.3 (17.7)	16.9 (30.5)	13.0 (14.4)	20.8 (40.7)	0.09
With IVH (n=151, 25.7%)							
Volume, ABC/2 (cm3)	18.5 (23.6)	17.7 (18.3)	19.2 (27.8)	31.8 (52.2)	21.1 (20.6)	40.1 (67.9)	0.018
IVH Volume (ml)	4.8 (7.3)	4.2 (5.0)	5.4 (9.0)	7.2 (6.2)	7.1 (5.7)	7.3 (6.8)	0.18
Shape index[363]	2.4 (3.7)	2.2 (1.9)	2.6 (4.8)	3.2 (2.1)	3.3 (2.9)	3.2 (1.5)	0.35
Density index	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.3 (0.1)	0.006
Graeb score (/12) [240]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 5.0]	4.0 [2.5, 6.0]	4.0 [2.0, 6.0]	4.0 [3.0, 6.0]	0.047
Without IVH (n=436, 74.3%)							
Volume, ABC/2 (cm3)	11.4 (12.6)	11.7 (13.9)	11.1 (11.2)	11.0 (11.8)	10.3 (11.1)	11.7 (12.9)	0.87
Shape index [363]	1.2 (1.1)	1.2 (1.2)	1.2 (1.0)	1.4 (1.1)	1.3 (0.9)	1.5 (1.3)	0.73

Density index[362]	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.0)	0.2 (0.1)	0.52

bpm: beats per minute; ICH: intracranial haemorrhage; IVH: intraventricular haemorrhage; MCA: middle cerebral artery; mRS: modified Rankin scale; NIHSS: National Institute of Health Stroke scale; SSS: Scandinavian Stroke Scale; TACS: total anterior circulation syndrome.

† Lobar: borderzone regions, cerebellar and or brainstem, ACA, PCA territory and MCA territory excluding striatocapsular regions

‡ Deep: lacunar, MCA territory including striatocapsular regions

Shape index was calculated as perimeter of haematoma/4∏ x surface area.[363] Density index was determined as standard deviation/mean Hounsfield attenuation unit.[362]

Table 4.2 Additional information on baseline neuroimaging data for all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), median [interquartile range], or mean (standard deviation).

Neuroimaging	All	GTN	No GTN	<6 hours	GTN	No GTN
Number of patients (N)	629	310	319	61	29	32
Participants with a scan available	587 (93.3)	296 (95.5)	291 (91.2)	57 (93.4)	28 (96.6)	29 (90.6)
Adjudicated findings						
Haematoma location (%)						
Lacune	155 (26.4)	83 (28.0)	72 (24.7)	13 (22.8)	6 (21.4)	7 (24.1)
Borderzone	16 (2.7)	6 (2.0)	10 (3.4)	1 (1.8)	1 (3.6)	0 (0)
Cerebellum and/or brainstem	17 (2.9)	9 (3.0)	8 (2.7)	2 (3.5)	1 (3.6)	1 (3.4)
MCA territory	372 (63.4)	183 (61.8)	189 (64.9)	38 (66.7)	19 (67.9)	19 (65.5)
ACA or PCA territory	27 (4.6)	15 (5.1)	12 (4.1)	3 (5.3)	1 (3.6)	2 (6.9)
Longest diameter (cm)						
<3	235 (40.4)	119 (40.8)	116 (40.1)	24 (42.1)	12 (42.9)	12 (41.4)
3-5	242 (41.7)	120 (41.1)	122 (42.2)	19 (33.3)	10 (35.7)	9 (31.0)
5-8	93 (16.0)	45 (15.4)	48 (16.6)	12 (21.1)	4 (14.3)	8 (27.6)
>8	11 (1.9)	8 (2.7)	3 (1.0)	2 (3.5)	2 (7.1)	0 (0)

Sub-arachnoid haemorrhage (%)	94 (16.0)	47 (15.9)	47 (16.2)	10 (17.5)	4 (14.3)	6 (20.7)
Subdural haematoma (%)	4 (0.7)	2 (0.7)	2 (0.7)	1 (1.8)	1 (3.6)	0 (0)
Remote ICH (%)	4 (0.7)	3 (1.0)	1 (0.3)	0 (0)	0 (0)	0 (0)
Measured CT scan findings						
Diameter, max (cm)	3.4 (1.4)	3.4 (1.4)	3.5 (1.4)	3.6 (1.4)	3.5 (1.4)	3.6 (1.5)
With IVH (n=151, 25.7%)						
Shape (/5) [378]	5.0 [2.0]	5.0 [2.0]	5.0 [1.0]	5.0 [0.5]	5.0 [1.0]	5.0 [0.0]
Density (/5) [378]	3.0 [2.0]	3.0 [2.0]	3.0 [2.0]	3.0 [3.0]	2.0 [2.0]	4.0 [2.0]
Modified Graeb score (/32) [241]	3.0 [4.5]	3.0 [4.0]	3.0 [5.0]	6.5 [7.5]	4.0 [5.0]	7.0 [6.0]
Without IVH (n=436, 74.3%)						
Shape (/5) [378]	3.0 [2.0]	3.0 [2.0]	3.0 [2.0]	2.0 [2.5]	2.0 [2.0]	3.0 [3.0]
Density (/5) [378]	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]	2.0 [2.0]

ACA: anterior cerebral artery; ICH: intracerebral haemorrhage; MCA: middle cerebral artery; PCA: posterior cerebral artery. Intracerebral haemorrhage shape and density were determined using a 5-point ordered categorical scale.

Table 4.3 Secondary outcomes at day 7 and day 90 for all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), mean (standard deviation) with 95% confidence intervals. Data are number of patients (%), mean (standard deviation) or median [interquartile range]. Comparison by logistic regression, ordinal regression or multiple regression with adjustment for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, total anterior circulation syndrome, volume of intracerebral haemorrhage, systolic blood pressure, feeding status and time to randomisation.

Outcome	N	GTN	No GTN	OR/MD (95% CI)	2p	≤6 hours	GTN	No GTN	OR/MD (95% CI)	2p
Patients	629	310	319			61	29	32		
Day 7 (or discharge)	627	310	317							
Death (%)	627	10 (3.2)	10 (3.2)	1.03 (0.38, 2.88)	0.95	60	2 (6.9)	4 (12.5)	-	1.00
SSS (/58)	625	34.5 (15.4)	34.8 (16.0)	0.18 (-1.30, 1.69)	0.80	60	33.4 (16.4)	27.1 (19.6)	7.0 (1.0, 13.1)	0.033

Outcome	N	GTN	No GTN	OR/MD (95% CI)	2p	≤6 hours	GTN	No GTN	OR/MD (95% CI)	2p
Recurrence (%)	626	8 (2.6)	4 (1.3)	2.43 (0.63, 9.29)	0.19	60	0	1 (3.1)	-	1.00
Hospital events	623	308	315			59	29	30		
Died in hospital (%)	623	28 (9.0)	32 (10.2)	0.92 (0.48, 1.76)	0.79	59	2 (6.9)	9 (30.0)	-	-
Death or discharge to institution (%)	623	121 (39.3)	131 (41.6)	0.84 (0.59, 1.22)	0.37	59	14 (48.3)	14 (46.7)	1.20 (0.32, 4.43)	0.79
Day 90	623	309	316			61	29	32		
Death (%)	625	42 (13.6)	47 (14.9)	0.91 (0.55, 1.55)	0.76	61	2 (6.9)	12 (37.5)	†	0.006
Modified Rankin Scale (/6)	625	3 [2]	3 [2]	1.04 (0.78, 1.38)	0.81	61	3 [2]	4 [4]	0.19 (0.06, 0.59)	0.004
Barthel Index	622	62.3 (38.1)	61.4 (39.7)	1.26 (-3.65, 6.17)	0.62	61	66.9 (36.4)	46.9 (45.7)	20.71 (6.34, 35.07)	0.005

Outcome	N	GTN	No GTN	OR/MD (95% CI)	2p	≤6 hours	GTN	No GTN	OR/MD (95% CI)	2p
t-MMSE	369	10 (7.2)	10.1 (7.4)	0.04 (-1.20, 1.28)	0.95	38	11.9 (6.4)	6.5 (8.3)	3.38 (-0.29, 7.10)	0.008
TICS-M	370	11.9 (9.3)	12.7 (9.3)	-0.64 (-2.20, 0.93)	0.43	39	16.6 (9.1)	7.1 (9.3)	7.17 (2.20, 12.12)	0.005
Animal naming (/∞)	376	8.2 (7.8)	7.9 (7.4)	0.28 (-1.09, 1.65)	0.69	39	12.8 (8.0)	4.8 (7.3)	7.92 (2.93, 12.92)	<0.001
ZDS (/100)	516	60.1 (24.2)	59.6 (24.3)	0.62 (-3.12, 4.43)	0.73	50	54.2 (20.6)	71.8 (28.6)	-17.58 (-32.25, -3.01)	<0.001
HUS (/1)	621	0.45 (0.31)	0.46 (0.32)	-0.01 (-0.05, 0.03)	0.60	61	0.53 (0.3)	0.53 (0.32)	0.19 (0.06, 0.32)	0.003
EQ-VAS (/100)	543	54.6 (31.3)	55.1 (31.5)	-0.44 (-5.16, 4.27)	0.85	57	60.9 (26.7)	40.4 (38.1)	21.28 (6.31, 36.25)	0.005
Dead or institution (%)	616	97 (31.4)	92 (29.1)	1.09 (0.72, 1.67)	0.68	61	13 (44.8)	14 (43.8)	0.51 (0.12, 2.18)	0.36

BI: Barthel Index; EQ-VAS: EQ-Visual Analogue Scale; HUS: health utility status; ICH: intracranial haemorrhage; mRS: modified Rankin Scale; t-MMSE: Modified telephone Mini-Mental State Examination; SAE: serious adverse event; SBP: systolic blood pressure; SSS: Scandinavian Stroke Scale; TICS-M: Modified Telephone Interview for Cognitive Status; ZDS: Zung Depression Scale. † Fisher's exact test

Table 4.4 Serious adverse events at day 90 for all patients with intracerebral haemorrhage at day 90 and those randomised within 6 hours. Data are number of patients (%) and mean (standard deviation). NA denotes not applicable.

	All			<6 hours		
	GTN	No GTN	2p	GTN	No GTN	2p
Complication of initial stroke	13 (4.2)	9 (2.8)	0.35	0	2 (6.3)	0.50
Extension of initial stroke	13 (4.2)	4 (1.3)	0.027	1 (3.4)	3 (9.4)	0.61
Recurrent stroke	7 (2.3)	7 (2.2)	0.96	0	0	NA
Myocardial infarction	1 (0.3)	2 (0.6)	1.00	0	2 (6.3)	0.49
Other cardiovascular cause	10 (3.2)	20 (6.3)	0.07	1 (3.4)	3 (9.4)	0.61
Pulmonary embolism	4 (1.3)	4 (1.3)	1.00	0	0	NA
Pneumonia	13 (4.2)	25 (7.8)	0.06	1 (3.4)	2 (6.3)	1.00
Sudden cardiac death	1 (0.3)	1 (0.3)	1.00	0	1 (3.1)	1.00
Other cause	4 (1.3)	4 (1.3)	1.00	2 (6.9)	1 (3.1)	1.00
Total SAEs	75 (24.2)	70 (21.9)	0.50	5 (17.2)	14 (43.8)	0.026

Table 4.5 Relationships between baseline imaging characteristics and functional outcome (modified Rankin Scale) at day 90. Results are odds ratio or mean difference with 95% confidence interval with comparison by logistic regression, ordinal regression or multiple regression; results are unadjusted, and adjusted for age, sex, severity (Scandinavian Stroke Scale) and time from stroke onset to imaging.

Haematoma characteristics	Univariate analyses OR/MD (95% CI)	2p	Co-variate adjusted OR/MD (95% CI)	2p
Haematoma location				
Lobar	1.32 (0.87, 2.00)	0.19	1.31 (0.85, 2.03)	0.22
Deep	1.08 (0.76, 1.53)	0.68	0.84 (0.58, 1.21)	0.35
Side of the brain				
Left	0.89 (0.67, 1.37)	0.40	0.76 (0.57, 1.01)	0.18
Right	1.10 (0.83, 1.45)	0.50	1.29 (0.97, 1.71)	0.09

Bilateral	2.41 (0.51, 11.50)	0.50	2.50 (0.41, 15.35)	0.32
Mass effect	2.30 (1.61, 3.29)	<0.0001	1.35 (0.93, 1.96)	0.18
Leukoaraiosis	2.14 (1.58, 2.90)	<0.0001	1.34 (0.96, 1.86)	0.09
Previous stroke lesion	1.19 (0.90, 1.59)	0.23	1.18 (0.88, 1.59)	0.28
Remote haemorrhage	5.21 (1.11, 24.57)	0.04	1.39 (0.20, 9.03)	0.75
Subarachnoid haemorrhage	2.22 (1.50, 3.28)	<0.0001	1.47 (0.97, 2.21)	0.07
Intraventricular haemorrhage	2.61 (1.86, 3.67)	<0.0001	1.92 (1.35, 2.74)	<0.0001
Cerebral atrophy	2.70 (1.99, 3.66)	<0.0001	1.46 (1.14, 1.86)	0.002
Volume ABC/2 (cm3)	1.02 (1.01, 1.03)	<0.0001	1.01 (0.99, 1.02)	0.56
Largest measured diameter (cm)	1.12 (1.07, 1.32)	<0.001	0.88 (0.74, 1.04)	0.14
Largest visual diameter	2.52 (1.69, 3.76)	<0.0001	1.24 (0.81, 1.89)	0.32
Haemorrhage shape (/5)	1.36 (1.23, 1.51)	<0.0001	1.28 (1.15, 1.42)	<0.0001
Haemorrhage density (/5)	1.42 (1.27, 1.60)	<0.0001	1.27 (1.13, 1.42)	<0.0001

Haematoma characteristics	Univariate analyses OR/MD (95% CI)	2p	Co-variate adjusted OR/MD (95% CI)	2p
Shape index	1.04 (0.98, 1.12)	0.22	1.03 (0.96, 1.11)	0.38
Density index	1.00 (1.00, 1.01)	0.24	1.00 (0.99, 1.01)	0.45
Haemorrhages with IVH				
Volume (ABC/2 cm3)	1.01 (0.99, 1.02)	0.19	1.00 (0.97, 1.03)	0.94
IVH volume (cm3)	1.02 (0.98, 1.06)	0.40	1.01 (0.97, 1.06)	0.56
Haemorrhage shape (/5)	1.31 (1.03, 1.67)	0.026	1.42 (1.11, 1.82)	<0.0001
Haemorrhage density (/5)	1.69 (1.37, 2.11)	<0.0001	1.49 (1.19, 1.86)	<0.0001
Graeb score (12)	1.07 (0.94, 1.22)	0.31	1.03 (0.90, 1.18)	0.67
Modified Graeb score (32)	1.03 (0.96, 1.10)	0.45	1.00 (0.94, 1.08)	0.80

Shape index	0.98 (0.91, 1.06)	0.63	0.99 (0.92, 1.08)	0.89
Density index	1.00 (1.00, 1.00)	0.13	1.00 (0.99, 1.00)	0.63

Table 4.6 Effect of treatment on neuroimaging measures at day 7 in 181 patients with a baseline scan prior to randomisation, for all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), median [interquartile range], or mean (standard deviation), and odds ratio or mean difference with 95% confidence intervals. Comparison by logistic regression, ordinal regression or multiple regression with adjustment for baseline value.

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Haematoma location	93	88		
Lobar (%)	10 (10.8)	11 (12.5)	1.24 (0.49, 3.15)	0.66
Deep (%)	83 (89.2)	77 (42.5)	0.63 (0.10, 3.85)	0.61

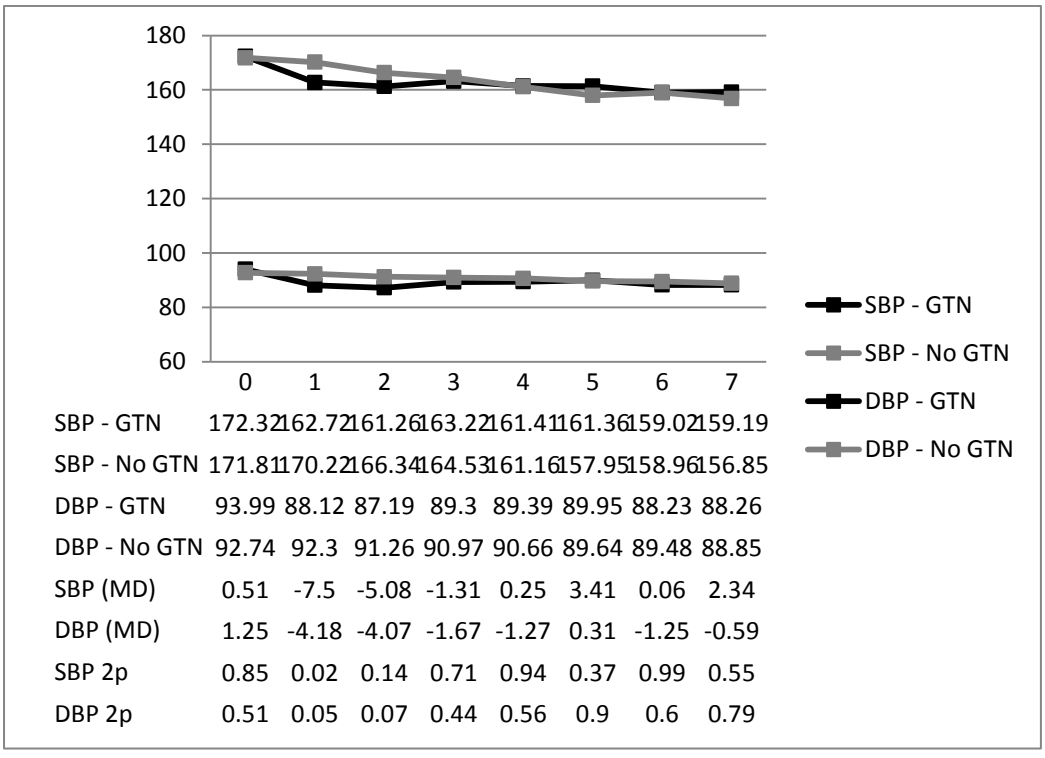
Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Intraventricular haemorrhage (%)	25 (26.9)	19 (21.6)	0.85 (0.43, 1.70)	0.65
Subarachnoid haemorrhage (%)	7 (7.5)	11 (12.5)	0.50 (0.17, 1.49)	0.21
Mass effect (%)	79 (84.9)	81 (92.0)	1.04 (0.72, 1.50)	0.84
Brain tissue reduction (%)	53 (57.0)	59 (67.0)	0.51 (0.24, 1. 10)	0.09
Cortical atrophy (%)	44 (47.3)	42 (47.7)	1.26 (0.47, 3.36)	0.64
Central atrophy (%)	48 (51.6)	58 (65.9)	0.92 (0.60, 2.10)	0.73
Leukoaraiosis (%)	64 (68.8)	63 (71.6)	0.83 (0.37, 1.87)	0.66
Previous stroke lesion (%)	41 (44.1)	51 (60.0)	0.57 (0.28, 1.16)	0.12
Visual longest diameter (cm)			0.66 (0.34, 1.27)	0.21

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
<3	38 (40.1)	36 (40.9)		
3-5	46 (49.5)	28 (31.8)		
5-8	6 (6.5)	20 (22.7)		
>8	3 (3.2)	4 (4.5)		
Volume ABC/2 (cm3)	15.4 (16.0)	19.2 (21.4)	-4.30 (-8.78, 0.23)	0.06
Largest measured diameter	3.6 (1.3)	3.8 (1.6)	-0.04 (-0.33, 0.25)	0.81
Shape index	1.7 (0.8)	1.7 (1.0)	-0.04 (-0.31, 0.24)	0.80
Shape [/5]	2 [2,3]	2 [1,3]	0.14 (-0.19, 0.47)	0.41
Density index	0.4 (0.7)	0.3 (0.5)	0.10 (-0.07, 0.28)	0.27

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Density [/5]	2 [1,3]	2 [1,3]	0.12 (-0.18, 0.43)	0.43
No IVH (n=137)				
Volume ABC/2(cm3)	14.7 (15.3)	18.4 (18.4)	-4.52 (-9.05, 0.01)	0.05
Shape index	1.5 (0.6)	1.7 (1.0)	-0.12 (0.42, 0.17)	0.42
Shape [/5]	2 [1,3]	2 [2,3]	0.04 (-0.31, 0.39)	0.82
Density index	0.4 (0.9)	0.3 (0.7)	0.15 (-0.11, 0.41)	0.26
Density [/5]	2 [1,3]	2 [1,3]	0.34 (-0.03, 0.71)	0.07
With IVH (n=44)				

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Volume ABC/2(cm3)	17.1(17.9)	18.4 (17.4)	-0.64 (-8.53, 7.24)	0.87
IVH volume (cm3)	3.0 (6.0)	3.7 (5.9)	0.52 (-4.96, 6.01)	0.85
Shape index	2.0 (1.0)	2.1 (1.2)	-0.12 (-0.79, 0.55)	0.73
Shape [/5]	4 [3,5]	4 [3,5]	1.00 (0.50, 1.99)	0.99
Density index	0.3 (0.1)	0.3 (0.1)	-0.01 (-0.06, 0.04)	0.66
Density [/5]	2 [1,3]	2 [1,3]	0.00 (-0.64, 0.63)	1.00
Graeb score	2.9 (1.8)	2.1 (1.3)	0.94 (-0.25, 2.12)	0.12
Modified Graeb score	3.4 (2.7)	2.5 (2.2)	1.23 (-0.59, 3.05)	0.18

Figure 4.1 Blood pressure levels for patients with intracerebral haemorrhage during 7 days treatment for GTN versus no GTN group. Blood pressure was 172/93 mm Hg at baseline and after the first dose was significantly lower in 310 patients allocated to GTN as compared to 319 patients randomised to no GTN: difference -7.5/-4.2 mm Hg. There was no significant difference thereafter. MD signifies mean difference in systolic and diastolic blood pressure between the two treatment groups.



SBP - GTN	172.32	162.72	161.26	163.22	161.41	161.36	159.02	159.19
SBP - No GTN	171.81	170.22	166.34	164.53	161.16	157.95	158.96	156.85
DBP - GTN	93.99	88.12	87.19	89.3	89.39	89.95	88.23	88.26
DBP - No GTN	92.74	92.3	91.26	90.97	90.66	89.64	89.48	88.85
SBP (MD)	0.51	-7.5	-5.08	-1.31	0.25	3.41	0.06	2.34
DBP (MD)	1.25	-4.18	-4.07	-1.67	-1.27	0.31	-1.25	-0.59
SBP 2p	0.85	0.02	0.14	0.71	0.94	0.37	0.99	0.55
DBP 2p	0.51	0.05	0.07	0.44	0.56	0.9	0.6	0.79

Figure 4.2 Distribution of modified Rankin scores for all 625 patients with intracerebral haemorrhage at day 90: glyceryl trinitrate versus no glyceryl trinitrate. Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomisation, and allocation to continue or stop pre-stroke antihypertensive drugs. Adjusted common odds ratio 1.04 (95% CI 0.78, 1.38), p=0.81.

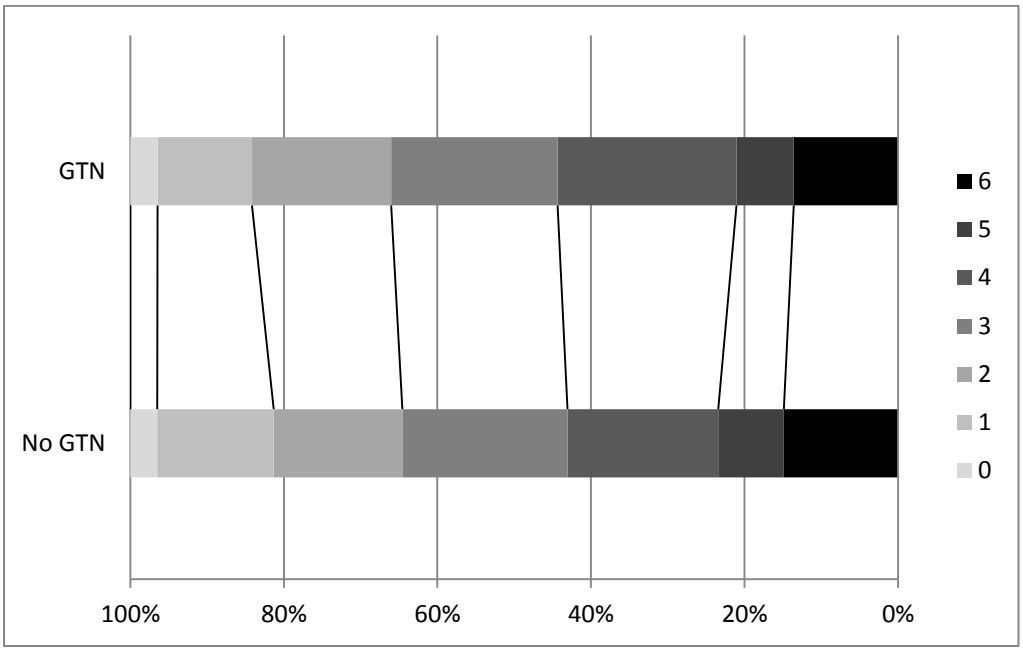


Figure 4.3 Effect of glyceryl trinitrate versus no glyceryl trinitrate on distribution of modified Rankin Scale in pre-specified clinical subgroups of patients with intracerebral haemorrhage at day 90. Analysis adjusted for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, total anterior circulation syndrome, volume of intracerebral haemorrhage, systolic blood pressure, feeding status and time to randomisation. Black squares indicate point estimates (with the area of the square proportional to the number of events) and the width of the horizontal lines is the 95% confidence interval of the estimate. The rectangle at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within categories.

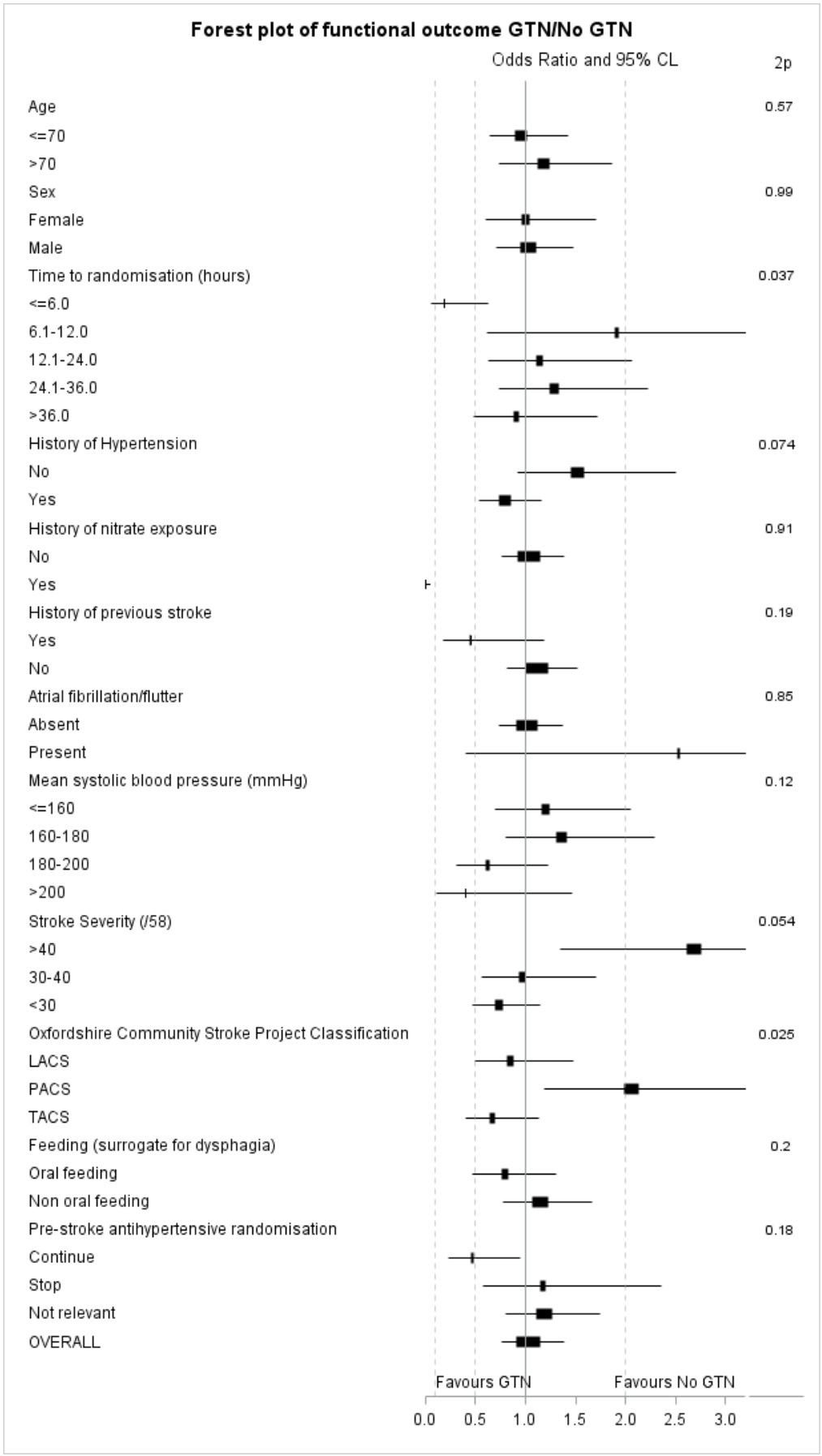

Forest plot of functional outcome GTN/No GTN
Odds Ratio and 95% CL
2p
Age
0.57
<=70
>70
Sex
0.99
Female
Male
Time to randomisation (hours)
0.037
<=6.0
6.1-12.0
12.1-24.0
24.1-36.0
>36.0
History of Hypertension
0.074
No
Yes
History of nitrate exposure
0.91
No
Yes
History of previous stroke
0.19
Yes
No
Atrial fibrillation/flutter
0.85
Absent
Present
Mean systolic blood pressure (mmHg)
0.12
<=160
160-180
180-200
>200
Stroke Severity (/58)
0.054
>40
30-40
<30
Oxfordshire Community Stroke Project Classification
0.025
LACS
PACS
TACS
Feeding (surrogate for dysphagia)
0.2
Oral feeding
Non oral feeding
Pre-stroke antihypertensive randomisation
0.18
Continue
Stop
Not relevant
OVERALL
Favours GTN
Favours No GTN
0.0
0.5
1.0
1.5
2.0
2.5
3.0

Figure 4.4 Effect of glyceryl trinitrate versus no glyceryl trinitrate on the primary outcome of modified Rankin Scale in pre-specified neuroimaging subgroups at day 90. Analysis adjusted for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, total anterior circulation syndrome, volume of intracerebral haemorrhage, systolic blood pressure, feeding status and time to randomisation. Black squares indicate point estimates (with the area of the square proportional to the number of events) and the width of the horizontal lines is the 95% confidence interval of the estimate. The rectangle at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within categories.

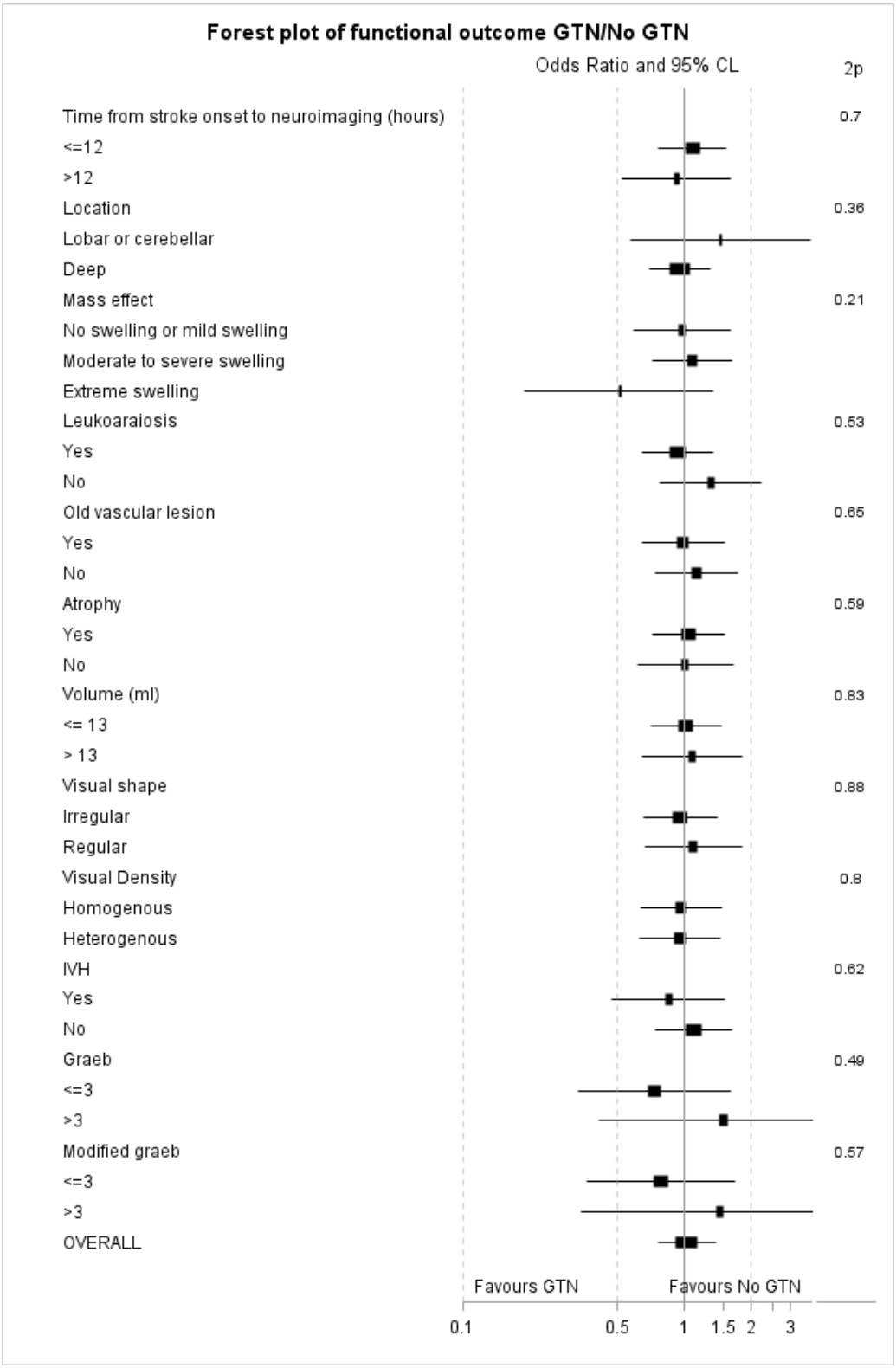

Forest plot of functional outcome GTN/No GTN
Odds Ratio and 95% CL
2p
Time from stroke onset to neuroimaging (hours)
0.7
<=12
>12
Location
0.36
Lobar or cerebellar
Deep
Mass effect
0.21
No swelling or mild swelling
Moderate to severe swelling
Extreme swelling
Leukoaraiosis
0.53
Yes
No
Old vascular lesion
0.65
Yes
No
Atrophy
0.59
Yes
No
Volume (ml)
0.83
<= 13
> 13
Visual shape
0.88
Irregular
Regular
Visual Density
0.8
Homogenous
Heterogenous
IVH
0.62
Yes
No
Graeb
0.49
<=3
>3
Modified graeb
0.57
<=3
>3
OVERALL
Favours GTN
Favours No GTN
0.1
0.5
1
1.5
2
3

Figure 4.5 Effect of glyceryl trinitrate versus no glyceryl trinitrate on survival to day 90 in patients with intracerebral haemorrhage. Comparison by Cox proportional hazards regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomisation, and allocation to continue versus stop pre-stroke antihypertensive drugs. Adjusted hazard ratio 1.02 (95% CI 0.67-1.56), p=0.92.

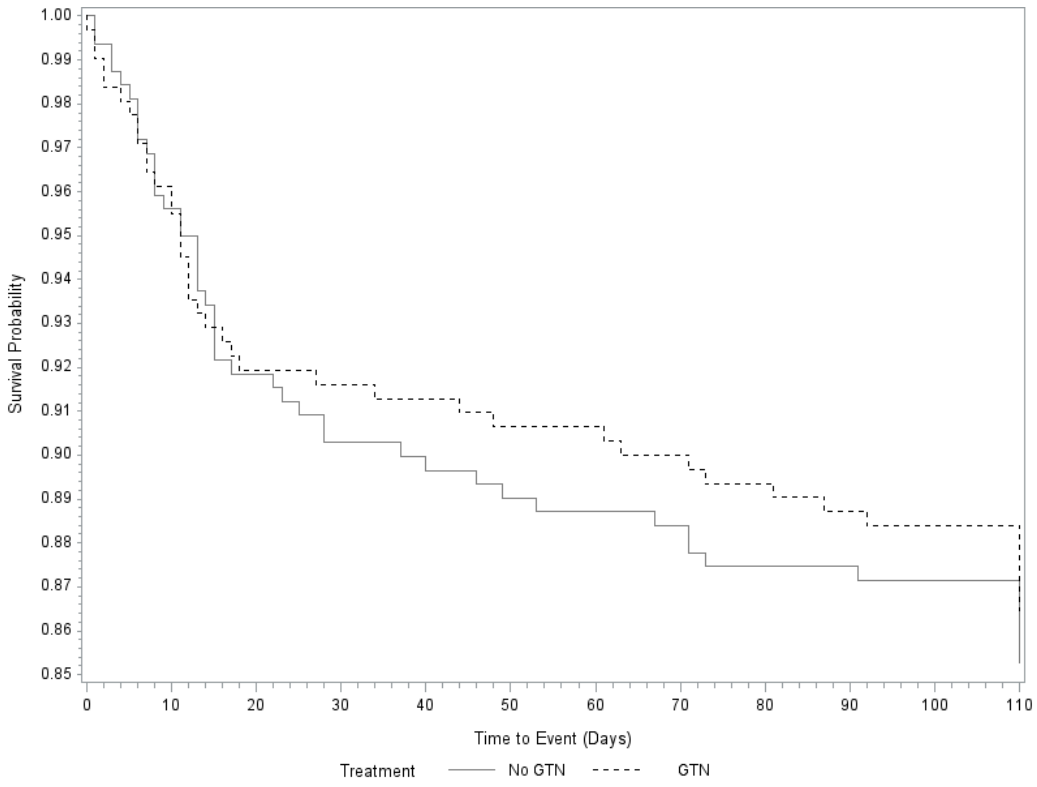
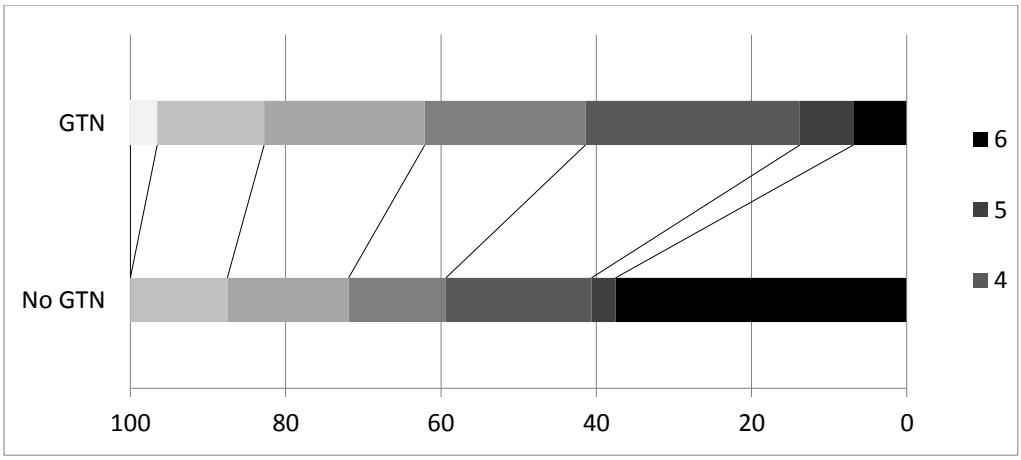


Figure 4.6 Distribution of modified Rankin scores for patients randomised within 6 hours at day 90: glyceryl trinitrate (n=29) versus no glyceryl trinitrate (n=32). Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomisation, and allocation to continue versus stop pre-stroke antihypertensive drugs. Adjusted common odds ratio 0.19 (95% CI 0.06, 0.59), p=0.004.



Chapter 5 - The effects of continue versus stopping pre-stroke antihypertensive drugs in acute intracerebral haemorrhage

Publications contributing to this chapter:

Continue versus stopping pre-stroke antihypertensive therapy in acute intracerebral haemorrhage: a subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) trial

Kailash Krishnan, Polly Scutt, Lisa Woodhouse, Alessandro Adami, Jennifer L Becker, Lesley A Cala, Ana M Casado, Valeria Caso, Christopher Chen, Hanna Christensen, D Ronan Collins, Anna Czlonkowska, Robert A Dineen, John Gommans, Panos Koumellis, Kennedy R Lees, George Ntaios, Serefnur Ozturk, Stephen J Phillips, Stuart J Pocock, Asita de Silva, Nikola Sprigg, Szabolcs Szatmari, Joanna M Wardlaw, Philip M Bath

Journal of Stroke and Cerebrovascular Diseases 2016; 25(5): 1017-26

ABSTRACT

Background and purpose

More than 50% of patients with acute intracerebral haemorrhage (ICH) are taking antihypertensive drugs before ictus. Although antihypertensive therapy should be given long term for secondary prevention, whether to continue or stop such treatment during the acute phase of ICH remains unclear, a question that was addressed in the Efficacy of Nitric oxide in Stroke (ENOS) trial.

Methods

ENOS was an international multicentre, prospective, randomised, blinded end-point trial. Among 629 patients with ICH and systolic blood pressure between 140-220 mm Hg, 246 patients who were taking antihypertensive drugs were assigned to continue (n=119) or stop temporarily (n=127) drugs for 7 days. The primary outcome was the modified Rankin Score at 90 days. Secondary outcomes included death, length of stay in hospital, discharge destination, activities of daily living, mood, cognition and quality of life.

Results

Blood pressure (baseline 171/92 mm Hg) fell in both groups but was significantly lower at 7 days in those patients assigned to continue antihypertensive drugs (difference 9.4/3.5mm Hg; $p<0.01$). At 90 days, the primary outcome did not differ between the groups, adjusted common odds ratio for worse outcome with continue versus stop drugs; OR 0.92 (95 % CI, 0.45-1.89; $p=0.83$). There was no difference between the treatment groups for any secondary outcome measure, or rates of death or serious adverse events.

Conclusion

Among patients with acute ICH, immediate continuation of antihypertensive drugs during the first week did not reduce death or major disability in comparison with stopping treatment temporarily.

5.1 Introduction

High blood pressure (BP) is present in 75% of patients with acute intracerebral haemorrhage (ICH) and is substantially higher than premorbid levels.[401-403] More than 50% of patients with acute ICH are taking antihypertensive drugs prior to their stroke and hospital admission.

Although lowering BP long term after stroke is key for secondary prevention,[404] it remains unclear whether pre-stroke antihypertensive drugs should be continued or stopped temporarily during the acute phase.[405] Arguments both for and against each strategy can be postulated and guidelines lack firm recommendations related to this subject.[135, 406] Continuing prior antihypertensive drugs after ICH might limit haematoma expansion, reduce the development of cerebral oedema and early recurrence, and improve long-term outcome.[404, 407] And yet, continuing treatment may lead to the development of hypotension thereby compromising regional cerebral perfusion because of dysfunctional cerebral autoregulation.[408] Further, continuing treatment involves administering tablets at a time when many patients have dysphagia and limited enteral access, a risk for aspiration pneumonia. Stopping treatment may result in secondary

prevention being forgotten thereby raising the risk of recurrent events and worsening outcomes long term.

Two trials have examined the question of whether pre-stroke BP drugs should be continued or stopped temporarily during the acute phase of stroke. COSSACS found no difference in functional outcome, death, or serious adverse events, although it had low statistical power with only 763 participants recruited of a planned 2900 patients.[409] No differential effect in patients with ICH versus ischaemic stroke were reported. The Efficacy of Nitric Oxide trial (ENOS) trial assessed the effects of glyceryl trinitrate (GTN) versus no GTN in 4011 participants with acute stroke; patients who were taking pre-stroke antihypertensive medications were also randomised to continue or stop these for seven days in a partial factorial design.[364] Although ENOS was neutral for both interventions,[137] a subgroup of patients randomised to continue treatment within 12 hours had a worse functional outcome (unpublished data), an effect also seen in a meta-analysis of individual patient data from COSSACS and ENOS combined (Woodhouse et al, unpublished). Here, we report the results of a pre-planned subgroup analysis of patients enrolled into ENOS with ICH and who were randomised to

continue versus stop pre-stroke antihypertensive therapy,[387] including those randomised within 12 hours of stroke onset.

5.2 Methods

5.2.1 ENOS trial

Details of the ENOS study protocol, statistical analysis plan, patient characteristics at baseline, and main results, have been published (ISRCTN99414122).[137, 374, 387]

In participants assigned to continue antihypertensive drugs, medication was administered orally and those with dysphagia received treatment through a nasogastric feeding tube. If oral or tube feeding was not possible, treatment was withheld until feasible. Open label antihypertensive drugs could be administered during the treatment period according to clinical need. During treatment, BP was measured once daily using a validated automatic clinical monitor (Omron HEM-705 CP or HEM-757, Illinois, USA)[388] with a cuff of suitable size. After day 7, antihypertensive therapy that had been stopped was re-started according to clinical need. In this subgroup analysis, we included all patients with ICH recruited into the

continue versus stop pre-stroke antihypertensive drugs part of ENOS.

5.3 Outcomes

As detailed in chapter 2, the primary outcome was the modified Rankin Scale (mRS, scores: 0=no residual disability; 5= bedbound and requiring 24 hour care; 6=death[410]) assessed at day 90. Key secondary outcomes were activities of daily living (Barthel Index, BI, scores: 0=severe disability to 100=no disability[411]), cognition (modified telephone Mini-Mental State Examination, t-MMSE, scores: 0=severe dementia to 18=normal;[390] Telephone Interview for Cognition Scale, TICS-M, scores: 0=severe dementia to 37=normal;[391] verbal fluency as animal naming, scores: 0=none to infinity); health-related quality of life (European Quality of Life-5 dimensions, EQ-5D,[392] from which health utility status (HUS) was calculated, scores: -0.594=very poor, 0=death to 1.0=perfect;[392] European Quality of Life-Visual analogue scale, EQ-VAS, scores: 0=very poor to 100=excellent) and mood (short Zung depression Score, ZDS, scores: 0=normal to 100=severe depression [394]). Safety outcomes included death, early neurologic deterioration (defined as a decrease of at least 5 points on the SSS from baseline to day 7 and/or

decrease in consciousness of more than 2 points on the SSS consciousness domain), recurrent stroke by day 7, hypotension (requiring intervention such as leg elevation or administration of fluids), hypertension (requiring treatment to lower BP) and serious adverse events. Serious adverse events whether related to treatment (definite, uncertain, no causality, unknown) and the systems affected by the adverse event were recorded by the local investigators.

5.4 Imaging

Brain imaging adjudication and haemorrhage quantification in ENOS are detailed in chapter 2 and 3. All imaging assessments were performed by a single investigator (KK), masked to clinical data and treatment assignment.

5.5 Analyses

As for the mRS and HUS, which have a separate category for death, we assigned an extreme score for death when analysing each of the other outcome scale. Values used were: -5: Barthel Index; -1: EQ-VAS, SSS, t-MMSE, TICS-M, verbal fluency; 0: EQ-5D/HUS; 102.5: ZDS.[137, 387] Comparisons were performed with binary logistic regression (dichotomous data), Cox regression (death), ordinal logistic regression (ordered

categorical data),[412] or multiple linear regression (continuous data). Analyses were adjusted for prognostic covariates: age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity (Scandinavian Stroke Scale, SSS), stroke syndrome (total anterior circulation vs other), systolic BP, feeding status, time to randomisation, and treatment assignment (GTN vs no GTN). Heterogeneity of treatment effect was assessed by including an interaction term in the adjusted statistical model for each of the following pre-defined subgroups: age, time to randomisation, presence of ipsilateral carotid stenosis, number of pre-stroke antihypertensive drugs, feeding status, stroke severity, blood pressure level at time of randomisation, feeding status, and treatment with GTN or no GTN. Analysis was performed using SPSS software (SPSS Statistics, Chicago, IL) version 22 on an Apple iMac computer. P values <0.05 were considered as statistically significant.

5.6 Results

Recruitment into ENOS ran between July 2001 and October 2014. During this period 629 patients with ICH were recruited into the trial, with 246 patients randomised to continue (n=119) or stop (n=127) antihypertensive drugs (Table 5.1). 39 patients were randomised within 12 hours (continue 18,

stop 21). The treatment groups were well matched at baseline, with mean age 69 years; male 59%, mean BP 171/92 mmHg and severity SSS 29.6 (NIHSS ~13.0 with mean ICH volume 12.0 cm3). Most haematomas (89%) were located primarily in the deeper brain regions and many patients had leukoaraiosis (70%) and/or evidence of a previous stroke (51%) (Table 5.2); 72% of neuroimaging was performed within 12 hours of stroke onset.

5.6.1 Blood pressure

Mean blood pressure was 171/92 mmHg at baseline and declined in both groups over the seven days of randomised treatment; by day 7, BP was lower by 9/4 mmHg in the group randomised to continue treatment (Figure 5.1). Baseline BP was 176/97 mmHg in patients randomised with 12 hours, and was lower by 28/16 mmHg at day 7 in those continuing treatment (Figure 5.2).

5.6.2 Clinical outcomes

There was no difference in mRS between the treatment groups at day 90, common odds ratio (OR) for worse outcome in the continue group 0.92 (95%CI 0.45-1.89; p=0.83) (Figure 5.3). A test of 'goodness-of-fit' showed no evidence that the assumption of proportional odds had been violated (p=0.07). There were no significant interactions between the effect of randomised treatment on mRS in pre-selected subgroups (Figure 5.4). Additionally, there was no difference in mRS in patients randomised within 12 hours to continue versus stop prestroke BP drugs (Figure 5.5). The rates of clinical hypotension and hypertension were similar between the two groups (Table 5.3). There were no significant differences between the two groups at day 90 in any of the secondary clinical outcomes (Table 5.3) or death (Figure 5.6), or serious adverse rates (Table 5.4).

5.7 Discussion

In this pre-planned subgroup analysis of patients in ENOS with acute ICH, there was no difference in the primary outcome of function between patients randomised to 7 days of continuing

versus stopping pre-stroke antihypertensive therapy;[387] this finding was consistent across all pre-specified subgroups of patients. Similarly, there were no differences in safety outcomes, or secondary outcome measures at day 90.

The overall neutral results seen for the continue versus stop comparison in ENOS (including both ischaemic stroke and ICH)[137] are similar to those seen in the smaller COSSACS trial.[409] COSSACS recruited only 38 patients with ICH and has not reported these results separately; hence this subgroup cannot be compared with the present substudy. Nevertheless, the two trials differed in several key aspects including time window for recruitment, exclusion or inclusion of dysphagia (and so differences in baseline severity), baseline BP, length of treatment, and timing of measurement of the primary endpoint. In an individual patient data meta-analysis of COSSACS and ENOS combined, no difference in mRS was seen in 284 patients with ICH who were randomised to continue versus stop pre-stroke antihypertensive therapy (Woodhouse *et al*, unpublished). In that meta-analysis, mRS was worse in patients randomised to continue treatment, irrespective of stroke type, if enrolled within 12 hours of onset. This finding was present in ENOS (unpublished data) but is not replicated in the present sub-study, presumably due to the small number

of patients and wide confidence intervals. Blood pressure lowering might reduce death or major disability if treatment is started within 6 hours of stroke.[260, 261, 264] However, the present analysis assessed the issue of continuing or stopping pre-existing antihypertensive treatment (where differences in BP between the treatment groups take days to develop), whereas the other trials initiated antihypertensive treatment in the hyperacute phase of stroke. Since it took several days for BP to differ between the randomised groups, it appears that short term high BP, as occurred in the group that were randomised to stop treatment temporarily, is not detrimental providing the difference occurs after the hyperacute period. Importantly, this observation appears to apply to those recruited within 12 hours where BP was higher by 28/16 mmHg at one week in those stopping treatment temporarily, a BP difference that was not associated with a worse outcome.

The strengths of the present study are two-fold. First, it assessed a broad population of patients with ICH, with international enrolment from multiple race-ethnicity groups, and inclusion of patients with a wide range of severity, including those with dysphagia. And second, the data come from a high fidelity trial with blinded assessment of outcomes, independent and masked adjudication of events, and near

complete follow-up.[137] However, two limitations should be noted. First, ENOS excluded patients with very high blood pressure, reduced consciousness (GCS<8), or without motor signs. As a result, patients with large haemorrhages may have been underrepresented. Second, fewer than 5% of patients had bleeding into the posterior fossa and therefore the results cannot be extrapolated to a population with posterior fossa haemorrhages. Recent observational data have shown that the blood pressure rise is steeper, and final levels higher, in such patients as compared with lobar haemorrhages.[403]

In conclusion, this subgroup analysis of ENOS was neutral and did not identify any beneficial effects in continuing pre-stroke antihypertensive drugs in patients during the first week after acute ICH. Although BP lowering reduces chronic stroke recurrence, the present results suggest it is reasonable to withhold antihypertensive drugs taken before the onset of ICH until patients are neurologically stable and appropriate enteral or oral access has been established.

Table 5.1 Baseline clinical characteristics of 246 patients with intracerebral haemorrhage and those randomised within 12 hours. Data are number (%), mean (standard deviation) or median [interquartile range]. Comparison of patients randomised within 12 hours versus those later by Fischer's exact test, Mann-Whitney U test or t test.

Characteristics	All	Continue	Stop	≤12 hours	Continue	Stop	2p
Number of patients (N)	246	119	127	39	18	21	
Country, UK (%)	138 (56.1)	68 (57.1)	70 (55.1)	20 (51.3)	10 (55.6)	10 (47.6)	0.52
Age (years)	69.2 (11.5)	68.8 (11.3)	69.6 (11.6)	68.3 (13.0)	67.1 (13.7)	69.3 (12.6)	0.58
Sex, male (%)	144 (58.5)	70 (58.8)	74 (58.3)	25 (64.1)	13 (72.2)	12 (57.1)	0.44
Smoking, current (%)	37 (15.5)	20 (17.4)	17 (13.8)	4 (10.8)	2 (11.8)	2 (10.0)	0.19
Pre-morbid mRS>0 (%)	81 (32.9)	43 (36.1)	38 (29.9)	9 (23.1)	5 (27.8)	4 (19.0)	0.23
Previous stroke (%)	45 (18.3)	20 (16.8)	25 (19.7)	3 (7.7)	0	3 (14.3)	0.06
Prior antihypertensive (%)	241 (98.0)	116 (97.5)	125 (98.4)	39 (100.0)	18 (100.0)	21 (100.0)	0.33

Number of BP drugs (%)							
0	3 (1.2)	1 (0.8)	2 (1.6)	-	-	-	-
1	107 (43.5)	55 (46.2)	52 (40.9)	20 (51.3)	13 (72.2)	7 (33.3)	0.22
2	58 (23.6)	28 (23.5)	30 (23.6)	9 (23.1)	3 (16.7)	6 (28.6)	0.47
3	25 (10.2)	8 (6.7)	17 (13.4)	5 (12.8)	1 (5.6)	4 (19.0)	1.00
4	11 (4.5)	4 (3.4)	7 (5.5)	2 (5.1)	1 (5.6)	1 (4.5)	1.00
5	1 (0.4)	1 (0.8)	0	-	-	-	-
Treated BP agent (%)							
ACE-inhibitor	106 (43.1)	51 (42.9)	55 (43.3)	17 (43.6)	6 (33.3)	11 (52.4)	0.29
ARA	49 (19.9)	24 (20.2)	25 (19.7)	5 (12.8)	1 (5.6)	4 (19.0)	0.35
ß-receptor antagonist	70 (28.5)	26 (21.8)	44 (34.6)	10 (25.6)	3 (16.7)	7 (33.3)	0.73
Calcium channel blocker	95 (38.6)	43 (36.1)	52 (40.9)	18 (46.2)	5 (27.8)	13 (61.9)	0.12
Centrally acting agent	8 (3.3)	4 (3.4)	4 (3.1)	2 (5.1)	1 (5.6)	1 (4.8)	1.00
Diuretic	63 (25.6)	34 (28.6)	29 (22.8)	11 (28.2)	7 (38.9)	4 (19.0)	0.53

Alpha-receptor antagonist	13 (5.3)	8 (6.7)	5 (3.9)	3 (7.7)	2 (11.1)	1 (4.8)	1.00
Other	3 (1.2)	1 (0.8)	2 (1.6)	0	-	-	-
Previous high BP (%)	238 (96.7)	115 (96.6)	123 (96.9)	39 (100.0)	18 (100.0)	21 (100.0)	0.21
Diabetes mellitus (%)	49 (19.9)	22 (18.5)	27 (21.3)	10 (25.6)	4 (22.2)	6 (28.6)	0.33
Ischaemic heart disease (%)	39 (15.9)	18 (15.1)	21 (16.5)	4 (10.3)	1 (5.6)	3 (14.3)	0.58
Atrial fibrillation (%)	28 (11.4)	13 (10.9)	15 (11.8)	5 (12.8)	1 (5.6)	4 (19.0)	0.75
TACS (%)	89 (36.2)	44 (37.0)	45 (35.4)	10 (25.6)	8 (44.4)	2 (9.5)	0.15
SSS (/58)	29.6 (12.6)	28.5 (12.3)	30.6 (12.9)	31.3 (11.4)	27.4 (12.4)	34.6 (9.4)	0.37
NIHSS (/42), calculated [379]	13.0 (5.4)	13.4 (5.3)	12.5 (5.5)	12.2 (4.9)	13.9 (5.4)	10.8 (5.4)	0.37
Glasgow Coma Scale [/15]	15 [1]	15 [1]	15 [1]	15 [1]	15 [1]	15 [0]	0.13
Systolic BP (mmHg)	170.8 (18.4)	169.5 (16.9)	172.1 (19.7)	175.8 (17.9)	175.0 (16.6)	176.4 (19.3)	0.07
Diastolic BP (mmHg)	92.3 (13.4)	93.3 (14.0)	91.4 (12.8)	96.5 (11.7)	95.6 (14.1)	97.3 (9.5)	0.031

Heart rate (bpm)	77.4 (15.8)	77.9 (15.9)	77.0 (15.9)	79.2 (17.9)	80.3 (15.1)	78.2 (20.3)	0.22
Feeding status							
Normal diet	77 (31.3)	43 (36.1)	34 (26.8)	15 (38.5)	6 (33.3)	9 (42.9)	0.28
Soft diet	58 (23.6)	22 (18.5)	36 (28.3)	10 (25.6)	7 (38.9)	3 (14.3)	0.09
Nasogastric tube feeding	15 (6.1)	7 (5.9)	8 (6.3)	2 (5.1)	1 (5.6)	1 (4.8)	1.00
Percutaneous feeding tube	0	-	-	-	-	-	-
IV/SC fluids	45 (18.3)	20 (16.8)	25 (19.7)	4 (10.3)	2 (11.1)	2 (9.5)	1.00

ARA: angiotensin receptor antagonist; BP: blood pressure; bpm: beats per minute; IV: intravenous; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke scale; NIHSS: National Institute of Health Stroke scale; SC: subcutaneous; SSS: Scandinavian Stroke Scale; TACS: total anterior circulation syndrome.

Table 5.2 Baseline neuroimaging characteristics of 246 patients with intracerebral haemorrhage and those randomised within 12 hours. Data are number (%) or mean (standard deviation). Comparison of patients randomised within 12 hours with those randomised later by Fisher's exact test, Mann-Whitney U test or t test.

Neuroimaging parameters	All	Continue	Stop	≤12 hours	Continue	Stop	2p
Participants with a scan available	234 (95.1)	115 (96.6)	119 (93.7)	35 (89.7)	17 (94.4)	18 (85.7)	
Time, onset to neuroimaging (%)							
<12 hours	169 (72.2)	84 (73.0)	85 (71.4)	33 (94.3)	17 (100.0)	16 (88.9)	0.89
12-24 hours	38 (16.2)	19 (16.5)	19 (16.0)	1 (2.9)	-	1 (5.6)	-
>24 hours	27 (11.5)	12 (10.4)	15 (12.6)	1 (2.9)	-	1 (5.6)	-

Location of haematoma (%)							
Lobar †	18 (7.7)	6 (5.2)	12 (10.1)	3 (8.6)	2 (11.8)	1 (5.6)	0.41
Deep ‡	207 (88.5)	107 (93.0)	100 (84.0)	32 (91.4)	15 (88.2)	17 (94.4)	0.10
Posterior ¶	9 (3.8)	2 (1.7)	7 (5.9)	-	-	-	0.28
ICH Volume ABC/2 (cm3)[413]	12.1 (14.0)	11.5 (13.6)	12.8 (14.5)	13.1 (17.0)	21.1 (20.5)	5.2 (6.3)	0.67
IVH volume (cm3)	3.1 (4.6)	3.1 (4.5)	3.0 (4.8)	3.9 (3.4)	5.1 (3.5)	1.8 (2.3)	0.61
Longest diameter (cm)	3.2 (1.4)	3.2 (1.3)	3.3 (1.5)	3.3 (1.5)	3.8 (1.6)	2.8 (1.2)	0.76
Visual ICH size category (cm)[367]							
<3	113 (49.1)	53 (46.9)	60 (51.3)	17 (48.6)	5 (29.4)	12 (66.7)	0.25
3-5	80 (34.8)	42 (37.2)	38 (32.5)	10 (28.6)	6 (35.3)	4 (22.2)	

5-8	35 (1.2)	17 (15.0)	18 (15.4)	8 (22.9)	6 (35.3)	2 (11.1)	
>8	2 (0.9)	1 (0.9)	1 (0.9)	-	-	-	
Shape (/5)[212]	3.3 (1.3)	3.4 (1.5)	3.2 (1.4)	3.4 (1.5)	4.0 (1.4)	2.8 (1.3)	0.69
Index [363]	1.7 (3.1)	1.8 (4.0)	1.6 (1.7)	1.7 (1.3)	2.2 (1.4)	1.3 (1.1)	0.34
Density (/5) [378]	2.7 (1.4)	2.6 (1.3)	2.8 (1.4)	2.7 (1.4)	2.8 (1.4)	2.5 (1.4)	0.84
Index [362]	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.34
Graeb score [240]	3.4 (2.2)	3.3 (2.1)	3.4 (2.3)	4.9 (2.1)	6.2 (0.8)	2.7 (1.5)	0.033
Modified[241]	5.0 (4.4)	4.9 (3.5)	5.2 (4.8)	8.0 (4.4)	10.4 (3.5)	4.0 (2.0)	0.034
Leukoaraiosis (%)	171 (73.1)	82 (71.3)	89 (78.8)	21 (60.0)	10 (58.8)	11 (61.1)	1.00
Mass effect (%)							
No swelling to mild swelling (%)	98 (41.9)	47 (40.9)	51(42.9)	17 (48.6)	5 (29.4)	12 (66.7)	0.55

Moderate to severe swelling (%)	33 (14.1)	18 (15.7)	15 (12.6)	18 (51.4)	12 (70.6)	6 (33.3)	0.14
Previous stroke lesion (%)	126 (53.8)	60 (52.2)	66 (55.5)	20 (57.1)	10 (58.8)	10 (55.6)	0.06
Brain tissue reduction (%)	153 (65.4)	77 (67.0)	76 (63.9)	22 (62.9)	12 (70.6)	10 (55.6)	0.42
Cortical atrophy (%)	119 (50.9)	58 (50.4)	61 (51.3)	15 (42.9)	6 (35.3)	9 (50.0)	0.70
Central atrophy (%)	146 (62.4)	72 (62.6)	74 (62.2)	22 (62.9)	12 (70.6)	10 (61.1)	0.65

† Lobar: ICH centred on borderzone regions, ACA, PCA territory and MCA territory excluding striatocapsular regions

‡ Deep: ICH centred on lacunar, MCA territory including striatocapsular regions

¶ Posterior: ICH centred on cerebellum and or brainstem

Shape index[363] = haematoma perimeter / 4∏ x surface area

Density index[362] = standard deviation/mean of Hounsfield units

Table 5.3 Primary and secondary outcomes at day 7 and day 90: continue versus stop pre-stroke antihypertensive drugs. Data are number of patients (%), median [interquartile range], or mean (standard deviation). Comparison by logistic regression, ordinal regression or multiple regression, shown as odds ratio (OR) or mean difference (MD), with adjustment for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, stroke severity, stroke syndrome (total anterior circulation), systolic blood pressure, feeding status, time to randomisation, and treatment assignment (glyceryl trinitrate versus none).

Outcome	N	All	Continue	Stop	Unadjusted OR/MD (95%CI)	2p	Adjusted OR/MD (95% CI)	2p
Day 7 (or discharge)		246	119	127				
Death (%)	246	6 (2.4)	2 (1.7)	4 (3.2)	0.53 (0.09, 2.92)	0.46	0.47 (0.07, 3.01)	0.58
SSS (/58)	244	33.2 (16.1)	33.1 (16.3)	33.3 (15.9)	-0.3 (-4.3, 3.8)	0.90	-0.8 (-4.0, 2.5)	0.64
Recurrent stroke (%)	245	6 (2.5)	3 (2.5)	3 (2.4)	1.06 (0.21, 5.36)	0.37	1.01 (0.18, 5.92)	0.99

SBP (mmHg)	210	155.4 (26.0)	150.6 (26.4)	160 (24.9)	-6.2 (-12.2, -0.2)	0.043	-7.5 (-14.7, -0.3)	0.037
Hypotension (%)	246	3 (1.2)	2 (1.7)	1 (0.8)	2.15 (0.19, 24.07)	0.53	0.09 (0.00, 6.06)	0.26
Hypertension (%)	246	36 (14.6)	15 (12.6)	21 (16.5)	0.73 (0.36, 1.49)	0.39	0.77 (0.57, 2.92)	0.54
Hospital events		244	118	126				
Died in hospital (%)	244	28 (11.5)	14 (11.9)	14 (11.1)	1.08 (0.49, 2.37)	0.86	1.03 (0.35, 2.38)	0.85
Hospital Stay (days)	244	11 [7,33]	12 [7,33]	11 [7,27]	-1.67 (-8.38, 5.03)	0.62	-0.68 (-7.09, 5.72)	0.83
Death or institution (%)	244	105 (43.0)	51 (43.2)	54 (42.9)	0.76 (0.45, 1.27)	0.29	0.69 (0.38, 1.24)	0.22
Day 90			119	126				
Death (%)	245	42 (17.1)	19 (16.0)	23 (18.3)	0.85 (0.44, 1.66)	0.64	0.82 (0.37, 1.82)	0.72
mRS (/6)	245	3.5 (1.7)	3.5 (1.7)	3.5 (1.6)	1.0 (0.7, 1.6)	0.94	1.0 (0.7, 1.6)	0.86
Barthel Index	245	57.4 (39.8)	57.1 (39.8)	57.6 (40.0)	-0.6 (-10.6, 9.5)	0.91	-3.2 (-11.7, 5.3)	0.45
tMMSE	141	9.1 (7.43)	9.0 (7.4)	9.2 (7.5)	-0.2 (-2.7, 2.3)	0.89	-1.1 (-3.2, 0.9)	0.28
TICS-M	130	18.9 (15.9)	19.2 (15.9)	18.6 (15.9)	0.7 (-4.9, 6.2)	0.82	-1.4 (-6.1, 3.3)	0.55

Animal naming (/∞)	136	7.2 (7.5)	7.2 (7.3)	7.2 (7.7)	-0.6 (-3.1, 1.9)	0.64	-0.6 (-3.3, 2.1)	0.66
ZDS (/100)	197	64.3 (24.0)	64.1 (23.4)	64.4 (24.7)	-0.3 (-7.1, 6.4)	0.92	1.7 (-4.2, 7.7)	0.57
EQ-5D/HUS (/1)	244	0.42 (0.31)	0.40 (0.30)	0.43 (0.33)	-0.03 (-0.11, 0.05)	0.52	-0.04 (-0.11, 0.03)	0.24
EQ-VAS (/100)	213	50.1 (31.5)	50.9 (31.0)	49.4 (32.1)	1.6 (-7.0, 10.1)	0.72	-1.9 (-9.6, 5.9)	0.64

BI: Barthel Index; EQ-5D: EuroQol-5 dimensions; EQ-VAS: EuroQol-Visual Analogue Scale; HUS: Health utility status; ICH: intracranial haemorrhage; mRS: modified Rankin Scale; t-MMSE: Modified telephone Mini-Mental State Examination; SAE: serious adverse event; SBP: systolic blood pressure; SSS: Scandinavian Stroke Scale; TICS-M: Modified Telephone Interview for Cognitive Status; VAS: Visual Analogue Scale; ZDS: Zung Depression Scale.

Range of scores:

Scandinavian Stroke Scale (SSS): -1 (death) to 0 (coma with quadriplegia) to 58 (normal neurological status).

Barthel Index: -5 (death) to 0 (severe disability) to 100 (no disability).

Modified telephone Mini-Mental State Examination (t-MMSE): -1 (death), 0 (severe dementia) to 18 (normal).

Modified Telephone Interview for Cognitive Status (TICS-M): -1 (death, 0 (severe dementia) to 37 (normal).

Verbal fluency (number of animals named in one minute): -1 (death), 0 (none named) to infinity.

Health utility status (HUS, derived from European Quality of Life-5 dimensions, EQ-5D): -0.5 (very poor quality of life, 0 (death) to 1.0 (perfect quality of life). European Quality of Life-Visual Analogue Scale (EQ-VAS): -1 (death), 0 (very poor) to 100 (excellent). Zung Depression Scale (ZDS): 0 (normal), 100 (severe depression) to 102.5 (death)

Table 5.4 Serious adverse events at day 90 for continue versus stop pre-stroke antihypertensive drugs in 246 patients with intracerebral haemorrhage. Data are number of patients (%) and mean (standard deviation).

Adverse event	Continue	Stop	2p	Continue	Stop	2p
		All			Fatal	
Neurological †	10 (8.4)	14 (11.0)	0.50	6 (5.0)	8 (6.3)	0.67
Cardiac ‡	4 (3.4)	10 (7.9)	0.17	2 (1.7)	2 (1.6)	1.00
Pulmonary embolism	1 (0.8)	2 (1.6)	1.00	1 (0.8)	0 (0.0)	0.48
Pneumonia	8 (6.7)	8 (6.3)	0.89	6 (5.0)	4 (3.1)	0.53
Other causes	0 (0.0)	1 (0.8)	1.00	-	-	-
Total	27 (22.7)	35 (27.6)	0.38	6 (33.3)	4 (19.0)	0.46

† Includes complication of initial stroke, extension of initial stroke, symptomatic intracranial haemorrhage and recurrent stroke

‡ Includes myocardial infarction, sudden cardiac death and other cardiovascular causes

Figure 5.1 Blood pressure levels in patients with intracerebral haemorrhage who were randomised to continue or stop pre-stroke antihypertensive drugs. Day 0 is at randomisation; day 1 is 2 hours post-randomisation. MD is the mean difference in systolic and diastolic blood pressure for the continue versus stop groups. Comparisons by independent t test at each time point (with Bonferroni correction), and repeated analysis of variance: $p<0.01/0.01$. Both systolic and diastolic blood pressure had significantly diverged by day 4 ($2p=0.010/2p<0.026$).

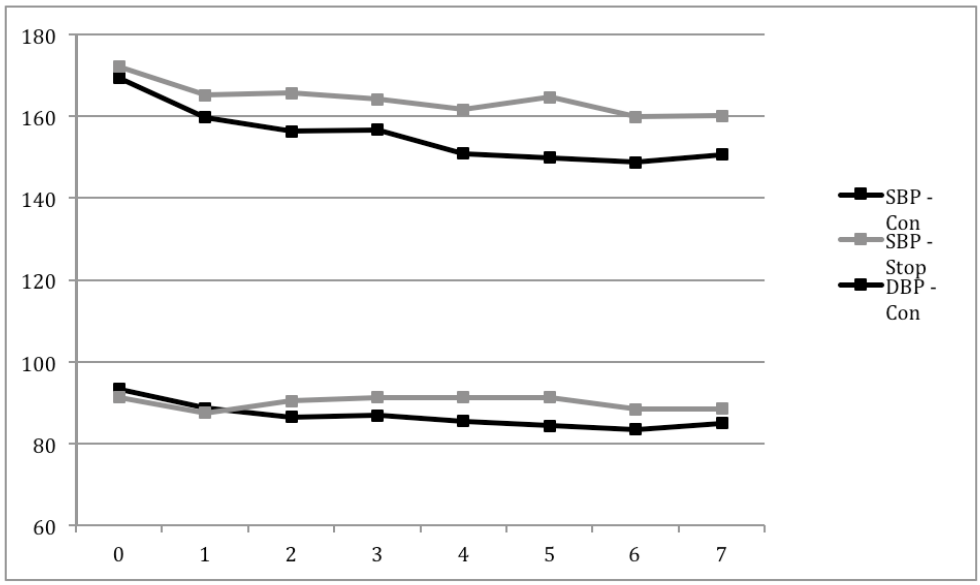


Figure 5.2 Blood pressure levels in patients with intracerebral haemorrhage who were randomised within 12 hours to continue or stop pre-stroke antihypertensive drugs. Day 0 is at randomisation; day 1 is 2 hours post-randomisation. MD is the mean difference in systolic and diastolic blood pressure for the continue versus stop groups. Comparisons by independent t test at each time point (with Bonferroni correction), and repeated analysis of variance: $p<0.01/<0.01$. Both systolic and diastolic blood pressure had significantly diverged by day 5 ($p<0.001$).

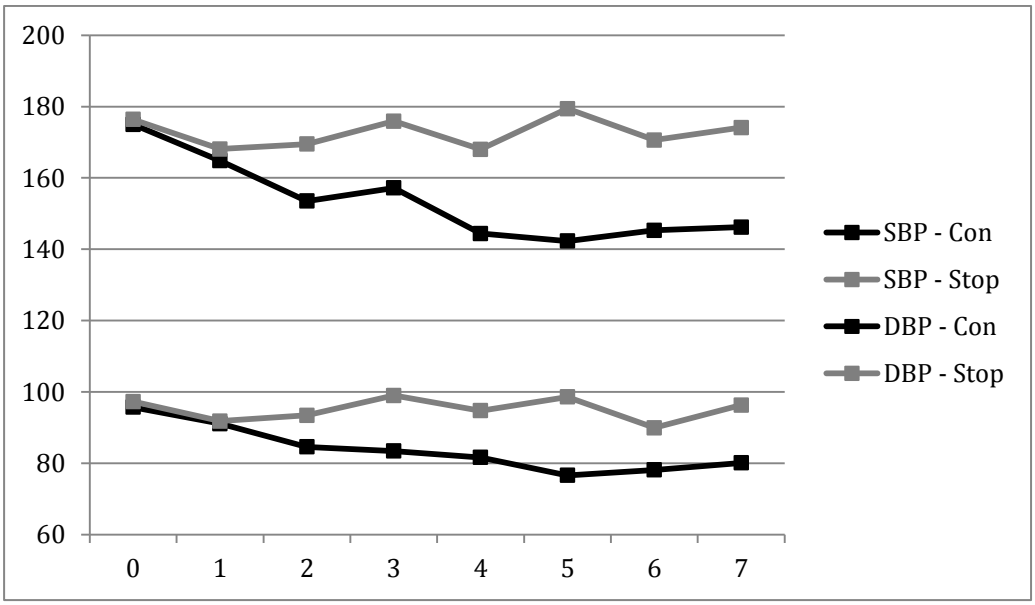


Figure 5.3 Distribution of modified Rankin scores at day 90 in patients randomised to continue versus stop pre-stroke antihypertensive drugs. Comparison by ordinal logistic regression with adjustment: common odds ratio 0.96 (95% CI 0.60 -1.51; p=0.84).

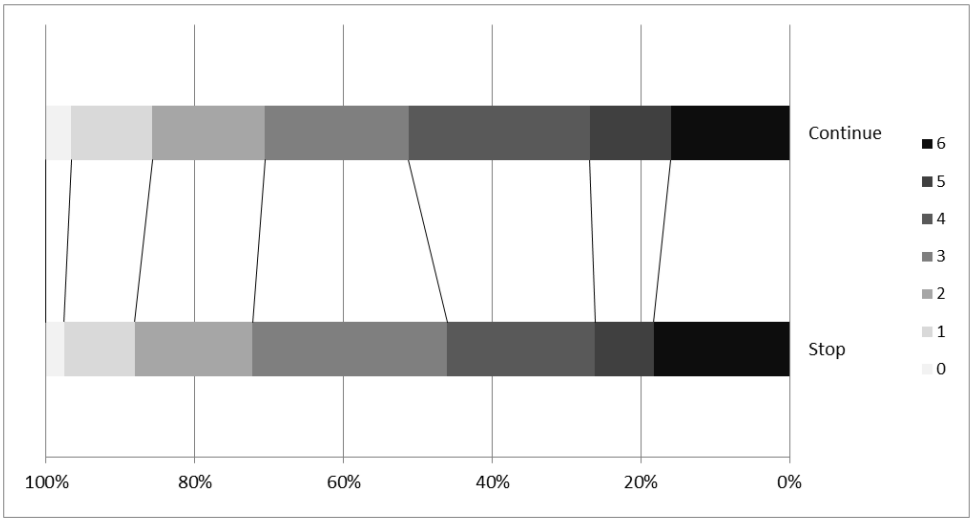


Figure 5.4 Subgroup analysis on the effects of functional outcome at day 90: continue versus stop. 2p is test for interaction.

ACE-I: angiotensin converting enzyme-inhibitor; GTN: glyceryl trinitrate; LACS: lacunar syndrome; PACS: partial anterior circulation syndrome; POCS: posterior circulation syndrome; RAAS: renin-angiotensin-aldosterone system; TACS: total anterior circulation syndrome

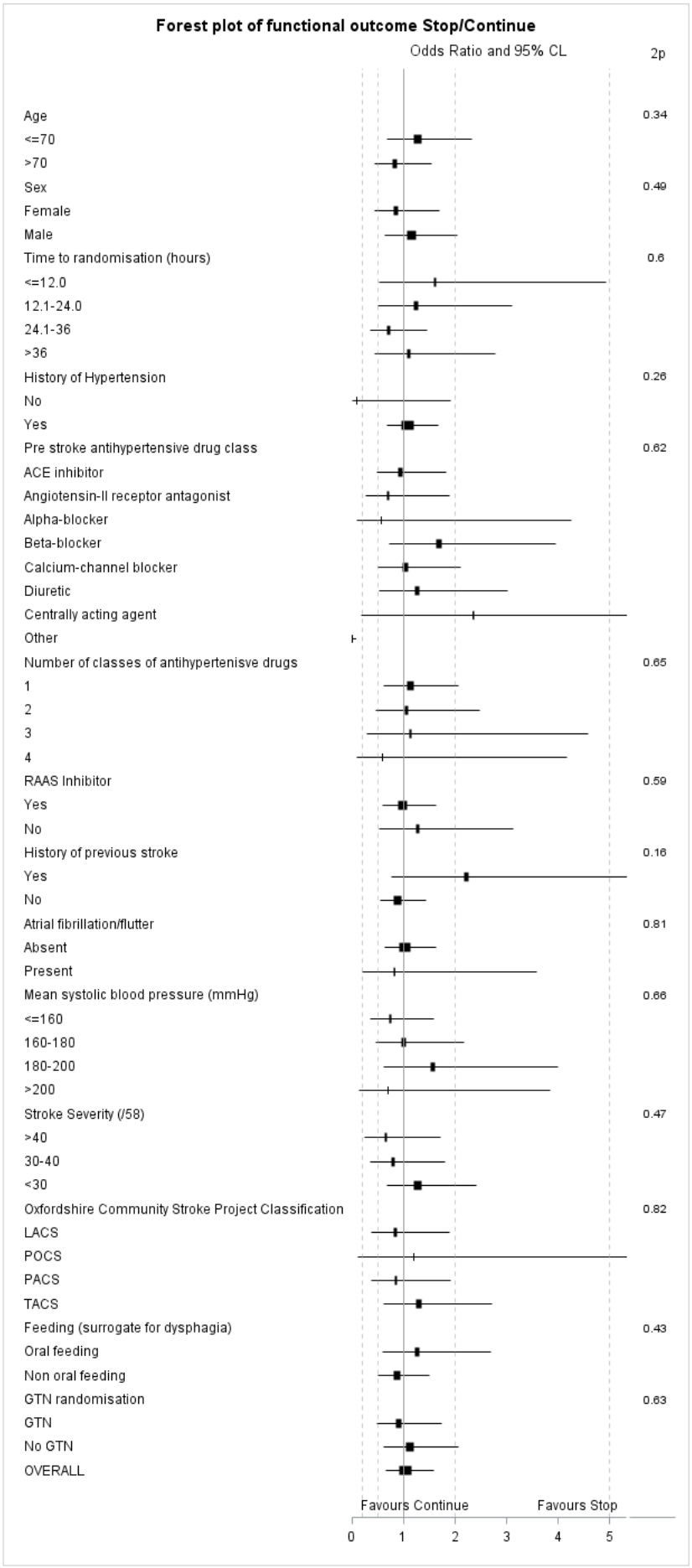

Forest plot of functional outcome Stop/Continue
Odds Ratio and 95% CL
2p
Age
0.34
<=70
>70
Sex
0.49
Female
Male
Time to randomisation (hours)
0.6
<=12.0
12.1-24.0
24.1-36
>36
History of Hypertension
0.26
No
Yes
Pre stroke antihypertensive drug class
0.62
ACE inhibitor
Angiotensin-II receptor antagonist
Alpha-blocker
Beta-blocker
Calcium-channel blocker
Diuretic
Centrally acting agent
Other
Number of classes of antihypertenisve drugs
0.65
1
2
3
4
RAAS Inhibitor
0.59
Yes
No
History of previous stroke
0.16
Yes
No
Atrial fibrillation/flutter
0.81
Absent
Present
Mean systolic blood pressure (mmHg)
0.66
<=160
160-180
180-200
>200
Stroke Severity (/58)
0.47
>40
30-40
<30
Oxfordshire Community Stroke Project Classification
0.82
LACS
POCS
PACS
TACS
Feeding (surrogate for dysphagia)
0.43
Oral feeding
Non oral feeding
GTN randomisation
0.63
GTN
No GTN
OVERALL
Favours Continue
Favours Stop
0
1
2
3
4
5

Figure 5.5 Distribution of modified Rankin scores at day 90 in 39 patients randomised within 12 hours to continue versus stop pre-stroke antihypertensive drugs. Comparison with Mann-Whitney U-test (p=0.43).

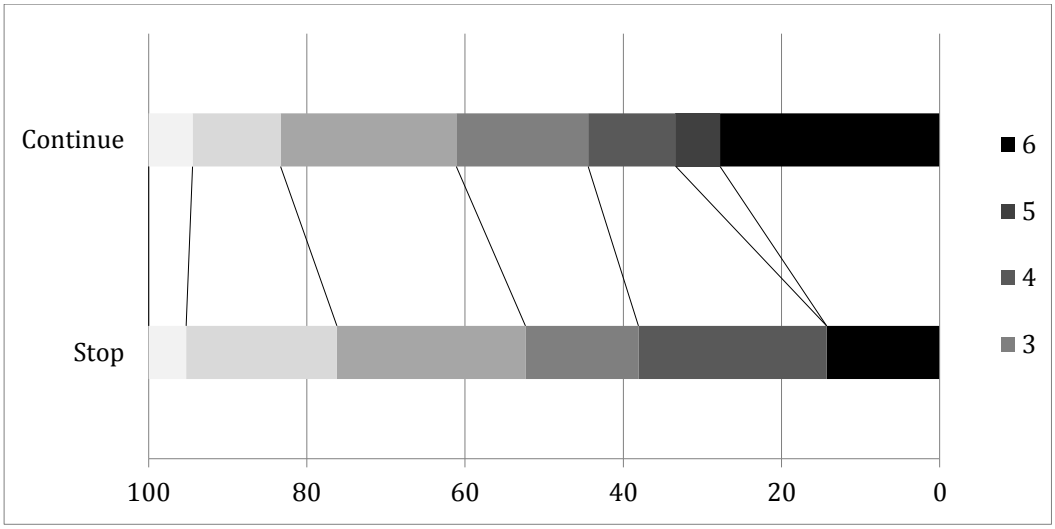
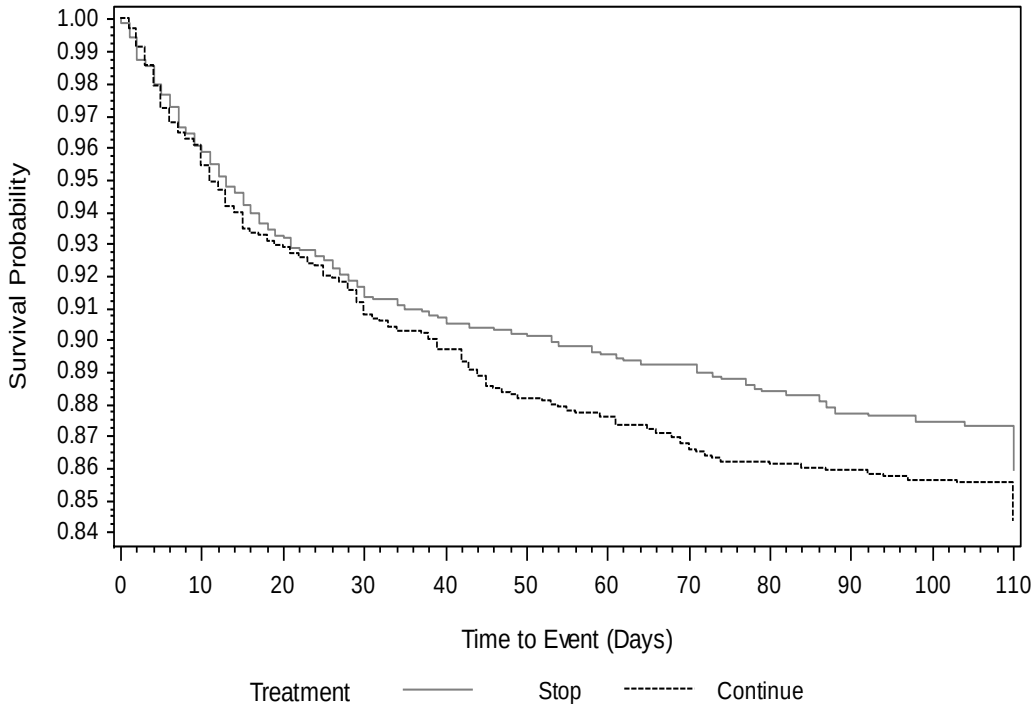


Figure 5.6 Comparison of survival between continue versus stop groups at day 90. Comparison using Cox proportional hazards model: hazard Ratio 1.01 (95% CI 0.81-1.27; p=0.88).



Chapter 6 - Relationship between baseline characteristics and outcome in Asian, Black and Caucasian patients with spontaneous intracerebral haemorrhage

Publications contributing to this chapter:

Kailash Krishnan, Lucy Beishon, Eivind Berge, Hanne Christensen, Robert A Dineen, Serefnur Ozturk, Nikola Sprigg, Joanna M Wardlaw, Philip M Bath, on behalf of the VISTA-ICH collaboration and ENOS Investigators.

Relationship between race and outcome in Asian, Black and Caucasian patients with spontaneous intracerebral haemorrhage: data from the Virtual International Stroke Trials Archive (VISTA) and Efficacy of Nitric Oxide in Stroke trial (ENOS).

(submitted November 2016)

Abstract

Background and purpose

Although poor prognosis after intracerebral haemorrhage relates to risk factors and haematoma characteristics, there is limited evidence for the effect of race-ethnicity.

Methods

Data from 1011 patients with intracerebral haemorrhage enrolled into hyperacute trials and randomised to control were obtained from the Virtual International Stroke Trials Archive (VISTA) and Efficacy of Nitric Oxide in Stroke (ENOS) Trial. Clinical characteristics and functional outcome were compared among three racial groups – Asians, Blacks and Caucasians.

Results

The majority of patients were Caucasian (78.1%) followed by Asians (14.5%) and Blacks (5.5%). At baseline, Caucasians were older and had larger haematoma volumes; Blacks had lower Glasgow Coma Scale and higher systolic blood pressure (all $p<0.05$). Although the primary outcome of modified Rankin scale (mRS) did not differ at 90 days ($p=0.14$), there were significant differences in mortality ($p<0.0001$) and quality of life (EQ-5D $p<0.0001$; EQ-VAS p 0.015). In test of

multiple comparisons, Caucasians were more likely to die (p=0.0003) and had worse quality of life (EQ-5D p=0.003; EQ-VAS p<0.0001) as compared to Asians.

Conclusion

Race-ethnicity appears to explain some of the variation in clinical characteristics and outcomes after acute intracerebral haemorrhage. Factors that explain this variation need to be identified.

6.1 Introduction

Spontaneous intracerebral haemorrhage (ICH) is a severe cause of stroke associated with significant morbidity and mortality.[414] In contrast to ischaemic stroke where incidence has declined in recent decades, the number of admissions for ICH continues to increase.[14, 18] Variations in ICH incidence and outcome occur between different race-ethnicity groups. A higher incidence of ICH is observed among black and Hispanic populations when compared with Caucasians.[15, 17, 415] The SINO-MONICA-Beijing study reported greater mortality due to ICH in China compared to other countries.[416] Death caused by stroke was reported to be higher in Asians compared to Caucasian patients in the UK and Canada.[417, 418] The causes for these observations are unclear and might be explained by increased prevalence of risk factors such as diabetes and hypertension among Asians.[419-422] Additional explanatory factors also appear to include blood pressure at presentation.[17, 423-425] However, studies assessing ICH in different race-ethnicity groups have mostly involved small centres with limited numbers of patients, and have restricted comparisons to differences between two racial populations.[16, 17, 415, 426]

In this study, we compared baseline clinical characteristics and functional outcome in three racial groups in patients with ICH. The data came from the Virtual International Stroke Trials Archive (VISTA) collaboration,[427] and the Efficacy of Nitric Oxide in Stroke (ENOS) trial.[137]

6.2 Methods

6.2.1 Data sources

Included patients came from the VISTA-ICH archive, which includes data from a number of completed randomised controlled trials,[427] and the acute ENOS blood pressure trial.[137, 374] Patients were those with spontaneous ICH, as diagnosed locally using routine neuroimaging, and who were treated within 6 hours of onset. We included patients allocated to the control group in ENOS, as patients assigned to intervention are not included in VISTA. Patients were excluded if: age<18, ICH attributed to trauma, planned surgical evacuation, previously dependent (mRS $\geq$2), concurrent illness with life expectancy <6 months, pregnant or breast feeding women, and those already participating in a study involving another drug or device.

6.2.2 Baseline data

Data at baseline were obtained for age, sex, time from ictus to treatment, medical history (previous stroke, hypertension, ischaemic heart disease, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and prior antithrombotic use), level of consciousness (Glasgow Coma Scale, GCS), stroke severity (National Institutes of Health Stroke Scale, NIHSS), systolic blood pressure (SBP), and heart rate. In VISTA, race (and ethnicity) was defined as Asian (Filipino, Oriental, Asian, Indian, Palestinian and Arabic), Black (black, African/American, Caribbean), Caucasian (white or Caucasian) and Others (American Indian, mixed-coloured, mixed, Hispanic, coloured, Hawaiian and Pacific Islanders).

6.2.3 Outcome data

Outcome at day 90 was assessed using the modified Rankin scale (mRS) and all cause mortality; where available, data on disability (Barthel Index, BI) and quality of life (Euro-QoL, EQ-5D) were also assessed.

6.2.4 Neuroimaging

Depending on trial protocol, CT scans were performed following treatment and then again at 72 hours. As in ENOS, information from CT scans in VISTA was sought for haemorrhage location, lesion volume, oedema volume, presence of mass effect, subarachnoid bleeding, intraventricular haemorrhage, brain atrophy and leukoaraiosis.

6.3 Statistical analysis

The primary outcome was the mRS at day 90. Baseline characteristics and outcomes were compared by Pearson χ^2 test for categorical variables, and analysis of variance for continuous variables. The relationship between baseline haematoma volume and mRS between ethnic groups was analysed using multiple regression. Individual comparisons between ethnic groups were made using Bonferroni correction. Mortality was assessed using Kaplan-Meier curves and Cox Regression. Analyses were adjusted for age, NIHSS, ICH volume and time to treatment. Confidentiality agreements precluded identification of the individual trials in VISTA-ICH and so analyses were not adjusted for trial. Since death is present in outcome scores such as mRS (6), HUS (0) and BI (-

5), death was scored for EQ-VAS as -1. Statistical significance was set at $p \leq 0.05$. All analyses were performed using SPSS (version 21) running on an Apple Mac computer.

6.4 Results

6.4.1 Baseline clinical and neuroimaging characteristics

A total of 1011 patients were identified: 979 recruited from VISTA-ICH,[427] and 32 from ENOS.[137] The mean age was 66.2 years, 63.2% were male, the average time to treatment was 3.7 hours, and the mean GCS was 13.8 (Table 6.1). The majority of patients were Caucasian (78.1%), followed by Asians (14.5%) and Blacks. Less than 2% were in the 'other group' and these were removed from further analyses. When analysed by baseline characteristics, Black patients were younger and more likely to have a previous history of hypertension and higher SBP at baseline. Caucasian patients trended to have more atrial fibrillation, and Asian patients were less likely to have a prior history of antithrombotic use. The mean ICH volume was 22.7 cm^3 and most haematomas were located in the deep subcortical white matter of the brain (Table 6.1).

6.4.2 Clinical outcomes

Table 6.2 shows clinical and radiological outcome measures by ethnicity. The primary outcome, mRS, did not differ between race groups at either day 7 or 90 (Figure 6.1). Similarly, there was no difference in NIHSS during the first 7 days. Whilst the Barthel Index differed at 7 days, it was not significant at day 90 using a test of multiple comparisons. Quality of life, assessed using two measures (health utility status derived from EQ-5D, and EQ-VAS), differed between the three groups (Table 6.2, Figure 6.2); following adjustment for multiple comparisons, Caucasians had worse quality of life scores for both EQ-5D and EQ-VAS as compared to Asians (Table 6.2). Adjusted survival rates differed between race-ethnicity groups (Table 6.2, Figure 6.3), explained by a significant difference between Asians and Caucasians ($p=0.005$). There were no other significant differences for other outcomes.

6.4.3 Neuroimaging outcomes

ICH volume differed across the race groups on both the first follow-up scan (Table 6.2, Figure 6.4) and at 72 hours. (Table 6.2); in both cases, Caucasians tended to have larger haematoma (Table 6.2). Similarly, oedema volumes differed across the race groups on both the first follow-up scan and at

day 7 with Caucasian patients have large oedema volumes than Black patients. The presence of hydrocephalus also differed and was highest in Caucasians. The presence of intraventricular haemorrhage, subarachnoid haemorrhage and midline shift did not differ between the race groups (Table 6.2).

When assessing the relationship between baseline haematoma volume and mRS, there was a significant difference in the slope of the regression lines between the race-ethnicity groups; Blacks and Asians appeared to have a worse mRS for a given haematoma volume ($p=0.047$; Figure 6.5). There were no other significant differences between any of the other comparison groups.

6.5 Discussion

To our knowledge, this is the first study to examine clinical and neuroimaging features and outcomes in ICH patients across three race groups. Significant differences in age, the frequency of previous stroke and hypertension, Glasgow coma scale, blood pressure and ICH volume were present between Caucasian, Asian and Black patients. Similarly, differences in neuroimaging features were present for haematoma location

and volume, oedema volume, and the presence of subarachnoid haemorrhage, hydrocephalus, leukoaraiosis and cerebral atrophy. Although there was no difference in the primary outcome of mRS at day 90, significant differences in case fatality and quality of life were seen. Similarly, differences in ICH and oedema volume, and the presence of hydrocephalus, were present between the race groups.

Black patients were younger and a larger proportion had a history of hypertension which could be associated with increased smoking, alcohol and drug abuse.[16, 426] It is noteworthy that BP in Blacks was higher on admission and probably reflects inadequate control, poor compliance with treatment or treatment resistance.[426, 428] Higher BP in the acute phase of ICH is common [210] and associated with neurological deterioration through haematoma expansion and re-bleeding.[210, 429, 430] The treatment implications of racial difference in BP lowering needs investigation as evidence suggests that early treatment is both safe and feasible,[261] and is now recommended in guidelines.[431, 432] In contrast to a previous report of greater mortality in Blacks for every stroke subtype,[433] VISTA-ENOS found reduced survival in Caucasians with ICH. This finding is difficult to explain and may relate to haemorrhage location, inherent susceptibility to ICH or quality

of care or simply that race-ethnic differences persist even after controlling for such characteristics.

As would be expected, ICH survivors had a quality of life worse than that reported in the general population.[434, 435] The difference between Caucasians and Asians has been reported previously,[423, 436] and may relate to family values, cultural attitudes and care preferences.[436, 437] In one study, Asians were more likely to be living at home whilst Caucasians were less likely to be discharged home despite better functional improvement.[438] Apart from cultural and family factors, age, female sex, stroke severity, persistent neglect and socioeconomic status have also been shown to affect quality of life after stroke.[439, 440]

The strengths of the study include a relatively large sample size for a study population with detailed clinical, radiological information and multiple functional endpoints. The included patients were from neutral RCT's or control group and therefore assessment of the race-ethnic differences avoided the confounding effects of active treatment. However, there are some limitations. First, the analysis of observational data from RCT's has the disadvantage that patients were included on the basis of pre-specified selection criteria. Therefore, the

results may not be applicable to a population of unselected ICH patients. Second, the VISTA collaboration does not reveal the identities of the individual trials and so it is uncertain as to what inclusion criteria were used to select patients. Additionally, analyses could not be adjusted for the source trials, which is important since trials themselves are a determinant of outcome. Third, ethnicity relates to culture, geography, language and it is not clear from the data if this was self-reported or defined by the investigator. Fourth, to compensate for limited numbers, distinct subpopulations were grouped into one ethnic group (for example Asians included people from China, Philippines, the Indian subcontinent, and Arabian peninsula) whilst small groups, present in the 'others' category were excluded. This may have not been appropriate as stroke risk and functional outcome vary within subpopulations living in the same country and between countries.[441, 442] Last, the analysis is limited to trials sharing information within the collaboration and therefore those studies that are not represented in VISTA would not have been included.

In conclusion, this analysis from hyperacute trials in acute haemorrhagic stroke found significant race differences in baseline clinical characteristics and haematoma measures.

There were no difference in the primary outcome of death or dependency but differences in death rates and quality of life were apparent. Further studies are needed to which factors explain race-ethnic differences and whether these differences become larger over time. This could include developing countries or those without access to specialist stroke care teams.

Table 6.1 Baseline characteristics of 1011 patients with intracerebral haemorrhage by ethnicity. Data are number (%) or mean (standard deviation). Comparisons by chi-square test or one-way analysis of variance.

Demographics	N	All	Caucasian	Asian	Black	Other	2p	C v A 2p	C v B 2p	A v B 2p
Number of patients (%)		1011	790 (78.1)	147 (14.5)	56 (5.5)	18 (1.8)				
Clinical findings										
Age (years)	1011	66.2 (12.5)	67.7 (12.1)	61.3 (12.5)	58.4 (11.3)	61.9 (11.0)	<0.001	<0.0001	<0.0001	0.13
Sex, male (%)	982	621 (63.2)	489 (63.3)	40 (65.6)	32 (57.1)	10 (71.4)	0.56	0.64	0.39	0.33
OTT (hrs)	1007	3.7 (1.2)	3.7 (1.2)	3.6 (1.4)	3.4 (1.2)	3.7 (1.2)	0.08	0.26	0.035	<0.0001
Medical history										
Previous stroke (%)	1011	106 (10.5)	71 (9.0)	24 (16.3)	8 (14.3)	3 (16.7)	0.017	0.011	0.23	0.83
Hypertension (%)	1011	813 (80.4)	613 (77.6)	133 (90.5)	52 (92.9)	15 (83.3)	<0.0001	<0.0001	0.006	0.78
IHD (%)	1011	105 (10.4)	92 (11.6)	10 (6.8)	3 (5.4)	0 (0)	0.07	0.11	0.19	1.00
Diabetes mellitus (%)	1011	177 (17.5)	135 (17.1)	25 (17.0)	11 (19.6)	6 (33.3)	0.89	1.00	0.59	0.68
HC (%)	997	49 (4.8)	43 (5.4)	5 (3.4)	1 (1.8)	0 (0)	0.49	0.40	0.42	1.00
Atrial fibrillation (%)	1011	68 (6.7)	62 (7.8)	4 (2.7)	2 (3.6)	0 (0)	0.047	0.022	0.43	0.67
Antithrombotic(s) (%)	162	162 (16.0)	143 (18.1)	8 (5.4)	7 (12.5)	4 (22.2)	0.005	1.00	0.77	0.87

NIHSS (/42) †	1008	13.7 (1.9)	13.7 (5.6)	13.3 (6.0)	15.1 (7.4)	13.7 (1.9)	0.12	0.37	0.08	0.07
GCS (/15)	1010	13.8 (1.8)	13.8 (1.8)	13.4 (1.9)	13.2 (2.2)	14.1 (1.7)	0.010	0.037	0.015	0.37
Systolic BP (mmHg)	1008	174.4 (29.2)	173.1 (29.3)	176.7 (26.5)	185.7 (40.0)	174.4 (29.2)	0.005	0.18	0.002	0.041
Diastolic BP (mmHg)	1007	93.2 (19.0)	91.6 (18.5)	97.1 (18.5)	106.0 (21.1)	93.8 (20.8)	<0.001	0.001	<0.0001	0.003
Heart rate (bpm)	1005	80.0 (15.1)	78.1 (15.4)	76.6 (13.8)	79.9 (14.6)	78.2 (14.1)	0.34	0.27	0.40	0.14
Neuroimaging										
Haematoma location (%)										
Lobar	863	134 (13.3)	122 (15.4)	5 (3.4)	7 (12.5)	0	0.001	<0.0001	0.57	0.045
Subcortical white matter	893	685 (67.8)	541 (68.5)	93 (63.3)	42 (75.0)	9 (50.0)	0.006	0.30	0.73	0.34
Thalamus	600	217 (21.5)	181 (22.9)	22 (15.0)	10 (17.9)	4 (22.2)	1.00	1.00	1.00	1.00
Brain stem/cerebellum	893	21 (2.1)	17 (2.2)	2 (1.4)	1 (1.8)	1 (5.6)	0.82	0.75	1.00	1.00
Haematoma volume (cm^3)	996	22.7 (23.1)	24.2 (24.9)	17.8 (13.1)	15.8 (14.1)	18.5 (17.3)	0.005	0.03	0.014	0.34
Oedema volume (cm^3)	874	13.9 (15.7)	14.9 (16.9)	11.1 (9.2)	9.9 (10.4)	8.1 (7.8)	0.007	0.015	0.041	0.48
Midline shift (%)	885	623 (61.6)	488 (61.8)	90 (61.2)	38 (67.9)	7 (38.9)	0.62	0.67	0.43	0.71
SAH (%)	1007	80 (7.9)	73 (9.2)	3 (2.0)	1 (1.8)	3 (16.7)	0.003	0.02	0.05	1.00
IVH (%)	876	286 (28.3)	234 (29.6)	33 (22.4)	17 (30.4)	2 (11.1)	0.22	0.14	0.75	0.26
Hydrocephalus (%)	860	619 (61.2)	517 (65.4)	64 (43.5)	29 (51.8)	9 (50.0)	<0.001	<0.0001	0.004	0.74
Leukoaraiosis (%)	619	287 (28.4)	251 (31.8)	21 (14.3)	12 (21.4)	3 (21.4)	0.28	0.29	0.18	0.66
Cerebral atrophy (%)	1007	552 (54.6)	469 (59.4)	50 (34.0)	21 (37.5)	12 (66.7)	<0.001	<0.0001	0.002	0.74

† Calculated [379] from Scandinavian Stroke Scale in ENOS

BP: blood pressure; GCS: Glasgow Coma Scale; HC: hypercholesterolemia; IHD: ischaemic heart disease; IVH: intraventricular haemorrhage; OTT: onset to treatment; SAH: subarachnoid haemorrhage

Table 6.2 Clinical and radiological outcomes by race groups**.** Data are number (%) and mean (standard deviation). Comparisons between group differences made by chi-square test or analysis of variance; multiple comparisons include Bonferroni correction.

	n	All	Caucasian	Asian	Black	Other	2p	C v A	C v B	A v B
Patients		1011	790	147	56	18		2p	2p	2p
Clinical										
mRS (/6)										
Day 7	538	4.1 (1.1)	4.2 (1.1)	4.2 (0.8)	3.9 (1.3)	4.6 (0.5)	0.36	1.00	0.07	0.12
Day 90	873	3.2 (1.6)	3.2 (1.6)	3.0 (1.6)	3.4 (1.7)	3.1 (1.8)	0.14	0.18	1.00	0.37
NIHSS (/42) †										
Day 1	936	13.1 (7.0)	13.1 (7.0)	12.8 (6.7)	13.2 (8.1)	12.4 (6.5)	0.89	1.00	1.00	1.00
Day 3	564	12.5 (8.0)	12.7 (8.2)	11.0 (6.3)	11.6 (8.3)	14.8 (7.0)	0.29	0.42	1.00	1.00
Day 7	534	10.8 (7.1)	10.9 (7.9)	10.2 (6.1)	10.7 (7.5)	13.1 (6.7)	0.80	1.00	1.00	1.00
Day 90	958	8.1 (9.8)	8.1 (10.1)	6.0 (5.7)	9.6 (10.4)	9.7 (10.6)	0.31	0.88	0.96	0.41
Barthel Index (/100)										

Day 7	539	28.9 (31.1)	28.6 (31.2)	30.6 (29.1)	33.9 (36.5)	14.4 (16.1)	0.010	1.00	1.00	1.00
Day 90	872	63.0 (37.4)	62.9 (37.6)	66.0 (35.7)	56.4 (39.0)	66.5 (39.1)	0.28	1.00	0.68	0.34
Day 90										
Death (%)	1011	211 (20.9)	189 (23.3)	11 (7.5)	9 (16.1)	2 (11.1)	<0.001	<0.001	0.59	0.33
EQ-5D (/1)	487	0.29 (0.37)	0.25 (0.36)	0.46 (0.40)	0.31 (0.40)	0.40 (0.39)	<0.001	<0.001	1.00	0.18
EQ-VAS (/100)	321	46.0 (33.5)	43.3 (33.6)	57.0 (30.2)	44.2 (35.2)	42.5 (60.1)	0.015	0.012	1.00	0.34
Neuroimaging										
ICH vol. (cm^3)										
Follow up scan	523	32.3 (32.2)	34.7 (34.4)	26.2 (23.8)	23.7 (23.6)	18.9 (24.1)	0.017	0.07	0.14	1.00
72 hours	930	27.3 (28.6)	28.7 (30.4)	23.3 (19.7)	20.1 (20.3)	21.6 (20.4)	0.019	0.13	0.09	1.00
Oedema vol. (cm^3)										
Follow up scan	428	31.8 (31.8)	34.1 (33.9)	29.1 (25.7)	19.7 (20.8)	19.7 (18.4)	0.030	0.65	0.038	0.46
72 hours	924	33.6 (30.9)	33.6 (30.9)	29.9 (22.1)	22.0 (19.6)	24.8 (23.4)	0.009	0.53	0.012	0.26
IVH (%)										
Follow up scan	399	195 (19.3)	145 (18.4)	35 (23.8)	14 (25.0)	1 (5.6)	0.98	0.90	1.00	1.00
72 hours	811	344 (34.0)	277 (35.1)	46 (31.3)	19 (33.9)	2 (11.1)	0.41	0.54	0.55	1.00
72 hours										
SAH (%)	566	97 (9.6)	87 (11.0)	7 (4.8)	2 (3.6)	1 (5.6)	0.23	0.21	0.20	0.71

Hydrocephalus (%)	791	605 (59.8)	498 (63.0)	67 (45.6)	31 (55.4)	9 (50.0)	<0.001	<0.001	0.016	0.60
Midline shift (%)	790	628 (62.1)	490 (62.0)	94 (63.9)	37 (66.1)	7 (38.9)	0.54	0.25	0.72	0.37

A: Asians; B: Blacks; C: Caucasians; EQ-5D: European Quality of Life-5 dimensions; EQ-VAS: European Quality of Life-Visual Analogue Scale; ICH: intracerebral haemorrhage; IVH: intraventricular haemorrhage; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; SAH: subarachnoid haemorrhage

†Calculated from Scandinavian Stroke Scale in the ENOS trial [379]

Range of scores for patients in ENOS:

Barthel Index: -5 (death) to 0 (severe disability) to 100 (no disability).

Health utility status (HUS, derived from European Quality of Life-5 dimensions, EQ-5D): -0.5 (very poor quality of life, 0 (death) to 1.0 (perfect quality of life). European Quality of Life-Visual Analogue Scale (EQ-VAS): -1 (death), 0 (very poor) to 100 (excellent).

Zung Depression Scale (ZDS): 0 (normal), 100 (severe depression) to 102.5 (death)

Figure 6.1 Distribution of modified Rankin scores between the three race groups at day 90.

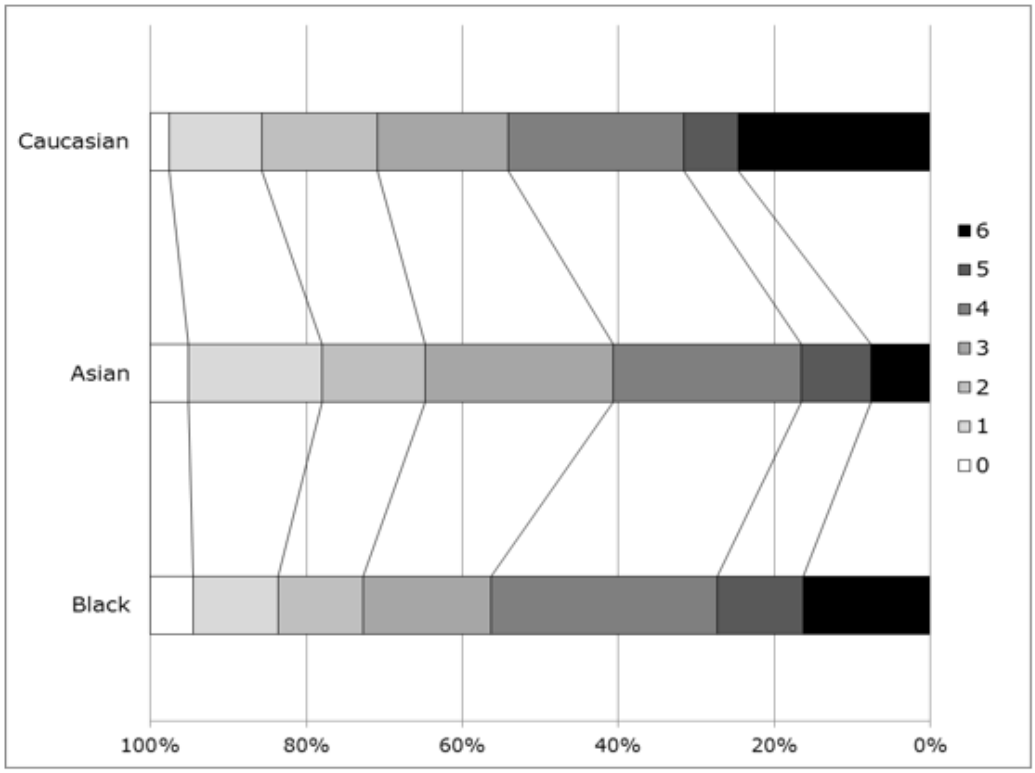


Figure 6.2 Box plots of Euro Quality of Life-5Dimension-3 level scores (n=487) at day 90. Comparison by ANOVA 2p<0.001; Caucasian vs Asian 2p<0.001, Caucasian vs Black 1.00, Asian vs Black 2p=0.18.

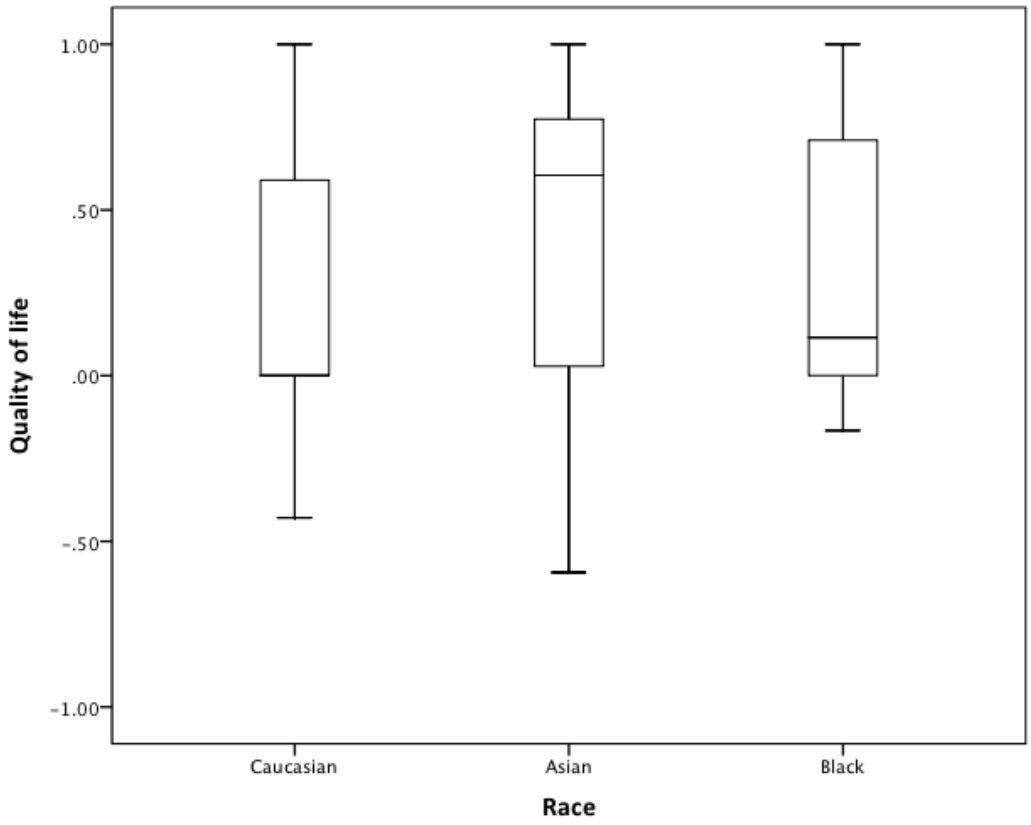


Figure 6.3 Cox regression with adjustment for age, baseline systolic blood pressure, stroke severity (NIHSS), haematoma volume and time to treatment: overall p=0.021; Asians vs Caucasians, hazard ratio 0.42 (95% CI 0.22, 0.77); p=0.005.

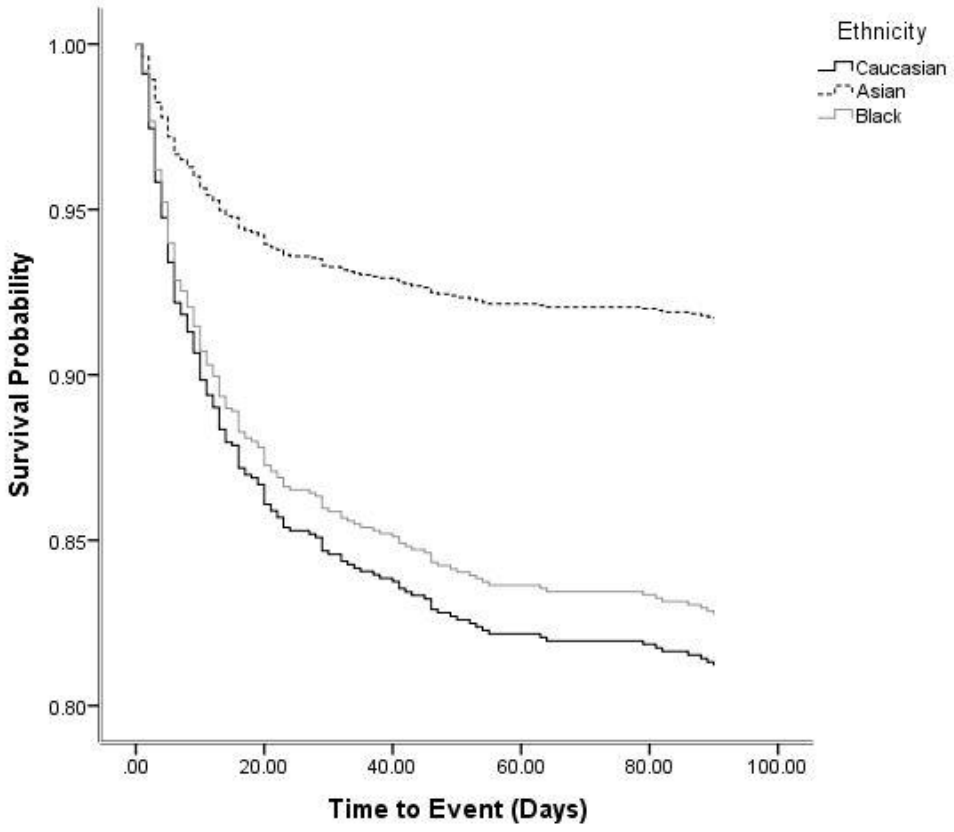


Figure 6.4 Intracerebral haematoma volume (n=523) on first follow-up imaging by race. Comparison by ANOVA 2p=0.017; Caucasian vs Asian 2p=0.07, Caucasian vs black 0.14, Asian vs black 2p=1.0.

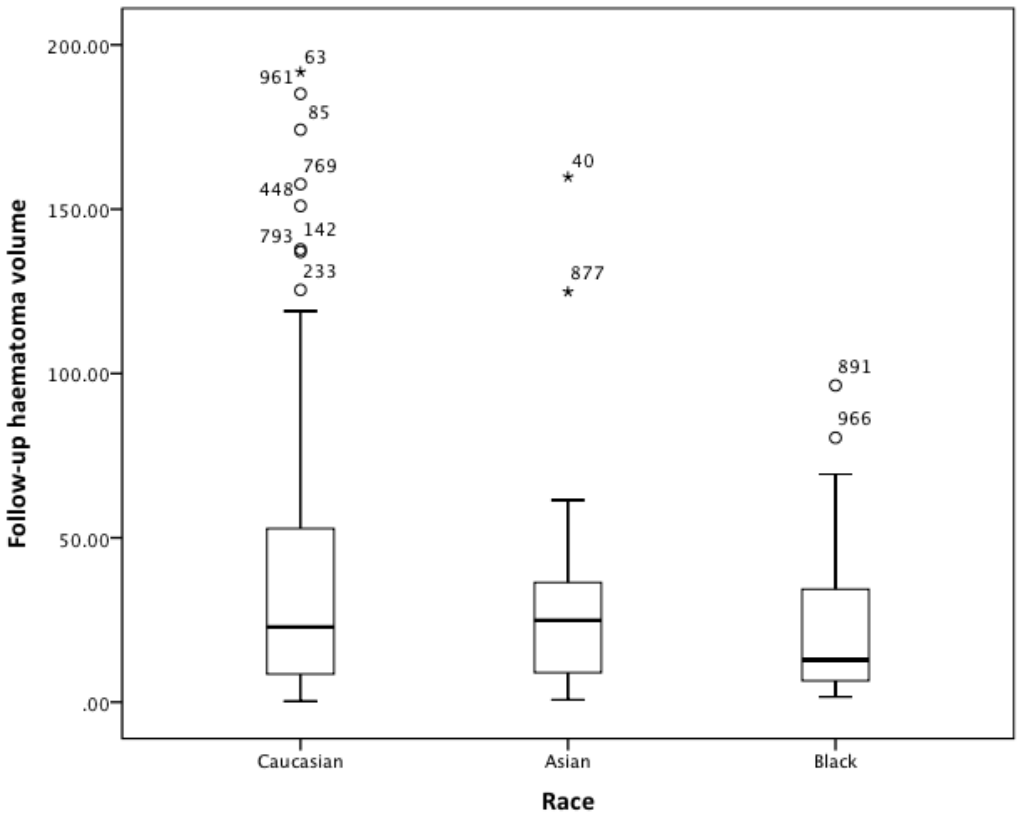
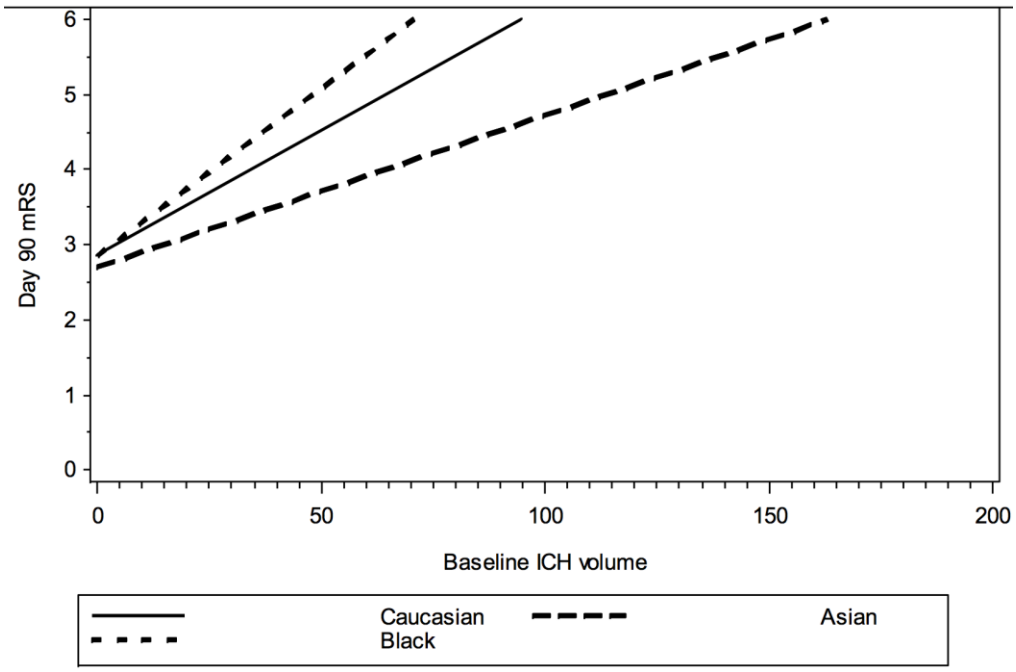


Figure 6.5 Relationship between haematoma volume at baseline and functional outcome, assessed as the modified Rankin Scale (mRS), at day 90 for Caucasians, Asians and Blacks. The continuous and dotted lines indicate the regression lines.



Overall comparison between the three ethnicities (using ANCOVA) showed a difference in the slopes of the regression lines between the three groups ($p<0.0001$). Individual comparisons found significant difference in the slopes of the regression lines between Blacks vs Asians ($p=0.047$; using Bonferroni correction). There were no significant differences between any of the other ethnic group comparisons. Analysis was adjusted for age, baseline NIHSS, ICH volume and time to treatment.

Chapter 7 - The effects of deliberately altering blood pressure in acute stroke: a systematic review and meta-analysis

Publications contributing to this chapter:

1. PMW Bath, K Krishnan. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD000039.
2. Kailash Krishnan, Philip MW Bath. Interventions for deliberately altering blood pressure in acute stroke. Stroke. 2015; 46:00-00.
3. Kailash Krishnan, Philip MW Bath. Interventions for deliberately altering blood pressure in acute stroke. Oral presentation at the UK Stroke Forum 2014.

Introduction

This chapter is an abbreviated version of a systematic review and meta-analysis of published and unpublished randomised controlled trials aimed at altering BP within 1 week of acute ischaemic or haemorrhagic stroke and a review of the methodology is described in this section.

Background

Traditional medical review articles broadly narrate the literature and attempt to synthesise results and conclusions of a particular subject. However, this approach is subject to personal bias of the author/s, a bias in the selection of the included studies and inferences may not be easily verified.[443, 444] By comparison, a systematic review poses a specific research question taking into account all relevant literature including studies with and without conflicting results, appraises their quality and provides an answer that is reproducible and free of bias.[445] In addition to identifying whether certain groups of studies (e.g. small studies, studies with negative results) are excluded in the analysis, a systematic review offers the following advantages:

- summarises large amounts of information
- reports the generalisibility and consistency in studies

- discusses when the study data is sparse or of poor quality
- identifies common definitions for outcomes
- extracts estimates of outcomes
- describes the robustness of the results
- allows hypothesis generation in subgroups
- discusses why an intervention may work thereby reducing delay between research findings and implementation in clinical practice. The conclusions in a systematic review are reliable because of the thorough and standardised methods used.

After defining a precise question, a comprehensive literature search is undertaken appropriate to the topic of interest. Between 30-80% of all randomised controlled trials can be found on MEDLINE and other standard database search engines and therefore other sources are used, including hand searching references listed in the primary source, reviewing conference abstracts, internet trial registers, 'grey literature' (e.g. non peer reviewed journals, product information from pharmaceutical companies), contacting investigators for unpublished information and 'raw data' via personal communication.[445, 446] Involvement of more than one reviewer at this stage is important to determine the level of detail in

each search strategy, reasons for study inclusion or exclusion and to avoid losing relevant data.[445, 447] Once selected, the studies should be evaluated for quality. Various scoring systems are available,[446, 448] but in essence all included studies are assessed for the following: whether the selected participants are similar to those in clinical practice, adequate concealment of random allocation, use of appropriate statistical tests, withdrawal reporting and blinding in outcome assessment.

The statistical techniques used to analyse data from all included studies is known as meta-analysis.[443] This is performed in two steps. First, the treatment effect is computed for each study. For continuous data, the mean difference or standardised mean difference is used. The former is used when the outcome is measured on the same scale (e.g. blood pressure measurement) and the latter is calculated when different scales are used to measure the same outcome (e.g. scoring of pain). With categorical data, risk ratio (RR), odds ratio (OR), absolute risk reduction (AR) and number needed to treat (NNT) are used as measures of effect.

The second stage of a meta-analysis is combining the extracted data to derive an overall pooled effect with greater weightage given to studies with more information. The approach chosen to combine data depends whether heterogeneity between the individual studies is present. Heterogeneity suggests that the results of each individual study are not compatible with the results of the others. Common sources of this variation include clinical (e.g. differences in patient selection, drug dosage, frequency, route of administration, measuring outcomes) or methodological (trial design, comparators, time to assess outcome and methods to ascertain outcome) differences. Advanced software such as the Review Manager (RevMan) endorsed by the Cochrane collaboration will investigate for statistical heterogeneity using the χ^2 and the I^2 tests. χ^2 assesses whether the differences in study results are attributed to chance alone and a value of 0.10 is considered significant.[443, 445] The I^2 computes heterogeneity as a percentage and a value >40% suggests this. If statistical heterogeneity is demonstrated, explanations such as clinical heterogeneity or differences between participants or trial design should be sought. If the latter is thought to be present, the analysis will use a random effects model;[449] this means that the meta-

analysis result is an un-weighted average effect size across all the included studies.

Another important factor to be taken into account is publication bias, where studies are more likely to be published if their results are 'significant' than if their results are negative or inconclusive. This can be assessed using a funnel plot,[450] which visually depicts the effect estimates (e.g. OR) from each study on the horizontal axis against a measure of study precision (standard error) on the vertical axis. In the absence of any bias, the plot will display as an inverted funnel with the apex centred on the summary estimate and 95% of all studies included within 1.96 standard errors on each side.[451]

The results of the meta-analysis are displayed in a standard graphical way using a forest plot.[452] The figure can be sectioned into five columns.[449, 453] All included studies are displayed as rows. The first column usually shows the study ID's, usually the first author followed by the year. The second and third columns indicate the intervention and control groups. The fourth column gives the visual display of the study results. The line in the middle represents' the line of no effect' and assigned a value of 1 for a binary outcome variable (OR, RR) or 0 for a continuous outcome variable. The square

is the mean effect estimate for that study and the area is proportional to the weighting given to that study. The horizontal line through each square is the length of the 95% confidence interval. The longer the line, the greater is the width of the confidence interval. The fifth column gives the numerical value for each study identical to the visual display of the graph in the fourth column. The diamond at the bottom row of the graph is the summary result; the middle of the diamond lies on the value for the overall effect estimate and the horizontal tips represent the confidence interval.

If the diamond does not cross the 'line of no effect', then the result represents an overall positive or negative effect. Conversely if the diamond crosses the vertical line, there is no statistical difference between the groups.

As with all papers, the last step is writing which includes a summary of the results, recommendations for clinical work (for example, in whom the intervention is likely to benefit, under what conditions) and what areas or topics require more research.

ABSTRACT

Background

It is unclear whether blood pressure should be altered actively during the acute phase of stroke. This is an update of a Cochrane review first published in 1997, and previously updated in 2001 and 2008.

Methods

Randomised controlled trials of interventions that would be expected on pharmacological grounds to alter BP within one week of acute ischaemic or haemorrhagic stroke were identified through electronic searches of databases and patient data collated. The effect of altering BP on functional outcome (modified Rankin scale, mRS; Barthel Index, BI) and blood pressure were assessed both overall and in pre-specified subgroups, including by time to treatment. Results were reported as odds ratio (OR) with 95% confidence interval (CI) for dichotomous data and as mean difference (MD) for continuous data.

Results

Twenty-six trials involving 17,011 participants were included (8497 participants were assigned active therapy and 8514 participants received placebo/control). Not all trials contributed to each outcome. Most data came from trials that had a wide time window for recruitment; four trials gave treatment within six hours and one trial within eight hours. The trials tested alpha-2 adrenergic agonists (A2AA), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor antagonists (ARA), calcium channel blockers (CCBs), nitric oxide donors, thiazide-like diuretics, and target-driven BP lowering. One trial tested phenylephrine.

Blood pressure lowering did not reduce death or dependency by stroke type (OR 0.98, 95% CI 0.92 to 1.05) or time to treatment (OR 0.98, 95% CI 0.92 to 1.05). Treatment within six hours of stroke appeared effective in reducing death or dependency (OR 0.86, 95% CI 0.76 to 0.99) but not death (OR 0.70, 95% CI 0.38 to 1.26) at end of trial. Although death or dependency did not differ between patients who continued pre-stroke antihypertensive treatment versus those who stopped it temporarily (worse outcome with continuing treatment, OR 1.06, 95% CI 0.91 to 1.24), disability scores at

end of trial were worse in patients randomised to continue treatment (Barthel Index, MD -3.2, 95% CI -5.8, -0.6)

Conclusions

There is insufficient evidence that lowering blood pressure during the acute phase of stroke improves functional outcome. Continuing pre stroke antihypertensive drugs immediately may be harmful. It is reasonable to withhold BP-lowering drugs until patients are medically and neurologically stable, and have suitable oral or enteral access, after which drugs can than be reintroduced. Further trials are needed to identify which patients are most likely to benefit from early treatment, in particular whether treatment started very early is beneficial**.**

7.1 Introduction

Acute stroke, whether due to infarction or haemorrhage is associated with high blood pressure in 75% of patients of whom 50% have a previous history of high blood pressure.[454, 455] The mechanisms underlying high blood pressure in stroke are complex and the adverse effects on outcome in both ischaemic stroke and haemorrhagic stroke was discussed in chapter 1. Haematoma expansion is related to high blood pressure in patients with intracerebral haemorrhage although this relationship may be confounded by stroke severity and time to presentation.[115, 210, 361, 456]

A Cochrane review of BP intervention in stroke published in 2001 and updated in 2008 included more information from thirteen randomised controlled trials analysing 1153 patients.[457] With a relatively small amount of data, there was insufficient evidence to evaluate the effect of altering blood pressure during the acute phase of stroke. The presented review and meta-analysis includes all new trials completed and published since 2008. Although many of the data are from trials testing BP alteration in the acute phase (<=48 hours), some recent trials have examined specific questions such as BP lowering in intracerebral haemorrhage,[260, 261] the use of an

ARA to lower BP,[458] the use of glyceryl nitrate in stroke[137] or lowering BP in the pre-hospital setting phase of stroke.[264, 459] Furthermore, two trials[136, 137] have now investigated whether to continue or stop temporarily pre-stroke antihypertensive therapy. This systematic review includes these this data and provides new information of deliberate blood pressure intervention in acute stroke.

7.2 Methods

7.2.1 Types of studies

Published and unpublished randomised controlled trials of vasoactive drugs in acute ischaemic stroke or acute intracerebral haemorrhage (ICH) where the aim of the trial was to alter blood pressure, and drug therapy was initiated within one week of stroke onset. We excluded uncontrolled studies, confounded controlled studies where two or more active interventions were compared, and studies of patients with subarachnoid haemorrhage.

7.2.2 Types of participants

Adults (age 18 or older) of either sex with acute ischaemic stroke or ICH who were eligible for randomisation to either active treatment, or placebo or open control.

7.2.3 Types of interventions

We sought randomised controlled trials evaluating single or multiple agents of deliberate blood pressure lowering or elevation in acute stroke, regardless of dosage or route of treatment, as compared against placebo or open control. We also included trials with two groups receiving different doses of the same BP lowering agent, and studies assessing effects of continuing or stopping pre-existing antihypertensive treatment.

7.2.4 Types of outcome measures

Primary outcomes

- Combined death or disability/dependency at end of trial (>= one month after stroke).
- Death or dependency was defined as modified Rankin Scale (mRS) >2 (or >3 as available). Death or disability was defined as Barthel Index <60.

Secondary outcomes

- Blood pressure when first measured after randomisation
- Early case fatality (< one month).
- Late case fatality (>= one month).

- Early neurological deterioration (< one month).

As there is no consensus on how early neurological deterioration should be standardised, we used the trial-specific definition as a decrease in SSS of >5points or a decrease in consciousness part of the SSS by > 2 points,[137] increase in NIHSS of 2[460] or more[136, 261, 262] or decline of 2 or more points in GCS.[261]

- Late disability or dependency (Barthel Index >=one month)
- Baseline and on-treatment blood pressure and heart rate

7.2.5 Search methods

These comprised electronic searches and assessment of studies referenced in published systematic and non-systematic reviews. No language restrictions were applied.

7.2.5.1 Electronic searches

We searched the Cochrane Stroke Group Trials Register, (last searched by the Managing Editor in February 2014), the Cochrane Database of Systematic reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2014), MEDLINE (Ovid) (1966 to

May 2014), EMBASE (Ovid) (1974 to May 2014), Science Citation Index (ISI, Web of Science, 1981 to May 2014) and the Stroke Trials Registry (www.strokecenter.org/trials/)(searched May 2014). The search terms included those used in a previous review and listed in the Appendix I.

7.2.5.2 Searching other resources

We searched reviews of in acute stroke relating to drugs which may alter blood pressure, including: calcium channel blockers (CCBs) (Horn 2001), nitric oxide (Bath 2002), pentoxifylline (Bath 2004a) and prostacyclin (Bath 2004b). In addition, we searched reference lists of included trials and relevant papers. We contacted principal investigators and researchers when we required additional information. For a previous version of this review (BASC 2001), one author (PB) contacted the following pharmaceutical companies: Bayer (nimodipine), Napp (pentoxifylline), Novartis (isradipine), Lipha Sante (naftidrofuryl), Hoffmann la Roche (N-methyl-D-aspartate), Hoechst (flunarizine) and UCB Pharma (piracetam).

7.3 Data collection

Review authors extracted data using a standard proforma; KK entered data into Review Manager (RevMan 2012) and PB checked the data.

7.3.1 Selection of studies

For this update, one review author (KK) screened the records obtained from the electronic searches and excluded obviously irrelevant studies. We obtained the full paper copy of the remaining studies and both review authors (KK and PB) selected trials for inclusion criteria detailed previously. We resolved any disagreements by discussion.

7.3.2 Data extraction and management

We extracted data from published and unpublished material where available. We recorded information on the method of randomisation, concealment of allocation, blinding of treatment administration, stroke type (ischaemia, haemorrhage, or mixed), drug dose, route of administration (oral, sublingual, intravenous, transdermal) and timing, blood pressure and heart rate before and during treatment, numbers

of deaths, functional disability, quality of life, and length of stay.

7.3.3 Assessment of risk of bias in included studies

We assessed the methodological quality of the trials using the following criteria:

- Method of randomisation.
- Balance of prognostic factors.
- Allocation concealment.
- Blinding of treatment administration.
- Intention to treat analysis.
- Blinding of outcome assessment.
- Follow up.

The quality criteria were used to derive an overall assessment bias score as 'low risk' (all criteria met), moderate risk (one or more criteria unclear) and high risk (one or more criteria absent).[461]

7.3.4 Measures of treatment effect

We calculated the weighted estimate of the typical treatment effect across trials using the Cochrane Review Manager software, RevMan 5 (RevMan 2012): odds ratio (OR) using the Mantel-Haenszel with random-effects model for binary data,

and mean difference (MD) using the inverse variance method for continuous data, each with 95% confidence intervals (CI).

7.3.5 Unit of Figure issues

The primary outcome was based on the modified Rankin Scale (mRS 0 to 6, where death =6) assess using the binary outcome of combined death or dependency (mRS >1 or >2 depending on trial definition). The Barthel Index (disability measure of activities of daily living) was also assessed (BI 100 to -5, where death =-5). Where functional outcome was not assessed, we excluded the trial from the analysis of functional outcome.

7.3.6 Dealing with missing data

We attempted to collect missing data from trial investigators. In instances where on-treatment blood pressure data were not provided or could not be obtained from study authors, we obtained data (mean, SD) from graphs in the trial publication; where the SD was not presented graphically, baseline data were used, a conservative strategy. We excluded trials from individual analyses when summary data were omitted in the trial publication.

7.3.7 Assessment of heterogeneity

Heterogeneity between RCTs' results was assessed using the I^2 statistic based on the DerSimonian-Laird formula.

7.4 Data synthesis

We performed statistical analysis using RevMan version 5.2 (RevMan 2012). We reported outcomes as odds ratio (OR) with 95% confidence intervals (CI) for dichotomous data, and mean difference (MD) with 95% CI for continuous data. We used a random-effects model to analyse individual results regardless of whether there was heterogeneity or not; this is a conservative strategy and takes into account that the trials had heterogenous designs and participant populations.

7.5 Subgroup analysis and investigation of heterogeneity

We assessed the primary outcomes in pre-specified subgroups:

- Class or type of intervention.
- Type of stroke: ischaemic; intracerebral haemorrhage.

We planned a priori subgroup analysis on the number of patients in the treated and control groups who were dead or

dependent at the end of follow up according to stroke location: cortical versus subcortical ischaemic stroke, deep intracerebral haemorrhage versus others.

The definition of deep haemorrhage was not defined in all the trials and we therefore used the data as provided.

- Timing of intervention: ultra-acute (<=4 hours) and pre-hospital; hyper-acute (<=6 hours) and in hospital; acute (<=48 hours); sub-acute (<=168 hours).

We considered I^2 greater than 50% to have significant heterogeneity. If significant heterogeneity was present, we looked for potential causes, e.g. differences in trial design and study participants.

7.6 Sensitivity Analysis

The analyses were based on all trials. No sensitivity analyses were performed.

7.7 Results

The results of the search process of the present review are shown in Figure 7.1.

7.7.1 Description of studies

Twenty-six trials involving 17,011 patients (8497 active, 8514 placebo/control) were included in this analysis.

7.7.2 Results of the search

The quantity of outcome data varied between studies:

- Outcomes not universally collected.
- Some data still to be published.
- 'Raw data' available by personal communication.

If a trial used more than one dose of a particular drug then the trial identifier is written as author followed by year and dose of the drug. Referencing the whole trial was given by author and year. For example the Fagan 1988 trial comprises: (Fagan 1988 120 mg; Fagan 1988 240 mg).[462]

7.7.3 Included studies

Twenty six trials were identified and fulfilled the inclusion criteria.

Three trials compared more than one drug against the control group[262, 463, 464] and two studies compared different doses.[385, 462]

Trial protocols and group data were obtained from published material for nineteen studies,[136, 137, 262, 264, 266, 458, 460, 462, 463, 465-474] whilst individual patient data were provided by seven sets of authors.[385, 463, 475-477] We obtained unpublished SBP, DBP and heart rate data for active and control groups by contacting the authors for three trials.[136, 465, 468]

A variety of strategies and drug classes were used to lower blood pressure:

- Alpha-2-adrenoceptor agonist, oral centrally-acting (clonidine: two participants): One trial[463]
- ACE-I (captopril, perindopril or lisinopril: 152 participants): Five trials[262, 266, 463, 468, 476]
- Angiotensin receptor antagonist (ARA), oral (candesartan or telmisartan: 4190 participants): Six trials [458 466, 474, 478-480]
- Beta-receptor antagonist (labetalol: 56 participants): One trial [262]
- CCBs (nimodipine or nicardipine: 75 participants): Three trials [462, 463, 475]
- Diuretic, oral thiazide-like (bendrofluazide: 18 participants): One trial [467]

- Nitric oxide donor (NO) donor, transdermal nitrate (glyceryl trinitrate, GTN: 4197 participants): Five trials [137, 385, 477, 481, 482]
- Intensive versus guideline blood pressure targets (7421 participants): Five trials [261, 460, 469, 472, 483]
- Continue versus Stop pre-stroke antihypertensive drugs (2860 participants): Two trials [136, 137]

One strategy was used to raise blood pressure**:** Sympathomimetic, intravenous (phenylephrine: 9 participants): One trial [465]

The trials recruited patients with only ischaemic stroke, mixed stroke (IS and ICH), or only ICH:

- Ischaemic stroke: 12 trials [462, 463, 465-468, 471, 474, 476, 478, 480, 483]

  In the Fagan study (Fagan 1988 120 mg; Fagan 1988 240 mg) patients were recruited with presumed 'ischaemic' stroke based on history and neurological examination.[462]
- Mixed stroke: 10 trials [136, 137, 262, 266, 385, 458, 475, 477, 481, 482]
- Intracerebral haemorrhage (ICH): 4 trials [261, 460, 464, 469]

Trials recruited participants at different time frames after stroke:

Ultra-acute (<4 hours of onset)/pre-hospital: 2 trials [266, 482]

Hyper-acute (<6 hours)/hospital: 2 trials [261, 469]

Acute (<48 hours): 11 trials [136, 262, 458, 460, 464, 466, 468, 475, 480, 483]

Sub-acute (<168 hours): 10 trials[385, 463, 465, 467, 474, 476-479, 481]

Timing unclear: 1 trial [462]

Trials variously defined enrolment blood pressure levels:

- Hypertension (systolic BP >120-170 and <=220 mm Hg): 19 trials[137, 262, 266, 385, 458, 463, 466-469, 471-474, 476, 477, 480, 484]
- Normotension (systolic BP <140 mmHg): 2 trials [465, 478]
- No BP criteria: 3 trials [136, 462, 475]

Trials treated participants for varying lengths of time:

- For 1 day: 1 trial[464]
- For up to two days: 3 trials[460, 465, 475]
- For up to three days: 1 trial[463]
- For 7-12 days: 13 trials[137, 385, 458, 466, 467, 469, 472, 473, 477, 480, 481]
- For 14 days: 5 trials[136, 262, 468, 476, 483]
- For 21 days: 1 trial[462]
- For 28 days: 1 trial[478]

- For 3 months: 1 trial[474]
- For up to 2.5 years: 1 trial;[471] outcomes at 1-3 months are used and longer-term follow-up data are ignored.

The trials recruited from one or more centres:

- Single centre: 14 trials[264, 266, 385, 460, 463, 465, 467, 468, 474-478, 481]
- Multicentre: 12 trials[136, 137, 262, 458, 462, 466, 469, 472, 473, 479, 480, 483]

17,011 participants received placebo or control treatment across the studies. Three trials compared two or more active treatment groups (8497 participants) with one control group (8512 participants).[385, 462, 463] One study reported on 19 participants from a larger randomised controlled trial[462]; further information on the main study is not available. One trial was performed in two stages: this review includes the first phase, a double-blind comparison of candesartan versus placebo[478] and excludes the second open-label comparison of candesartan and an ACE-I. One study expressly included patients with either ICH, who were given intravenous nimodipine (treatment: eight participants; placebo: three participants), or ischaemic stroke, who were given oral nimodipine (treatment: 38 participants; placebo: 39

participants);[475] 10 participants (treatment: two participants; placebo: eight participants) were treated with antihypertensive agents for malignant hypertension, and two participants treated with intravenous nimodipine for subarachnoid haemorrhage were excluded.[475] Data from two trials were only available from published abstract.[478, 480]

7.7.4 Blood pressure measurements

Sixteen studies reported the method by which blood pressure was measured, including equipment model type and patient posture.[136, 137, 262, 264, 385, 458, 463, 467, 468, 474, 476, 477, 483] The Fagan trial only reported the average blood pressure measurements at, and for one hour after, morning dosing over seven days of treatment (Fagan 1988 120 mg/Fagan 1988 240 mg); in the absence of individual patient data, it is not possible to determine the blood pressure at selected time points during treatment.[462] Furthermore, this trial co-administered beta blockers to some patients, although these were always given at least two hours before or after nimodipine. In the ACCESS study during the first three days blood pressure measurements were performed by nurses as part of routine clinical care; on day seven, an automatic 24-hour blood pressure recording was performed.[466] The other

nine trials[266, 462, 465, 466, 469, 472, 473, 475, 480] made no mention of patient posture or how blood pressure was measured.

Three trials recorded systolic but not diastolic BP after the first intervention.[261, 460, 464]

7.7.5 Outcomes

The trials reported a variety of outcomes:

- Modified Rankin Scale (mRS) and/or Barthel Index (BI) at >=1 months: 15 trials.[136, 137, 262, 264, 385, 458, 466-469, 473, 477, 479, 481, 483] Historically, trials dichotomised outcome as death or dependency, defined as mRS>2, or mRS>3, or BI<60. Ordinal analysis of ordered categorical data is more efficient statistically and provides information on severity of outcome[412] and recent trials have used ordinal analysis of mRS data.[137, 262, 458, 469, 473, 474, 479, 483]
- Case fatality at >=1 months: 15 trials[136, 137, 262, 264, 385, 458, 466-469, 473, 477, 479, 481, 483]
- Early neurological impairment (e.g. National Institutes of Health Stroke Scale, Scandinavian Stroke Scale) at <1 month: 11 trials[136, 262, 463, 465, 467-469, 472, 473, 476, 483]
- Hospital length of stay: four trials[137, 262, 264, 483]

7.7.6 Excluded studies

66 studies were excluded because they: lacked randomisation, were irrelevant to the questions addressed in the current review, and/or failed to provide BP or outcome assessments.

7.7.7 Other studies

8 studies are either awaiting assessment[485-488] or are ongoing.[400, 489-491]

7.8 Statistical Analyses

Four trials compared more than one treatment against a common control group.[262, 385, 462, 463] The most appropriate analysis according to a previous update of this review involved dividing the control group participants equally between treatment groups to prevent control participants being counted more than once and thereby artificially narrowing the confidence intervals.

7.9 Risk of bias in included studies

Ten trials used CT prior to entry to identify[460, 469, 472, 473, 475] or exclude[463, 465-467, 476] patients with ICH. The Fagan study attempted to exclude ICH through information from the

history and neurological examination; it may therefore have inadvertently included some patients with ICH.[462]

7.9.1 Allocation bias

We classified allocation concealment as 'low risk', 'high risk' or 'unclear risk' according to the Cochrane Handbook for Systematic Reviews.[461]

7.9.2 Blinding (performance and detection bias)

The method of randomisation was given for 23 trials.[136, 137, 262, 264, 266, 385, 458, 460, 465-469, 472-474, 476-481, 483] Two authors were unable to describe the method of randomisation[463, 475] and one did not respond to our communication.[462]

Patients and investigators were blinded to treatment as follows:

- Double-blind (patient and investigator blinded): 13 trials[262, 266, 458, 462, 463, 466-468, 474, 476, 478, 479, 481]
- Single-blind (patient-blinded): 4 trials[137, 264, 385, 477]
- Open-label: six trials[136, 385, 460, 472, 473, 480]

7.9.3 Incomplete outcome data (attrition bias)

Sixteen trials were analysed by intention to treat (ITT).[136, 137, 262, 264, 385, 458, 460, 462, 463, 469, 473, 477, 479, 481, 483, 492] In one study we excluded 10 patients from the analysis because they had been treated with antihypertensive agents for concurrent accelerated (malignant) hypertension.[475] Cardiovascular data were analysed on a per-protocol basis and outcome data by intention to treat in a trial of lisinopril.[468]

7.9.4 Selective reporting (reporting bias)

We assessed selective reporting as low risk, high risk or unclear risk according to the Cochrane Handbook for Systematic Reviews.[461] We did not see evidence of selective reporting in any of the trials.

7.9.5 Other potential sources of bias

One trial randomised patients before neuroimaging and those having a non-ischaemic stroke were subsequently withdrawn from the study.[468] Two trials did not state the method of randomisation.[465, 467] We did not find any other potential risks to the validity of the included studies.

7.10 Effects of interventions

The result section is split into three parts:

- Comparisons of BP lowering with control
- Comparisons of continuing versus stopping temporarily pre-stroke antihypertensive drugs
- Comparisons of BP elevation with control

7.10.1 Blood pressure lowering

7.10.1.1 Clinical outcomes

Twenty- one trials provided data on one or more outcomes relating to treatment with:

- ACE-I (lisinopril): three trials[262, 266, 468]
- ARA (candesartan, telmisartan): five trials[458, 466, 474, 479, 480]
- Beta-receptor antagonist (labetalol): one trial[262]
- Calcium channel blockers (nimodipine): one trial[475]
- NO donors (glyceryl trinitrate):five trials[137, 264, 385, 477, 481]
- Intensive BP-lowering: six trials[262, 460, 469, 472, 473, 483]
- BP elevation (phenylephrine): one trial[465]

7.10.1.1.1 Death or dependency, end of trial

7.10.1.1.1.1 Stroke type

The effect of lowering BP did not vary by stroke subtype (ischaemic stroke, mixed stroke, ICH) across 14 trials (Figure 7.2).

7.10.1.1.1.2 Stroke location

The effect of lowering BP did not vary by stroke location (ICH deep or not, ischaemic stroke cortical or subcortical) across six trials with 11951 patients (Figure 7.3). Although there was insufficient evidence for heterogeneity, BP lowering in deep ICH almost reached significance (OR 0.86, 95% CI 0.73-1.00, p=0.06) (Figure 7.3).

7.10.1.1.1.3 Time to treatment

Data from 15 trials involving 15,520 patients are available. There was significant reduction in death or dependency if treatment was administered during the hyperacute period and in hospital (OR 0.87, 95% CI 0.76-0.99, p=0.03). Recruitment of participants later than this was associated with no benefit (Figure 7.4).

7.10.1.1.2 Death, early and end of trial

There was no overall effect of treatment on early death or death at end of trial when analysed by stroke type (Figure 7.5, Figure 7.7) or time to treatment (Figure 7.6, Figure 7.8).

7.10.1.1.3 Barthel Index (disability), end of trial

Barthel Index was assessed at the end of follow-up in 2 trials with 4350 patients (Figure 7.9). Although no significant difference was observed with stroke type (Figure 7.9), BI scores were lower if treatment was started within six 6 hours of stroke onset (Figure 7.10).

7.10.1.1.4 Early neurological deterioration

Subgroup differences were not present when analysed by stroke type (Figure 7.11). However, subgroup differences were apparent when assessed by time to treatment (Figure 7.12); specifically, an increase in neurological deterioration was seen in participants with acute stroke (<=48 hours post stroke) (OR 1.39, 95% CI 1.07-1.81, p=0.01) but not when trials specifically treated earlier during the ultra-acute and hyper-acute periods.

7.10.1.1.5 Quality of life

Quality of life, assessed using the EQ-5D and transformed into a Health Utility Status, was assessed in three trials (Figure 7.13). Health Utility HUS scores were higher/better with BP lowering (MD 0.03, 95% CI 0.01-0.04 MD 0.02, p=0.19). However, subgroup differences were heterogeneity was apparent between studies (I^2=76.0%) with a significant result in INTERACT-2 but not ENOS-GTN.[137, 473] When broken down into stroke types, patients with intracerebral haemorrhage in INTERACT-2 treated with BP lowering tended to report better quality of life.[261] When assessed by time to treatment, HUS scores were higher in participants treated <=6 hours (MD 0.06, 95% CI 0.03-0.08), but not when treated later (Figure 7.14).

7.10.1.1.6 Length of stay

Length of stay was not influenced by lowering blood pressure and there were no subgroup differences by stroke type or time to treatment (Figure 7.15 and Figure 7.16).

7.10.1.2 Haemodynamic measures

7.10.1.2.1 Blood pressure

The effect of different BP-lowering strategies on BP after the first dose are summarised in Figures 7.17, 7.18 and 7.19. Altogether, 24 trials studied 15,432 participants; most participants received an ARA, a NO donor or intensive BP-lowering. The focus for the following comments are on systolic rather than diastolic BP. The magnitude of BP reduction varied between -4.6/-2.5 mmHg for oral ARA (primarily candesartan and telmisartan) and -13.7/-7.9 mmHg for ACE-Is. When assessed by stroke type, heterogeneity was present; slightly larger reductions in BP were seen in patients with ICH (-11.8/-5.1 mmHg) with mixed stroke intermediate (-7.9/-3.0 mmHg) and ischaemic stroke least (-7.0/-3.1 mmHg) (Figure 6.18). Similarly, the magnitude of reduction varied by time to randomisation or treatment (I^2=89%); a graded decrease was seen by time with the largest reduction occurring in participants treated during the ultra-acute/pre-hospital (-16.0/-15.0 mmHg), hyper-acute/hospital (-13.4/-7.5 mmHg), acute (-8.2/-2.8 mmHg) and sub-acute (-7.3/-4.9 mmHg) periods.

7.10.2 Continue versus stop pre-stroke antihypertensive drugs

Two trials, COSSACS and ENOS tested whether pre-stroke antihypertensives should be continued in the immediate post-stroke period, or stopped temporarily.[136, 137] The total number of participants numbered 2860.

7.10.2.1 Clinical outcomes

7.10.2.1.1Death or dependency, end of trial

There was no significant difference in mRS at day 90 between those patients assigned to continue or stop antihypertensives by stroke type or time to treatment across both trials (Figure 7.20 and Figure 7.21).

7.10.2.1.2 Death, early and end of trial

The rates of death at the end of treatment, and end of trial, did not differ by stroke type or time to treatment (Figure 7.22, Figure 7.24, Figure 7.23 and Figure 7.25).

7.10.2.1.3 Barthel Index

Barthel Index scores were lower in patients assigned to continue treatment (MD -3.2, 95% CI -0.6, -5.8, p=0.02) (Figure 7.26).

7.10.2.1.4 Neurological deterioration, early

The rate of early neurological deterioration at the end of treatment did not differ between the treatment groups (Figure 7.27).

7.10.2.1.5 Quality of life

Quality of life, assessed using the EQ-5D and transformed into a Health Utility Status, was lower (i.e. worse) in patients randomised to continue pre-stroke antihypertensive drugs (MD -0.03, 95% CI -0.05, +0.01, p=0.008) (Figure 7.28).

7.10.2.2 Haemodynamic measures

7.10.2.2.1 Blood pressure

Blood pressure was lower by -7.9/-1.2 mmHg at the first measurement after randomisation in participants randomised to continue treatment with the reduction in systolic BP much greater in COSSACS than in ENOS (Figure 7.29 and Figure

7.30). By the end of treatment, BP was lower by -11.3/-6.4 mmHg in the continue group (Figure 7.30 and Figure 7.31).

7.10.3 Blood pressure elevation therapy in acute stroke

7.10.3.1 Phenylephrine

Phenylephrine non-significantly increased systolic BP at 24 hours (MD 21 mmHg, 95% CI -13, +55 mmHg), but had no significant effect on diastolic BP (Figure 7.33 and Figure 7.34).[465] However the results came from only one study and so definite conclusions can be made.

7.11 Discussion

Twenty-six trials, involving 17,011 participants with stroke, assessed the effects of deliberate BP alteration.

7.11.1 BP lowering

The results come from 25 trials that studied 15,432 participants.

7.11.1.1 Clinical outcomes

Overall, lowering BP did not improve outcome, whether assessed as death, combined death or dependency,

neurological deterioration or quality of life. The findings were consistent irrespective of type of stroke. However, when assessed by time to treatment, very early BP-lowering (before hospital presentation or within six hours of stroke onset) was associated with reduced death or dependency, and improved quality of life.[264, 473]

7.11.1.2 Haemodynamic effects

All the studied antihypertensive drug classes lowered BP during the period of treatment. Reductions in BP after the first treatment varied between -4.6/-2.5 mmHg for oral ARA and -21.0/-7.9 mmHg for ACE-I. Slightly larger reductions in BP were seen in patients with ICH (-11.8/-5.1 mmHg) than in those with ischaemic stroke (-7.0/-3.1 mmHg). The largest reductions were seen if treatment was started very early before hospital presentation (-16.0/-15.0 mmHg); smaller reductions occurred if treatment was started beyond 48 hours after stroke onset (-7.3/-4.9 mmHg).

7.11.1.3 Comments

A variety of hypotheses can be postulated for why functional outcome was better if BP lowering was started very early after stroke. First, the magnitude of BP-lowering may be important

since the greatest improvement in outcome occurred when treatment was started early. Second, the type of intervention may be important since improved outcome was seen with early intensive BP lowering,[261] and early nitrate administration.[137, 264] Conversely, apparent hazard was seen with ARA drugs.[383, 458] Perhaps surprisingly, stroke type may not be particularly relevant since differential effects on outcome were not seen for IS versus ICH.

In summary, very early treatment with an appropriate agent or target BP may be the most important strategy to test in the future, irrespective of stroke type.

7.11.2 Continue versus Stop pre-stroke antihypertensive drugs

The results come from two trials that studied 2860 participants.[136, 137]

7.11.2.1 Clinical outcomes

The findings were mixed with some comparisons, in particular dependency (mRS), death, and neurological deterioration, neutral for the comparison of continue versus stop pre-stroke antihypertensive drugs. In contrast, measures of disability (BI) and quality of life (EQ-5D, transformed into a Health

Utility Status) were worse in patients randomised to continue treatment immediately.

7.11.2.2 Haemodynamic effects

Immediately continuing antihypertensive drugs taken before stroke was associated with a lower BP by -7.9/-1.2 mmHg at the first measurement after randomisation, and -11.3/-6.4 mmHg by end-of-treatment.

7.11.2.3 Comments

The discrepancy in findings for two measures of functional outcome, mRS and BI, is challenging to explain. First, it may represent chance such that no difference exists between the interventions. Second, it could reflect outcome bias since it is not possible to test this question in a double-blind placebo-controlled design. Nevertheless, both trials used blinded outcome assessment for both mRS and BI. Further, since a majority of stroke physicians tend to continue treatment in routine practice,[493] the result seen across the two results is counter-intuitive. Last, the difference may be real in which case mRS, usually considered to be the optimal functional outcome in stroke trials,[370] failed to detect a difference in contrast to a comparison of BI scores.

If continuing drugs immediately is, indeed, hazardous, then the two trials do not identify the cause. Drugs that attenuate stress hormones, in particular that down-regulate the renin-angiotensin-aldosterone-system (RAAS) were commonly taken before stroke, e.g. ACE-I, ARA and ß-receptor antagonists. Initiating these drugs in the acute phase of stroke has been associated with harm.[458, 494] So it can be postulated that continuing these during the acute phase of stroke is potentially harmful. Alternatively, continuing drugs in patients who are dysphagic and who do not have safe enteral access for feeding may be hazardous through aspiration of these drugs and then the development of pneumonia. The ENOS trial gives some support for this hypothesis.[137]

The main implication for clinicians is that it is reasonable to withhold BP-lowering drugs until patients are medically and neurologically stable, and have suitable oral or enteral access, after which drugs can then be reintroduced.

7.11.3 General

An important problem with some of the trials was the absence of detailed information on how blood pressure was measured. Hence, the quality of blood pressure readings is unknown. It is

essential that future trials describe in detail how blood pressure is measured by including the following information.

- Equipment: manufacturer, model, measurement method (mercury, anaeroid or oscillometry, and manual or automatic), and whether the equipment has been independently validated, and if so by whom.
- Measurer: who measured blood pressure, and how they were trained, assessed, re-trained and re-assessed.
- Measurements: the number of readings at each time point, site of measurement (brachial, finger, etc) and what position the patient was in (supine, sitting, standing).

Little is known on the effect of BP altering in older patients with acute stroke, who comprise the largest group of patients, including those with IS who need thrombolysis. Of the trials, only two had mean age over 75 years contributing to a total of 98 patients.[262, 264] The number and proportion of older patients is likely to increase with population ageing. As the variation in response by individuals to BP modulating agents increases with age, e.g. related to concurrent isolated systolic hypertension or cardiac dysfunction, it may be inappropriate to assume that the effects of changing BP seen in younger populations will necessarily be the same in older ones.

This review is Part 1 of the Blood pressure in Acute Stroke Collaboration and reports only those trials which specifically set out to alter blood pressure in patients with acute stroke. Part 2 of the project assesses all randomised controlled trials in acute stroke where vasoactive drugs were administered and includes all those studies covered in Part 1. Although progress has been made in the number and quality of stroke trials in the last few years, substantial number of questions remain. The number of patients included in this review is very small in comparison to the global burden of stroke (about 15,000,000 per year worldwide). At present, any benefit of treatment is small, and additional data are required to recommend changes to routine clinical practice. The centres which took part in the trials were interested and familiar with the management of acute stroke. To extrapolate these results in routine clinical practice to less specialist centres could result in greater hazard or completely negate any potential benefit. Therefore, there is a need for new centres to participate in trials.

Further evidence is needed on:

- How to select patients
- The influence of age, time of onset, stroke subtype, severity, choice of drug, dose, route of administration

and blood pressure variability, on response to active changes in BP.

Recent guidelines based on largely observational data recommend that hypertension should not be treated for up to two weeks after an IS unless severe hypertension, hypertensive encephalopathy, heart failure, cardiac ischaemia, aortic dissection, or continued intracerebral bleeding are present.[495-497] Persistent hypertension after two weeks should be treated since the risk of stroke in patients with cerebrovascular disease is dependent on systolic and diastolic blood pressure.[498] In the PROGRESS trial, perindopril (with or without indapamide) reduced the risk of stroke among both hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack.[499] Further, evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial suggests that an ACE-I may reduce stroke and other vascular events in patients with prior cerebrovascular disease.[500] Overall lowering blood pressure in patients with chronic stroke reduces the subsequent risk of recurrence.[404]

7.12 Conclusions

7.12.1 Implications for practice

- The lack of definitive results for BP lowering, and very limited data for raising BP, mean that no firm recommendations can be made.

- There is no evidence to support the routine policy of immediately continuing prestroke antihypertensive drugs; treatment may be re-started once patients have stabilised medically and neurologically, and once safe feeding or enteral access is available.

- The very limited data related to BP elevation mean that no recommendations can be made.

7.12.2 Implications for research

Large randomised controlled trials of blood pressure lowering are needed to:

- Test the effect of ultra-acute/pre-hospital lowering of BP in RCTs.

- Test the effect of hyper-acute/hospital lowering of BP in RCTs. Two trials are important examples of ongoing studies[400, 489]
- Determine the effects on long -term survival (>=one year).
- Determine the effects on quality of life and cost-effectiveness.

An individual patient data (IPD) meta-analysis is required to:

- Identify subgroups of patients who are likely to benefit or be harmed, e.g. by age, sex, race-ethnicity group, baseline BP, history of hypertension, stroke type (IS, ICH).
- Identify what type of treatment is required, e.g. drug class, route, dose of administration.

Table 7.1 Characteristics of included studies

Trial	Size A/C	Male (%)	Stroke type	Enrolment time (hrs)	Intervention	Rx duration (days)	Primary outcomes
ACCESS[466]	173/166	51	IS	24-48	candesartan 4 mg/ placebo (po)	7	BP, BI at 3 months
ACCOST[478]	19/19	-	IS	120	candesartan 4 mg/ placebo (po)	28	BP, all death and death due to vascular causes, NIHSS, mRS, BI at 3 months
Bath	16/21	49	IS, PICH	120	GTN/placebo (td)	12	24 hour ABPM at day 0,1 and 8, mRS, BI at 3 months
CATIS[470]	2033/2033	62	IS	48	Intensive (iv/po)/ stop prestroke BPdrugs	14	BP at day 1,7,14, death/dependency at day 14 and 90
CHHIPS-	57/30	53	IS, ICH	24	Lisinopril/placebo (po/sl/iv)	14	mRS at 2 weeks

lis[262]							
CHIPPS-lab[262]	56/29	61	IS, PICH	24	Labetalol/placebo (po/sl/iv)	14	mRS at 2 weeks
COSSACS[136]	379/384	74	IS, PICH	48	Continue/stop prestroke BP drugs	14	mRS at 2 weeks
Dyker[476]	14/14	61	IS	168	Perindopril 4mg/ placebo (po)	15	BP, NIHSS at baseline and day 15
ENOS[137]	2000/2011	57	IS, PICH	48	GTN 5 mg/placebo (td); continue/stop prestroke BP drugs	7	mRS at day 90
Eveson[468]	18/22	63	IS	24	Lisinopril/placebo (po)	14	NIHSS at day 14, mRS and BI at day 14 and 90
Fagan[462] 120 mg	10/9	45+	IS	-	Nimodipine 20 mg/ placebo (po)	21	BP for 7 days

Fagan[462] 240 mg	10/9	45+	IS	-	Nimodipine 20 mg/ placebo (po)	21	BP for 7 days
Hillis[465]	9/6	27	IS	168	Phenylephrine (iv)/conventional management	3	NIHSS at day 3, cognition
ICH-ADAPT[472]	39/36	67	PICH	24	Intensive/guideline (iv)	1	Perihaematoma CBF
INTERACT pilot[469]	203/201	65	PICH	6	Intensive/guideline (po/iv)	7	Proportional change in haematoma volume
INTERACT 2013[473]	1382/1412	64	PICH	6	Intensive/guideline (po/iv)	7	mRS at day 90
Koch[460]	21/21	61	PICH	8	Intensive/guideline	2	NIHSS, GCS at 24 and 48 hours
Lisk[463]	10/6	25	IS	72	Nicardipine 20 mg, captopril 12.5 mg, clonidine 0.1	3	NIHSS, BP

					mg/placebo (po)		
PILFAST[459]	6/8	100	IS, PICH	3	Lisinopril 5 mg/placebo (po/sl/ng)	7	BP
PRoFESS[479]	647/713	64	IS	72	Telmisartan/placebo (po)	2.5 years	BP, HR at day 7, 30 and 90
Rashid 1[385]	20/30	46	IS, PICH	72	GTN 5mg/control (td)	10	mRS, BI, quality of life at 3 months
Rashid 2[385]	20/30	46	IS, PICH	72	GTN 5mg/control (td)	10	mRS, BI, quality of life at 3 months
Rashid 3[385]	20/30	46	IS, PICH	72	GTN 5mg/control (td)	10	mRS, BI, quality of life at 3 months
RIGHT[264]	25/16	60	IS, PICH	4	GTN 5mg/control (td)	7	SBP at 2 hours, mRS day 90
SCAST[458]	1017/1012	60	IS,	30	Candesartan/placebo (po)	7	mRS at 6 months, composite of

			PICH				vascular death, nonfatal MI or non-fatal stroke in first 6 months
TAST[474]	12/7	83	IS	120	Telmisartan/placebo (po/ng)	90	Ipsilateral hemispheric CBF
Uzuner iv[475]	8/3	63	IS, PICH	24	Nimodipine/placebo (iv)	2	BP, HR
Uzuner po[475]	38/39	63	IS, PICH	24	Nimodipine/placebo (po)	2	BP, HR
VENTURE[480]	203/202	-	IS	24	Valsartan/no valsartan	7	mRS at day 90
Willmot[477]	12/6	70	Clinical stroke	120	GTN 5mg/no patch (td)	7	Central, peripheral BP

A: active; BI: Barthel index; BP: blood pressure; C: control/placebo; HR: heart rate; IS: Ischaemic stroke; mRS: modified Rankin scale; PICH: primary intracerebral haemorrhage; po:per oral; sl: sublingual; td: transdermal; iv: intravenous; Rx: treatment

Figure 7.1 Search process of relevant studies

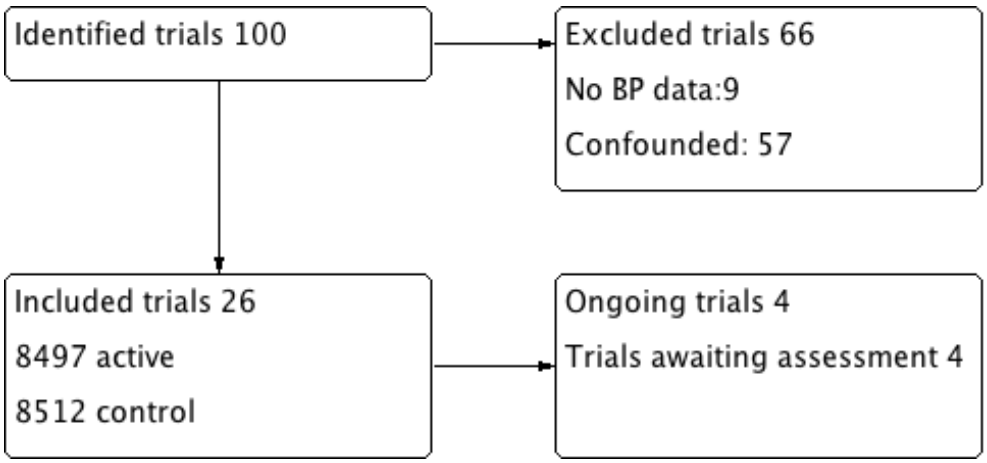


Figure 7.2 Death or dependency, end of trial by stroke type

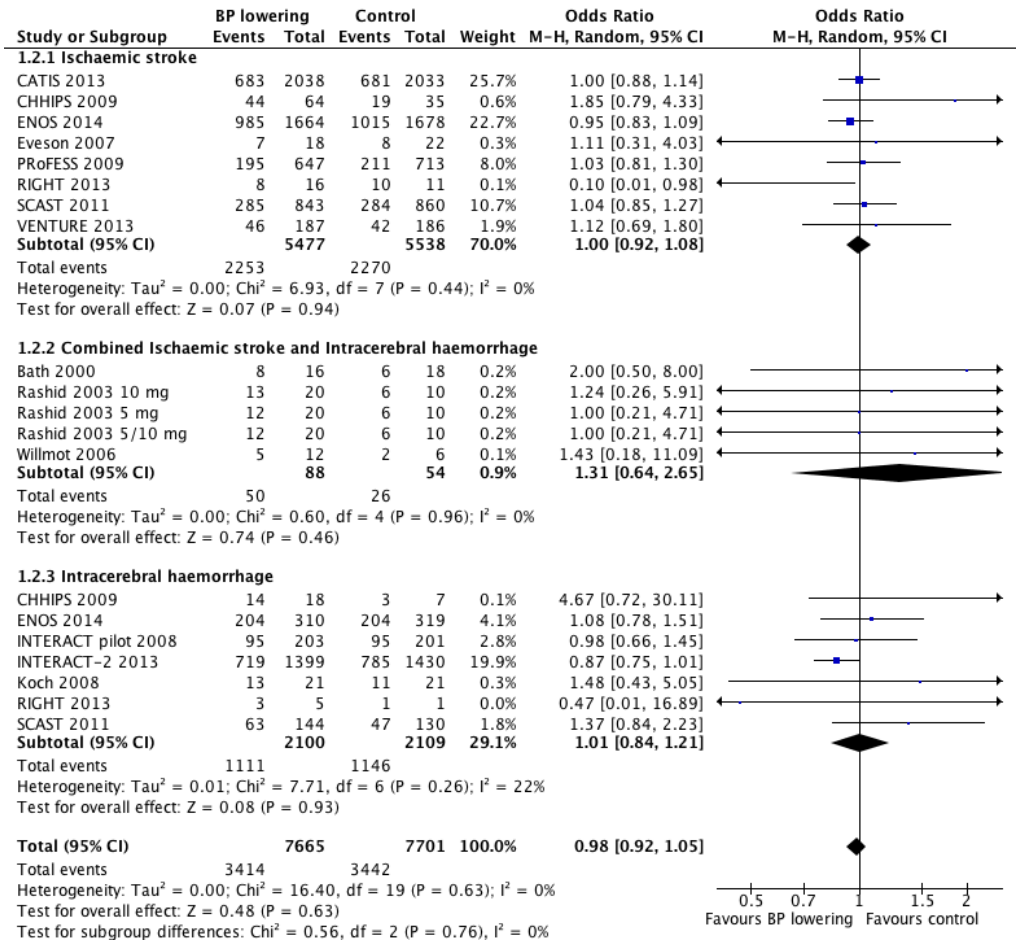


Figure 7.3 Death or dependency, end of trial by stroke location

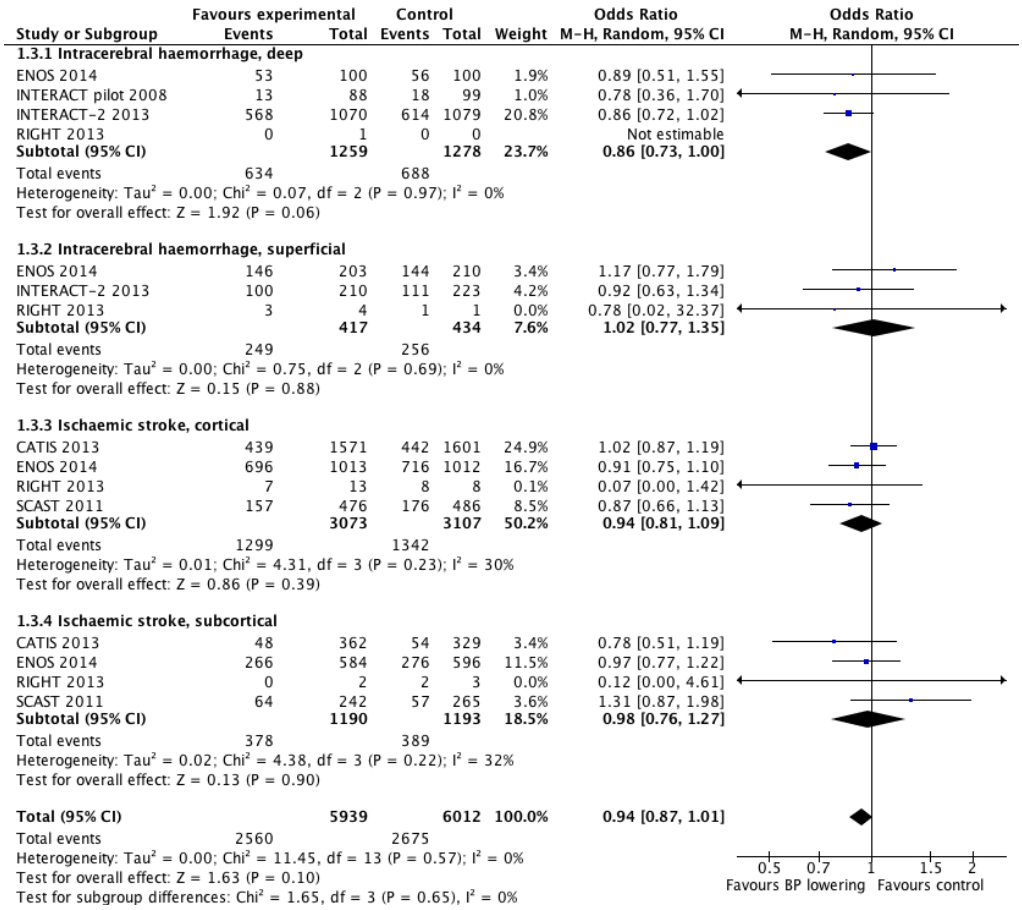


Figure 7.4 Death or dependency, end of trial by time to treatment

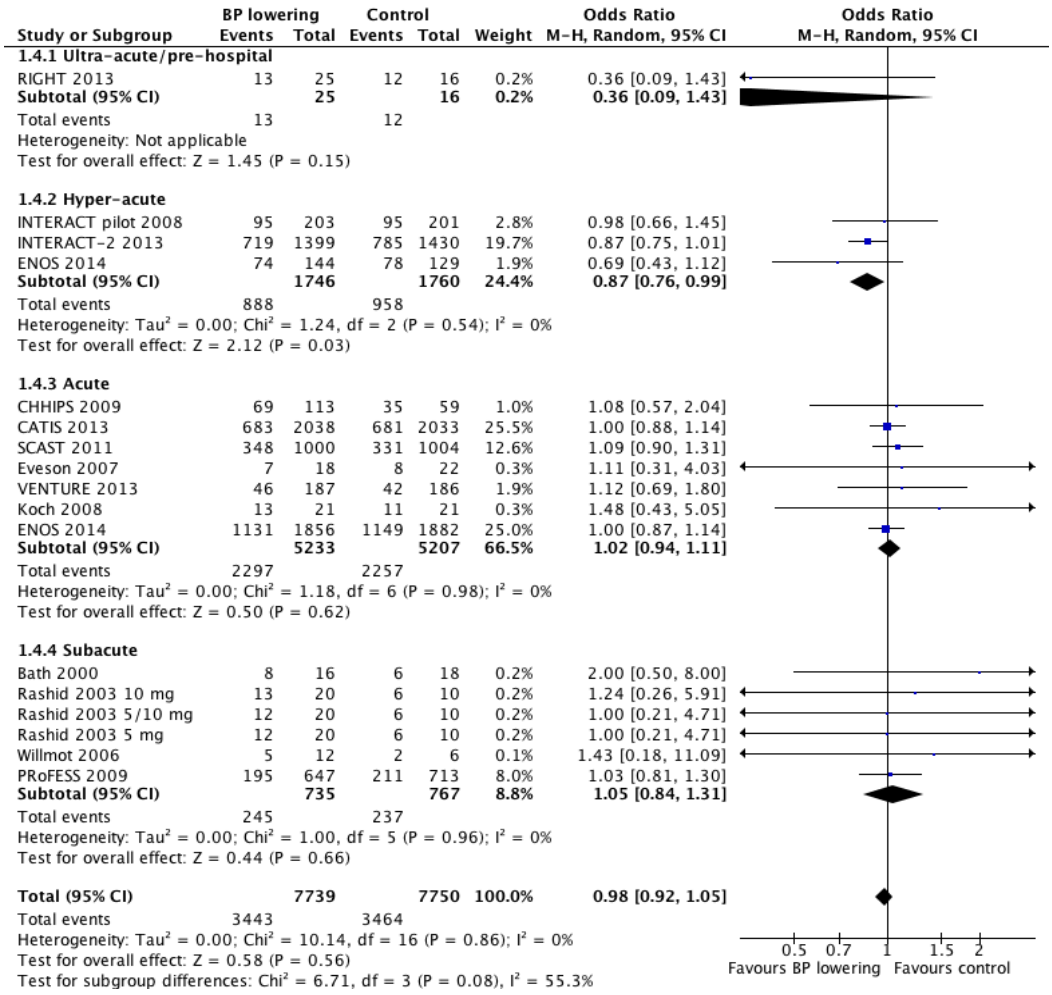


Figure 7.5 Death early, by stroke type

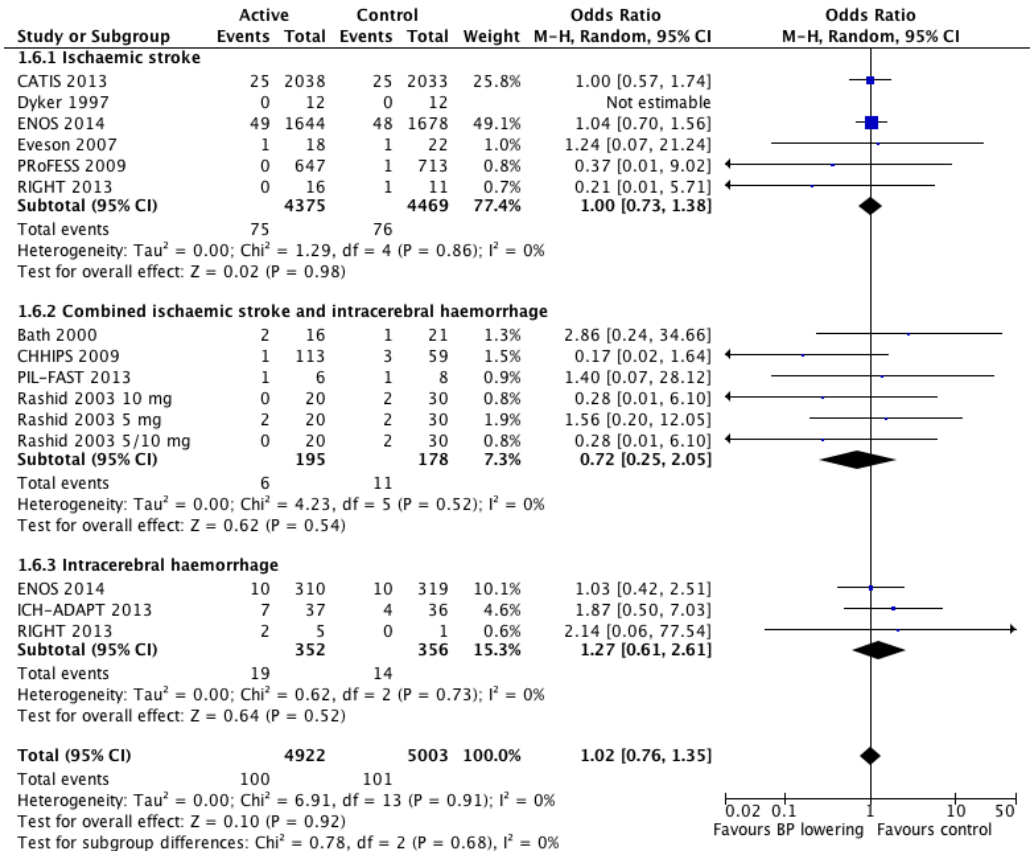


Figure 7.6 Death, early by time to treatment

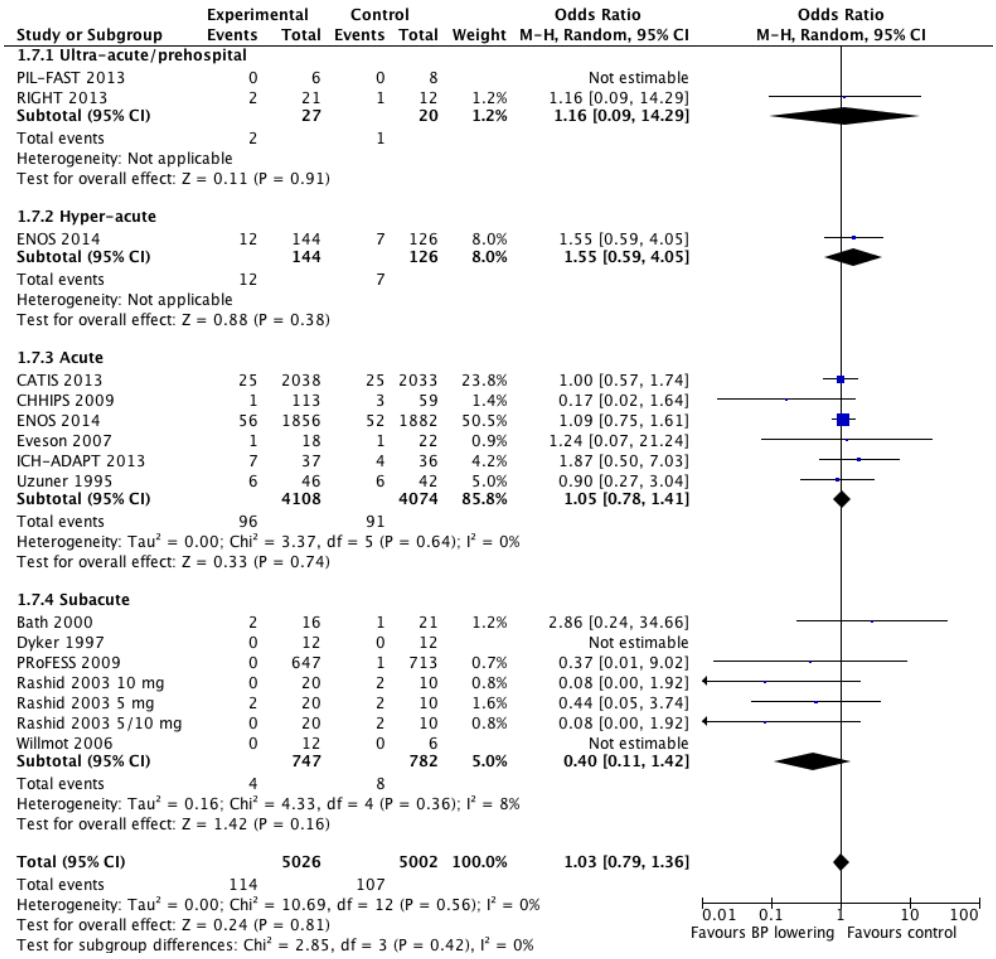


Figure 7.7 Death, end of trial by treatment

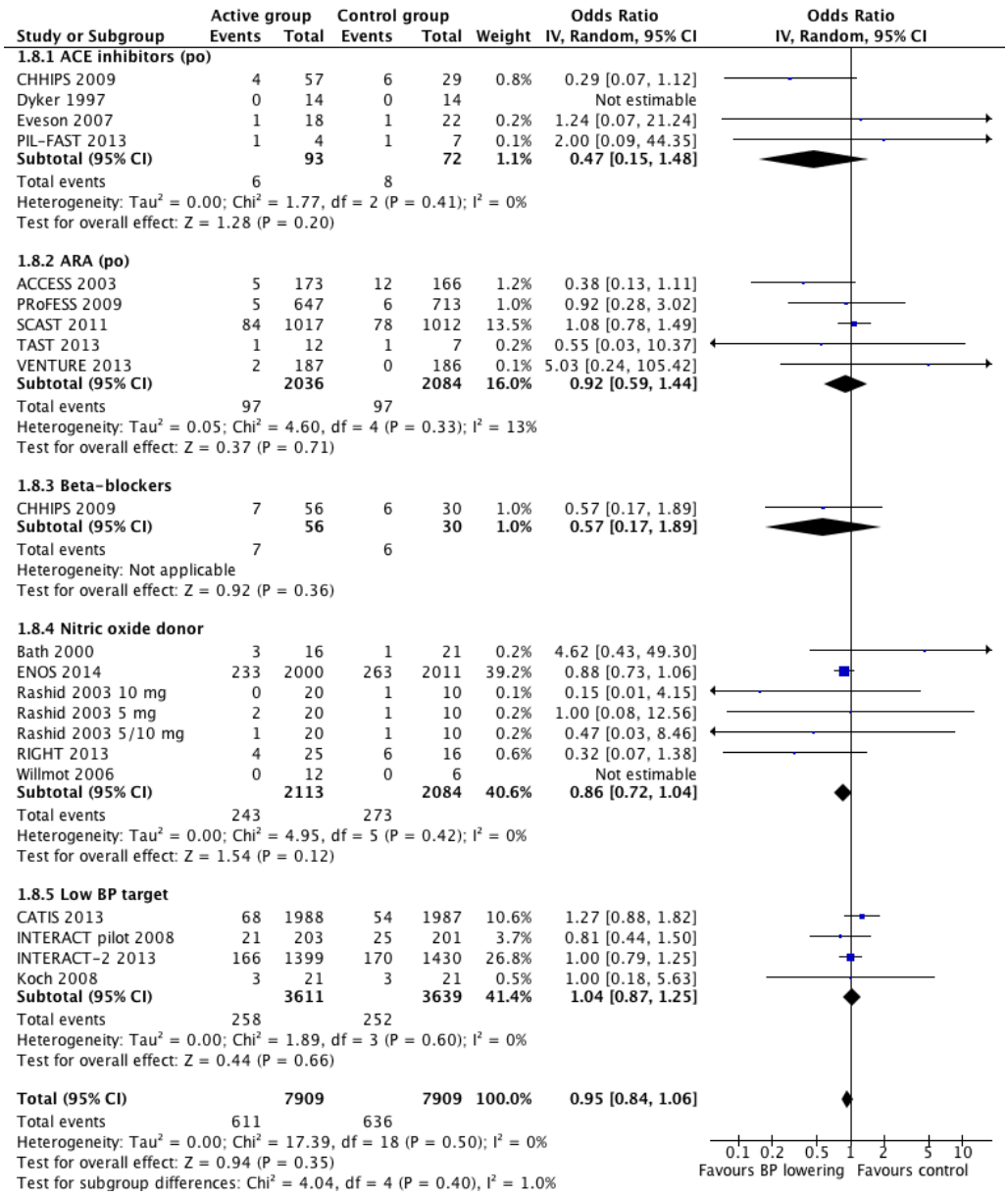


Figure 7.8 Death, end of trial by time to treatment

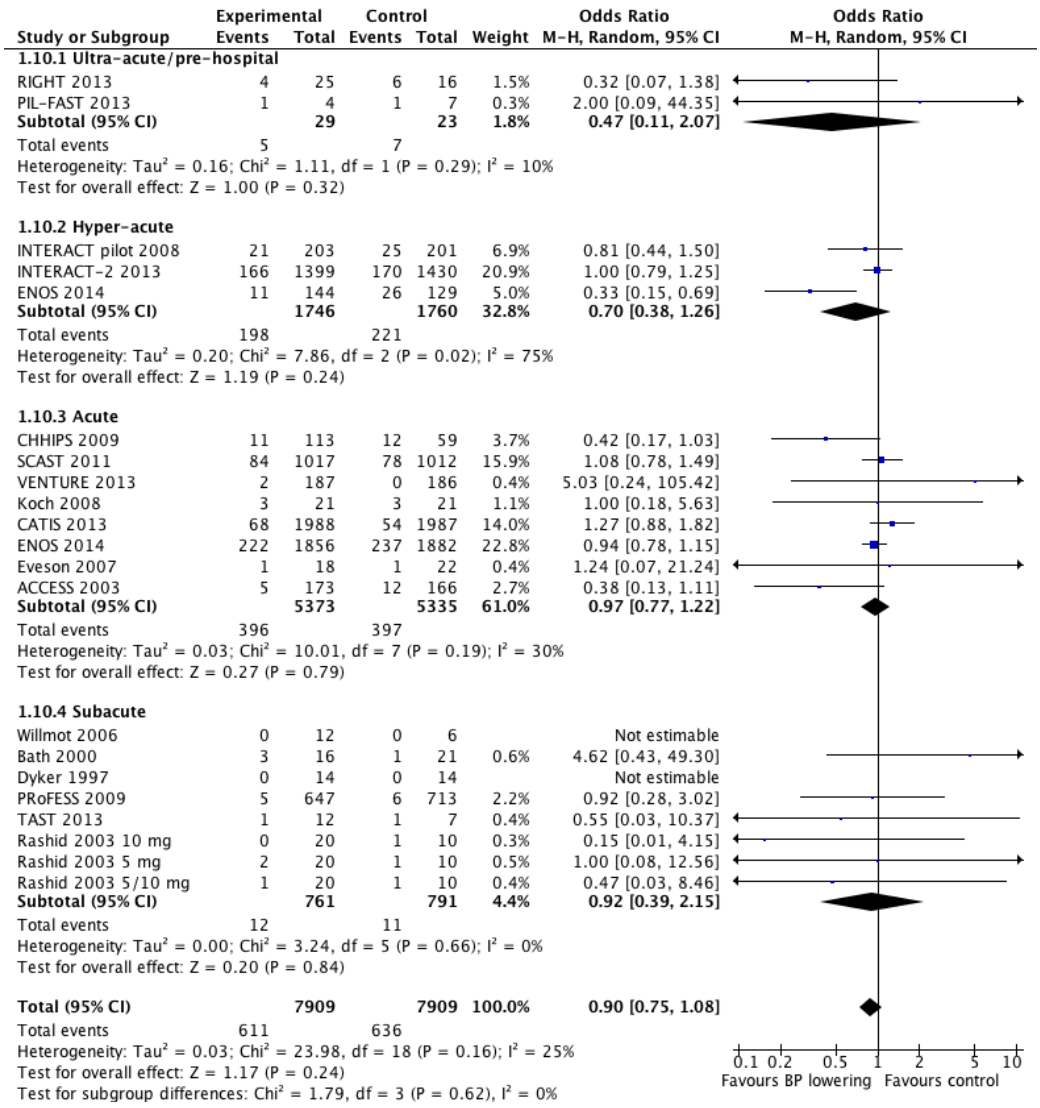


Figure 7.9 Barthel Index, end of trial, by stroke type

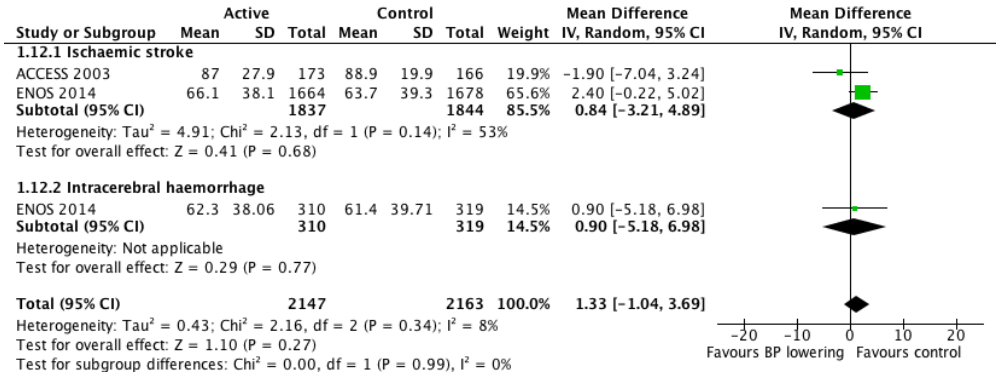


Figure 7.10 Barthel Index, end of trial by time to treatment

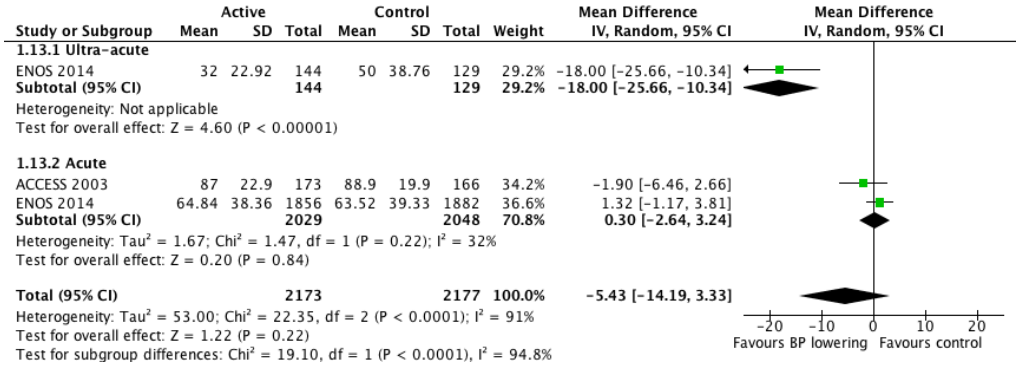


Figure 7.11 Early neurological deterioration, by stroke type

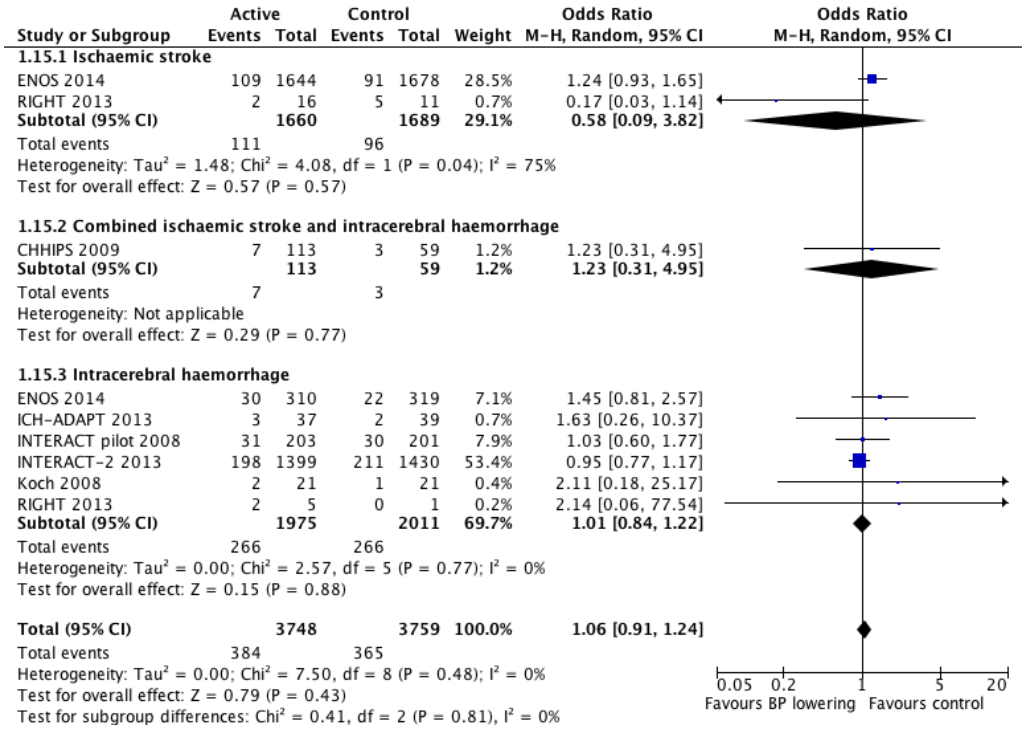


Figure 7.12 Early neurological deterioration, by time to treatment

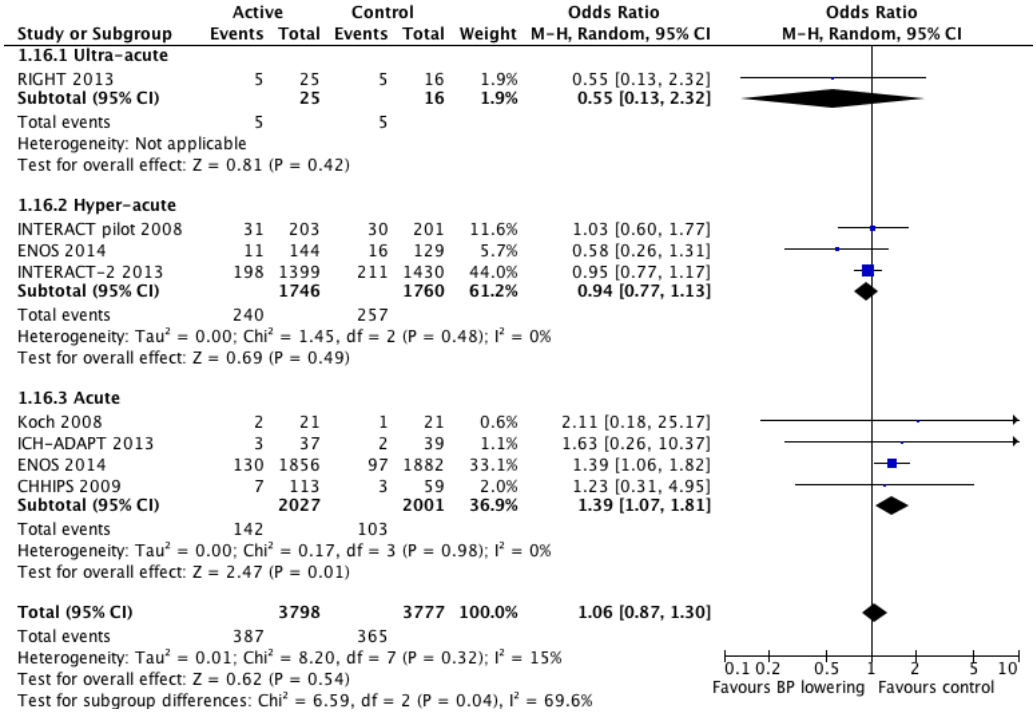


Figure 7.13 Quality of life (EuroQoL) at end of trial, by stroke type

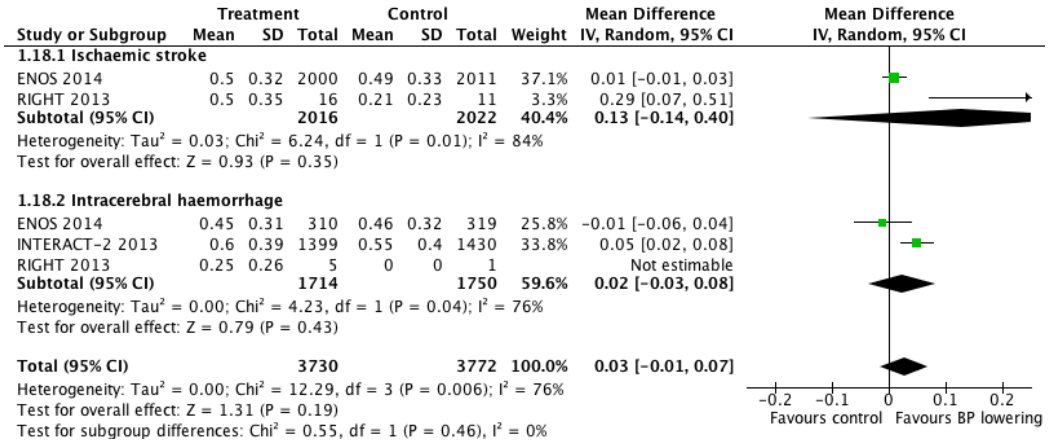


Figure 7.14 Quality of life (EuroQoL) at end of trial, by time to treatment

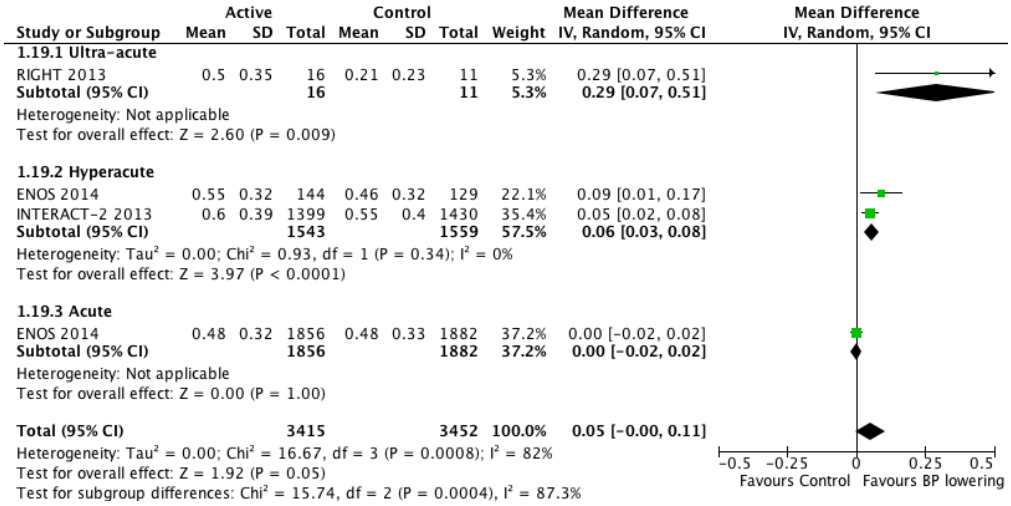


Figure 7.15 Length of stay, by stroke type

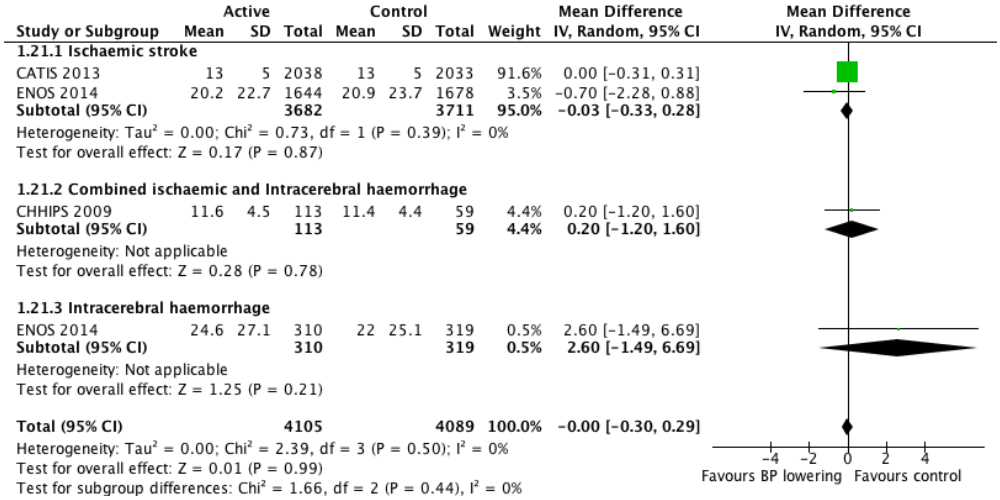


Figure 7.16 Length of stay, by time to treatment

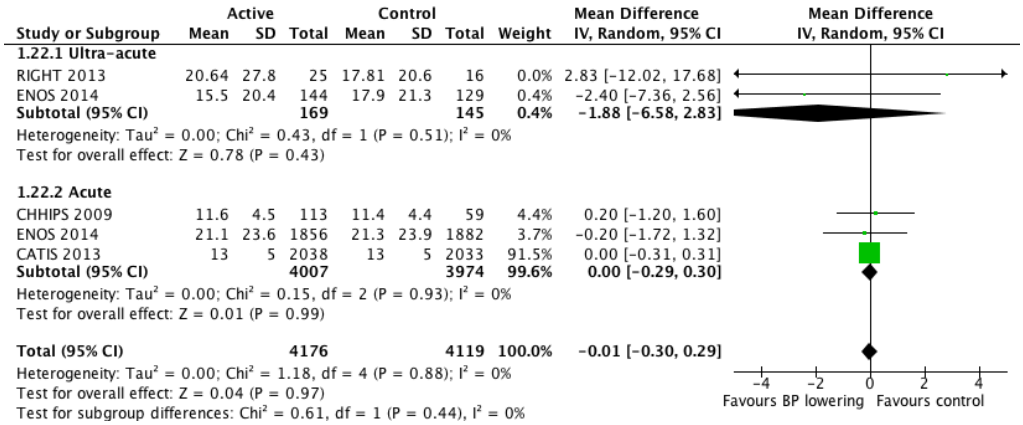


Figure 7.17 SBP, first after randomisation by intervention

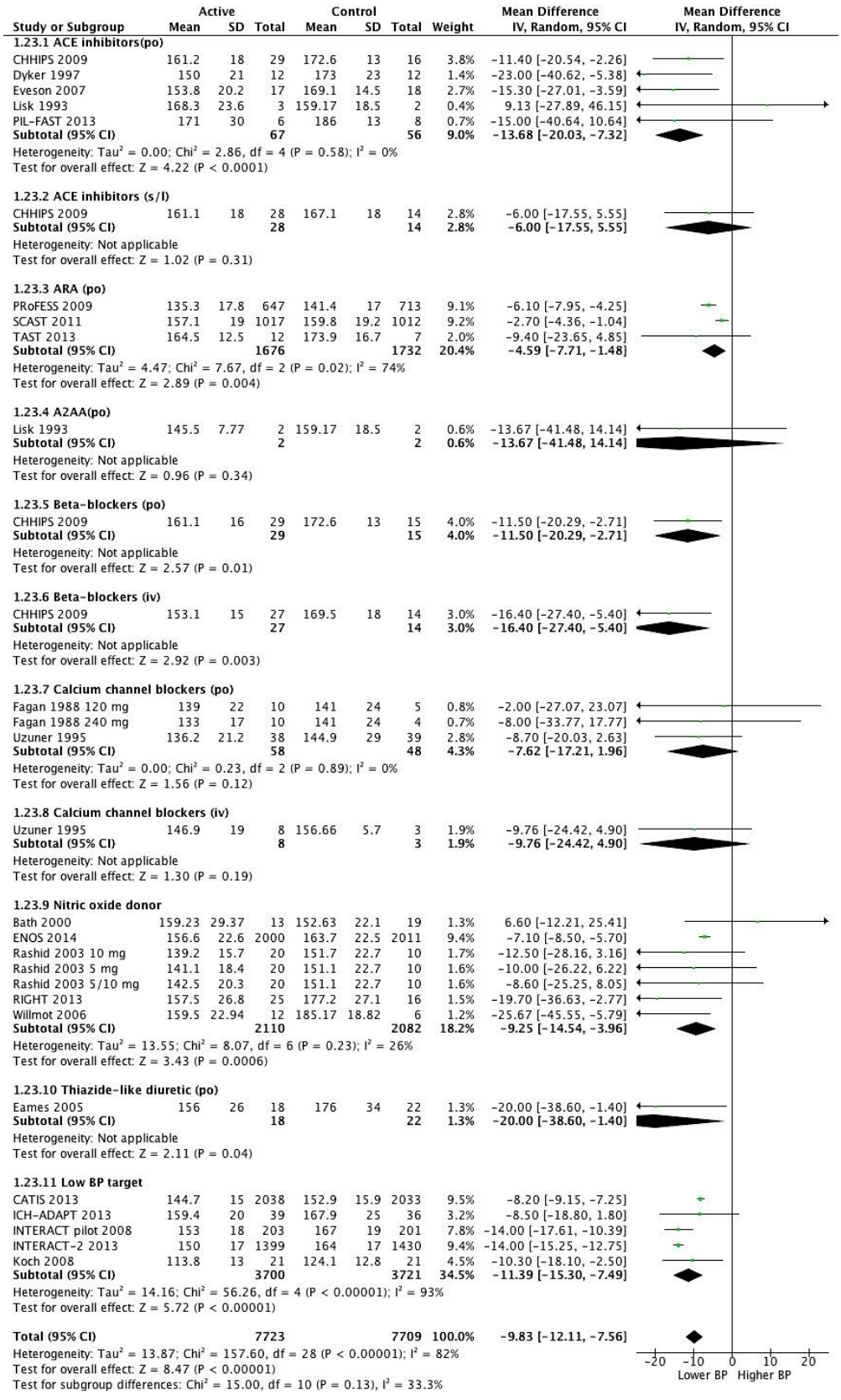

Active
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.23.1 ACE inhibitors(po)
CHHIPS 2009 161.2 18 29 172.6 13 16 3.8% -11.40 [-20.54, -2.26]
Dyker 1997 150 21 12 173 23 12 1.4% -23.00 [-40.62, -5.38]
Eveson 2007 153.8 20.2 17 169.1 14.5 18 2.7% -15.30 [-27.01, -3.59]
Lisk 1993 168.3 23.6 3 159.17 18.5 2 0.4% 9.13 [-27.89, 46.15]
PIL-FAST 2013 171 30 6 186 13 8 0.7% -15.00 [-40.64, 10.64]
Subtotal (95% CI) 67 56 9.0% -13.68 [-20.03, -7.32]
Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 4 (P = 0.58); I² = 0%
Test for overall effect: Z = 4.22 (P < 0.0001)
1.23.2 ACE inhibitors (s/l)
CHHIPS 2009 161.1 18 28 167.1 18 14 2.8% -6.00 [-17.55, 5.55]
Subtotal (95% CI) 28 14 2.8% -6.00 [-17.55, 5.55]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)
1.23.3 ARA (po)
PRoFESS 2009 135.3 17.8 647 141.4 17 713 9.1% -6.10 [-7.95, -4.25]
SCAST 2011 157.1 19 1017 159.8 19.2 1012 9.2% -2.70 [-4.36, -1.04]
TAST 2013 164.5 12.5 12 173.9 16.7 7 2.0% -9.40 [-23.65, 4.85]
Subtotal (95% CI) 1676 1732 20.4% -4.59 [-7.71, -1.48]
Heterogeneity: Tau² = 4.47; Chi² = 7.67, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 2.89 (P = 0.004)
1.23.4 A2AA(po)
Lisk 1993 145.5 7.77 2 159.17 18.5 2 0.6% -13.67 [-41.48, 14.14]
Subtotal (95% CI) 2 2 0.6% -13.67 [-41.48, 14.14]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
1.23.5 Beta-blockers (po)
CHHIPS 2009 161.1 16 29 172.6 13 15 4.0% -11.50 [-20.29, -2.71]
Subtotal (95% CI) 29 15 4.0% -11.50 [-20.29, -2.71]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.57 (P = 0.01)
1.23.6 Beta-blockers (iv)
CHHIPS 2009 153.1 15 27 169.5 18 14 3.0% -16.40 [-27.40, -5.40]
Subtotal (95% CI) 27 14 3.0% -16.40 [-27.40, -5.40]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.92 (P = 0.003)
1.23.7 Calcium channel blockers (po)
Fagan 1988 120 mg 139 22 10 141 24 5 0.8% -2.00 [-27.07, 23.07]
Fagan 1988 240 mg 133 17 10 141 24 4 0.7% -8.00 [-33.77, 17.77]
Uzuner 1995 136.2 21.2 38 144.9 29 39 2.8% -8.70 [-20.03, 2.63]
Subtotal (95% CI) 58 48 4.3% -7.62 [-17.21, 1.96]
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)
1.23.8 Calcium channel blockers (iv)
Uzuner 1995 146.9 19 8 156.66 5.7 3 1.9% -9.76 [-24.42, 4.90]
Subtotal (95% CI) 8 3 1.9% -9.76 [-24.42, 4.90]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
1.23.9 Nitric oxide donor
Bath 2000 159.23 29.37 13 152.63 22.1 19 1.3% 6.60 [-12.21, 25.41]
ENOS 2014 156.6 22.6 2000 163.7 22.5 2011 9.4% -7.10 [-8.50, -5.70]
Rashid 2003 10 mg 139.2 15.7 20 151.7 22.7 10 1.7% -12.50 [-28.16, 3.16]
Rashid 2003 5 mg 141.1 18.4 20 151.1 22.7 10 1.6% -10.00 [-26.22, 6.22]
Rashid 2003 5/10 mg 142.5 20.3 20 151.1 22.7 10 1.6% -8.60 [-25.25, 8.05]
RIGHT 2013 157.5 26.8 25 177.2 27.1 16 1.5% -19.70 [-36.63, -2.77]
Willmot 2006 159.5 22.94 12 185.17 18.82 6 1.2% -25.67 [-45.55, -5.79]
Subtotal (95% CI) 2110 2082 18.2% -9.25 [-14.54, -3.96]
Heterogeneity: Tau² = 13.55; Chi² = 8.07, df = 6 (P = 0.23); I² = 26%
Test for overall effect: Z = 3.43 (P = 0.0006)
1.23.10 Thiazide-like diuretic (po)
Eames 2005 156 26 18 176 34 22 1.3% -20.00 [-38.60, -1.40]
Subtotal (95% CI) 18 22 1.3% -20.00 [-38.60, -1.40]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.04)
1.23.11 Low BP target
CATIS 2013 144.7 15 2038 152.9 15.9 2033 9.5% -8.20 [-9.15, -7.25]
ICH-ADAPT 2013 159.4 20 39 167.9 25 36 3.2% -8.50 [-18.80, 1.80]
INTERACT pilot 2008 153 18 203 167 19 201 7.8% -14.00 [-17.61, -10.39]
INTERACT-2 2013 150 17 1399 164 17 1430 9.4% -14.00 [-15.25, -12.75]
Koch 2008 113.8 13 21 124.1 12.8 21 4.5% -10.30 [-18.10, -2.50]
Subtotal (95% CI) 3700 3721 34.5% -11.39 [-15.30, -7.49]
Heterogeneity: Tau² = 14.16; Chi² = 56.26, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.72 (P < 0.00001)
Total (95% CI) 7723 7709 100.0% -9.83 [-12.11, -7.56]
Heterogeneity: Tau² = 13.87; Chi² = 157.60, df = 28 (P < 0.00001); I² = 82%
Test for overall effect: Z = 8.47 (P < 0.00001)
Test for subgroup differences: Chi² = 15.00, df = 10 (P = 0.13), I² = 33.3%
-20 -10 0 10 20
Lower BP Higher BP

Figure 7.18 SBP, first after randomisation by stroke type

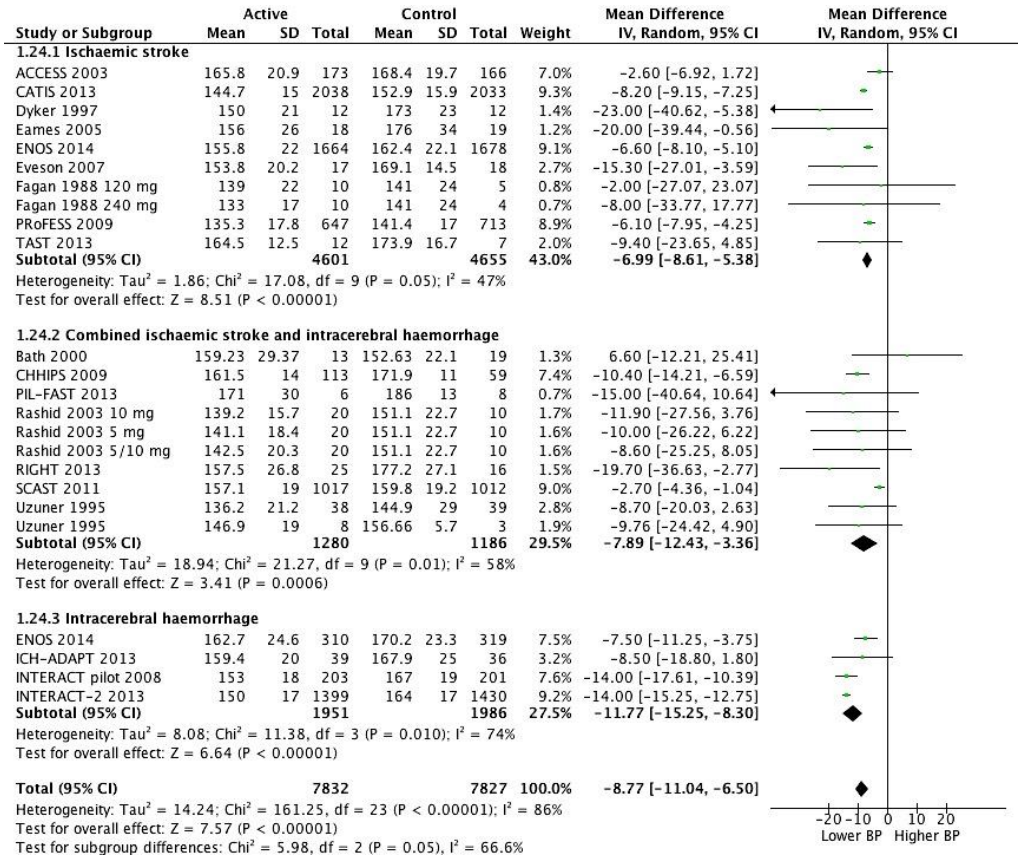


Figure 7.19 SBP, first after randomisation by time to treatment

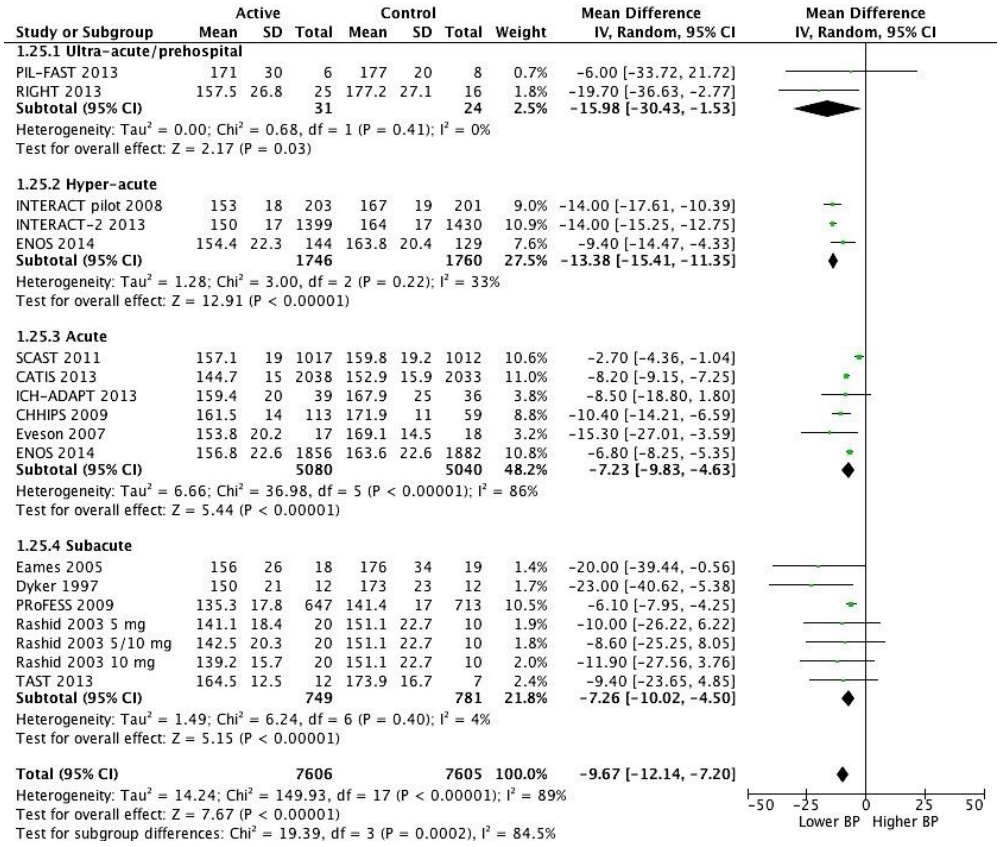


Figure 7.20 Death or dependency, end of trial by stroke type, continue vs stop

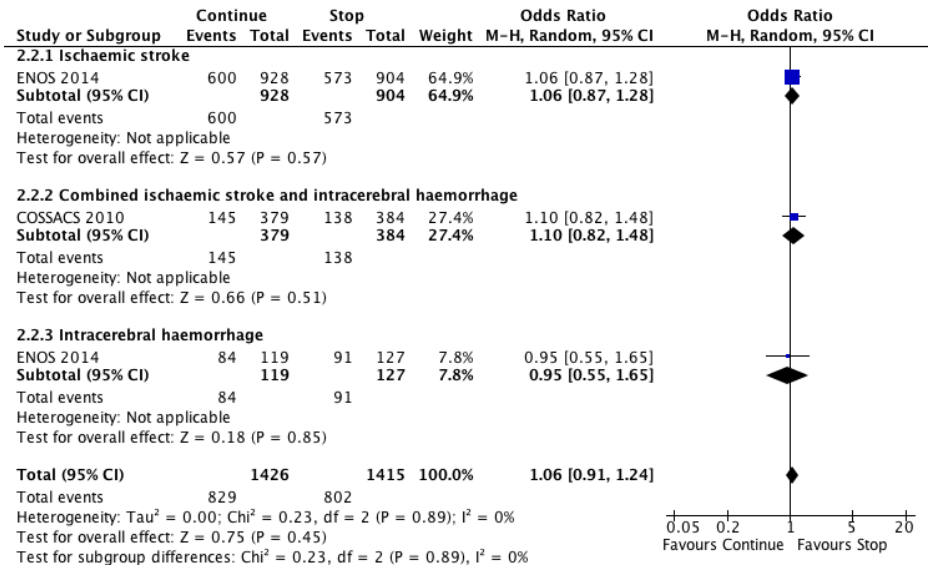


Figure 7.21 Death or dependency, end of trial by time to treatment, continue vs stop

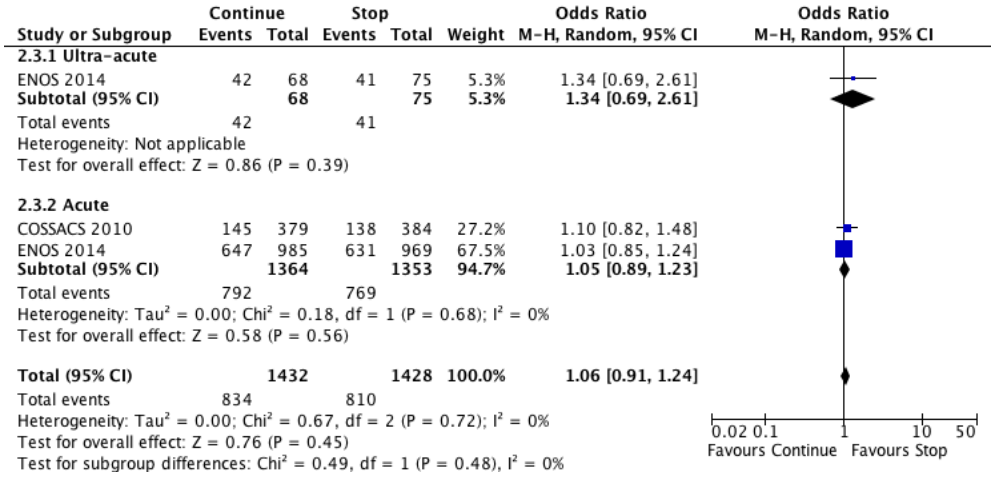


Figure 7.22 Death early, by stroke type, continue vs stop

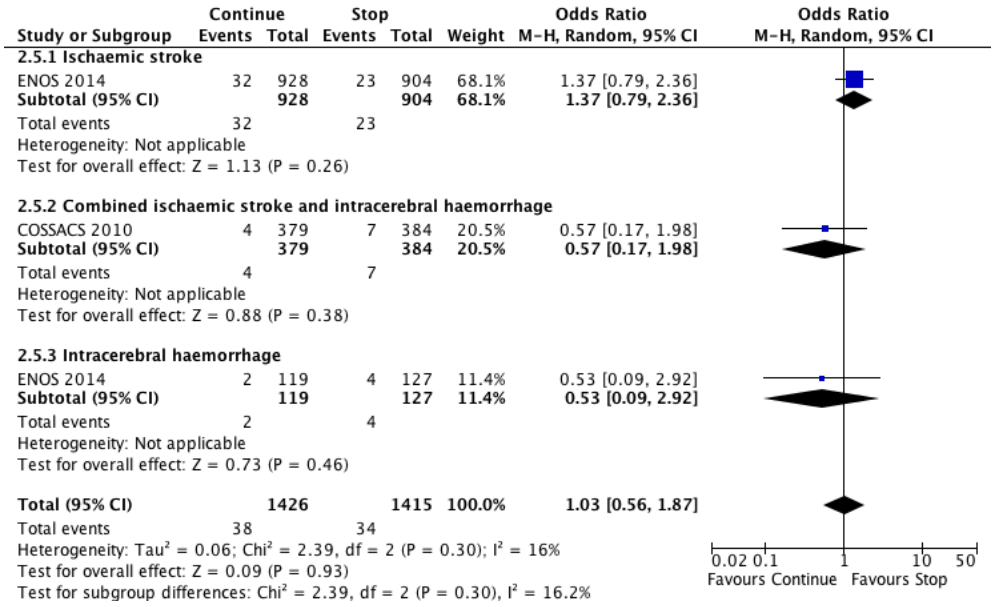


Figure 7.23 Death early, by time to treatment, continue vs stop

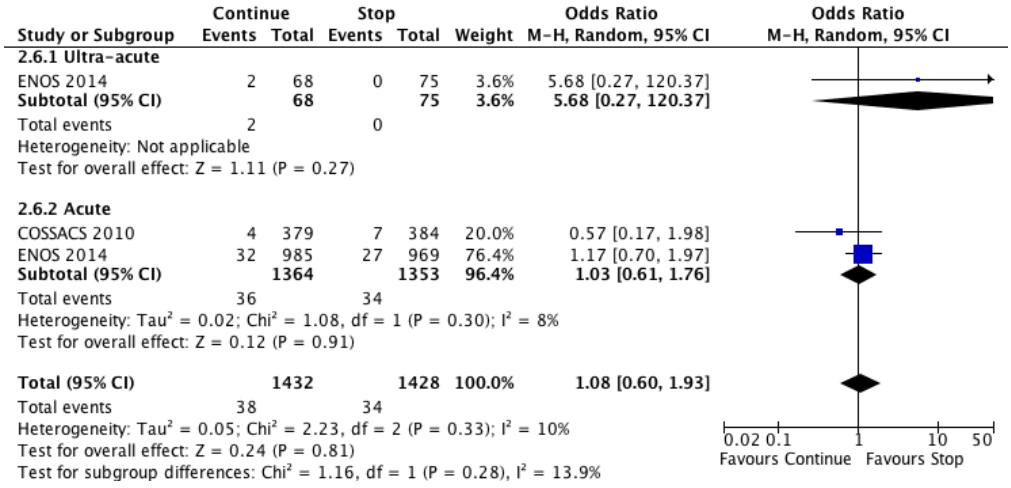


Figure 7.24 Death, end of trial, by stroke type, continue vs stop

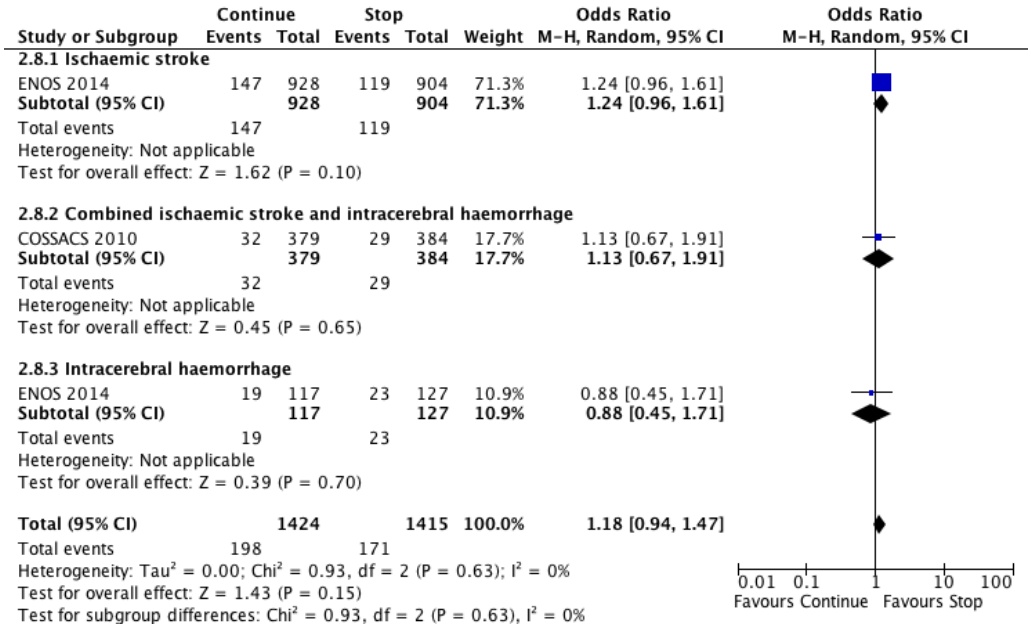


Figure 7.25 Death, end of trial, by time to treatment, continue vs stop

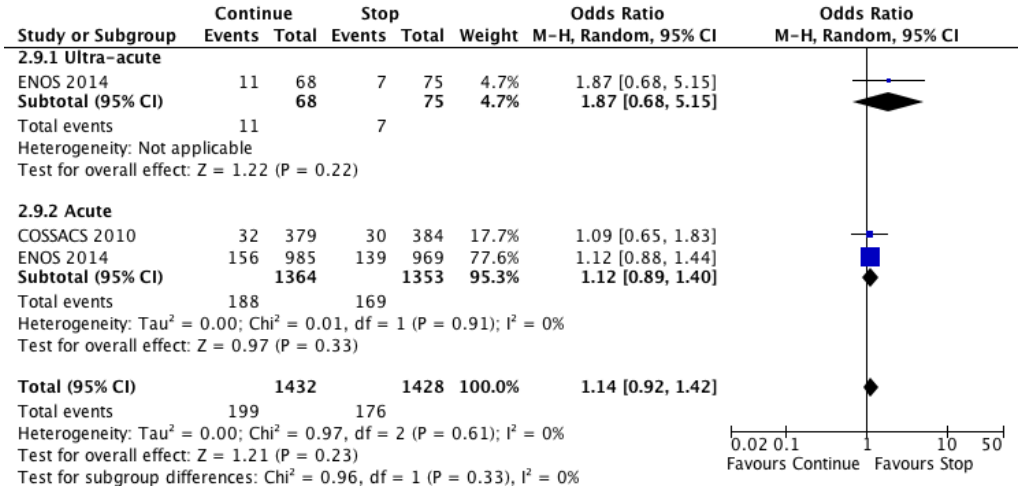


Figure 7.26 Barthel index, end of trial, by continue vs stop

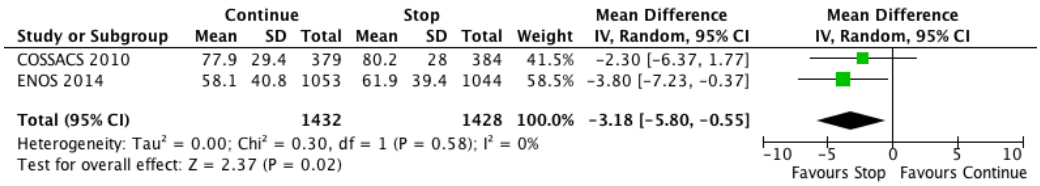


Figure 7.27 Early neurological deterioration, by continue vs stop

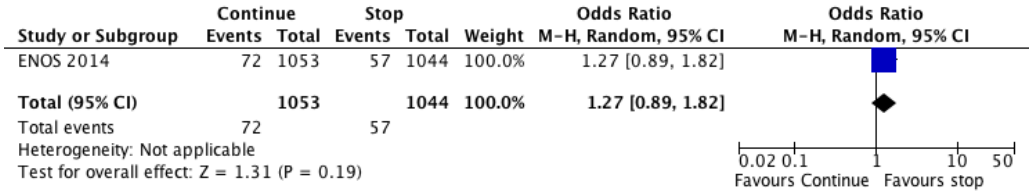


Figure 7.28 Quality of life (EuroQoL) at end of trial, by continue vs stop

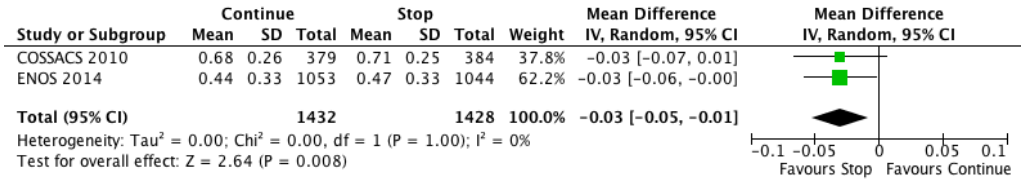


Figure 7.29 SBP, first after randomisation, by continue vs stop

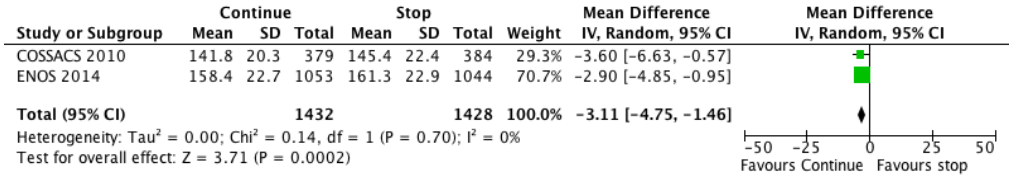


Figure 7.30 DBP, first after randomisation, by continue vs stop

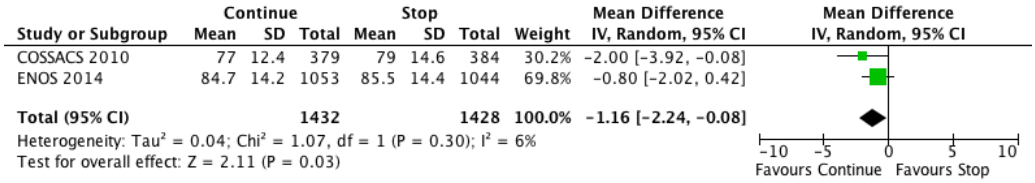


Figure 7.31 SBP, at end of treatment by continue vs stop

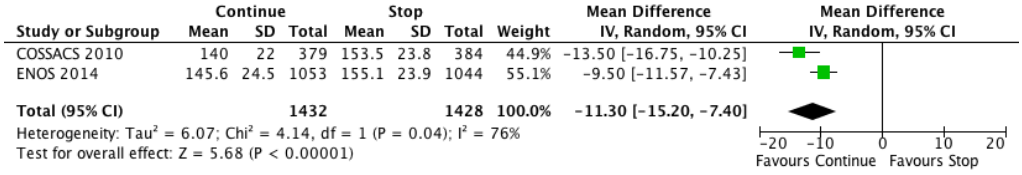


Figure 7.32 DBP, at end of treatment by continue vs stop

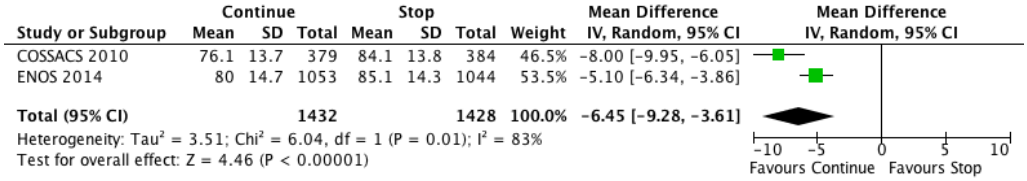


Figure 7.33 SBP at day 1

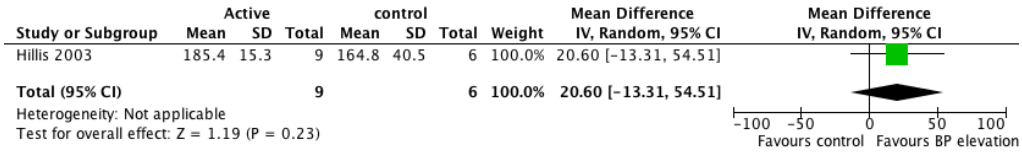
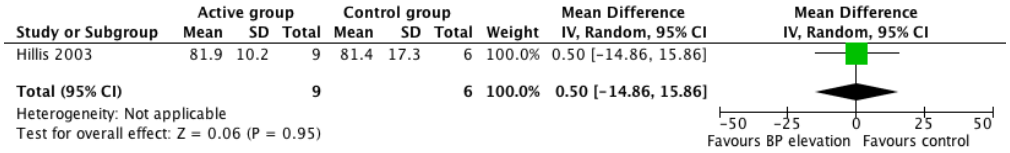


Figure 7.34 DBP at day 1



Chapter - 8 Discussion

8.1 Introduction

The management of acute intracerebral haemorrhage has been a topic of debate and focus of research especially in the last few decades. Systematic work has revealed the following: haematoma volume and early expansion is frequent with potential consequences of neurological deterioration and death;[211, 225] strong association exists between high blood pressure and poor outcome after stroke[124, 501] and treating high blood pressure which is low cost and widely available appears attractive. Whilst new research relating to these topics adds insight into a small area in this vast subject, attempts to answer one question often reveals new areas of uncertainty.

I return to some of the objectives outlined in the introduction and discuss under various headings.

8.2 Assess the performance characteristics of the methods used to measure intracerebral haemorrhage volume

Haematoma volume is the most potent predictor of poor prognosis after ICH.[225] Limiting haemorrhage expansion is used as a surrogate marker of functional outcome in recent trials of blood pressure lowering, haemostatic therapy or surgery[260, 261, 277, 310, 502, 503] and therefore the ability to accurately calculate volume becomes critical. The ABC/2 formula and its modified version (where slices of haemorrhage are excluded if less than 25% of the largest surface area)[251, 352] are commonly used but researchers have doubted the accuracy and reliability as the implicit assumption is haematoma volume is approximated to an ellipsoid.[250, 252-254, 355, 356] Computer assisted SAS or 3-D automatic volume rendering are also used but rely on good quality electronic scan images and advanced software.[246, 252, 355] Previous work examining these methods highlighted issues relating to measurement time, type of data, accuracy, availability of computer and sample size, all studied in part.[246, 252-254]

With this background, a study was undertaken to investigate the reliability and causes for variation and error between three methods commonly used to measure haemorrhage volume:

ABC/2, modified ABC/2 and SAS. In addition, the reliability of a novel way of estimating longest haemorrhage diameter in an ordered category (less than 3 cm, 3-5 cm, 5-8 cm and >8 cm) was also assessed. This is the largest study in the field of spontaneous ICH and CT scans from the large multinational trial ENOS was used for this purpose (details listed in chapter 2). The results revealed that volume calculation by each of the methods: ABC/2, modified ABC/2 and SAS had minimal intra and inter-observer variation demonstrating excellent internal validity. Standard ABC/2 was easy to use, quick to perform and produced similar volumes compared to SAS. By comparison, haemorrhage volumes calculated using modified ABC/2 were significantly lower compared with ABC/2 and SAS and the difference enlarged as haematomas became bigger. When assessing qualitative estimates of haemorrhage size in a ordered escalation, our results found that visual categorisation was quick, consistent and reliable making it potentially useful in emergency situations when moved images preclude accurate volumetric measurements or measuring tools are not accessible.

To compare our study results with those previously published, a review of studies analysing ABC/2, modified ABC/2 and SAS was undertaken and 11 studies identified. Although the overall

patient numbers were small, sufficient methodological information was available to conclude that consistent ICH volumetric calculation can be achieved using standard ABC/2. This is relevant from a practical perspective, as in the absence of a readily available computerised software program, clinicians will be able to obtain a reliable calculation of ICH volume using ABC/2. Such crucial information might influence treatment decisions such as surgical intervention or prevent incorrect initiation of 'do not resuscitate' orders.

We extended the hypothesis by examining the reliability between volume computed by ABC/2, modified ABC/2 and SAS according to haematoma shape. It is known that irregular shaped haematomas are more likely to expand and affect survival after stroke.[361] The results showed that ICH volumes produced by standard ABC/2 were reliable and consistent compared with SAS, irrespective of haemorrhage shape. By comparison, ICH volume was significantly lesser using the modified ABC/2 method for small, regular shaped haemorrhages and the difference larger as haemorrhages became bigger and more irregular. It is possible that the haemorrhage volumes in ENOS were too small to detect any difference between standard ABC/2 and SAS as previous work

has questioned the accuracy in more larger and complex shaped irregular haemorrhages.[250]

One report suggested that haematoma shape may depend on brain location and degree of cerebral atrophy.[253] As such criteria were not used to select our dataset, these questions were not tested and need further exploration. In our study, it was also not possible to examine whether an individual haematoma shape at one given time point on a CT changed to another shape as in ENOS patients had scans at the time of entry into the trial and a second scan if possible at 7 days. Ongoing trials should take this into account and hopefully will provide answers in this area.[220, 280, 504]

Our report that the settings for computer assisted SAS is being cumbersome and extremely time consuming is consistent with previous studies.[246, 252, 253] We were also not able to assess the reliability of fully automated 3-D rendering using Osirix; this is reflected in the small number of volumes calculated making it difficult even for hypothesis generation. This is because Osirix was unable to handle scans with variable slice thickness. Other software packages are able to manage this issue but experience significant delays in image acquisition.[246, 252] In a small study of patients with

intracerebral haemorrhage, acquisition time ranged between 20-30 minutes for each CT raising questions of the use of fully automated 3-D rendering in clinical situations and therefore more work to develop faster algorithms is needed.[252] Even with faster software, it is important not to forget that the SAS and 3-D rendering still require user discretion and manual intervention for final ICH volume estimation. Future work should test whether various computer-assisted methods supported by different software produce similar results.[246]

The present study did not assess the accuracy and reliability of these methods in larger and more complex warfarin related haemorrhages as ENOS examined the effect of blood pressure lowering in a population of spontaneous ICH. Warfarin related ICH is associated with more morbidity and mortality [205, 505] as the propensity for haematoma expansion is greater.[205] Hence, work analysing the reliability of volumetry in this area is crucially needed. Similarly, work should be encouraged in the field of novel anticoagulants because of lack of data and increasing use in an ageing population with atrial fibrillation.[506] Assessing the reliability of these methods in perihaematoma oedema is also needed as it has been shown to affect clinical outcome.[232, 233]

8.3 Blood pressure lowering with transdermal glyceryl trinitrate (GTN) in acute intracerebral haemorrhage

As detailed in chapter 4, a subgroup analysis of ENOS was performed to investigate whether blood pressure lowering with transdermal GTN was associated with improved functional outcome after acute haemorrhagic stroke. Functional outcome was measured using the modified Rankin scale at 90 days (0 to 6, 0 indicating no symptons, five meaning severe dependency and 6 denoting death). Patients were recruited worldwide and received care in different healthcare systems and therefore represent a wide perspective of stroke care. The results revealed that in 629 patients, GTN reduced SBP by 8 mm Hg but did not improve functional outcome. Given concerns about worsening functional outcome with an ARA agent like candesartan,[507] the absence of worsening on neuroimaging measures at day 7 (end of treatment) and adverse events including hypotension, early and late fatality with GTN is reassuring and supports trials further testing of this agent in acute stroke.[133, 134]

When examined by prespecified time windows as in INTERACT-2 (within 6 hours),[261] participants treated with GTN were less likely to die and reported better quality of life and

scored higher on cognitive assessment. Although careful interpretation should be made given the small numbers of patients, GTN when given very early is postulated to have other effects in addition to BP lowering such as neuroprotection and improving reperfusion by opening collateral circulation as supporting evidence was shown in a pilot trial of the drug in hyperacute stroke, RIGHT.[264] RIGHT demonstrated that paramedics could successfully screen patients with stroke symptons, consent, randomise and start BP lowering in a pre-hospital setting.[264] The mean time from stroke onset to randomisation was 55 minutes and after 2 hours of treatment with GTN, SBP was lowered by 18 mm Hg.[264] Taking together the results from ENOS and RIGHT and a previous large trial in acute intracerebral haemorrhage,[137, 261, 264] the results support further testing whether very early BP lowering might benefit in improving functional outcome as is being undertaken in ongoing randomised controlled trials.[133, 134, 268] In addition, parameters such as blood pressure variability, central and cerebral haemodynamics could also be assessed as evidence suggests that these factors could impact short term and long term functional outcome.[508, 509] Future trials could also examine changes to haemorrhage characteristics at various time points during treatment as this

may provide information on potential mechanisms of drug action.

It is important to highlight that the data came from a randomised controlled trial with prespecified inclusion and exclusion criteria. Patients with very high blood pressure (>220 mm Hg) were excluded from ENOS and so no results are available for those with severe hypertension. As a result, strength of the relationship between BP lowering and functional outcome as a result might have been underestimated. Patients with comorbidities such as MI and cardiac failure with SBP pressure levels less than 140 mm Hg will have been excluded and therefore information on such patients is not available. Low BP may result in poor perfusion of the penumbra surrounding the haematoma and result in poor outcome.[510, 511] Another issue is that a low proportion of patients with IVH were recruited into ENOS and therefore such patients with will have been underrepresented. This may have affected the strength of the relationship between BP lowering and functional outcome. One other factor to highlight is time. ENOS allowed recruitment upto 48 hours and so it is possible that some haemorrhages may have already expanded and this will have affected the ability of BP lowering to have any effect. Furthermore, some patients with higher blood pressure will

have been missed as it is known blood pressure falls within the first few hours after stroke onset.[512]

That functional outcome may be predicted using simple visual assessments of characteristics such as haematoma shape and density is highly relevant for treating clinicians. Rapid assessment of shape and density might identify those at high risk of haematoma growth and allow recruitment into clinical trials aimed at detecting any treatment effect. Alternatively, including a large irregular ICH with extension into the ventricles may not translate into favourable effect.

The present work is novel adding more information to this area of ICH but more work to identify clinical and radiological factors at stroke onset. To-date, most predictors of poor outcome in ICH are irreversible including age, haemorrhage location and baseline level of consciousness leaving only one factor haemorrhage volume as potentially modifiable.[225, 513] Finding the 'spot sign' on CT angiography might be useful but questions surround the time dependent variability and interpretation in the presence of potential confounders such as blood pressure lowering and haemostatic agents.[44, 514] However, it is known of the association between 'spot positive' status of haematoma and adverse clinical outcome[515] and

therefore clinical trials in this group of patients are needed.[280, 281, 296] Future work should also examine pathophysiological factors or possible mechanisms. With this knowledge, agents targeting patients who might benefit most may be identified.

8.4 Effects of continue versus stopping prestroke antihypertensive drugs in acute intracerebral haemorrhage

Upto 50% of patients admitted with acute stroke are on blood pressure lowering tablets and it was unclear whether they should be continued or stopped temporarily during the acute phase of stroke. Treating hypertension by continuing prior antihypertensive drugs in the immediate period after ICH seems advantageous by reducing stroke recurrence, haematoma expansion and improving functional outcome.[404] The issue may become complicated by the fact that many patients develop swallowing problems after stroke and may not be able to take the tablets even if prescribed. On the other hand, lowering blood pressure by continuing treatment might cause profound hypotension and dehydration, a common problem in acute stroke patients who may not be taking fluids appropriately. Stopping treatment might limit hazard as seen in trials of angiotensin receptor antagonists, β-receptor

antagonists and calcium channel blockers.[494, 507, 516] The clinical equipoise that resulted from these opposing arguments led onto research in this area. The COSSACS trial attempted to answer this question and did not show any potential harm from treatment continuation, but was statistically underpowered.[136] Keeping this in mind, Chapter 5 of this thesis explored this question in a subgroup analysis using data from ENOS.

Among 629 patients with haemorrhagic stroke, 246 patients were assigned to continue or stop pre-existing antihypertensive drugs temporarily for 7 days. For those assigned to continue, medication was administered orally and those with dysphagia received treatment through a nasogastric feeding tube. The results revealed no significant difference in the functional outcome assessed using mRS at day 90 among those who continued prior antihypertensive drugs compared to those stopped treatment. When analysing rates of survival, more deaths seemed to occur in those assigned to stop antihypertensive drugs implying they did worse. This was even after confirming that the timing of ascertainment of death between the groups was similar and the data and figures checked for any numerical or labelling errors. The observed result is difficult to explain but overall

there was no significant difference. The analysis is novel as it examined the association between clinical and neuroimaging parameters in haemorrhagic stroke during the acute phase.

A combined analysis including the results of ENOS and COSSACS revealed that measures of disability and quality of life were worse in patients randomised to continue treatment. Although the primary outcome of mRS was not significantly affected by treatment continuation, the signs of possible harm in key secondary variables suggest that it seems sensible to withhold blood pressure lowering drugs until patients are stable and ensure suitable oral and enteral access is established. Given practical issues in implementing this complex question in the setting of a large trial,[136] it is unlikely there will be any future studies looking into continue versus stopping pre-existing antihypertensives in acute stroke. Guidelines do not advise on this issue,[517] but will need to update the recommendations based on the results of COSSACS and ENOS.

8.5 Compare the baseline characteristics and outcomes of patients with intracerebral haemorrhage from different ethnic backgrounds

Whilst previous work indicates ethnic variation in risk factors for ICH, little is known whether these manifest as differences in clinical characteristics, haematoma parameters or functional outcome. With this background, an analysis was conducted in Chapter 6 using data from ENOS and the VISTA collaboration (Virtual International Stroke Trials Archive). Only those patients randomised to control were included to avoid any potential confounding treatment factors. This is the first study addressing this aspect of haemorrhagic stroke and the results found significant differences in age, GCS, BP and ICH volume at baseline among 3 ethnic groups- Caucasians, Asians and Blacks. Although no difference was observed in mRS at day 90, there were significant differences in mortality rates and quality of life. After adjusting for baseline characteristics, Asians were less likely to die and scored higher in the 5 domains of the European-Quality of life questionnaire compared to Caucasians. The causes for these disparities are open to question and may be partly explained by lifestyle factors. Whether genetic or cultural differences impacted upon the findings was beyond the scope of this study and needs further exploration.

More than three-quarter of patients in this cohort were Caucasians suggesting that future trials need to achieve better balance of treatment and control allocation within populations. This would be of relevance when drawing conclusions about outcomes between hospitals within regions or between countries. It is equally important to mention that in this analysis distinct subpopulations were combined into one ethnic group (for example including Filipinos, Indian and Arabics as Asians) and this might have not been appropriate. Although this was undertaken to compensate for small patient numbers, it would be important for future studies to examine for differences among subpopulations. This is because stroke incidence and outcomes are known to differ between population groups living in the same country and between countries.[420, 518, 519]

Most patients with ICH in this cohort were males reflecting a higher incidence but whether clinical and outcome differences exist within or between sexes are limited[520] and need further assessment. This would be important as interactions between sex and ethnicity will affect the incidence of ICH. For example, a higher incidence of ICH is observed in Japanese men compared to women.[521, 522] In a population-based study of

Chinese men, a higher incidence was observed in those living in Changsha but not in Beijing or Shanghai.[523] When exploring the question of sex-difference in future research, examining variation in haematoma according to location, volume and expansion might also help.

It is important to highlight that patients in this study came from randomised controlled trials with specific inclusion and exclusion criteria and this may have led to selection bias. Therefore, the results may not be applicable to a population of unselected patients. The information was limited to trials sharing information with the VISTA collaboration and therefore those that are not represented need to be examined. Future analysis could also include developing countries and those which do not have access to specialist stroke teams.

8.6 Deliberate BP intervention in acute stroke

Whilst previous work indicates high BP is associated with poor early and late outcome after acute stroke, it is still debated as to whether it should or should not be treated during the acute phase. Pathophysiological evidence argues against in the context of impaired cerebral autoregulation during the acute phase whilst observational data favours lowering. Current

guidelines recommend blood pressure lowering only if the blood pressure is greater than 220/120 mm Hg, greater than 200/100 with end-organ damage (concomitant hypertensive encephalopathy, aortic dissection, cardiac ischaemia, renal failure) or more than 200/120 mm Hg in primary ICH.[268, 495, 517]

As detailed in Chapter 7, a meta-analysis of blood pressure altering trials aimed at improving clinical outcome in acute stroke was performed. This was an update since the first review in 2001, updated again in 2008 and included 17,011 patients. The new trials included tested BP alteration using single agents, blood pressure lowering to no target to pre-specified targets and functional outcomes ranged from near-negative to neutral to near-positive. The overall result was that blood pressure lowering did not improve functional outcome irrespective of type of stroke. However, there were signs that treatment initiated very early might reduce death or dependency and therefore justifies further research as is being undertaken in ongoing randomised controlled trials.[133, 134]

Few aspects relating to blood pressure lowering in this review warrant discussion. Despite the evidence, it remains unclear as to which antihypertensive agent should be used to lower

blood pressure in acute stroke. Trials involving angiotensin receptor antagonists reduced blood pressure but appeared to cause harm whereas trials of outcome with nitrates ranged from neutral to signs of benefit when administered early.[137, 264, 507] No significant benefit on outcome was seen with thiazide diuretics although the information came from one trial.[467] Agents such as alpha-receptor antagonists, hydralazine, diuretics and centrally acting drugs were used in combination in trials of target driven BP lowering making it difficult to analyse the effects of any single agent. More homogeneous data is therefore needed and crucial information will become available when ongoing trials of single agents are completed.[133, 134] Another important clinical issue during BP lowering is dysphagia which occurs in a significant proportion of patients after stroke and therefore starting tablets might not be an option. Alternative approaches include applying a transdermal GTN patch or to use short acting intravenous agents such as nicardipine and clevidipine but more work in this area is needed.

Another important issue is the lack of knowledge as to when to start BP lowering after acute stroke. Whilst the present meta-analysis does not give the answer in a precise manner, it attempts in a way by showing that functional outcome was

better if BP lowering was started within 6 hours of onset and delay beyond 6 hours was not associated with clinical benefit. The observed results were probably relate to the magnitude of BP lowering as seen in INTERACT-2 and the postulated neuroprotective effect of GTN very early after stroke but no firm conclusions can be made as the summary result was neutral. Of recent, the ATACH-2 investigators attempted to extend this knowledge using intravenous nicardipine in ICH patients presenting within 4.5 hours of ictus with GCS over 5 and randomly assigned patients to 140 to 179 mmHg or 110 to 139 mmHg.[524] The trial planned to enrol more patients, but was stopped prematurely after 1000. Although nicardipine appeared to an effect on haematoma expansion, there was no significant difference in the primary outcome of death or disability which occurred in 38.7% of the intensive group compared to 37.7% of the standard group (adjusted relative risk, 1.04; 95% confidence interval, 0.85 - 1.27; p= 0.72).[524]

One other issue related to this analysis was the lack of clarity as to what magnitude of reduction might benefit. Whilst previous work showed that a 8-14 mm Hg reduction may reduce the risk of poor outcome, the number of included studies were few and patient numbers small.[132] The trials in this review differed in the blood pressure level for enrolment

and treatment targets varied from intensive control to guideline based to no pre-specified level. Repeating the meta-regression with the current data and results from ongoing trials might provide more clear answers.

If blood pressure lowering is thought to benefit, it is not clear from the data as to how long patients should be treated for. Trials in this review varied from 1 day upto 2.5 years making the shift from primary to secondary prevention after stroke appear indistinct. The work from a previous meta-analysis suggests that treatment for a short period may be effective[132] and supporting further testing in this area of stroke research.[134, 525]

There was limited information on long-term follow-up, as most trials (including the most recent ones) performed follow up at three months. This might be early as patients with severe stroke (included in the trials) can experience recovery upto six months. Moreover, a longer time-point on functional outcome might highlight continued benefit or potential harm as shown recently by the SCAST study group with candesartan.[526] Future trials may therefore consider long-term follow up but it should be remembered that outcome assessment may be

confounded by concurrent interventions such as physiotherapy.

One of the key limitations of this analysis was the lack of information on how blood pressure was measured including equipment, who took the measurement and how they were trained, the number of readings at each time point and what position the patient was in (supine, sitting or standing). Of the included 26 studies, only 16 reported on BP equipment, the measurer and how the measurements were taken. Some studies had no recording of blood pressure and therefore excluded from the analysis. Although attempts were made to contact the individual trialists, only few provided data and the rest did not respond. It is essential that future studies should report such information as significant imbalances in values will affect treatment effect. The outcomes in this review were not adjusted for key variables such as age, baseline stroke severity, blood pressure, stroke type and this is important as they might have had a significant impact upon the results. [384, 466, 527] Some of these factors might have been addressed by providing individual patient data and therefore future trialists should be encouraged to do so. One approach would be to share and publish results under the auspices of a collaboration.

The data in these trials was derived from patients with little comorbidity and as yet little is known about altering BP in older patients with multiple medical problems who comprise the largest population in both ischaemic and haemorrhagic stroke. It should also be remembered that the responses of older patients with reduced cerebrovascular reactivity and those with severe hypertension might not show similar responses to younger population during blood pressure modulation.

Conclusions

In conclusion, this thesis has investigated several questions in acute haemorrhagic stroke. It provides new information on assessment of acute intracerebral haemorrhage descriptors and assessed their relationship with clinical outcomes. The data from a multinational international randomised clinical trial from which the body of this thesis is derived provides more information of the management of blood pressure in acute haemorrhagic stroke. It showed that transdermal GTN 5 mg lowered blood pressure, tended to reduce haematoma volume but did not reduce death or dependency. A meta-analysis including recently published trials in acute stroke demonstrated that beta-receptor antagonists, oral calcium

channel blockers, angiotensin converting enzyme inhibitors, angiotensin-receptor antagonists blockers deliberately altered blood pressure in acute stroke. This updated work also established that immediately re-starting prior antihypertensive drugs taken before stroke may increase disability and worsen quality of life. The current work demonstrates that lowering blood pressure early in acute haemorrhagic stroke may benefit, and therefore justifies ongoing randomised clinical trials in this area. Work in this thesis has also shown that clinical features and outcomes in acute intracerebral haemorrhage vary among ethnic groups. However, more research is needed to examine whether genetic susceptibility, socio-economic factors or cultural differences play a role.

References

1. Tunstall-Pedoe H. The who monica project monitoring trends and determinants in cardiovascular disease a major international collaboration. *Journal of Clinical Epidemiology*. 1988;41:105-114
2. Pessin MS, Duncan GW, Mohr JP, Poskanzer DC. Clinical and angiographic features of carotid transient ischemic attacks. *New England Journal of Medicine*. 1977;296:358-362
3. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al. Transient ischemic attack--proposal for a new definition. *N Engl J Med*. 2002;347:1713-1716
4. Sudlow CLM, Warlow CP. Comparable studies of the incidence of stroke and its pathological types - results from am international collaboration. *Stroke*. 1997;28:491-499
5. Reducing brain damage: Faster access to stroke care. . *In: Health Do. ed.: National Audit Office*. 2005
6. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the united kingdom. *Pharmacoeconomics*. 2003;21:43-50
7. Fernandez RL, Nicola Paul LM, Alastair M. Gray, Sarah T. Pendlebury, Linda M. Bull, Sarah J.V. Welch, et al. Population-based study of disability and institutionalization after transient ischemic attack and stroke. *Stroke*. 2013
8. Feigin V, Lawes C, Bennett D, Barker-Collo S, Parag V. Changing worldwide stroke epidemiology in the 21st century: Stroke incidence rates in developing countries for the first time exceed those in developed countries and parallel changes in official stroke mortality rates. *Circulation*. 2010;122:E82-E82
9. Feigin V, Lawes C, Bennett D, Barker-Collo S, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurology*. 2009;8:355-369
10. Asplund K, Karvanen J, Giampaoli S, Jousilahti P, Niemela M, Broda G, et al. Relative risks for stroke by age, sex, and population based on follow-up of 18 european populations in the morgam project. *Stroke*. 2009;40:2319-2326
11. Bonita R. Epidemiology of stroke. *Lancet*. 1992:342-344
12. Williams GR, Jiang JG, Matchar DB, Samsa GP. Incidence and occurrence of total (first-ever and recurrent) stroke. *Stroke*. 1999;30:2523-2528
13. Rolfe C. *British Medical Bulletin* 2000: 275-286
14. Islam M, Anderson C, Hankey GJ, Hardie K, Carter K, Broadhurst R, et al. Trends in incidence and outcome of stroke in perth, western australia during 1989 to 2001: The perth community stroke study. *Stroke*. 2008;39:776-782
15. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks and hispanics. *Neurology*. 2005;65:518-522

16. Qureshi AI, Safdar K, Patel M, Janssen RS, Frankel MR. Stroke in young black patients. Risk factors, subtypes, and prognosis. *Stroke*. 1995;26:1995-1998
17. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, et al. Stroke in a biracial population: The excess burden of stroke among blacks. *Stroke*. 2004;35:426-431
18. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in oxfordshire, uk from 1981 to 2004 (oxford vascular study). *Lancet*. 2004;363:1925-1933
19. Warlow CP. Epidemiology of stroke. *Lancet*. 1998;352:SIII1-SIII4
20. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Long-term risk of first recurrent stroke in the perth community stroke study. *Stroke*. 1998;29:2491-2500
21. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural-history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337
22. Warlow CP DM, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM, Wardlaw J. *Stroke. A practical guide to management.*: Oxford: Blackwell Science; 1996.
23. Lindley RI, Warlow CP, Wardlaw JM, Dennis MS, Slattery J, Sandercock PAG. Interobserver reliability of a clinical classification of acute cerebral infarction. *Stroke*. 1993;24:1801-1804
24. Wardlaw J. What causes lacunar stroke? *Journal of Neurology Neurosurgery and Psychiatry*. 2005;76:617-619
25. Michael Brainin, Heiss. W-D. *Textbook of stroke medicine*. New York, United States of America: Cambridge University Press; 2010.
26. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon Dl, et al. Classification of subtype of acute ischemic stroke - definitions for use in a multicenter clinical trial. *Stroke*. 1993;24:35-41
27. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the national registry of atrial fibrillation. *JAMA*. 2001;285:2864-2870
28. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272
29. Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. *Stroke*. 2005;36:891-901
30. Hart RG, Diener H-C, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: The case for a new clinical construct. *Lancet Neurology*. 2014;13:429-438
31. Wardlaw J, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P. Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke*. 2004;35:2477-2483

32. Writing committee. Diagnosis and initial management of acute stroke and transient ischaemic attack. *NICE Clinical guideline 68*. 2008
33. The Intercollegiate Stroke working party. National clinical guideline for stroke. *Royal College of Physicians*. 2016;5th edition
34. Rother J. Ct and mri in the diagnosis of acute stroke and their role in thrombolysis. *Thrombosis Research*. 2001;103:S125-S133
35. Wardlaw J, Keir S, Seymour J, Lewis S, Sandercock P, Dennis M, et al. What is the best imaging strategy for acute stroke? *Health Technology Assessment*. 2004;8:1-+
36. José G. Merino, Warach. S. Imaging of acute stroke. *Nature Reviews Neurology*.6:560-571
37. Wardlaw JM, Muir KW, Macleod MJ, Weir C, McVerry F, Carpenter T, et al. Clinical relevance and practical implications of trials of perfusion and angiographic imaging in patients with acute ischaemic stroke: A multicentre cohort imaging study. *Journal of Neurolgy Neurosurgery and Psychiatry*. 2013
38. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, et al. Comparison of mri and ct for detection of acute intracerebral hemorrhage. *Jama-Journal of the American Medical Association*. 2004;292:1823-1830
39. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, et al. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. 2009
40. Wardlaw JM, Statham PF. How often is haemosiderin not visible on routine mri following traumatic intracerebral haemorrhage? *Neuroradiology*. 2000;42:81-84
41. Barber PA, Demchuk AN, Hudon ME, Pexman JHW, Hill MD, Buchan AM. Hyperdense sylvian fissure mca "dot" sign - a ct marker of acute ischemia. *Stroke*. 2001;32:84-88
42. Ozdemir O, Leung A, Bussiere M, Hachinski V, Pelz D. Hyperdense internal carotid artery sign - a ct sign of acute ischemia. *Stroke*. 2008;39:2011-2016
43. Al-Nakshabandi NA. The swirl sign. *Radiology*. 2001;218:433
44. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. Ct angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. 2007;38:1257-1262
45. Almekhlafi MA, Kosior JC, Dowlatshahi D, Demchuk AM. Spot sign and live-imaged dramatic intracerebral hematoma expansion. *Neurology*. 2011;76:1275-1276; author reply 1276
46. Kim J, Smith A, Hemphill JC, Smith WS, Lu Y, Dillon WP, et al. Contrast extravasation on ct predicts mortality in primary intracerebral hemorrhage. *AJNR Am J Neuroradiol*. 2008;29:520-525
47. Sun SJ, Gao PY, Sui BB, Hou XY, Lin Y, Xue J, et al. "Dynamic spot sign" on ct perfusion source images predicts haematoma expansion in acute intracerebral haemorrhage. *European Radiology*. 2013

48. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults. *Stroke*. 2007;38:e391-e413
49. WHO-Stroke. Recommendations on stroke prevention, diagnosis and therapy. Report of the who task force on stroke and other cerebrovascular disorders. *Stroke*. 1989
50. Abbott RD, Yin Y, Reed DM, Yano K. Risk of stroke in male cigarette smokers. *New England Journal of Medicine*. 1986;315:717-720
51. Romero JR, Morris J, Pikula A. Stroke prevention: Modifying risk factors. *Therapeutic advances in cardiovascular disease*. 2008;2:287-303
52. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha 4 beta 2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation - a randomized controlled trial. *Jama-Journal of the American Medical Association*. 2006;296:47-55
53. Lancaster T, Stead L, Silagi C, Sowden A, Cochrane Tobacco Addiction R. Effectiveness of interventions to help people stop smoking: Findings from the cochrane library. *British Medical Journal*. 2000;321:355-358
54. Lancaster T, Stead LF. Self-help interventions for smoking cessation. *The Cochrane database of systematic reviews*. 2000:CD001118-CD001118
55. Reynolds K, Lewis LB, Nolen JDL, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke - a meta-analysis. *Jama-Journal of the American Medical Association*. 2003;289:579-588
56. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke - a guideline from the american heart association/american stroke association stroke council: Cosponsored by the atherosclerotic peripheral vascular disease interdisciplinary working group; cardiovascular nursing council; clinical cardiology council; nutrition, physical activity, and metabolism council; and the quality of care and outcomes research interdisciplinary working group - the american academy of neurology affirms the value of this guideline. *Stroke*. 2006;37:1583-1633
57. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack - a statement for healthcare professionals from the american heart association/american stroke association council on stroke - co-sponsored by the council on cardiovascular radiology and intervention - the american academy of neurology affirms the value of this guideline. *Stroke*. 2006;37:577-617
58. Zhang H, Thijs L, Staessen JA. Blood pressure lowering for primary and secondary prevention of stroke. *Hypertension*. 2006;48:187-195

59. Anonymous. Post-stroke antihypertensive treatment study. A preliminary result. Pats collaborating group. *Chinese Medical Journal*. 1995;108:710-717
60. Arima H, Anderson C, Omae T, Woodward M, Hata J, Murakami Y, et al. Effects of blood pressure lowering on major vascular events among patients with isolated diastolic hypertension the perindopril protection against recurrent stroke study (progress) trial. *Stroke*. 2011;42:2339-2341
61. Sleight P. The hope study (heart outcomes prevention evaluation). *Journal of the renin-angiotensin-aldosterone system : JRAAS*. 2000;1:18-20
62. Drayer JIM, Weber MA, Sealey JE, Laragh JH. Low and high renin essential- hypertension: A comparison of clinical and biochemical characteristics. *American Journal of the Medical Sciences*. 1981;281:135-142
63. Williams B. Treatment of hypertension in the uk: Simple as abcd? *Journal of the Royal Society of Medicine*. 2003;96:521-522
64. Collins R, Peto R, Hennekens C, Doll R, Bubes V, Buring J, et al. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849-1860
65. Sandercock PAG, Counsell C, Gubitz GJ, Tseng MC. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database of Systematic Reviews*. 2008
66. Halkes PHA, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A, Esprit Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (esprit): Randomised controlled trial. *Lancet*. 2006;367
67. Diener H, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention - study 2 - dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Nervenheilkunde*. 1999;18:380-390
68. Bath P, Cotton D, Martin R, Palesch Y, Yusuf S, Sacco R, et al. Effect of combined aspirin and extended-release dipyridamole versus clopidogrel on functional outcome and recurrence in acute, mild ischemic stroke profess subgroup analysis. *Stroke*. 2010;41:732-738
69. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *New England Journal of Medicine*. 2006;354:1706-1717
70. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (match): Randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331-337
71. Benavente O, Hart R, McClure L, Szychowski J, Coffey C, Pearce L, et al. Effects of clopidogrel added to aspirin in patients with recent

lacunar stroke. *New England Journal of Medicine*. 2012;367:817-825
72. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *The New England journal of medicine*. 2013;369:11-19
73. Bath PMW, TARDIS Trial Investigators. Results of the triple antiplatelets for reducing dependency after ischaemic stroke. *International Stroke Conference, Texas, USA*. 2017
74. Sandercock P, Bamford J, Dennis M, Burn J, Slattery J, Jones L, et al. Atrial-fibrillation and stroke - prevalence in different types of stroke and influence on early and long-term prognosis (oxfordshire community stroke project). *British Medical Journal*. 1992;305:1460-1465
75. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have onvalvular atrial fibrillation. *Annals of Internal Medicine*. 2007;146:857-867
76. Sandercock P. Immediate anticoagulation for acute stroke in atrial fibrillation:No. *Stroke*. 2006;37:3054-3055
77. Hylek E, Skates S, Sheehan M, Singer D. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *New England Journal of Medicine*. 1996;335:540-546
78. Sandercock PA GL, Liu LM. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. 2009
79. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM, Carotid Endarterectomy Trialists C. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915-924
80. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. 2011
81. Carotid stenting trialists' collaboration. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: A preplanned meta-analysis of individual patient data. *Lancet*. 2010;376:1062-1073
82. Abbott AL, Adelman MA, Alexandrov AV, Barber PA, Barnett HJM, Beard J, et al. Why calls for more routine carotid stenting are currently inappropriate. *Stroke*. 2013;44:1186-1190
83. Huisa BN SA, Zivin JA. Atorvastatin in stroke: A review of sparcl and subgroup analysis. *Vascular Health and Risk Management*. 2010;6:229-236
84. Collins R, Armitage J, Parish S, Sleight P, Peto R, Collaborat HPS, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757-767
85. Shahar E, Chambless L, Rosamond W, Boland L, Ballantyne C, McGovern P, et al. Plasma lipid profile and incident ischemic stroke - the atherosclerosis risk in communities (aric) study. *Stroke*. 2003;34:623-631

86. Amarenco P, Bogousslavsky J, Callahan A, III, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *New England Journal of Medicine*. 2006;355:549-559
87. Lee SH, Bae HJ, Yoon BW, Kim H, Kim DE, Roh JK. Low concentration of serum total cholesterol is associated with multifocal signal loss lesions on gradient-echo magnetic resonance imaging - analysis of risk factors for multifocal signal loss lesions. *Stroke*. 2002;33:2845-2849
88. Divani AA, Majidi S, Luo X, Souslian FG, Zhang J, Abosch A, et al. The abcs of accurate volumetric measurement of cerebral hematoma. *Stroke*. 2011;42:1569-1574
89. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-1913
90. Roberta Ravenni, Joe F. Jabre, Alberto Mazza. Primary stroke prevention and hypertension treatment: Which is the first-line strategy? *Neurology International*. 2011;5
91. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension - prognostic information provided by pulse pressure. *Hypertension*. 1999;34:375-380
92. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895-905
93. Webb AJS, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. *Lancet*. 2010;375:906-915
94. Johansson BB. Hypertension mechanisms causing stroke. *Clinical and Experimental Pharmacology and Physiology*. 1999;26:563-565
95. Wardlaw J, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *Lancet Neurology*. 2013;12:483-497
96. Wardlaw J, Doubal F, Valdes-Hernandez M, Wang X, Chappell F, Shuler K, et al. Blood-brain barrier permeability and long-term clinical and imaging outcomes in cerebral small vessel disease. *Stroke*. 2013;44:525-527
97. Poels MM ZK, Verwoert GC, Vernooij MW, Hofman A, van der Lugt A, Witteman JC, Breteler MM, Mattace-Raso FU, Ikram MA. Arterial stiffness and cerebral small vessel disease: The rotterdam scan study. *Stroke*. 2012:2637-2642
98. Leenders Kl, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJR, et al. Cerebral blood flow, blood volume and oxygen utilization - normal values and effect of age. *Brain*. 1990;113:27-47

99. Strandgaard S, Mackenzie ET, Jones JV, Harper AM. Studies on cerebral-circulation of baboon in acutely induced hypertension. *Stroke*. 1976;7:287-290
100. Auer LM, Ishiyama N, Pucher R. Cerebrovascular response to intracranial hypertension. *Acta Neurochirurgica*. 1987;84:124-128
101. Qureshi AI, Harris-Lane P, Kirmani JF, Ahmed S, Jacob M, Zada Y, et al. Treatment of acute hypertension in patients with intracerebral hemorrhage using american heart association guidelines. *Crit Care Med*. 2006;34:1975-1980
102. Shah QA, Ezzeddine MA, Qureshi AI. Acute hypertension in intracerebral hemorrhage: Pathophysiology and treatment. *Journal of the Neurological Sciences*. 2007;261:74-79
103. Sacco S, Carolei A. Autoregulation might explain why blood pressure is not associated with haematoma enlargement in acute intracerebral haemorrhage. *European Journal of Neurology*. 2008;15
104. Grabowski M, Mattsson B, Nordborg C, Johansson B. Brain capillary density and cerebral blood flow after occlusion of the middle cerebral artery in normotensive wistar-kyoto rats and spontaneously hypertensive rats. *Journal of Hypertension*. 1993;11
105. Markus HS. Cerebral perfusion and stroke. *Journal of Neurology Neurosurgery and Psychiatry*. 2004;75:353-361
106. Strangaard S, Poulson OB. Regulation of cerebal blood flow in health and disease. *Journal of Cardiovascular Pharmacology*.19:89-83
107. Strandgaard S, Paulson OB. Cerebral blood flow and its pathophysiology in hypertension. *American Journal of Hypertension*. 1989;2:486-492
108. Baron J-C. Perfusion thresholds in human cerebral ischemia: Historical perspective and therapuetic implications. *Cerebrovascular Diseases*. 2001;11:2-8
109. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients - modifying influence of prolonged antihypertensive treatment on tolerance to acute, drug-induced hypotension. *Circulation*. 1976;53:720-727
110. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the nhs. *Health Technology Assessment 2002*.6
111. Wardlaw J, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley R, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: An updated systematic review and meta-analysis. *Lancet*. 2012;379:2364-2372
112. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al. Determinants of intracerebral hemorrhage growth - an exploratory analysis. *Stroke*. 2007;38:1072-1075
113. Adnan I. Qureshi RAH, Jawad F. Kirmani, Abutaher M. Yahia, L.Nelson Hopkins. Cerebral blood flow changes associated with

intracerebral hemorrhage. *Neurosurgery Clinics of North America*.13:355-370
114. Alqadri SL, Qureshi AI. Management of acute hypertensive response in patients with intracerebral hemorrhage. *Curr Atheroscler Rep*. 2012;14:322-327
115. Bath P, Chalmers J, Powers W, Beilin L, Davis S, Lenfant C, et al. International society of hypertension (ish): Statement on the management of blood pressure in acute stroke. *Journal of Hypertension*. 2003;21:665-672
116. Arboix A, Roig H, Rossich R, Martinez EM, Garcia-Eroles L. Differences between hypertensive and non-hypertensive ischemic stroke. *European Journal of Neurology*. 2004;11:687-692
117. Christensen H, Meden P, Overgaard K, Boysen G. The course of blood pressure in acute stroke is related to the severity of the neurological deficits. *Acta Neurologica Scandinavica*. 2002;106:142-147
118. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome - a systematic review. *Hypertension*. 2004;43:18-24
119. Hachinski VC, Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF. Asymmetry of sympathetic consequences of experimental stroke. *Arch Neurol*. 1992;49:697-702
120. Sevoz-Couche C, Comet MA, Bernard JF, Hamon M, Laguzzi R. Cardiac baroreflex facilitation evoked by hypothalamus and prefrontal cortex stimulation: Role of the nucleus tractus solitarius 5-ht2a receptors. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology*. 2006;291:R1007-R1015
121. Szilagyi JE, Taylor AA, Skinner JE. Cryoblockade of the ventromedial frontal-cortex reverses hypertension in the rat. *Hypertension*. 1987;9:576-581
122. Resstel LBM, Correa FMA. Medial prefrontal cortex nmda receptors and nitric oxide modulate the parasympathetic component of the baroreflex. *European Journal of Neuroscience*. 2006;23:481-488
123. Vidale S. “Relation between change in blood pressure in acute stroke and risk of early adverse events and poor outcome”. *Stroke*. 2012;43
124. Qureshi AI. Acute hypertensive response in patients with stroke - pathophysiology and management. *Circulation*. 2008;118:176-187
125. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome - a systematic review. *Hypertension*. 2004;43
126. Weaver CS, Leonardi-Bee J, Bath-Hextall FJ, Bath PMW. Sample size calculations in acute stroke trials: A systematic review of their reporting, characteristics, and relationship with outcome. *Stroke*. 2004;35
127. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford G, Kaste M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis retrospective analysis from safe implementation of thrombolysis in

stroke-international stroke thrombolysis register (sits-istr). *Stroke*. 2009;40:2442-2449
128. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the international stroke trial. *Stroke*. 2002;33:1315-1320
129. Arakawa S, Saku Y, Ibayashi S, Nagao T, Fujishima M. Blood pressure control and recurrence of hypertensive brain hemorrhage. *Stroke*. 1998;29:1806-1809
130. Sare GM, Bath PMW, Gray LJ, Moulin T, Woimant F, England T, et al. The relationship between baseline blood pressure and computed tomography findings in acute stroke data from the tinzaparin in acute ischaemic stroke trial (taist). *Stroke*. 2009;40:41-46
131. Geeganage CM, Bath PM. Interventions for deliberately altering blood pressure in acute stroke. *Stroke*. 2009
132. Geeganage CM, Bath PMW. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke a metaregression. *Hypertension*. 2009;54:775-U180
133. Bath PMW. Rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2. *Trials Registry*. 2015;ISRCTN26986053
134. Sanossian N. Field administration of stroke therapy-blood pressure lowering (fast-bp). *ClinicalTrials.gov(NCT01811693)*.
135. Hemphill 3rd JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke*. 2015;46:2032-2060
136. Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the continue or stop post-stroke antihypertensives collaborative study (cossacs): A prospective, randomised, open, blinded-endpoint trial. *Lancet Neurology*. 2010;9:767-775
137. Bath PMW, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (enos): A partial-factorial randomised controlled trial. *Lancet*. 2015;385:617-628
138. Anonymous. 'Know stroke. Know the signs. Act in time.'. 2008
139. Nor A, McAllister C, Louw S, Dyker A, Davis M, Jenkinson D, et al. Agreement between ambulance paramedic- and physician-recorded neurological signs with face arm speech test (fast) in acute stroke patients. *Stroke*. 2004;35:1355-1359
140. Govan L, Weir CJ, Langhorne P, Stroke Unit Trialists Collaboration. Organized inpatient (stroke unit) care for stroke. *Stroke*. 2008;39:2402-2403
141. Langhorne P, Tong B, Stott D. Association between physiological homeostasis and early recovery after stroke. *Stroke*. 2000;31:2526-2527
142. Laird E, Coates V. Systematic review of randomized controlled trials to regulate glycaemia after stroke. *Journal of Advanced Nursing*. 2013;69:263-277

143. Sandercock PA CC, Tseng MC. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. 2008
144. Dennis M, Cranswick G, Deary A, Fraser A, Graham C, Grant S, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (clots trial 1): A multicentre, randomised controlled trial. *Lancet*. 2009;373:1958-1965
145. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (clots 3): A multicentre randomised controlled trial. *Lancet* 2013;382:516-524
146. Chen Z, Hui J, Liu L, Liu Z, Peto R, Sandercock P, et al. Cast: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641-1649
147. Sandercock P, Collins R, Counsell C, Farrell B, Peto R, Slattery J, et al. The international stroke trial (ist): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. *Lancet*. 1997;349:1569-1581
148. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute stroke. *New England Journal of Medicine*. 1995;333:1581-1587
149. Sandercock P, Lindley R, Wardlaw JM. Antiplatelet, anticoagulant and fibrinolytic agents in acute ischemic stroke and tia. *British Journal of Hospital Medicine*. 1992;47:731-&
150. Menon BK, Saver JL, Prabhakaran S, Reeves M, Liang L, Olson DM, et al. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator. *Stroke*. 2012;43:2293-2299
151. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee T-H, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *New England Journal of Medicine*. 2016;374:2313-2323
152. Eric Sussman CK, Michael McDowell, Peter Yang, Eric Nelson, Sophie Greenberg, Daniel Sahlein, Sean Lavine, Philip Meyers and E. Sander Connolly Endovascular thrombectomy following acute ischemic stroke: A single-center case series and critical review of the literature. *Brain Sciences*. 2013;3:521-539
153. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. *N Engl J Med*. 2013;368:893-903
154. Ciccone A VL, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, Boccardi E; SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke. *N Engl J Med.* 2013;368(10):904-913.
155. Kidwell CS JR, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer JR, Olson S, Schwamm LH, Yoo AJ, Marshall RS, Meyers PM, Yavagal DR, Wintermark M, Guzy J, Starkman S, Saver JL, MR RESCUE Investigators. A trial of imaging selection and endovascular

treatment for ischaemic stroke. *The New England journal of medicine*. 2013:914 - 923
156. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38:948-954
157. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: Successful recanalisation by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42:1775-1777
158. Zaidat OO, Suarez JI, Santillan C, Sunshine JL, Tarr JW, Paras VH, et al. Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. *Stroke*. 2002;33:1821-1826
159. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intra-arterial treatment for acute ischemic stroke. *New England Journal of Medicine*. 2015;372:11-20
160. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessmen of rapid endovascular treatment for acute ischemic stroke. *New England Journal of Medicine*. 2015;372:1019-1030
161. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *New England Journal of Medicine*. 2015;372:1009-1018
162. Saver JL, Goyal M, Bonafe A, Diener H, Levy E, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-pa vs t-pa alone in stroke. *New England Journal of Medicine*. 2015;372:2285-2295
163. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *New England Journal of Medicine*. 2015;Epub ahead of print
164. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731
165. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
166. Treadwell SD, Thanvi B. Malignant middle cerebral artery (mca) infarction: Pathophysiology, diagnosis and management. *Postgraduate Medical Journal*. 2010;86:235-242
167. Symon L, Pasztor E, Branston NM. Distribution and density of reduced cerebral blood flow following acute middle cerebral artery occlusion - experimental study by technique of hydrogen clearance in baboons. *Stroke*. 1974;5:355-364
168. Huttner HB, Schellinger PD, Hartmann M, Köhrmann M, Juettler E, Wikner J, et al. Hematoma growth and outcome in treated

neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: Comparison of acute treatment strategies using vitamin k, fresh frozen plasma, and prothrombin complex concentrates. *Stroke*. 2006;37:1465-1470
169. Staykov D, Gupta R. Hemicraniectomy in malignant middle cerebral artery infarction. *Stroke*. 2011;42:513-516
170. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard J-P, et al. Sequential-design, multicenter, randomized controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (decimal trial). *Stroke*. 2007;38:2506-2517
171. Juttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (destiny). *Stroke*. 2007;38:2518-2525
172. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, Worp VD, et al. Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial (hamlet): A multi-centre, open, randomised trial. *Lancet*. 2009;8:326-333
173. Rahme R, Zuccarello M, Kleindorfer D, Adeoye OM, Ringer AJ. Decompressive hemicraniectomy for malignant middle cerebral artery territory infarction: Is life worth living? *Journal of Neurosurgery*. 2012;117:749-754
174. Touzani O, Young AR, Mackenzie ET. The window of therapeutic opportunity following focal cerebral ischaemia. *Pharmacology of Cerebral Ischemia 1994*. 1994:575-588
175. The European Ad Hoc Consensus Group. Neuroprotection as initial therapy in acute stroke. *Cerebrovascular Diseases*. 1998;8:59-72
176. White A, Murphy A. Administration of thiazolidinediones for neuroprotection in ischemic stroke: A pre-clinical systematic review. *Journal of Neurochemistry*. 2010;115:845-853
177. Shejun Feng QY, Ming Liu, Weizheng Li, Wenming Yuan, Shihong Zhang, Bo Wu, Juntao Li. Edaravone for acute ischaemic stroke. 2011
178. van der Worp HB, Macleod MR, Kollmar R, European Stroke Res Network H. Therapeutic hypothermia for acute ischemic stroke: Ready to start large randomized trials? *Journal of Cerebral Blood Flow and Metabolism*. 2010;30:1079-1093
179. Kollmar R, Gebhardt B, Schwab S. Eurohyp-1 trial. Eu-funded therapy study on the effectiveness of mild therapeutic hypothermia for acute ischemic stroke. *Nervenarzt*. 2012;83:1252-+
180. Belenichev IF SI, Dunaev VV, Orlovskiĭ MA, Bukhtiiarova NV, Kovalenko SI. Pharmacological neuroprotection against experimental acute cerebral ischemia of neurons of sensomotor area of frontal cortex and hippocampus in rats. *Eksp Klin Farmakol.* 2006;69(5)
181. The Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. *Cochrane Database of Systematic Reviews*. 2001

182. Sherman D, Atkinson R, Chippendale T, Levin K, Ng K, Futrell N, et al. Intravenous ancrod for treatment of acute ischemic stroke - the stat study: A randomized controlled trial. *Jama-Journal of the American Medical Association*. 2000;283:2395-2403
183. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke - the proact ii study: A randomized controlled trial. *Jama-Journal of the American Medical Association*. 1999;282:2003-2011
184. Davalos A, Castillo J, Alvarez-Sabin J, Secades J, Mercadal J, Lopez S, et al. Oral citicoline in acute ischemic stroke - an individual patient data pooling analysis of clinical trials. *Stroke*. 2002;33:2850-2857
185. Gaist D, Wallander M, Gonzalez-Perez A, Garcia-Rodriguez L. Incidence of hemorrhagic stroke in the general population: Validation of data from the health improvement network. *Pharmacoepidemiology and Drug Safety*. 2013;22:176-182
186. Dubas F. Small vessel pathology and cerebral hemorrhage. *Journal of Neuroradiology*. 2003;30:298-302
187. Pleşea IE CA, Georgescu CC, Enache SD, Zaharia B, Georgescu CV, Tenovici M. Study of cerebral vascular structures in hypertensive intracerebral haemorrhage. *Rom J Morphol Embryol*. 2005;2005;46(3):249-256
188. Fonseca A, Ferro J. Drug abuse and stroke. *Curr Neurol Neurosci Rep*. 2013
189. Aguilar MI, Brott TG. Update in intracerebral hemorrhage. *The Neurohospitalist*. 2011;1:148-159
190. Brouwers HB, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. *Cerebrovascular Diseases*. 2013;35:195-201
191. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med*. 2001;344:1450-1460
192. Broderick J, Diringer M, Hill M, Brun N, Mayer S, Steiner T, et al. Determinants of intracerebral hemorrhage growth: An exploratory analysis. *Stroke*. 2007;38:1072-1075
193. Hemphill J, Bonovich D, Besmertis L, Manley G, Johnston S. The ich score - a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-896
194. Moussouttas M, Malhotra R, Fernandez L, Maltenfort M, Holowecki M, Delgado J, et al. Role of antiplatelet agents in hematoma expansion during the acute period of intracerebral hemorrhage. *Neurocritical Care*. 2010;12:24-29
195. Moussouttas M. Challenges and controversies in the medical management of primary and antithrombotic-related intracerebral hemorrhage. *Therapeutical Advances in Neurological Disorders*. 2012
196. Naidech A, Bassin S, Bernstein R, Batjer H, Alberts M, Lindholm P, et al. Reduced platelet activity is more common than reported anti-platelet medication use in patients with intracerebral hemorrhage. *Neurocritical Care*. 2009;11:307-310

197. Naidech A, Bendok B, Garg R, Bernstein R, Alberts M, Bleck T, et al. Reduced platelet activity is associated with more intraventricular hemorrhage. *Neurosurgery*. 2009;65:684-688
198. Siddiqui FM, Qureshi AI. Effect of pre-morbid aspirin use on hematoma expansion, disability and death among 4734 patients with spontaneous intracerebral hemorrhage. *Neurology*. 2011;76:A630-A630
199. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage - facts and hypotheses. *Stroke*. 1995;26:1471-1477
200. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy - a genetic and pathologic study. *Neurology*. 2000;55:947-951
201. Goodnough LT, Shander A. How i treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage. *Blood*. 2011;117:6091-6099
202. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy recent - data and ideas. *Stroke*. 2005;36:1588-1593
203. Flibotte JJ HN, O'Donnell J, Greenberg SM, Rosand J. . Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. . *Neurology*. 2004:1059–1064.
204. Ichikawa K, Yanagihara C. Sedimentation level in acute intracerebral hematoma in a patient receiving anticoagulation therapy: An autopsy study. *Neuroradiology*. 1998;40:380-382
205. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P, Investigators C, et al. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke*. 2008;39:2993-2996
206. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *Journal of Neuropathology and Experimental Neurology*. 1971;30:536-550
207. Greenberg SM, Nandigam RNK, Delgado P, Betensky RA, Rosand J, Viswanathan A, et al. Microbleeds versus macrobleeds evidence for distinct entities. *Stroke*. 2009;40:2382-2386
208. Brouwers HB, Biffi A, Ayres AM, Schwab K, Cortellini L, Romero JM, et al. Apolipoprotein e genotype predicts hematoma expansion in lobar intracerebral hemorrhage. *Stroke*. 2012;43:1490-+
209. Almandoz JED, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, et al. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion the spot sign score. *Stroke*. 2009;40:2994-3000
210. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28:2370-2375
211. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5

212. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al. Density and shape as ct predictors of intracerebral hemorrhage growth. *Stroke*. 2009;40:1325-1331
213. Silva Y, Leira R, Tejada J, Lainez JM, Castillo J, Davalos A, et al. Molecular signatures of vascular injury are associated with early growth of intracerebral hemorrhage. *Stroke*. 2005;36:86-91
214. Steiner T, Boesel J. Options to restrict hematoma expansion after spontaneous intracerebral hemorrhage. *Stroke*. 2010;41:402-409
215. Qureshi AI, Tariq N, Divani AA, Novitzke J, Hussein HH, Palesch YY, et al. Antihypertensive treatment of acute cerebral hemorrhage. *Critical Care Medicine*. 2010;38:637-648
216. Qureshi A, Wilson D, Hanley D, Traystman R. No evidence for an ischemic penumbra in massive experimental intracerebral hemorrhage. *Neurology*. 1999;52:266-272
217. Qureshi AI, Palesch YY, Investigators A. Antihypertensive treatment of acute cerebral hemorrhage (atach) trial: Final results. *Stroke*. 2009;40
218. Arima H, Huang Y, Wang JG, Heeley E, Delcourt C, Parsons M, et al. Earlier blood pressure-lowering and greater attenuation of hematoma growth in acute intracerebral hemorrhage interact pilot phase. *Stroke*. 2012;43:2236-U2429
219. Moussouttas M, Malhotra R, Fernandez L, Maltenfort M, Holowecki M, Delgado J, et al. Impact of intraventricular hemorrhage upon intracerebral hematoma expansion. *Neurocritical Care*. 2011;14:50-54
220. Sprigg N, Renton CJ, Dineen RA, Kwong Y, Bath PMW. Tranexamic acid for spontaneous intracerebral hemorrhage: A randomized controlled pilot trial. *Journal of Stroke and Cerebrovascular Diseases*. 2014;23:1312-1318
221. Hanley D. Minimally invasive surgery plus rt-pa for ich evacuation phase iii (mistie iii). *ClinicalTrials.gov (NCT01827046)*.
222. Dowlatshahi D, Kosior JC, Idris S, Eesa M, Dickhoff P, Joshi M, et al. Planimetric hematoma measurement in patients with intraventricular hemorrhage is total volume a preferred target for reliable analysis? *Stroke*. 2012;43:1961-1963
223. Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE, et al. Defining hematoma expansion in intracerebral hemorrhage relationship with patient outcomes. *Neurology*. 2011;76:1238-1244
224. Dowlatshahi D, Kosior JC, Idris S, Eesa M, Dickhoff P, Joshi M, et al. Planimetric hematoma measurement in patients with intraventricular hemorrhage: Is total volume a preferred target for reliable analysis? *Stroke*. 2012;43:1961-1963
225. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987-993
226. Yang GY, Betz AL, Chenevert TL, Brunberg JA, Hoff JT. Experimental intracerebral hemorrhage: Relationship between brain edema,

blood flow, and blood–brain barrier permeability in rats. *J Neurosurg*. 1994:pp. 93–102
227. Gebel JM, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, et al. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke*. 2002;33:2631-2635
228. Bullock R, Mendelow AD, Teasdale GM, Graham DI. Intracranial haemorrhage induced at arterial pressure in the rat. Part 1: Description of technique, icp changes and neuropathological findings. *Neurological research*. 1984;6:184-188
229. Zazulia AR, Diringer MN, Videen TO, Adams RE, Yundt K, Aiyagari V, et al. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. *J Cereb Blood Flow Metab*. 2001;21:804-810
230. Carhuapoma J, Wang P, Beauchamp N, Keyl P, Hanley D, Barker P. Diffusion-weighted mri and proton mr spectroscopic imaging in the study of secondary neuronal injury after intracerebral hemorrhage. *Stroke*. 2000;31:726-732
231. Kim-Han J, Kopp S, Dugan L, Diringer M. Perihematomal mitochondrial dysfunction after intracerebral hemorrhage. *Stroke; a journal of cerebral circulation*. 2006;37:2457-2462
232. Gebel J, Jauch E, Brott T, Khoury J, Sauerbeck L, Salisbury S, et al. Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke*. 2002;33:2636-2641
233. Arima H, Wang J, Huang Y, Heeley E, Skulina C, Parsons M, et al. Significance of perihematomal edema in acute intracerebral hemorrhage- the interact trial. *Neurology*. 2009;73:1963-1968
234. Hinson HE, Hanley DF, Ziai WC. Management of intraventricular hemorrhage. *Current Neurology and Neuroscience Reports*. 2010;10:73-82
235. Steiner T, Diringer MN, Schneider D, Mayer SA, Begtrup K, Broderick J, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: Risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor vii. *Neurosurgery*. 2006;59:767-773
236. Hallevi H, Albright KC, Aronowski J, Barreto AD, Martin-Schild S, Khaja AM, et al. Intraventricular hemorrhage - anatomic relationships and clinical implications. *Neurology*. 2008;70:848-852
237. Steinke W, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Thalamic stroke - presentation and prognosis of infarcts and hemorrhages. *Archives of Neurology*. 1992;49:703-710
238. Maas MB, Nemeth AJ, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Delayed intraventricular hemorrhage is common and worsens outcomes in intracerebral hemorrhage. *Neurology*. 2013;80:1295-1299

239. Young WB, Lee KP, Pessin MS, Kwan ES, Rand WM, Caplan LR. Prognostic-significance of ventricular blood in supratentorial hemorrhage - a volumetric study. *Neurology*. 1990;40:616-619
240. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB. Computed tomographic diagnosis of intraventricular hemorrhage-etiology and prognosis *Radiology*. 1982;143:91-96
241. Morgan T, Dawson J, Spengler D, Lees K, Aldrich C, Mishra N, et al. The modified graeb score an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. *Stroke*. 2013;44:635-641
242. Hallevi H, Dar NS, Barreto AD, Morales MM, Savitz SI, Martin-Schild S, et al. Rapid estimation of ivh volume using the ivh score: Research and clinical utility. *Neurology*. 2008;70:A245-A245
243. Hallevi H, Dar NS, Barreto AD, Morales MM, Martin-Schild S, Abraham AT, et al. The ivh score: A novel tool for estimating intraventricular hemorrhage volume: Clinical and research implications. *Critical Care Medicine*. 2009;37:969-974
244. Ruscalleda J, Peiro A. Prognostic factors in intraparenchymatous hematoma with ventricular hemorrhage. *Neuroradiology*. 1986;28:34-37
245. Sven Loncaric APD, Dubravko Cosic, Domagoj Kovacevic, Joseph Broderick, Thomas Brott. 3-d image analysis of intra-cerebral brain hemorrhage from digitized ct films. *Computer Methods and Programs in Biomedicine*. 1995;46(3):207-216
246. Kosior J, Idris S, Dowlatshahi D, Alzawahmah M, Eesa M, Sharma P, et al. Quantomo: Validation of a computer-assisted methodology for the volumetric analysis of intracerebral haemorrhage. *International Journal of Stroke*. 2011;6:302-305
247. Hussein HM, Tariq NA, Palesch YY, Qureshi AI, et al. Reliability of hematoma volume measurement at local sites in a multicenter acute intracerebral hemorrhage clinical trial. *Stroke*. 2013;44:237-239
248. Prionas ND, Ray S, Boone JM. Volume assessment accuracy in computed tomography: A phantom study. *J Appl Clin Med Phys*. 2010;11:3037
249. Gebel JM, Sila CA, Sloan MA, Granger CB, Weisenberger JP, Green CL, et al. Comparison of the abc/2 estimation technique to computer-assisted volumetric analysis of intraparenchymal and subdural hematomas complicating the gusto-1 trial. *Stroke*. 1998;29:1799-1801
250. Huttner HB, Steiner T, Hartmann M, Köhrmann M, Juettler E, Mueller S, et al. Comparison of abc/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. *Stroke*. 2006;37:404-408
251. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The abcs of measuring intracerebral hemorrhage volumes. *Stroke*. 1996;27:1304-1305
252. Freeman WD, Barrett KM, Bestic JM, Meschia JF, Broderick DF, Brott TG. Computer-assisted volumetric analysis compared with

abc/2 method for assessing warfarin-related intracranial hemorrhage volumes. *Neurocrit Care*. 2008;9:307-312
253. Sheth KN, Cushing TA, Wendell L, Lev MH, Romero JM, Schwab K, et al. Comparison of hematoma shape and volume estimates in warfarin versus non-warfarin-related intracerebral hemorrhage. *Neurocrit Care*. 2010;12:30-34
254. Maeda AK, Aguiar LZ, Martins C, Bichinho GL, Gariba MA. Hematoma volumes of spontaneous intracerebral hemorrhage: The ellipse (abc/2) method yielded volumes smaller than those measured using the planimetric method. *Arquivod de Neuro-Psiquiatria*. 2013;71:540-544
255. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181
256. Moon J-S, Janjua N, Ahmed S, Kirmani J, Harris-Lane P, Jacob M, et al. Prehospital neurologic deterioration in patients with intracerebral hemorrhage. *Critical Care Medicine*. 2008;36:172-175
257. Naval NS, Nquist PA, Carhuapoma R. Management of spontaneous intracerebral hemorrhage. *Neuro Clin*. 2008;26(2):373-384
258. Elliott J, Smith M. The acute management of intracerebral hemorrhage: A clinical review. *Anesthesia and Analgesia*. 2010;110:1419-1427
259. Butcher KS, Baird T, MacGregor L, Desmond P, Tress B, Davis S. Perihematomal edema in primary intracerebral hemorrhage is plasma derived. *Stroke*. 2004;35:1879-1885
260. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (interact): A randomised pilot trial. *Lancet Neurology*. 2008;7:391-399
261. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *New England Journal of Medicine*. 2013:2355-2365
262. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, et al. Controlling hypertension and hypotension immediately post-stroke (chhips): A randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurology*. 2009;8:48-56
263. Sandset EC, Bath PMW, Boysen G, Jatuzis D, Korv J, Luders S. The angiotensin-receptor blocker candesartan for treatment of acute stroke (scast): A randomised, placebo controlled, double-blind trial. *Lancet*. 2011;377:741-750
264. Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: The rapid intervention with glyceryl trinitrate in hypertensive stroke trial (right, isrctn66434824). *Stroke*. 2013;44:3120-3128
265. Jusufovic M, Sandset EC, Bath PMW, Berge E, SCAST study group. Blood pressure lowering treatment with candesartan in patients with acute hemorrhagic stroke. *Stroke*. 2014;45:3440-3442

266. Shaw L PL, McLure S, Howel D, McColl E, Younger P, Ford GA Paramedic initiated lisinopril for acute stroke treatment (pil-fast): Results from the pilot randomised controlled trial. *Emergency Medicine Journals*. 2013
267. Broderick JP, Brott TG, Duldner J, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid haemorrhage. *Stroke*. 1994;25:1342-1347
268. Hemphill III JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke*. 2015;46:[epub ahead of print]
269. Watson H, Baglin T, Laidlaw S, Makris M, Preston F. A comparison of the efficacy and rate of response to oral and intravenous vitamin k in reversal of over-anticoagulation with warfarin. *British Journal of Haematology*. 2001;115:145-149
270. Makris M GM, Phillips WS, Kitchen S, Rosendaal FR, Preston EF. Emergency oral anticoagulant reversal: The relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost.* 1997:470-480
271. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature. *American Journal of Hematology*. 2008;83:137-143
272. Steiner T, Poli S, Griebe M, Husing M, Hajda J, Freiberg A. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin k antagonists (inch): A randomised trial. *Lancet*. 2016;15:566-573
273. Skolnick BE, Mathews DR, Khutoryansky NM, Pusateri AE, Carr ME. Exploratory study on the reversal of warfarin with rfviia in healthy subjects (vol 116, pg 693, 2010). *Blood*. 2010;116:5079-5079
274. Tanaka KA, Szlam F, Dickneite G, Levy JH. Effects of prothrombin complex concentrate and recombinant activated factor vii on vitamin k antagonist induced anticoagulation. *Thrombosis Research*. 2008;122:117-123
275. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, et al. Safety and feasibility of recombinant factor viia for acute intracerebral hemorrhage. *Stroke*. 2005;36:74-79
276. Hedner U. Mechanism of action of factor viia in the treatment of coagulopathies. *Seminars in Thrombosis and Hemostasis*. 2006;32:77-85
277. Mayer S, Brun N, Begtrup K, Broderick J, Davis S, Diringer M, et al. Recombinant activated factor vii for acute intracerebral hemorrhage. *New England Journal of Medicine*. 2005;352:777-785
278. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Efficacy and safety of recombinant activated factor vii for acute intracerebral hemorrhage. *New England Journal of Medicine*. 2008;358:2127-2137
279. Mayer SA, Davis SM, Skolnick BE, Brun NC, Begtrup K, Broderick JP, et al. Can a subset of intracerebral hemorrhage patients benefit

from hemostatic therapy with recombinant activated factor vii? *Stroke*. 2009;40:833-840
280. Flaherty M. The spot sign for predicting and treating ich growth study "stop-it". *Clinical Trials Registry(NCT00810888)*. 2012
281. Gladstone D. ""Spot sign" selection of intracerebral hemorrhage to guide hemostatic therapy (spotlight)". 2011
282. Connolly SJ, Eikelboom J, Joyner C, Diener H-C, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *New England Journal of Medicine*. 2011;364:806-817
283. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*. 2009;361:1139-1151
284. Connolly SJ, Milling Jr TJ, Eikelboom JW, Gibson M, Curnutte JT, Gold A, et al. Andexanet alfa for acute major bleeding associated with factor xa inhibitors. *The New England journal of medicine*. 2016;375:1131-1141
285. Levy JH, Key NS, Azran MS. Novel oral anticoagulants implications in the perioperative setting. *Anesthesiology*. 2010;113:726-745
286. Gathier CS, Algra A, Rinkel GJ, van der Worp HB. Long-term outcome after anticoagulation-associated intracerebral haemorrhage with or without restarting antithrombotic therapy. *Cerebrovascular Diseases*. 2013;36:33-37
287. Viswanathan A, Rakich SM, Engel C, Snider R, Rosand J, Greenberg SM, et al. Antiplatelet use after intracerebral hemorrhage. *Neurology*. 2006;66:206-209
288. Goldstein JN. Should anticoagulation be resumed after intracerebral hemorrhage? *Cleveland Clinic Journal of Medicine*. 2010;77:791-799
289. Panduranga P, Al-Mukhaini M, Shehab A. Management dilemmas in patients with mechanical heart valves and warfarin-induced major bleeding. *World Journal of Cardiology*. 2012;4:54-59
290. Piriyawat P, Morgenstern LB, Yawn DH, Hall CE, Grotta JC. Treatment of acute intracerebral hemorrhage with epsilon-aminocaproic acid - a pilot study. *Neurocritical Care*. 2004;1:47-51
291. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (crash-2): A randomised, placebo-controlled trial. *Lancet*. 2010;376:23-32
292. Perel P, AlShahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, et al. Crash-2 (clinical randomisation of an antifibrinolytic in significant haemorrhage) intracranial bleeding study: The effect of tranexamic acid in traumatic brain injury - a nested, randomised, placebo-controlled trial. *Health Technology Assessment*. 2012;16:1-+
293. Sprigg N, Dineen R, Bath PM. Tranexamic acid for acute intracerebral haemorrhage (tich). 2010

294. Sprigg N, Renton CJ, Kwong Y, Dineen R, Bath PM. Tranexamic acid for acute intracerebral haemorrhage (tich): Results of the first randomised controlled trial. *UK Stroke Forum*. 2012
295. Sorimachi T, Fujii Y, Morita K, Tanaka R. Rapid administration of antifibrinolytics and strict blood pressure control for intracerebral hemorrhage. *Neurosurgery*. 2005;57:837-843
296. Davis SM. Stop-aust: The spot sign and tranexamic acid on preventing ich growth - australasia trial. *ClinicalTrials.gov (NCT01702636)*.
297. de Gans K, Haan RJ, Majoie CB, Koopman MM, Brand A, Dijkgraaf MG, et al. Patch: Platelet transfusion in cerebral haemorrhage:Study protocol for a multicentre, randomised, controlled trial. *BMC Neurology*. 2010;10
298. Naidech AM, Mass MB, Levasseur-Franklin KE, Liotta EM, J.C. G, Berman M, et al. Desmopressin improves platelet activity in acute intracerebral haemorrhage. *Stroke*. 2014;45:2451-2453
299. Naidech A, Jovanovic B, Liebling S, Garg R, Bassin S, Bendok B, et al. Reduced platelet activity is associated with early clot growth and worse 3-month outcomed after intracerebral hemorrhage. *Stroke*. 2009;40:2398-2401
300. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, Gans K, Koopman M, Brand A, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous intracerebral haemorrhage associated with antiplatelet therapy (patch): A randomised open-label, phase 3 trial. *Lancet*. 2016;387:2605-2613
301. Al-Shahi Salman R. Haemostatic drug therapies for acute spontaneous intracerebral haemorrhage. *The Cochrane database of systematic reviews*. 2009:CD005951-CD005951
302. Pantazis G, Tsitsopoulos P, Mihas C, Katsiva V, Stavrianos V, Zymaris S. Early surgical treatment vs conservative management for spontaneous supratentorial intracerebral hematomas: A prospective randomized study. *Surgical Neurology*. 2006;66:492-502
303. Mendelow AD GB, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MD, Barer DH; STICH investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (stich): A randomised trial. *Lancet*. 2005;365(9457):387-397
304. Fernandes HM, Mendelow AD. Spontaneous intracerebral haemorrhage: A surgical dilemma. *British Journal of Neurosurgery*. 1999;13:389-394
305. Kirollos R, Tyagi A, Ross S, van Hille P, Marks P. Management of spontaneous cerebellar hematomas: A prospective treatment protocol. *Neurosurgery*. 2001;49:1378-1386
306. Da Pian R, Bazzan A, Pasqualin A. Surgical versus medical treatment of spontaneous posterior fossa haematomas: A cooperative study on 205 cases. *Neurol Res*. 1984;6(3):145-151

307. Kanaya H, Saiki I, Ohuchi T, Mizukami M, Kanaya K, Yamori Y, et al. Hypertensive ich in japan: Update on surgical treatment. In:Hypertensive intracerebral hemorrhage. 1983;147
308. Jun Morioka MF, Shoichi Kato, Hirosuke Fujisawa, Tatsuo Akimura, Michiyasu Suzuki, Shotai Kobayashi, Japan Standard Stroke Registry Group Surgery for spontaneous intracerebral hemorrhage has greater remedial value than conservative therapy. *Surgical Neurology*. 2005;65:67-72
309. Barbara A. Gregson, Broderick JP, Ludwig M. Auer, Hunt Batjer, Xian-Cheng Chen, Seppo Juvela, et al. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke*. 2012;43:1496-1504
310. Mendelow AD GB, Rowan EN, Murray GD, Gholkar A, Mitchell PM; for the STICH II Investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (stich ii): A randomised trial. *Lancet*. 2013;382:397-403
311. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (stich ii): A randomised trial. *Lancet*. 2013
312. Gautschi OP, Schaller K. Surgery or conservative therapy for cerebral haemorrhage? *The Lancet*. 2013
313. Mitchell P, Gregson BA, Vindlacheruvu RR, Mendelow AD. Surgical options in ich including decompressive craniectomy. *Journal of the Neurological Sciences*. 2007;261:89-98
314. Mayer S, Brun N, Begtrup K, Broderick J, Davis S, Diringer M, et al. Efficacy and safety of recombinant activated factor vii for acute intracerebral hemorrhage. *New England Journal of Medicine*. 2008;358:2127-2137
315. Thiex R. Future perspectives on the fibrinolytic therapy of intracerebral hemorrhages. *Central Nervous System Agents in Medicinal Chemistry*. 2011;11:150-156
316. Johnson WD, Bouz PA. Use of intralesional tpa in spontaneous intracerebral hemorrhage: Retrospective analysis. *Acta Neurochir Suppl*. 2011;111:425-428
317. Huttner HB, Tognoni E, Bardutzky J, Hartmann M, Kohrmann M, Kanter IC, et al. Influence of intraventricular fibrinolytic therapy with rt-pa on the long-term outcome of treated patients with spontaneous basal ganglia hemorrhage: A case-control study. *European Journal of Neurology*. 2008;15:342-349
318. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D. Preliminary findings of the minimally-invasive surgery plus rtpa for intracerebral hemorrhage evacuation (mistie) clinical trial. *Acta Neurochir Suppl*. 2008:147-151
319. Mould WA, Carhuapoma JR, Muschelli J, Lane K, Morgan TC, McBee NA, et al. Minimally invasive surgery plus recombinant tissue-type

plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke*. 2013;44:627-634
320. Naff NJ, Carhuapoma JR, Williams MA, Bhardwaj A, Ulatowski JA, Bederson J, et al. Treatment of intraventricular hemorrhage with urokinase - effects on 30-day survival. *Stroke*. 2000;31:841-847
321. Webb AJS, Ullman NL, Mann S, Muschelli J, Awad IA, Hanley DF. Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic the clot lysis: Evaluating accelerated resolution of ivh (clear ivh) program. *Stroke*. 2012;43:1666-1668
322. Naff N, Williams MA, Keyl PM, Tuhrim S, Bullock MR, Mayer SA, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage the intraventricular hemorrhage thrombolysis trial. *Stroke*. 2011;42:3009-3016
323. Zhou X, Chen J, Li Q, Ren G, Yao G, Liu M, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage a meta-analysis of randomized controlled trials. *Stroke*. 2012;43:2923-2930
324. Ramanan M, Shankar A. Minimally invasive surgery for primary supratentorial intracerebral haemorrhage. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2013;20:1650-1658
325. Takeuchi S, Wada K, Nagatani K, Otani N, Mori K. Decompressive hemicraniectomy for spontaneous intracerebral hemorrhage. *Neurosurgical Focus*. 2013;34
326. Fung C, Murek M, Z'Graggen WJ, Kraehenbuehl AK, Gautschi OP, Schucht P, et al. Decompressive hemicraniectomy in patients with supratentorial intracerebral hemorrhage. *Stroke*. 2012;43:3207-3211
327. Hayes SB, Benveniste RJ, Morcos JJ, Aziz-Sultan MA, Elhammady MS. Retrospective comparison of craniotomy and decompressive craniectomy for surgical evacuation of nontraumatic, supratentorial intracerebral hemorrhage. *Neurosurgical Focus*. 2013;34
328. Murthy JMK, Chowdary GVS, Murthy T, Bhasha PSA, Naryanan TJ. Decompressive craniectomy with clot evacuation in large hemispheric hypertensive intracerebral hemorrhage. *Neurocritical Care*. 2005;2:258-262
329. Xi G, Keep R, Hoff J. Mechanisms of brain injury after intracerebral haemorrhage. *The Lancet*. 2006;5:53-63
330. Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage: An update. *Progress in Neurobiology*. 2010;92:463-477
331. Hua Y, Wu J, Keep RF, Nakamura T, Hoff JT, Xi G. Tumor necrosis factor-alpha increases in the brain after intracerebral hemorrhage and thrombin stimulation. *Neurosurgery*. 2006;58:542-550
332. Rosenberg GA. Matrix metalloproteinases in neuroinflammation. *Glia*. 2002;39:279-291

333. Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematomal edema after intracerebral hemorrhage measured by serial magnetic resonance imaging. *Stroke*. 2011;42:73-80
334. Lee SH, Park HK, Ryu WS, Lee JS, Bae HJ, Han MK. Effects of celecoxib on hematoma and edema volumes in primary intracerebral hemorrhage: A multicenter randomized controlled trial. *European Journal of Neurology*. 2013;20:1161-1169
335. Gonzales NR, Sangha N, Kauffman T, Cai C, Sline MR, Pandurengan R, et al. The safety of pioglitazone for hematoma resolution in intracerebral hemorrhage (shrinc): Safety results. *International Stroke Conference*. 2014;45
336. Tapia-Perez H, Sanchez-Aguilar M, Torres-Corzo JG, Rodriguez-Leyva I, Gonzalez-Aguirre D, Gordillo-Moscoso A, et al. Use of statins for the treatment of spontaneous intracerebral haemorrhage: Results of a pilot study. *Central European Neurosurgery*. 2009;70:15-20
337. Naval N. Simvastatin for intracerebral hemorrhage study. *Clinical Trials. gov*. 2008
338. Nagatsuna T, Nomura S, Suehiro E, Fujisawa H, Koizumi H, Suzuki M. Systemic administration of argatroban reduces secondary brain damage in a rat model of intracerebral hemorrhage: Histopathological assessment. *Cerebrovascular Diseases*. 2005;2005:192-200
339. Kitaoka T, Hua Y, Xi G, Hoff JT, Keep RF. Delayed argatroban treatment reduces edema in rat model of intracerebral haemorrhage. *Stroke*. 2002;33:3012-3018
340. Xi G, Reiser G, Keep RF. The role of thrombin and thrombin receptos in ischemic, hemorrhagic and traumatic brain injury. *Journal of Neurochemistry*. 2003;84:3-9
341. Matsuoka H, Hamada R. Role of thrombin in cns damage associated with intracerebral haemorrhage: Opportunity for pharmacological intervention? *CNS Drugs*. 2002;16:509-516
342. Okauchi M, Hua Y, Keep R, Morgenstern LB, Xi G. Effects of deferoxamine on intracerebral hemorrhage-induced brain injury in aged rats. *Stroke*. 2009;40:1858-1863
343. Nakamura T, Keep RF, Hua Y, Nagao S, Hoff JT, Xi G. Iron-induced oxidative brain injury after experimental intracerebral hemorrhage. *Acta Neurochir Suppl*. 2006;96:194-198
344. Nakamura T, Keep RF, Hua Y, Schallert T, Hoff JT, Xi G. Deferoxamine-induced attenuation of brain edema and neurological deficits in a rat model of intracerebral hemorrhage. *Neurosurgery*. 2004;100:672-678
345. Selim M. Deferoxamine mesylate: A new hope for intracerebral hemorrhage: From bench to clinical trials. *Stroke*. 2009;40:S90-91
346. Selim M, Yeatts S, Goldstein JN, et al. Safety and tolerability of deferoxamine mesylat in patients with acute intracerebral hemorrhage. *Stroke*. 2011;42:3067-3074

347. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: Mechanisms of injury and therapeutic targets. *Lancet Neurology*. 2012;11:720-731
348. Kawanishi M, Kawai N, Nakamura T, Luo C, Tamiya T, Nagao S. Effect of delayed mild brain hypothermia on edema formation after intracerebral hemorrhage in rats. *Journal of Stroke and Cerebrovascular Diseases*. 2008;17:187-195
349. Fingas M, Penner M, Silasi G, Colbourne F. Treatment of intracerebral hemorrhage in rats with 12 h, 3 days and 6 days of selective brain hypothermia. *Experimental Neurology*. 2009;219:156-162
350. Staykov D, Huttner HB, Kohrmann M, Bardutzky J, Schellinger PD. Novel approaches to the treatment of intracerebral haemorrhage. *International Journal of Stroke*. 2010;5:457-465
351. Kollmar R, Staykov D, Dorfler A, Schellinger PD, Schwab S, Bardutzky J. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2010;41:1684-1689
352. Kwak R, Kadoya S, Suzuki T. Factors affecting the prognosis in thalamic hemorrhage. *Stroke*. 1983;14:493-500
353. Newman GC. Clarification of abc2 rule for ich volume. *Stroke*. 2007
354. Broderick JP, Brott TG, Grotta JC. Intracerebral hemorrhage volume measurement. *Stroke*. 1994;25:1081
355. Sheth KN, Cushing TA, Wendell L, Lev MH, Romero JM, Schwab K, et al. Comparison of hematoma shape and volume estimates in warfarin versus non-warfarin-related intracerebral hemorrhage. *Neurocrit Care*. 2010;12:30-34
356. Yang W, Feng Y, Zhang Y, Yan J, Fu Y, Chen S. Volume quantification of acute infratentorial hemorrhage with computed tomography: Validation of the formula 1/2abc and 2/3sh. *Plos One*. 2013;8
357. Zimmerman RD, Maldjian JA, Brun NC, Horvath B, Skolnick BE. Radiologic estimation of hematoma volume in intracerebral hemorrhage trial by ct scan. *AJNR Am J Neuroradiol*. 2006;27:666-670
358. Kosior J, Idris S, Dowlatshahi D, Alzawahmah M, Eesa M, Sharma P, et al. Quantomo: Validation of a computer-assisted methodology for the volumetric analysis of intracerebral haemorrhage. *International Journal of Stroke*. 2011;6:302-305
359. Bhanu Prakash KN, Zhou S, Morgan TC, Hanley DF, Nowinski WL. Segmentation and quantification of intra-ventricular/cerebral hemorrhage in ct scans by modified distance regularized level set evolution technique. *International Journal of Computer Assisted Radiology and Surgery*. 2012;7:785-798
360. Liu J, Huang S, Ihar V, Ambrosius W, Lee LC, Nowinski WL. Automatic model-guided segmentation of the human brain ventricular system from ct images (vol 6, pg 718, 2010). *Academic Radiology*. 2010;17:1226-1226
361. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J Neurosurg*. 1994;80:51-57

362. Barras CD, Tress BM, Christensen S, Collins M, Desmond PM, Skolnick BE, et al. Quantitative ct densitometry for predicting intracerebral hemorrhage growth. *American Journal of Neuroradiology*. 2013;34:1139-1144
363. Pabst W, Gregerova E. Characterisation of particle and particle systems. *ICT*. 2007:1-123
364. The ENOS Trial Investigators. Glyceryl trinitrate vs. Control, and continuing vs. Stopping temporarily prior antihypertensive therapy, in acute stroke: Rationale and design of the efficacy of nitric oxide in stroke (enos) trial (isrctn99414122). *International Journal of Stroke*. 2006;1:245-249
365. O' Brien E, Mee F, Atkins F, Thomas M. Evaulation of three devices for self-measurement of blood pressure monitoring according to the revised british hypertension society protocol: The omron hem-705 cp, philips hp 5332 and nissei ds-175. *Blood Pressure Monitoring*. 1996;1:55-67
366. Wardlaw J, Bath P, Sandercock P, Perry D, Palmer J, Watson G, et al. The neurogrid stroke examplar clinical trial protocol. *International Journal of Stroke*. 2007;2:63-69
367. Wardlaw JM, Sellar RJ. A simple practical classification of cerebral infarcts on ct and its interobserver reliability. *American Journal of Neuroradiology*. 1994;15:1933-1939
368. Rosset A, Spadola L, Ratib O. Osirix: An open-source software for navigating in multidimensional dicom images. *Journal of Digital Imaging*. 2004;17:205-216
369. Heuberger J, Rosset A. *Osirix user manual the complete reference*. 266 rue de Bernex CH-1233 Bernex Switzerland Pixmeo 2012
370. Lees KR, Bath PMW, Schellinger PD, et al. Contemporary outcome measures in acute stroke research: Choice of primary outcome measure. *Stroke*. 2012;43:1163-1170
371. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Efficacy and safety of recombinant activated factor vii for acute intracerebral hemorrhage. *New England Journal of Medicine*. 2008;358:2127-2137
372. Sandercock P, Lindley R, Wardlaw J, Dennis M, Lewis S, Venables G, et al. The third international stroke trial (ist-3) of thrombolysis for acute ischaemic stroke. *Trials*. 2008;9:37
373. Shrout P, Fleiss J. Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*. 1979:420-428
374. ENOS Investigators. Baseline characteristics of the 4011 patients recruited into the "efficacy of nitric oxide in stroke (enos) trial. *International Journal of Stroke*. 2014;9:711-720
375. Wang CW, Juan CJ, Liu YJ, Hsu HH, Liu HS, Chen CY, et al. Volume-dependent overestimation of spontaneous intracerebral hematoma volume by the abc/2 formula. *Acta Radiol*. 2009;50:306-311
376. Zhao KJ, Liu Y, Zhang RY, Wang XQ, Gao C, Shen JK. A precise, simple, convenient and new method for estimation of intracranial hematoma volume-the formula 2/3sh. *Neurological Research*. 2009;31:1031-1036

377. Sucu HK, Gokmen M, Gelal F. The value of xyz/2 technique compared with computer-assisted volumetric analysis to estimate the volume of chronic subdural hematoma. *Stroke*. 2005;36:998-1000
378. Barras CD, Tress BM, Christensen S, et al. Density and shape as ct predictors of intracerebral hemorrhage growth. *Stroke*. 2009;40:1325-1331
379. Gray LJ, Ali M, Lyden PD, Bath PM. Interconversion of the national institutes of health stroke scale and scandinavian stroke scale in acute stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2009;18:466-468
380. Poon MTC, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: Systematic review and meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry*. 2014;85:660-667
381. Terayama Y, Tanahashi N, Fukuuchi Y, Gotoh F. Prognostic value of admission blood pressure in patients with intracerebral hemorrhage. Keio cooperative stroke study. *Stroke*. 1997;28:1185-1188
382. Qureshi AI, Mohammad YM, Yahia AM, Suarez JI, Siddiqui AM, Kirmani JF, et al. A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage. *Journal of Intensive Care Medicine*. 2005;20:34-42
383. Jusufovic M, Sandset E, Bath P, Berge E. Blood pressure lowering treatment with candesartan in patients with acute hemorrhagic stroke. *Stroke*. 2014;45:3440-3442
384. Bath PMW, Pathansali R, Iddenden R, Bath FJ. The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. *Cerebrovasc Dis*. 2001;11:265-272
385. Rashid P, Weaver C, Leonardi-Bee J, Bath F, Fletcher S, Bath P. The effects of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure, cerebral and cardiac hemodynamics, and plasma nitric oxide levels in acute stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2003;12:143-151
386. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension*. 2006;47:1209-1215
387. Bath P, Houlton A, Woodhouse L, Sprigg N, Wardlaw J, Pocock S. Statistical analysis plan for the 'efficacy of nitric oxide in stroke' (enos) trial. *International Journal of Stroke*. 2014;9:372-374
388. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised british hypertension society protocol: The omron hem-705cp, philips hp5332, and nissei ds-175. *Blood Pressure Monitoring*. 1996;1:55-61

389. Sulter G, Steen C, de Kayser J. Use of the barthel index and modified rankin scale in acute stroke trials. *Stroke*. 1999;1999:1538-1541
390. Metitieri T, Geroldi C, Pezzini A, et al. The itle-mmse: An italian telephone version of the mini-mental state examination. *International Journal of Geriatric Psychiatry*. 2001;16:166-167
391. Desmond DW, Tatemichi TK, Hanzawa L. The telephone interview for cognitive status (tics): Reliability and validity in a stroke sample. *International Journal of Geriatric Psychiatry*. 1994;9:803-807
392. Whynes DK, Sprigg N, Selby J, Berge E, Bath PMW. Testing for differential item functioning within the eq-5d. *Medical Decision Making*. 2013;33:252-260
393. Sprigg N, Selby J, Fox L, Berge E, Whynes D, Bath P. Very low quality of life after acute stroke: Data from the efficacy of nitric oxide in stroke trial. *Stroke*. 2013;44:3458-3462
394. Zung WWK. A self-rating depression scale. *Archives of General Psychiatry*. 1965;12:63-70
395. Ankolekar S, Renton C, Sare G, Ellender S, Sprigg N, Wardlaw JM, et al. Relationship between poststroke cognition, baseline factors, and functional outcome: Data from "efficacy of nitric oxide in stroke" trial. *Journal of Stroke and Cerebrovascular Diseases*. 2014;23:1821-1829
396. Qureshi AI, Palesch YY, Martin R, Novitzke J, Cruz-Flores S, Ehtisham A, et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: Results from the antihypertensive treatment of acute cerebral hemorrhage study. *Arch Neurol*. 2010;67:570-576
397. Willmot M, Gray L, Gibson C, Murphy S, Bath PMW. A systematic review of nitric oxide donors and l-arginine in experimental stroke; effects on infarct size and cerebral blood flow. *Nitric Oxide-Biology and Chemistry*. 2005;12:141-149
398. Morikawa E, Rosenblatt S, Moskowitz MA. L-arginine dilates rat pial arterioles by nitric oxide-dependent mechanisms and increases blood flow during focal cerebral ischaemia. *British Journal of Pharmacology*. 1992;107:905-907
399. The ENOS Trial Investigators. Glyceryltrinitrate vs. Control, and continuing vs.Stopping temporarily prior antihypertensive therapy in acute stroke:Rationale and design of the efficacy of nitric oxide (enos) trial (isrctn99414122). *Int J Stroke*. 2006;1:245-249
400. Qureshi AI, Palesch YY. Antihypertensive treatment of acute cerebral hemorrhage (atach) ii: Design, methods, and rationale. *Neurocrit Care*. 2011;15:559-576
401. Chen S, Chen S, Hsu C, Hogan E. Progression of hypertensive intracerebral hemorrhage. *Neurology*. 1989;39:1509-1514
402. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, et al. Early neurologic deterioration in intracerebral hemorrhage - predictors and associated factors. *Neurology*. 2004;63:461-467

403. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: A population-based study. *Lancet Neurology*. 2014;13:374-384
404. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and the secondary prevention of stroke and other vascular events: A systematic review. *Stroke*. 2003;34:2741-2749
405. Lees KR, Dyker AG. Blood pressure control after acute stroke. *J Hypertens Suppl*. 1996;14:S35-38
406. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European stroke organisation (eso) guidelines for the management of spontaneous intracerebral hemorrhage. *International Journal of Stroke*. 2014;9:840-855
407. Neal B, MacMahon S, Chapman N. Effects of ace inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. Blood pressure lowering treatment trialists' collaboration. *Lancet*. 2000;2000:1955-1964
408. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *British Medical Journal*. 1973;3:507-510
409. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, et al. Effects of antihypertensive treatment after acute stroke in the continue or stop post-stroke antihypertensives collaborative study (cossacs): A prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol*. 2010;9:767-775
410. Lees KR, Bath PMW, Schellinger PD, Kerr DM, Fulton R, Hacke W, et al. Contemporary outcome measures in acute stroke research: Choice of primary outcome measure *Stroke* 2012;43:1163-1170
411. Sulter G, Steen C, de Keyser J. Use of the barthel index and modified rankin scale in acute stroke trials. *Stroke*. 1999;30:1538-1541
412. Bath PM, Lees KR, Schellinger PD, et al. Statistical analysis of the primary outcome in acute stroke trials *Stroke* 2012;43:1171-1178
413. Krishnan K, Mukhtar SF, Lingard J, Houlton A, Walker E, Jones T, et al. Performance characteristics of methods for quantifying spontaneous intracerebral haemorrhage: Data from the efficacy of nitric oxide in stroke (enos) trial. *Journal of Neurology Neurosurgery and Psychiatry*. 2015;86:1258-1266
414. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373:1632-1644
415. Bruno A, Carter S, Qualls C, Nolte KB. Incidence of spontaneous intracerebral hemorrhage among hispanics and non-hispanic whites in new mexico. *Neurology*. 1996;47:405-408
416. Chen DY, Roman GC, Wu GX, Wu ZS, Yao CH, Zhang M, et al. Stroke in china (sin0-monica-beijing study) 1984-1986. *Neuroepidemiology*. 1992;11:15-23
417. Wild S, Mckeigue P. Cross sectional analysis of mortality by country of birth in england and wales, 1970–92. *BMJ*. 1997;314:705-710

418. Sheth T, Nair C, Nargundkar M, Anand S, Yusuf S. Cardiovascular and cancer mortality among canadians of european, south asian and chinese origin from 1979 to 1993: An analysis of 1.2 million deaths. *CMAJ*. 1999;161:132-138
419. Hsu RT, Ardron ME, Brooks W, Cherry D, Taub NA, Botha JLT. The 1996 leicestershire community stroke & ethnicity study: Differences and similarities between south asian and white strokes. *International Journal of Epidemiology*. 1999;28:853-858
420. Fang J, Foo SH, Jeng JS, Yip PK, Alderman MH. Clinical characteristics of stroke among chinese in new york city. *Ethn Dis*. 2004;14:378-383
421. Feigin V, Carter K, Hackett M, et al. Ethnic disparities in incidence of stroke subtypes: Auckland regional community stroke study, 2002–2003. *Lancet Neurology*. 2006;5:130-139
422. Gunarathne A, Patel JV, Gammon B, Gill PS, Hughes EA, Lip GY. Ischemic stroke in south asians: A review of the epidemiology, pathophysiology and ethnicity-related clinical features. *Stroke*. 2009;40:e415-e423
423. Khan NA, Quan H, Hill MD, Pilote L, McAlister F, Palepu A, et al. Risk factors, quality of care and prognosis in south asian, east asian and white patients with stroke. *BMC Neurology*. 2013;13
424. Qureshi AI, Giles WH, Croft JB. Racial differences in the incidence of intracerebral hemorrhage: Effects of blood pressure and education. *Neurology*. 1999;52:1617-1621
425. van Asch C, Luitse M, Rinkel G, van der Tweel I, Algra A, Klijn C. Incidence, case fatality, and functional outcome of intracerebral haemorrhage overtime, according to age, sex, and ethnic origin: A systematic review and meta-analysis. *Lancet Neurology*. 2010;9:167-176
426. Qureshi AI, Suri MA, Safdar K, Ottenlips JR, Janssen RS, Frankel MR. Intracerebral hemorrhage in blacks. Risk factors, subtypes, and outcome. *Stroke*. 1997;28:961-964
427. Ali M, Bath P, Brady M, David S, Diener H-C, Donnan G, et al. Development, expansion and use of a stroke clinical trials resource for novel exploratory analyses. *International Journal of Stroke*. 2012;7:133-138
428. Zahuranec DB, Wing JJ, Edwards DF, Menon RS, Fernandez SJ, Burgess RE. Poor long term blood pressure control after intracerebral hemorrhage. *Stroke*. 2012;43:2580-2585
429. Fogelholm R, Avikainen S, Murros K. Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. *Stroke*. 1997;28:1396-1400
430. Passero S, Burgalassi L, D' Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. *Stroke*. 1995;26:1189-1192
431. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European stroke organisation (eso) guidelines for the

management of spontaneous intracerebral hemorrhage. *International Journal of Stroke*. 2014;9:840-855
432. Hemphill J, Greenberg S, Anderson C, Becker K, Bendok B, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke*. 2015;46:2032-2060
433. Gillum RF. Stroke mortality in blacks. Disturbing trends. *Stroke*. 1999;30:1711-1715
434. de Haan RJ, Limburg M, Van der Muelen JHP, Jacobs HM, Aaronson NK. Quality of life after stroke: Impact of stroke type and lesion location. *Stroke*. 1995;26:402-408
435. Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Archives of General Psychiatry*. 1993;50:85-94
436. Xian Y, Holloway RG, Smith EE, Schwamm L, Reeves MJ, Bhatt DL, et al. Racial/ethnic differences in process of care and outcomes among patients hospitalized with intracerebral hemorrhage. *Stroke*. 2014;45:3246-3250
437. Ottenbacher KJ, Campbell J, Kuo YF, Deutsch A, Ostir GV, Granger CV. Racial and ethnic differences in postacute rehabilitation outcomes after stroke in the united states. *Stroke*. 2008;39:1514-1519
438. McNaughton H, Feigin V, Kerse N, Barber PA, Weatherall M, Bennett D, et al. Ethnicity and functional outcome after stroke. *Stroke*. 2010;42:960-964
439. de Haan RJ, Limburg M, Van der Meulen JHP, Jacobs HM, Aaronson NK. Quality of life after stroke. *Stroke*. 1995;26:402-408
440. Christensen MC, Mayer S, Ferran JM. Quality of life after intracerebral hemorrhage: Results of the factor seven for acute hemorrhagic stroke (fast) trial *Stroke*. 2009;40:1677-1682
441. Pickle LW, Munigole M, Gilum RF. Geographic variation in stroke mortality in blacks and whites in the united states. *Stroke*. 1997;28:1639-1647
442. Lackland DT, Egan BM, Jones PJ. Impact of nativity and race on "stroke belt" mortality. *Hypertension* 1999;34:57-62
443. Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ*. 1997;315:672-675
444. Uman LS. Systematic reviews and meta-analyses. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*. 2011;20:57-59
445. Crowther M, Lim W, Crowther MA. Systematic review and meta-analysis methodology. *Blood*. 2010;116:3140-3146
446. Higgins JPT, Green SG. Cochrane handbook for systematic reviews of interventions. 2011
447. Higgins JPT, Altman DG, Sterne JAC, (editors). Chapter 8: Assessing risk of bias in included studies. . *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011).* 2011

448. Jadad AR, Moore RA, Caroll D, all. e. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*. 1996;17:1-12
449. Ried K. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. . *The Australian Family Physician.* 2006;35
450. Copas J, Qing JS. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics*. 2000;1:247-262
451. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002
452. Sedgwick P. How to read a forest plot. *BMJ*. 2012;345:e8335
453. Lewis S, Clarke M. Forest plots: Trying to see the wood and the trees. *BMJ*.322:1479-1480
454. Britton M, de Faire U, Helmers C. Hazards of therapy for excessive hypertension in acute stroke. *Acta Medical Scandinavia*. 1980;207:253-257
455. Oppenheimer S, Hachinski V. Complications of acute stroke. *Lancet*. 1992;339:721-724
456. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. 1998;29:1160-1166
457. Geeganage CM, Bath PMW. Interventions for deliberately altering blood pressure in acute stroke. *Stroke*. 2009;40:390-391
458. Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (scast): A randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741-750
459. Shaw L, Price C, McLure S, Howel D, McColl E, Younger P, et al. Paramedic initiated lisinopril for acute stroke treatment (pil-fast): Results from the pilot randomised controlled trial. *Emerg Med J*. 2013
460. Koch S, Romano JG, Forteza AM, Otero CM, Rabinstein AA. Rapid blood pressure reduction in acute intracerebral hemorrhage: Feasibility and safety. *Neurocritical Care*. 2008;8:316-321
461. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions* 2011.
462. Fagan SC, Gengo FM, Bates V, Levine SR, Kinkel WR. Effect of nimodipine on blood pressure in acute ischemic stroke in humans. *Stroke*. 1988;19:401-402
463. Lisk DR, Grotta JC, Lamki LM, Tran HD, Taylor JW, Molony DA, et al. Should hypertension be treated after acute stroke? A randomized controlled trial using single photon emission computed tomography. *Archives of Neurology*. 1993;50:855-862
464. Kenneth S. Butcher TJ, Michael Hill, Andrew M. Demchuk, Dariush Dowlatshahi, Shelagh B. Coutts, Bronwen Gould, Rebecca McCourt, Negar Asdaghi, J. Max Findlay, Derek Emery and Ashfaq Shuaib for

the ICH ADAPT Investigators. The intracerebral hemorrhage acutely decreasing arterial pressure trial. *Stroke*. 2013;44:620-626
465. Hillis AE, Ulatowski JA, Barker PB, Tobey M, Ziai W, Beauchamp NJ. A pilot randomised trial of induced blood pressure elevation: Effects on function and focal perfusion in acute and subacute stroke. *Cerebrovascular Diseases*. 2003;16:236-248
466. Schrader J, Luders S, Kulschewski A, Berger J, Zidek W, Treib J, et al. The access study: Evaluation of acute candesarten cilexetil therapy in stroke survivors. *Stroke*. 2003;34:1699-1703
467. Eames PJ, Robinson TG, Panerai RB, Potter JF. Bendrofluazide fails to reduce elevated blood pressure levels in the immediate post-stroke period. *Cerebrovascular Diseases*. 2005;19:253-259
468. Eveson DJ, Robinson TG, Potter JF. Lisinopril for the treatment of hypertension within the first 24 hours of acute ischemic stroke and follow-up. *American Journal of Hypertension*. 2007;20:270-277
469. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (interact): A randomised pilot trial. *Lancet Neurol*. 2008;7:391-399
470. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The catis randomized clinical trial. *JAMA*. 2013
471. Bath PMW, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, et al. Effects of telmisartan on functional outcome, recurrence and blood pressure in patients with acute mild ischemic stroke: A profess subgroup analysis. *Stroke*. 2009;40:3541-3546
472. Butcher KS, Jeerakathil T, Hill M, Demchuk AM, Dowlatshahi D, Coutts SB, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. *Stroke*. 2013;44:620-626
473. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355-2365
474. Sare GM, Ghadami A, Ankolekar S, England T, Hammonds F, Adrian M, et al. Effect of telmisartan on cerebral and systemic haemodynamics in patients with recent ischaemic stroke stroke: A randomised controlled trial. *ISRN Stroke*. 2013:1-9
475. Uzuner N, Gucuyner D, Ozdemir G. The interaction between nimodipine and systemic blood pressure and pulse rate. *Pan-European consensus meeting on stroke management*. 1995
476. Dyker AG, Grosset DG, Lees K. Perindopril reduces blood pressure but not cerebral blood flow in patients with recent cerebral ischemic stroke. *Stroke*. 1997;28:580-583
477. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PMW. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension*. 2006;47:1209-1215

478. O'Brien. Acute candesartan cilexetil outcomes stroke trial (accost). *2nd International Conference on Hypertension, Lipids, Diabetes and Stroke Prevention*. 2008
479. Bath PMW, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, et al. Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: A profess subgroup analysis. *Stroke*. 2009;40:3541-3546
480. Yu K-H, Oh M-S, Hong K-S, Kang D-W, Park J-M, Bae H-J, et al. Safety and efficacy of modest blood pressure reduction with valsartan in acute ischemic stroke. *International Stroke Conference Poster*. 2013
481. Bath PMW, Pathansali R, Bath F. The effect of transdermal glyceryl trinitrate, a nitric oxide donor on blood pressure and platelet function in acute stroke. *Cerebrovascular Diseases*. 2000;11:265-272
482. Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke the rapid intervention with glyceryl trinitrate in hypertensive stroke trial (right, isrctn66434824). *Stroke; a journal of cerebral circulation*. 2013;44:3120-3128
483. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The catis randomized clinical trial. *JAMA*. 2013;311:479-489
484. Bath PMW, Pathansali R, Iddenden R, Bath FJ. The effect of nitric oxide, given as transdermal glyceryl trinitrate, on blood pressure in acute stroke. *Cerebrovascular Diseases*. 1999;9 Suppl 1:101
485. Hosomi N, Sueda Y, Masugata H, Dobashi H, Murao K, Ueno M, et al. The optimal timing of antihypertensive medication administration for morning hypertension in patients with cerebral infarction. *Hypertension Research*. 2012;35:720-724
486. Zanchetti A. Optimal blood pressure and cholesterol targets for preventing recurrent stroke in hypertensives esh-chl-shot. *Clinical Trials. gov [NCT01563731]*. 2013
487. MAPAS trial investigators. Manipulation of arterial pressure in acute ischemic stroke. *Clinical Trials. gov [NCT00848770]*. 2009
488. Stable ICAS investigators. Strategy for adequate blood pressure lowering in patients with intracranial atherosclerosis. *Clinical Trials.gov [NCT011004311]*. 2010
489. Huang Y, Sharma VK, Robinson T, Lindley RI, Chen X, Kim JS, et al. Rationale, design, and progress of the enhanced control of hypertension and thrombolysis stroke study (enchanted) trial: An international multicenter 2 × 2 quasi-factorial randomized controlled trial of low- vs. Standard-dose rt-pa and early intensive vs. Guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. *International Journal of Stroke*. 2015;Epub ahead of print
490. Sanossian N, on behalf of Field Administration of Stroke Therapy-Blood Pressure Lowering (FAST-BP) investigators. Fast-bp: Field

administration of stroke therapy- blood pressure lowering (fast-bp). *Clinical Trials. gov (NCT01811693)*. 2013
491. Bang OY. Safety and efficacy of therapeutic induced hypertension in acute non-cardioembolic stroke. *Clinical Trials. gov [NCT01600235]*. 2012
492. Dyker AG, Grosset DG, Lees KR. Effect of perindopril in blood pressure and cerebral blood flow after ischaemic stroke. *Heart Brain: Third Int.Conf.Stroke, Prague*. 1995
493. Bath P, Bath F, Rashid P, Weaver C. Large trial of effect of reducing blood pressure in acute stroke is being set up. *BMJ*. 2000;321:300
494. Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR. Low dose beta blockade in acute stroke ("best" trial): An evaluation. 1988;296:737-741
495. Jauch EC, Saver JL, Adams Jr HP, Connors B, Demaerschalk BM, Khatri P, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2013;44:870-947
496. Morgensetern L, Hemphill J, Anderson C, Becker K, Broderick J, Connolly S, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2010;41:2108-2129
497. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457-507
498. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C, et al. Blood pressure and risk of stroke in patients with cerebrovascular disease. *Br Med J*. 1996;313:147
499. MacMahon S, Neal B, Tzourio C, Rodgers A, Woodward M, Curler J, et al. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033-1041
500. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New Engl J Med*. 2000;342:145-153
501. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: A systematic review. *Cerebrovascular Diseases*. 2002;13 (suppl 3):95 (abstract)
502. Qureshi AI, Palesch YY, Martin R, Novitzke J, Cruz-Flores S, Ehtisham Aa, et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage results from the antihypertensive treatment of acute cerebral hemorrhage study. *Archives of Neurology*. 2010;67:570-576
503. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative

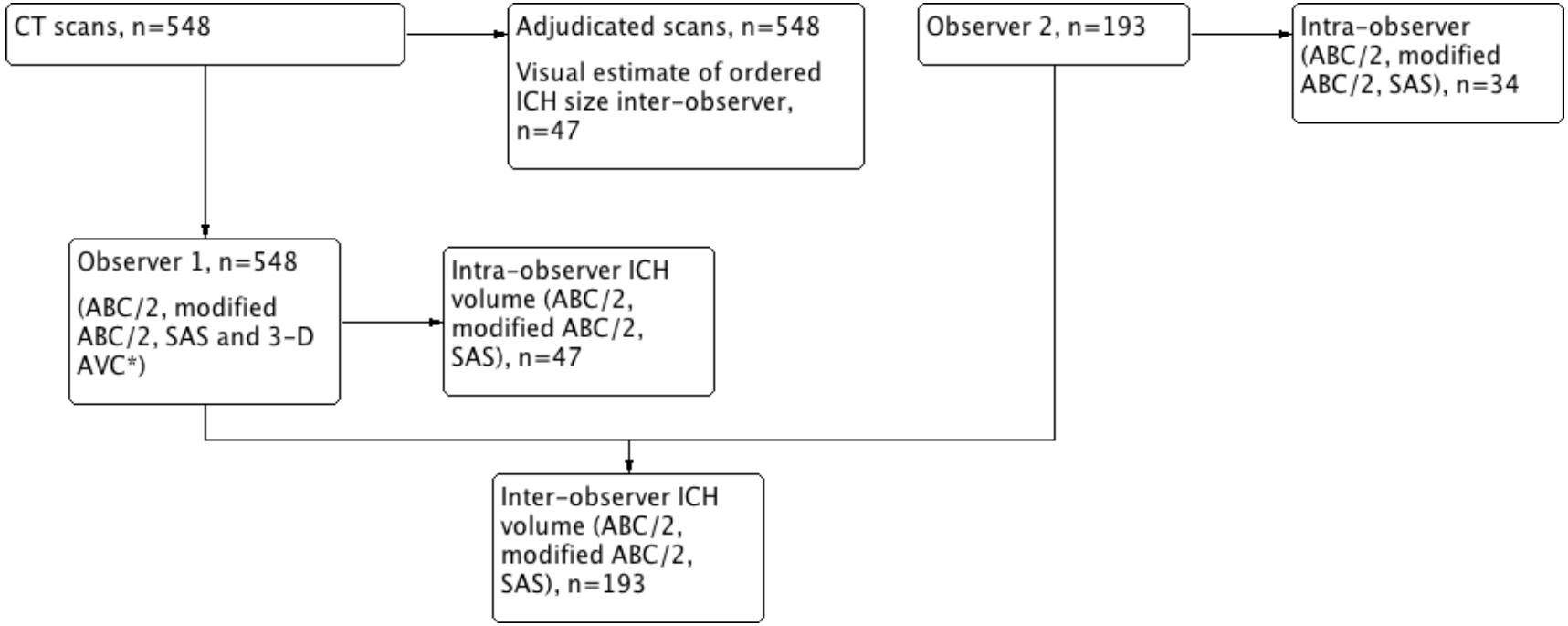
treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (stich): A randomised trial. *Lancet*. 2005;365(9457):387-397
504. Meretoja A, Churilov L, Campbell BC, Aviv RI, Yassi N, Barras C, et al. The spot sign and tranexamic acid on preventing ich growth-australasia trial (stop-aust): Protocol of a phase ii randomized, placebo-controlled, double-blind, multicenter trial. *International Journal of Stroke*. 2014;9:519-524
505. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. . *Neurology*. 2004:1059–1064.
506. Vernooij MW, Haag MDM, van der Lugt A, Hofman A, Krestin GP, Stricker BH, et al. Use of antithrombotic drugs and the presence of cerebral microbleeds. The rotterdam scan study. *Arch Neurol*. 2009;66:E1-7
507. Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (scast): A randomised, placebo-controlled double-blind trial. *Lancet*. 2011;377:741-750
508. Manning LS, Mistri AK, Potter J, Rothwell PM, Robinson TG. Short-term blood pressure variability in acute stroke: Post hoc analysis of the controlling hypertension and hypotension immediately post stroke and continue or stop post-stroke antihypertensives collaborative study trials. *Stroke*. 2015;[Epub ahead of print]
509. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: A post-hoc analysis of interact2, a randomised controlled trial. *The Lancet Neurology*. 2014;13:364-373
510. Sukhotinsky I, Dilekoz E, Moskowitz MA, Ayata C. Hypoxia and hypotension transform the blood flow response to cortical spreading depression from hyperemia into hypoperfusion in the rat. *Journal of Cerebral Blood Flow and Metabolism*. 2008;28:1369-1376
511. Sukhotinsky I, Yaseen MA, Sakadzic S, Ruvinskaya S, Sims JR, Boas DA, et al. Perfusion pressure-dependent recovery of cortical spreading depression is independent of tissue oxygenation over a wide physiologic range. *Journal of Cerebral Blood Flow and Metabolism*. 2010;30:1168-1177
512. Wong AA, Davis JP, Schluter PJ, Henderson RD, O' Sullivan JD, Read SJ. The time course and determinants of blood pressure within the first 48 hours after ischaemic stroke. *Cerebrovascular Diseases*. 2007;24:426-433
513. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al. Determinants of intracerebral hemorrhage growth: An exploratory analysis. *Stroke*. 2007;38:1072-1075
514. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Silva Blas Y, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the ct-

angiography spot sign (predict): A prospective observational study. *Lancet Neurology*. 2012;11:307-314
515. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA. Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. *Stroke*. 1999;30:20125-22032
516. Wahlgren NG, Macmahon DG, Dekeyser J, Indredavik B, Ryman T. Intravenous nimodipine west european stroke trial (inwest) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovascular Diseases*. 1994;4:204-210
517. The Intercollegiate Stroke working party of the Royal College of Physicians. National clinical guideline for stroke. 2012;4th Edition
518. Nguyen-Huynh MN, Johnston SC. Regional variation in hospitalization for stroke among asians/pacific islanders in the united states: A nationwide retrospective cohort study. *BMC Neurology*. 2005;5
519. Ayala C, Greenlund HJ, Croft JB, Keenan NL, Donehoo RS, Giles WH, et al. Racial/ethnic disparities in mortality by stroke subtype in the united states, 1995-1998. *American Journal of Epidemiology*. 2001;154:1057-1063
520. Gokhale S, Caplan LR, James ML. Sex differences in incidence, pathophysiology and outcome of primary intracerebral hemorrhage. *Stroke*. 2015;46:886-892
521. T Inagawa NO, A Takechi, M Shibukawa, K Yahara. Primary intracerebral hemorrhage in izumo city, japan: Incidence rates and outcome in relation to the site of hemorrhage. *Neurosurgery*. 2003:1283-1297
522. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a japanese community: The hisayama study. *Stroke*. 2003;23:2349-2354
523. Jiang B, Wang WZ, Chen H, Hong Z, Yang QD, Wu SP, et al. Incidence and trends of stroke and its subtypes in china: Results from three large cities. *Stroke*. 2006;37:63-68
524. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *New England Journal of Medicine*. 2016;[Epub ahead of print]
525. Bath PMW, on behalf of The Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke investigators. Right 2: Rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2.
526. Hornslein AG, Sandset EC, Igland J, Terent A, Boysen G, Bath PM, et al. Effects of candesartan in acute stroke on vascular events during long-term follow-up: Results from the scandinavian candesartan acute stroke trial (scast). *International Journal of Stroke*. 2015;10:830-835
527. Huczynski J, Kostka-Trabka E, Sotowska W, Bieron K, Grodzinska L, Dembinska-Kiec A, et al. Double-blind controlled trial of the

therapeutic effects of prostacyclin in patients with completed ischaemic stroke. *Stroke.* 1985;16:810-814

APPENDIX I

Flow chart of the number of CT scans from the ENOS trial used to assess intra and inter observer reliability



*Only 23 of 548 scans were amenable to analysis using AVC

APPENDIX II

This section lists the search terms used in Chapter 8 for a systematic review and meta-analysis of trials which deliberately altered blood pressure in acute stroke.

MEDLINE search strategy

1. blood pressure.tw.
2. hypertension.tw
3. acute/
4. stroke.tw.
5. or/1-4
6. and/1-4
7. 1-4.kf.
8.1-4.ti.
9. trials
10. 1-4 and 9
11. 1-4 and 9.ti.
12. ischaemic stroke.tw/ti.
13. haemorrhagic stroke.tw/ti.
14. intracerebral haemorrhage.tw./ti.
15. blood pressure lowering/
16. blood pressure increase/
17. 1-4 or 12
18. 1-4 or 13
19. 1-4 or 14
20. 1-4 and 15
21.1-4 and 16
22. cerebr
23. 1-4 or 22
24. vasoactive/
25. 12-16 or 24
26. nitrate.tw.
27. glyceryl trinitrate/GTN.tw
28. nitric Oxide Donors.tw.
29. 1-4 and/or 26-28
30. 9, 12-13, 16 and/or 26-28
31. thiazide.tw.
32. bendrofluazide.tw.
33. bendroflumethiazide.tw.
34. hydrochrlothiazide/HCT.tw.
35. 31-34 and/or 1-4
36. 31-34 and/or 12-15
37. beta blockers.tw

38. atenolol.tw.
39. propanalol.tw.
40. 37-39 and/or 1-4
41. 37-39 and or 12-15
42. calcium channel blockers.tw.
43. nimodipine.tw.
44. nicardipine.tw.
45. amilodipine.tw.
46. felodipine.tw.
47. isradipine.tw.
48. nifedipine.tw.
49. nisolodipine.tw.
50. 42-49 and or 1-4
51. 42-49 and or 12-15
52. angiotensin-converting enzyme inhibitors/ACE inhibitors.tw
53. captopril.tw.
54. enalapril.tw.
55. lisinopril.tw.
56. perindopril.tw.
57. ramipril.tw.
58. 52-57 and or 1-4
59. 52-57 and or 12-15
60. angiotensin receptor blockers/antagonists.tw.
61. candesartan.tw
62. losartan.tw.
63. telmisartan.tw
64. valsartan.tw.
65. clonidine.tw.
65. 60-65 and or 1-4
66. 60-65 and or 12-15
67. vasoconstrictors.tw.
68. dopamine.tw.
69. dobutamine.tw.
70. noradrenaline.tw.
71. phenylephrine.tw.
72. 67-71 and or 3, 4, 9, 16
73. cerebral blood flow
74. autoregulation
75. stroke outcome
76. 73-75 and or 1-4
77. 73-75 and or 12-16

EMBASE search strategy

1. blood pressure.tw.
2. hypertension.tw

3. acute/
4. stroke.tw.
5. or/1-4
6. and/1-4
7. 1-4.kf.
8.1-4.ti.
9. trials
10. 1-4 and 9
11. 1-4 and 9.ti.
12. ischaemic stroke.tw/ti.
13. haemorrhagic stroke.tw/ti.
14. intracerebral haemorrhage.tw./ti.
15. blood pressure lowering/
16. blood pressure increase/
17. 1-4 or 12
18. 1-4 or 13
19. 1-4 or 14
20. 1-4 and 15
21.1-4 and 16
22. cerebr
23. 1-4 or 22
24. vasoactive/
25. 12-16 or 24
26. nitrate.tw.
27. glyceryl trinitrate/GTN.tw
28. nitric Oxide Donors.tw.
29. 1-4 and/or 26-28
30. 9, 12-13, 16 and/or 26-28
31. thiazide.tw.
32. bendrofluazide.tw.
33. bendroflumethiazide.tw.
34. hydrochrlothiazide/HCT.tw.
35. 31-34 and/or 1-4
36. 31-34 and/or 12-15
37. beta blockers.tw
38. atenolol.tw.
39. propanalol.tw.
40. 37-39 and/or 1-4
41. 37-39 and or 12-15
42. calcium channel blockers.tw.
43. nimodipine.tw.
44. nicardipine.tw.
45. amilodipine.tw.
46. felodipine.tw.
47. isradipine.tw.
48. nifedipine.tw.
49. nisolodipine.tw.

50. 42-49 and or 1-4
51. 42-49 and or 12-15
52. angiotensin-converting enzyme inhibitors/ACE inhibitors.tw
53. captopril.tw.
54. enalapril.tw.
55. lisinopril.tw.
56. perindopril.tw.
57. ramipril.tw.
58. 52-57 and or 1-4
59. 52-57 and or 12-15
60. angiotensin receptor blockers/antagonists.tw.
61. candesartan.tw
62. losartan.tw.
63. telmisartan.tw
64. valsartan.tw.
65. clonidine.tw.
65. 60-65 and or 1-4
66. 60-65 and or 12-15
67. vasoconstrictors.tw.
68. dopamine.tw.
69. dobutamine.tw.
70. noradrenaline.tw.
71. phenylephrine.tw.
72. 67-71 and or 3, 4, 9, 16
73. cerebral blood flow
74. autoregulation
75. stroke outcome
76. 73-75 and or 1-4 77. 73-75 and or 12-16

Science Citation Index search strategy

1. blood pressure.TI.
2. hypertension.TI
3. acute/
4. stroke.TS.
5. OR/1-4
6. AND/1-4
7. 1-4.TI.
8.1-4.TI.
9. trials
10. 1-4 AND 9
11. 1-4 AND 9.ti.
12. ischaemic stroke.TI/TS.
13. haemorrhagic stroke.TI/TS.
14. intracerebral haemorrhage.TI./TS.
15. blood pressure lowering/
16. blood pressure increase/

17. 1-4 OR 12
18. 1-4 OR 13
19. 1-4 OR 14
20. 1-4 AND 15
21.1-4 AND 16
22. cerebr
23. 1-4 OR 22
24. vasoactive/
25. 12-16 OR 24
26. nitrate.TI./TS
27. glyceryl trinitrate/GTN.TI/TS
28. nitric Oxide Donors.TI./TS
29. 1-4 AND/OR 26-28
30. 9, 12-13, 16 AND/OR 26-28
31. thiazide.TI.
32. bendrofluazide.TI.
33. bendroflumethiazide.TI.
34. hydrochrlothiazide/HCT.TI.
35. 31-34 AND/OR 1-4
36. 31-34 AND/OR 12-15
37. beta blockers.TI
38. atenolol.TI.
39. propanalol.TI.
40. 37-39 AND/OR 1-4
41. 37-39 AND/OR 12-15
42. calcium channel blockers.TI.
43. nimodipine.TI.
44. nicardipine.TI.