Clinical and Radiological Associations with Outcome after a Severe Stroke

Ganesh Subramanian

Dissertation submitted to the University of Nottingham for the degree of MRes (School of Medicine)

November 2019

Acknowledgements

I would like to express my sincere gratitude to Professor Nikola Sprigg for giving me this opportunity to undertake the Masters in Research. Her original ideas, guidance and supervision were instrumental in completing this piece of work.

I would like to acknowledge the support provided by Prof Philip Bath (reviewing my research work and giving me invaluable advice) and Dr Kailash Krishnan for guiding me whilst I struggled with statistical analysis. I would like to thank Miss Lisa Woodhouse for providing me with all the data in the first instance and on all the subsequent times when I needed more information.

This work would not have been possible without the patients who participated in Efficacy of Nitric Oxide in Stroke Trial (ENOS). I am also indebted to my family who supported me throughout the programme without which I would not have been successful in completing this dissertation.

Index of Tables

		Page
Table 1.1	TOAST classification	16
Table 1.2	Effect of intravenous thrombolysis on morbidity - Classified by time, age and severity of stroke	18
Table 1.3	Effect of mechanical thrombectomy in those eligible and ineligible for intravenous thrombolysis	19
Table 1.4	ICH score	22
Table 1.5	Prognosis based on Oxford Classification of stroke subtypes	31
Table 1.6	Advantages and disadvantages of various scales	40
Table 1.7	Benefits and limitations of various imaging modalities	60
Table 2.1	Baseline clinical characteristics	88
Table 2.2	Baseline neuroimaging characteristics	90
Table 2.3	Clinical outcome based on baseline arm/hand score	92
Table 2.4	Radiological predictors of 90-day outcome in those	94

whose arm/hand score did not improve (i.e. < 4 on day 0 and 7)

Table 3.1 Baseline clinical characteristics 117

Table 3.2 Baseline neuroimaging characteristics 119

Table 3.3 Clinical outcomes based on arm/hand score on day 0 and 7 123

Table 3.4 Radiological predictors of 90-day outcome in those whose arm/hand score did not improve (i.e. < 4 on day 0 and 7) 125

Index of Figures

Page

Figure 1.1 PREP2 algorithm 34

Figure 2.1 Patient population included in ischaemic stroke 97

Figure 2.2 Probability of arm/hand score not improving in those presenting with arm/hand score of ≤ 4 on day 0 98

Figure 2.3 Probability of mRS > 3 on day 90 in those presenting with arm/hand score ≤ 4 on day 0 99

Figure 2.4 Probability of mRS > 4 on day 90 in those whose arm/hand score did not improve on day 7 (i.e. score of ≤ 4 on day 0 and 7) 100

Figure 2.5 Probability of having a mRS > 3 on day 90 vs. arm/hand score on day 0 101

Figure 2.6 Day 90 mRS outcome in patients with arm/hand score of ≤ 4 vs. ≥ 5 on day 0 102

Figure 3.1 Patient population included in ICH 130

Figure 3.2 Probability of arm/hand score not improving in those presenting with arm/hand score of ≤ 4 on day 0 131

Figure 3.3 Probability of mRS > 3 on day 90 in those presenting with arm/hand score ≤ 4 on day 0 132

Figure 3.4 Probability of mRS > 4 on day 90 in those whose arm/hand score did not improve on day 7 (i.e. score of ≤ 4 on day 0 and 7) 133

Figure 3.5 Probability of having a mRS > 3 on day 90 vs. arm/hand score on day 0 134

Figure 3.6 Day 90 mRS outcome in patients with arm/hand score of ≤ 4 vs. ≥ 5 on day 0 135

Contents

Acknowledgements 2

Index of Tables 3

Index of Figures 5

Chapter 1 – Introduction 9

1.1. Abstract 9

1.2. Introduction 11

1.3. Natural history of Stroke 12

1.4. Ischaemic stroke 13

1.4.1. Investigations 14

1.4.2. Acute management of ischaemic stroke 17

1.5. Primary Intracerebral Haemorrhage 20

1.6. Clinical and Radiological definitions of severe stroke 24

1.6.1. Clinical Scales that measure impairment after a stroke 26

1.6.2. Scales that are used to predict outcome 29

1.6.3. Scales used to measure outcomes 35

1.7. Neuroimaging markers that predict severity of stroke 46

1.7.1. CT scan of head 47

1.7.2. CT angiogram 52

1.7.3. Magnetic Resonance Imaging 54

1.7.4. Transcranial Magnetic Stimulation (TMS) 58

1.8. Other factors that predict functional outcome after Severe Stroke 64

1.8.1. Risk factors and post stroke complications 64

1.8.2. Clinical Features 66

1.9. Gaps in literature 67

1.10. Aims and Hypothesis 68

Chapter 2 – Ischaemic Stroke 71

2.1 Abstract 71

2.2 Introduction 72

2.3 Methods 74

2.3.1 Participants 74
2.3.2 Measures 75
2.3.3 Outcomes 76
2.3.4 Analysis 77
2.4 Results 78
2.4.1 Baseline outcomes 78
2.4.2 Clinical outcomes 79
2.4.3 Non-improvers (arm/hand score ≤ 4 on day 0 and 7) 80
2.5 Discussion 82
Chapter 3 – Intracerebral Haemorrhage (ICH) 105
3.1 Abstract 105
3.2 Introduction 106
3.3 Methods 108
3.3.1 Participants 108
3.3.2 Measures 108
3.3.3 Outcomes 110
3.3.4 Analysis 111
3.4 Results 111
3.4.1 Baseline characteristics 112
3.4.2 Arm/hand score vs. clinical outcome 112
3.4.3 Non-improvers (arm/hand score ≤ 4 on day 0 and day 7) 113
3.5 Discussion 114
Chapter 4 – Discussion 142
Appendices 153
Reference 166

Chapter 1 – Introduction

1.1. Abstract

Introduction: Stroke is a leading cause of neurological disability and the 4th common cause of death. It also costs both health and social care vast amounts of money. Baseline severity (of stroke) predicts outcome, but the use of clinical scale and radiological markers in those with severe stroke has been less well studied. We also know that some of the acute radiological markers can predict poor outcome in those with severe stroke.

Methods: I undertook a literature review on the various clinical and radiological predictors following an ischaemic and haemorrhagic stroke.

Results: I classified the various clinical scales in to one of 3 categories – those that measured impairment, those that predicted outcome and those that were used to measure outcomes. These scales were either non-specific, difficult to administer or not used in routine clinical practice. Radiological investigations were

predominantly used to predict medium term outcomes and they were either CT or MRI based. More advanced imaging modalities are not used in clinical practice routinely. There is very little literature on whether background (pre-existing) brain damage had any impact on the outcome. Do you need to talk about SAFE and PREP here or leave for next chapters?

Conclusion:

There is no simple clinical assessment that has been shown to predict poor outcome after a severe stroke. There is very little literature on the ability of background brain health in predicting poor outcome after severe stroke.

Hypotheses

This thesis will, for the first time, look at using a combination of clinical and radiological parameters to predict poor outcome in those who have suffered a severe stroke. The hypothesis included that those who had an arm/hand score of ≤ 4 and those with poor background brain health had a poor 90-day outcome in both ischaemic and haemorrhagic strokes.

1.2. Introduction

Stroke is defined as a clinical syndrome of presumed vascular origin, characterised by rapidly developing focal or global neurological deficit lasting at least 24 hours or leading to death. [1] Stroke association estimates that more than 100,000 people suffer from a stroke in UK every year; is a leading cause of disability and the 4th common cause of death; it also costs around £1.7 billion (both to health and social care combined). Rothwell et al[2] suggest that the incidence of stroke is 230 per 100,000 population and the UK Stroke audit (SSNAP) suggests that the 30- day mortality is around 14%. [3] According to the Royal College of Physicians Intercollegiate Stroke Working Party, around 80,000 patients are admitted to hospital every year with an acute stroke. Stroke is the 3rd leading cause of disability[4] in United Kingdom. A systematic review and meta-analysis found that the risk of recurrent stroke is estimated to be around 26% in the first 5 years after a stroke and as high as 39% over a 10 year period following the initial stroke. [5] Approximately 85% of strokes are related to ischaemia/infarct, 10% are related to primary (or secondary to underlying vascular abnormality) parenchymal haemorrhage and 5% are due to subarachnoid haemorrhage. For the purpose of this dissertation, I will discuss only

about infarction and intra parenchymal haemorrhage (but not subarachnoid haemorrhage).

1.3. Natural history of Stroke

The incidence of stroke increases with age and men are more at risk of having a stroke than females. It is estimated that 1 in 4 males and 1 in 5 females over the age of 45 will have a stroke in their lifetime[6] (assuming they live into their 80s). Although the risk of strokes is more in males, the risk of dying from a stroke is more in females, [7] perhaps related to older age at the onset of stroke. There is a variation in the incidence of strokes – blacks are at more risk of both ischaemic and haemorrhagic stroke. [8-10] It is estimated by the end of 1 year since the stroke onset, roughly 30% of patients are dead, 30% are independent and 40% are dependent with activities of daily living. [11] A recent overview has suggested that only 14% of patients achieve full recovery of activities of daily living while 25 – 50% require some assistance and up to 50% are dependent in the long term. [12] Upper limb function is essential for independent living after a stroke. [13, 14] Irrespective of whether stroke is due to ischaemia or haemorrhage, recovery of upper limb function is crucial to regaining independence after stroke. [15]

1.4. Ischaemic stroke

This accounts for roughly 85% of all strokes. Many risk factors that increase the risk which can be classified as modifiable and non-modifiable.

Modifiable risk factors include hypertension, atrial fibrillation, diabetes, smoking, ischaemic heart disease, congestive cardiac failure, renal dysfunction, excess alcohol consumption and hypercoagulable states (e.g. cancer, myeloproliferative disorders). Non-modifiable factors include increasing age, gender and previous history of stroke or TIA. In a younger person, other causes like cervical artery dissection, recreational drug usage, patent foramen ovale (causing paradoxical embolism), thrombophilic tendencies (e.g. lupus anticoagulant, antiphospholipid antibody syndrome), primary (or secondary) CNS vasculitis and genetic conditions (e.g. Fabry's disease, CADASIL, CARASIL, etc.).

1.4.1.Investigations

Stroke is a clinical diagnosis and the investigations are there to support the diagnosis (or rule out other causes). However, neuroimaging is the best (and only) way to establish if the cause of stroke is ischaemic or a haemorrhage. Although Computed Tomographic (CT) scan of head is very helpful in ruling out an acute intracranial haemorrhage, Magnetic Resonance Imaging (MRI) offers a lot of advantages – including superior visualisation of posterior cranial fossa, reliably rule out other pathologies like demyelination, tumours, etc., able to detect small infarcts (both in the presence and absence of chronic ischaemic changes), ability to detect old haemorrhages and with newer techniques, the ability to guide the clinicians about acute management/intervention. However, one major drawback of MRI scan is the fact that some people find it claustrophobic and hence unable to tolerate the procedure; in addition, there are some patients in whom MRI scan is contraindicated (e.g. those with permanent pace-maker or intracranial aneurysm clip). It also takes a lot longer to acquire MR images compared to CT images.

All patients with ischaemic stroke should have full blood count, renal and liver function tests, random plasma glucose, clotting screen, lipid profile and a 12 lead electrocardiogram. Further investigations should be directed by the clinical scenario e.g. thrombophilia and autoimmune screen in young patients with stroke, vessel imaging (e.g. CT or MR angiogram if dissection or unusual vascular pathology is suspected), echocardiogram (in those with cardioembolic stroke), genetic screen (e.g. Fabry's disease, CADASIL, etc.)

Trial of Org 10172 (TOAST)[16] – table 1.1 – classification uses clinical picture as well as the results of investigations to categorise patients into 5 categories – Large Artery Atherosclerosis, Cardio-embolism, Small Vessel disease, Stroke of Other Determined aetiology and Stroke of Undetermined aetiology. The risk factor for stroke in an individual varies depending on which TOAST category the patient falls under (Table 1.1). One study[17] suggests that although NIHSS score is a strong predictor of outcomes after an ischaemic stroke, TOAST lacunar subtype did not conform to that rule – those with lacunar subtype may have a moderate stroke in NIHSS score (< 12), but those with persistent severe weakness of limbs tend to be very disabled.

Table 1.1 – TOAST classification of stroke subtypes

TOAST category	% of ischaemic strokes	Risk factors
Large artery atherosclerosis	50%	Increasing age, male sex, cigarette smoking, excess alcohol consumption, hypertension, diabetes, obesity, family history, haemostatic factors, etc.
Cardio-embolism	30%	Atrial fibrillation, valvular heart disease (with or without atrial fibrillation), LV aneurysm and rarely tumours like atrial myxoma
Small vessel disease	20%	Somewhat similar to large artery atherosclerosis but more commonly hypertension and

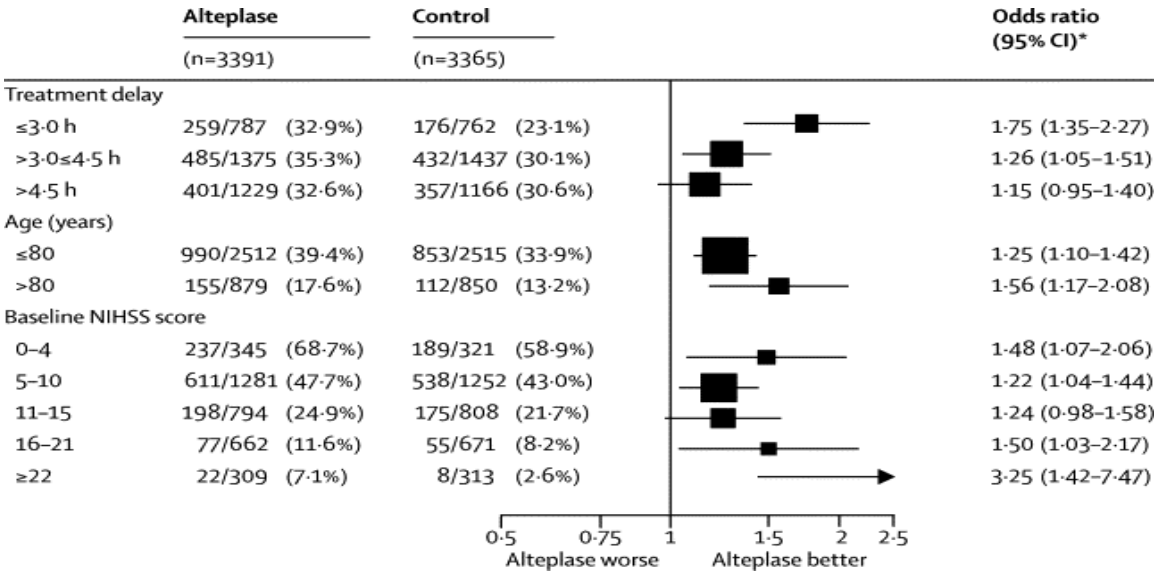
		diabetes. Alcohol and smoking to a lesser extent
Stroke of other determined aetiology	Rare	Rare conditions like vasculitis and other vasculopathies, inherited disorders of metabolism or genetic conditions
Stroke of undetermined aetiology	Rare	Risk factors may not be evident even after detailed investigations; occasionally due to paradoxical embolism

1.4.2.Acute management of ischaemic stroke

One of the immediate priorities in the management of acute ischaemic stroke is recanalization of the blocked artery as soon as possible to re-establish cerebral blood supply. A recent meta-analysis[18] (individual patient data analysis from randomised

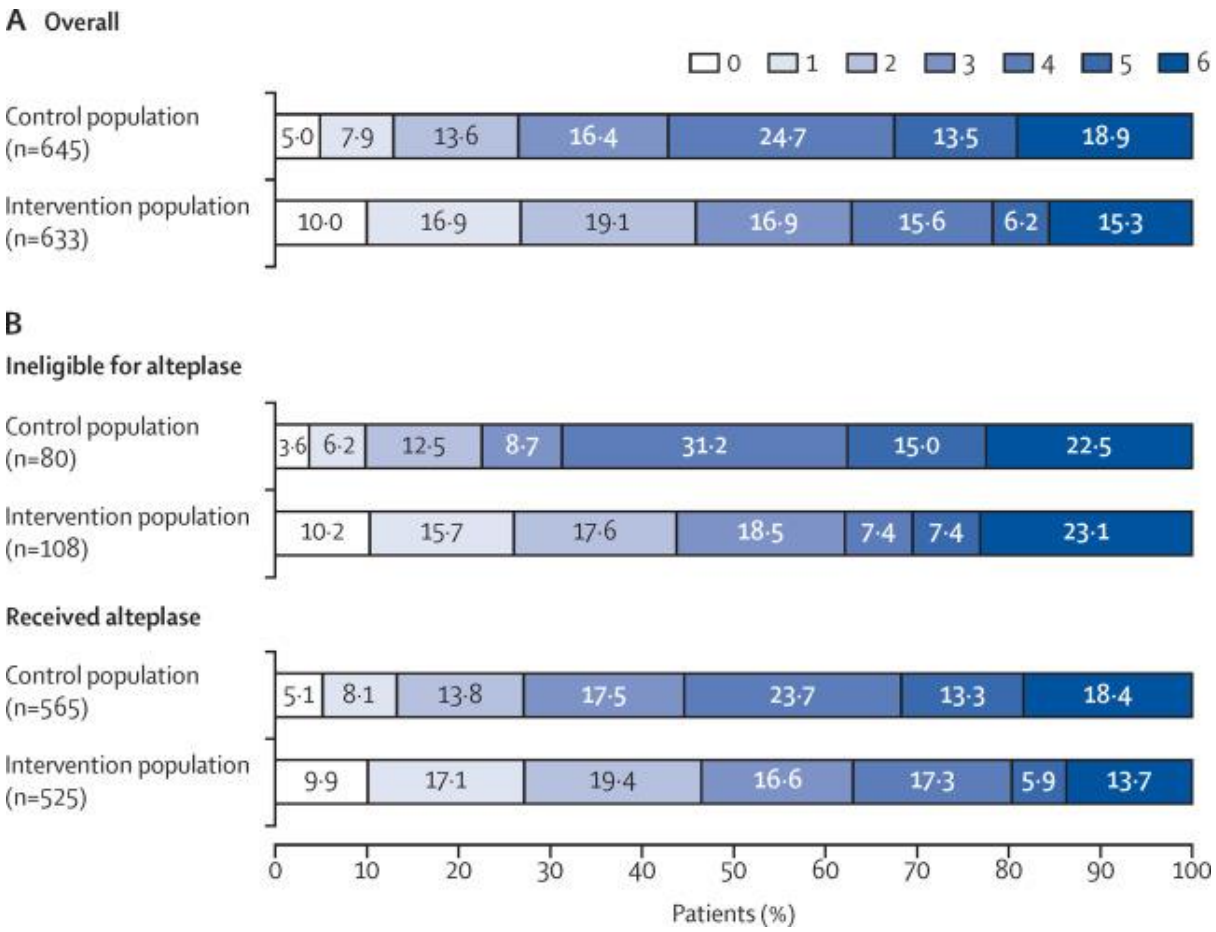
controlled trials) found that the sooner the thrombolytic was administered, the better the outcome (Table 2).

Table 1.2 – Effect of intravenous thrombolysis on morbidity – classified by time, age and severity of stroke



Another individual patient data meta-analysis[19] has shown that mechanical thrombectomy (with or without intravenous thrombolysis) improved morbidity although there was no difference in 90 day mortality.

Table 1.3 – Effect of mechanical thrombectomy in those eligible and ineligible for intravenous thrombolysis



However, one of the most powerful predictors of outcome in terms of mortality, morbidity and living at home a year after stroke is directly related to whether the patient was treated in a stroke unit or not. [20] Organised stroke unit care ensures commencement of early rehabilitation, multi-disciplinary input at appropriate time and

prevention of complications (e.g. venous thromboembolism, spasticity, etc.) in addition to appropriate secondary prevention measures.

Malignant middle cerebral artery (MCA) syndrome is a known and common complication after a severe ischaemic stroke; in those patients, decompressive hemicraniectomy increases the chance of survival significantly although at the expense of high levels of dependency. [21]

1.5. Primary Intracerebral Haemorrhage

Intracerebral haemorrhage accounts for about 10% of all strokes. The risk increases significantly as one gets older. The 2 major risk factors for intracerebral haemorrhage include hypertension and cerebral amyloid angiopathy (which is distinctly different to systemic amyloidosis). Other risk factors include iatrogenic (antiplatelets and more importantly anticoagulant medications and very rarely post carotid endarterectomy or stenting due to cerebral hyperperfusion syndrome), excess alcohol consumption, vascular malformations (aneurysms, arterio-venous malformations, dural arterio-venous

fistula), use of recreational drugs (in particular cocaine and amphetamine although other drugs can be causative as well) and inherited bleeding disorders.

Although it has been proposed that hypertensive bleeds tend to involve deeper structures like basal ganglia, thalamus, etc. and cerebral amyloid angiopathy causes superficial, lobar bleeds, the only certain way of diagnosing the latter is by brain biopsy.

When it comes to intracerebral haemorrhages, posterior fossa haemorrhages carry a poor prognosis[22] as there is a high risk of developing obstructive hydrocephalus. Intraventricular haemorrhage also carries of high risk of developing hydrocephalus (although the mechanism in the former is related to obstruction of CSF flow but in the latter, it is related to impaired absorption due to the blood and blood products coating the arachnoid villi). It is also known that an intraventricular haemorrhage of 20 mls in volume or increasing size of intraventricular haemorrhage is associated with poor prognosis[23-25].

In terms of anterior circulation ICH, there is good evidence that the bigger the volume of bleed, the worse is the prognosis[26]. Haematoma expansion can happen up to 24 hours after the ictus, although majority of the expansion happens in the first 6 hours[27, 28].

Hemphill et al[29] (Table 1.4) have proposed a simple ICH score using clinical and radiological parameters (Glasgow Coma Scale, Age, Infratentorial or Intraventricular haemorrhage and volume of the haematoma) to help with predicting prognosis – a higher score suggests worse prognosis.

Table 1.4 – ICH score as proposed by Hemphill et al[29]

Parameters	ICH score
GCS	
3 – 4	2
5 – 12	1
13 – 15	0
Age	
≥ 80 years	1
≤ 79	0

Infratentorial haemorrhage Yes No	 1 0
Intraventricular haemorrhage Yes No	 1 0
ICH volume ≥ 30 cm^3 ≤ 29 cm^3	 1 0

Diagnosis is established by neuroimaging. Rapid diagnosis and intensive monitoring is essential as early deterioration is common in the early hours and is likely related to haematoma expansion[27, 28] or increasing peri-haematomal oedema (although there remains debate about this).

Medical and supportive management remains the cornerstone in those with intracerebral haemorrhage. There is increasing evidence that we need to control hypertension more aggressively in the acute phase[30, 31]. Tranexamic acid administered in the acute phase

showed a reduction in early death but unfortunately did not alter the functional outcome. [32] If the patient is on anticoagulants, there is a strong rationale to consider reversing the anticoagulant effect (e.g. activated protein C concentrate for those on warfarin[33] and Idarucizumab for those on dabigatran[34]). Andexanet Alfa has been shown to be an effective antidote for Factor Xa inhibitors, [35] but currently licenced only for reversing the effects of Rivaroxaban and Apixaban (and not for Edoxaban). The role of neurosurgery is limited to those who have a large haematoma with evidence of mass effect[36].

1.6. Clinical and Radiological definitions of severe stroke

There is no generally accepted definition of severe stroke. Some have used the symptoms and signs at the time of presentation to describe stroke severity, whereas others have used various scales that are used to measure disability as a marker of stroke severity. Appelros et al[37] proposed that the amount of initial insult or risk of death on admission as a measure of severity of stroke, but on the other extreme, Nolfe et al[38] suggested that if the functional outcome is poor post rehabilitation (or higher risk of mortality), then it should be classified as severe stroke (and not based on initial presentation).

For the purpose of my dissertation, I am classifying the various clinical scales used in clinical and research setting following stroke into the 3 categories; but some of the scales may fall into more than 1 category.

- Those scales that are used to measure the impairment following a stroke (Oxford classification of stroke subtypes, National Institute of Health Stroke Scale, Scandinavian Stroke Scale, Canadian Neurological Scale and The 6S score)

- Those scales that are used to predict stroke outcomes (e.g. Oxford Classification of stroke subtypes, National Institute of Health Stroke Scale, Scandinavian Stroke Scale, Canadian Neurological scale, Orpington Prognostic Score, Functional Independence Measure, The 6S score, SAFE score, PREP2 algorithm)

- Those that are used to measure performance/functional outcome after stroke (e.g. Barthel Index, Modified Rankin

Scale, Functional Independence Measure and Fugl-Meyer Score)

Even though some scales appear in more than one category, they will be discussed in more detail in the most appropriate section below. More importantly, a recent analysis [39] of 8 different scales showed a varying prognostic accuracy; in addition, even the best performing scales were not good enough to be used for clinical decision making.

1.6.1.Clinical Scales that measure impairment after a stroke

1.6.1.1. National Institute of Health Stroke Scale (NIHSS)[40]

NIHSS is a systematic assessment tool for quantifying neurological deficit in those who have had an acute stroke – see Appendix 2. It uses 11 different domains to assess the neurological deficit. Initially it was used as a research tool to measure the baseline neurological deficit but currently it is used not only in research setting but also in clinical settings. It is simple to administer and has good inter-rater reliability[41]; it can be used not only by doctors but also by the nurses

and allied health professionals. NIHSS measures various domains of neurological deficit but critics argue that it does not measure cognitive deficit, nor it assesses the functional ability of the individual. NIHSS score can be used to predict the volume of brain damage (lower the score suggests smaller the area of damage). NIHSS has been shown to predict short and long term outcome after a stroke[42]. There is some disagreement regarding when one would classify as severe stroke. The National Institute of Neurological Diseases and Stroke which developed this scale suggested that a score of 1 – 4 would be classified as minor stroke, 5 – 15 as moderate stroke, 16 – 21 moderate to severe and > 21 would be classified as a severe stroke. However more recently, the neurointerventional studies[19, 43] have used a criterion of a NIHSS score of 6 or more to be suggestive of a large vessel occlusion, which indirectly suggests a severe stroke (please see section 1.5.2 for further information).

1.6.1.2. The 6S score [44]

Racosta et al[44] have recently developed a stroke severity score based on 6 signs and symptoms for quantifying stroke severity as well as predicting in hospital mortality. The scores were measured (prospectively) within 24 hours of symptom onset and included level

of consciousness, motor deficit, sensory deficit, aphasia, dysarthria, visual defects, neglect, ataxia and cranial nerve palsies (including facial palsy). They argue that it is as good as NIHSS scale when it comes to predicting in hospital mortality. However, this is a small study (only 210 patients) and it has not been validated in any other study.

1.6.1.3. Scandinavian Stroke Scale (SSS) [45]

Scandinavian Stroke Study Group proposed a new scale in 1985[45] (Appendix 3). This score has the advantage of having 2 different scores – prognostic and long term scores. Unlike the NIHSS score, in SSS, a higher score suggests more independence. Although this is a well validated and easy to use tool in acute stroke settings, it is infrequently used scoring system both in clinical practice and in more recent research trials. Gray et al[46] have developed a mathematical conversion system in which both NIHSS score and SSS score can be interconverted reliably and accurately using date from 5 acute stroke trials. More recently, in a small trial (involving 104 patients), SSS has been shown to be as good as NIHSS score in predicting prognosis in 3 months[47]. This scale is particularly useful as it has been shown to predict prognosis following a mild ischaemic stroke[48]. One of the

advantages of using SSS includes the assessment of hand function (compared to NIHSS assessment).

1.6.1.4. Canadian Neurological Scale [49]

First proposed in 1986[49], the Canadian Neurological scale – CNS – (Appendix 5) uses 8 items which include level of consciousness, orientation, speech, motor function and facial weakness. This scale has the advantage that it can be administered to those with receptive dysphasia – the A1 version is for those who have intact language comprehension and the A2 version is for those with receptive aphasia. As the score gets smaller, the prognosis gets worse. One of the biggest advantages is that CNS can be administered to people who are drowsy and can help in monitoring the progress of the individual. Nilanont et al[50] have described a model to reliably convert CNS into NIHSS score – this would allow simpler neurological assessment of acute stroke patients.

1.6.2.Scales that are used to predict outcome

1.6.2.1. Oxford classification of Stroke subtypes [51]

One of the commonly used classification in clinical practice is based on the Oxford Classification of Stroke (also known as Bamford Classification)[51] – see Appendix 1. This was originally developed by neurologists as part of a community-based study of first ever strokes. It has good interobserver reliability[52] and also has been shown to predict mortality and functional outcome[51] but also may help in determining if the stroke is related to large vessel or small vessel occlusion. Those with total anterior circulation stroke have the worst prognosis (1-year mortality being around 60%) and those with lacunar stroke have the best prognosis (1-year mortality 10%).

Table 1.5 – Prognosis based on Oxford classification of stroke subtyes[51]

Type of stroke	Case fatality (%)			Functionally dependent (mRS 3 – 5) (%)			Dead or dependent (%)		
	1 month	6 months	1 year	1 month	6 months	1 year	1 month	6 months	1 year
LACS	2	7	11	36	26	28	38	34	40
PACS	4	10	19	39	34	29	44	45	45
TACS	39	56	60	56	39	36	96	96	96
POCS	7	14	19	39	29	28	38	32	38

1.6.2.2. Orpington Prognostic Score (OPS) [53]

This scale was proposed by Kalra et al[53] in the early 90s (Appendix 4). It just used 4 items (motor, proprioception, balance and cognition) to predict prognosis. Lower the score, better the

prognosis. However, more recently[54], it is argued that even though the inter-rater and test-retest reliability is very good, it has poor accuracy in predicting discharge destination and is a poor predictor of follow up services.

1.6.2.3. SAFE and PREP algorithm [55, 56]

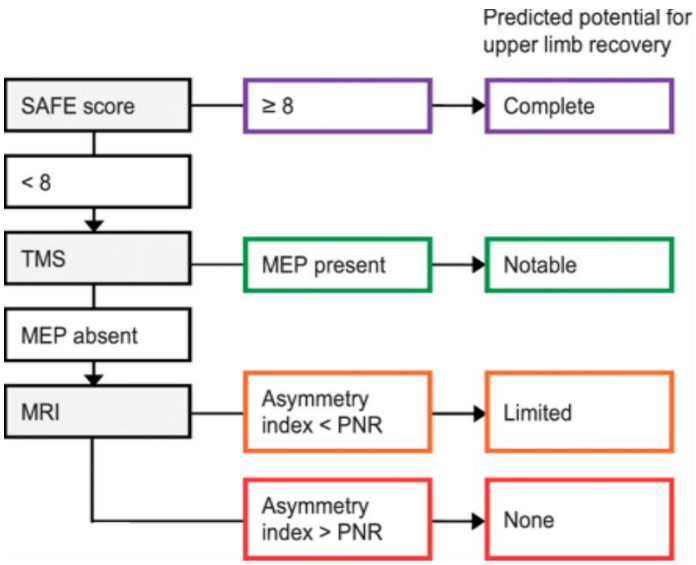
Recovery of upper limb motor function is crucial to regaining independence after stroke[15]. It is difficult to predict recovery of motor function after stroke as it depends on the site of the lesion, whether it is just the cortex or the cortex and the fibre tracts are affected and whether any other structures are affected (e.g. thalamus, brainstem, etc.). Thirumala et al[57] proposed (after fMRI) that it depends on "perilesional motor reorganisation, use of motor pathways in subcortical structures, use of collateral pathways in both ipsi and contralateral side or possibly development of new pathways".

Previous prospective cohort studies had shown that the early recovery of finger extension in the first 7 days[58, 59] and shoulder shrug and abduction in the first 11 days (on average) [60] were

important determinants of good functional outcome for the weak upper limb 6 months after stroke. EPOS study[61] suggested that the presence of Finger Extension and Shoulder Abduction within 72 hours of stroke predicted functional recovery of the hemiplegic arm at 6 months. However, the limitation of this study was the fact that they included only those with mild to moderate stroke and hence it may not be applicable to patients with severe stroke; they also did not include patients who had dysphasia, cognitive problems or altered sensorium. EPOS study also did not include patients with recurrent stroke.

Stinear et al[55, 56] tried to improve the Shoulder Abduction and Finger Extension (SAFE) prediction model further by adding investigations (Predicting Recovery Potential – PREP). The algorithm included TMS and diffusion weighted MR imaging (dw MRI) and the latter to look for anisotropy of corticospinal tract (Figure 1). The SAFE score was assessed at 72 hours after stroke onset.

Figure 1.1 PREP 2 algorithm (reproduced with permission from Dr Stinear) [62]



SAFE – Shoulder Abduction and Finger Extension
(scores calculated using MRC grading of power)
TMS – Transmagnetic stimulation
MEP – Motor Evoked Potential
MRI – Magnetic Resonance Imaging
PNR – Point of No Return

Using this algorithm, they not only showed that they can predict who was going to recover upper limb function in 3 and 6 months post stroke (in other words, functional independence)[55], they also allowed for modification of therapy that the patient received and also a reduced length of stay in hospital[56]. It is interesting to note that in the latter study[56], they recruited all the patients in the 'comparison' group (those who did not have their PREP measured) before they recruited any patients to the 'implementation' group – i.e. sequential study and not a randomised design. However, this study included only patients with mild to moderate stroke, did not include those

with cognitive impairment or dysphasia – similar to EPOS study[61]. The predictions were also made known to the treating clinicians which could have had an impact.

1.6.3.Scales used to measure outcomes

1.6.3.1. Modified Rankin Scale [63]

Modified Rankin Scale (mRS) – Appendix 7 – is one of the commonest tool used to assess degree of disability and dependence; it was first introduced by Dr Rankin[63], it has become the most commonly used tool to assess clinical outcome in stroke research. In general, it is accepted that if the mRS is 3 or more suggests a severe stroke (and significant dependence)[64]. In most research trials (including iv thrombolysis trials, mRS was used at 90 days after stroke onset to assess the disability. Some criticise mRS as it has a significant subjective element when applied to assess clinical outcome; however, this can be reduced to a large extent by using a structured questionnaire.

1.6.3.2. Barthel Index [65]

Barthel Index (BI) – Appendix 6 – is an ordinal measure of activities of daily living and is a commonly used tool not only in research but in day to day clinical practice in a variety of settings (e.g. inpatient rehabilitation, community setting, etc.). It is not a stroke specific tool in assessing the severity of stroke, but it has good inter-rater reliability and easy to use. Petra et al[66] have shown that BI even if administered via telephone is as valid and reliable as the one administered in person. It is one of the oldest measure introduced[65] to measure disability (in 1965); it uses 10 different items that includes aspects of activities of daily living and mobility – higher score suggests functional independence. Although the original BI score had a maximum score of 100, it is often reduced to a 20-point score (but using exactly the same 10 items). Some argue that if the BI is < 50/100[67] or <10/20[68] at the time of admission to rehabilitation, it predicts poor prognosis – suggesting that it is perhaps a severe stroke.

1.6.3.3. Functional Independence Measure [69]

Functional Independence measure (FIM) is an 18 item, which is based on Barthel Index, yields a motor, cognitive and a total score (Appendix 5). This is one of the most frequently used measures in rehabilitation trials not only just in Stroke but also in Traumatic brain injuries, spinal cord injuries and multiple sclerosis. Higher score in FIM score is consistent with more independence. It can be very useful in monitoring the progress of patients with rehabilitation. Alexander et al[70] suggested than a total FIM score of <40 soon after admission suggested a poor functional outcome, but this was a retrospective analysis of 520 patients. There are others who have looked at the motor component of the FIM score soon after admission[71, 72] but once again they are retrospective analysis.

This is a slightly more complex assessment tool to use for assessment compared to the other tools discussed in this section (e.g. Oxford classification or Orpington Prognostic Tool). If a patient achieves level 7, it suggests that they are completely independent and 6 is completely independent but needs some assistance of devices (in these 2 categories, they don't need any supervision); levels 5 – 3 are considered to be relatively independent but need a helper – level 5 just needs supervision but can undertake all activities of daily living (ADL), level 4 needs minimal assistance i.e.

patient can do 75% of ADLs and level 3 needs moderate assistance i.e. patient can do 50% of ADLs; level 2 is dependant for most tasks on a helper and level 1 suggests that the patient is totally dependent (or it is untestable).

1.6.3.4. Fugl-Meyer Assessment (FMA) [73]

Fugl-Meyer scale was first proposed in 1975[73, 74] (see Appendix 8), is a stroke specific, performance based impairment index. It is designed to assess motor functioning (upper and lower limbs), balance (7 tests – 3 seated and 4 standing), sensation (spinothalamic sensation on 2 surfaces of upper and lower limbs and proprioception in 8 joints) and joint functioning (range of movement) and joint pain in patients with post stroke hemiplegia – so, in total 5 domains and 155 items. Scoring is based on direct observation of performance. The advantage of this scale is the fact that any one of the 5 domains can be used on its own (without administering the other domains) to assess that particular functionality (e.g. motor scores, joint functioning scores, etc.). It has been shown to have high inter-rater reliability[75]. Although this has been shown to have excellent correlation with Barthel Index[76] and FIM[77], it has a poor

ceiling effect which makes it somewhat poor in detecting changes over a long period of time[78].

Table 1.6 – Advantages and disadvantages of various scales

Type of Assessment	Advantages	Disadvantages
NIHSS score[40]	Quantitative measure of neurological deficit Easy to measure Good inter rater reliability Helpful to monitor deterioration Can predict volume of brain damage Commonly used in clinical setting	Does not assess cognition Does not assess functional ability Poor in assessing posterior circulation strokes
The 6S score[44]	Easy to administer As reliable as NIHSS in predicting mortality	Not been validated yet in a different population or in other studies Not used in clinical setting

SSS[45]	Validated scale Has prognostic and long term scores Can be reliably converted to NIHSS score equivalent Includes assessment of hand function	Poor in assessing non motor component of neurological assessments Not been used in large scale drug trials (unlike NIHSS)
CNS[49]	Easy to administer 2 sections – one for those with intact comprehension and one for those with impaired comprehension Can be used to monitor change in neurological status	Telephone assessment is not feasible Poor in assessing posterior circulation strokes Used more in research setting

Oxford Classification[51]	Easy, clinical classification Good inter rater reliability Helpful in assessing prognosis Can measure severity of stroke Can predict mortality Commonly used in clinical setting	Does not assess functional ability It can be difficult to allocate them to appropriate subtype (e.g. ataxic hemiparesis)
OPS[53]	Easy to use (only 4 items) Good for prognosis Good inter-rater reliability	Poor in predicting discharge destination; hence in planning service provision Not routinely used
SAFE[61]	Very easy to administer Good prediction of outcome	Has not been validated in clinical setting (only in research) Not validated in larger studies Not used in clinical setting

PREP[55, 56]	Very easy to administer Good prediction of outcome	Has not been validated in clinical setting (only in research) Not validated in larger studies Not used in clinical setting Needs complex neuroimaging in addition to clinical assessment
mRS[63]	Easy to administer Can be done over a telephone Commonly used in clinical setting	Poor demarcation between various levels (e.g. patient may be classified less disabled if able to walk) Moderate inter-observer reliability Less sensitive to changes in neurological status Significant subjective element

BI[65]	Easy to administer Good inter-rater reliability Can be administered over a telephone Commonly used in clinical setting	Poor in assessing cognition Just assesses basic function Less sensitive to changes in neurological status
FIM[69]	Most commonly used assessment in stroke research Very detailed assessment Good correlation with mRS and BI	Difficult to administer 7 point scale is poorly defined Assesses physical function and environment – difficult to assess change if environment changes
FMA[73]	Very detailed assessment Each domain can be administered individually Excellent inter-rater reliability Excellent correlation with FIM and BI Very good for lower limb problems	Very time consuming Poor in detecting change over a period of time Not often used in clinical setting

NIHSS – National Institute of Health Stroke Scale

6S – 6 signs and symptoms

SSS – Scandinavian Stroke Scale

CNS – Canadian Neurological Scale

OPS – Orpington Prognostic Scale

SAFE – Shoulder Abduction and Finger Extension

PREP – Predicting Recovery Potential

mRS – Modified Rankin Scale

BI – Barthel Index

FIM – Functional Independence Measure

FMA – Fugl-Meyer Assessment

1.7. Neuroimaging markers that predict severity of stroke

There has been very little literature on defining severe stroke in radiological terms. Most neuroimaging techniques have looked at prognosis in the medium term rather than trying to define what is a severe stroke. This is somewhat understandable as stroke is a clinical syndrome and radiological investigations aid in the diagnosis by ruling out other causes of neurological deficit. Of course, it is essential in establishing whether the stroke is due to an infarct or haemorrhage. Even though certain neuroimaging findings are accepted by clinicians to represent severe stroke, they are usually accompanied by severe clinical syndrome.

There are several radiological investigations that are used in clinical practice that helps in predicting severity/outcome in clinical setting – e.g. CT Scan, CT angiogram and MR imaging (diffusion weighted imaging); however, there are other investigations that are used predominantly in research setting to help predicting severity/outcome after stroke – e.g. functional MR scan, MR spectroscopy, MR diffusion tensor imaging, transcranial magnetic stimulation

There has been a large volume of work done in this area using a variety of imaging modalities. The techniques have evolved to a tremendously in the last decade or so, but we are still in the very early phase of understanding some of the relevance of the certain findings in imaging and also that we are yet to realise the potential of technological advances.

1.7.1.CT scan of head

As mentioned above, CT scan is the most commonly used modality of neuroimaging in acute stroke. There has been a lot of debate whether it is the site of infarction or the volume of infarction is most relevant in predicting outcome.

There are a number of studies which has found a positive correlation between the infarct volume and a functional outcome[79, 80]. In a small study[81], it was suggested that an infarct size of ≥ 50 mm in diameter led to a poor outcome; another study suggests that an infarct volume of 28 cm^3 correlated with poor outcome[82]. Yoo et al[83] argue

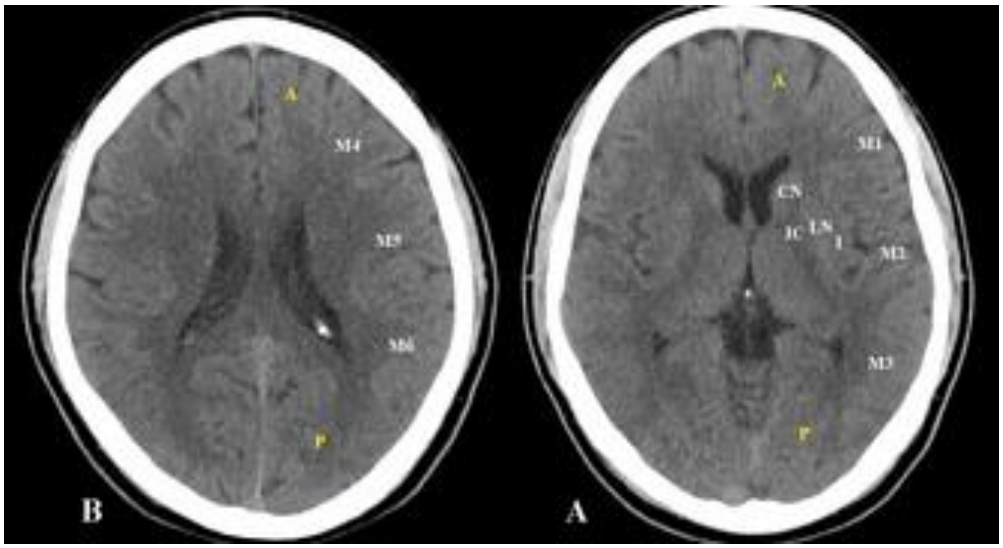
that the infarct volume was an important marker in terms of functional outcome following intra-arterial intervention after a ischaemic stroke. It is also clear that space occupying middle cerebral artery (MCA) territory infarcts carry a not only has a very high mortality rate but a very poor functional outcome as well[84] – this study looked at those who had an infarct volume of ≥ 60 mls with or without midline shift of ≥ 5 mm. The same study also suggested that concurrent anterior cerebral artery infarct worsened the prognosis. The hemicraniectomy trials significantly reduced mortality in this group of people but not necessarily the functional outcome[21].

On the other hand, there is a significant body of evidence to suggest that it is perhaps the lesion location that is significant. Nazzal et al[85] have suggested that there is a significant correlation between motor performance and presence of deep infarcts. Cheng et al[86] argue that those who had involvement of corona radiata or the insular cortex with surrounding frontal operculum had a poor outcome. Interestingly, they also found that there was a difference in lesion location and poor outcome which was dependent on the side of infarct (right inferior parietal lobule had a worse outcome than left and left superior/middle temporal lobe worse than the right).

Anterior choroidal artery territory infarctions are more likely to extend and hence tend to have a poorer prognosis[87].

1.7.1.1. Alberta Stroke Program Early CT Score (ASPECTS) [88]

CT scan of head is the commonest mode of neuroimaging worldwide when a patient presents with acute stroke as it is very cheap and much more widely available than MR scan. Barber et al[88] have described a simple, systematic and reliable way of analysing a CT scan of head in those presenting with acute ischaemic stroke. The MCA territory is divided in to 10 areas – 6 points for the cortex supplied by MCA and 1 each for Caudate Nucleus, Putamen, Internal Capsule and Insular ribbon. In the original article, a point was allocated only if the posterior limb of internal capsule was affected but it is now accepted that point is awarded if any part of the internal capsule is affected. The ASPECTS scoring system has an inverse relationship to NIHSS score and thus the outcome and if the score is less than 8, the outcome following intravenous thrombolysis is poor[89].



1.7.1.2. Hyperdense artery sign

Hyperdense artery sign may be seen in a non-contrast CT brain scan and may suggest a poor prognosis[90-92]. It is not particularly sensitive sign but quite specific of a clot in the artery and may be one of the earliest signs of cerebral ischaemia. It may also suggest that the patient may not respond well to intravenous thrombolytic therapy alone and may well need to undergo mechanical thrombectomy.

1.7.1.3. Malignant middle cerebral artery (MCA) syndrome

This is a devastating condition with nearly 80% mortality in those treated conservatively[93]. Almost in all patients who have had

ischaemic stroke, there is a degree of peri-infarct oedema. The significant difference in malignant middle cerebral artery syndrome relates to the (extensive) degree of brain damage and the subsequent development of 'space occupying oedema', which usually happens in the first 48 – 72 hours (can be much earlier in some patients). This leads on to midline shift and increasing intracranial pressure with or without associated brain herniation (which could be subfalcine or uncal herniations). The infarct itself affects the whole of the middle cerebral artery territory with or without affecting ipsilateral anterior cerebral or posterior cerebral artery territories.

Although CT scan of head is good in detecting this condition, there signs in early stages can be subtle and thus affected by significant intra and interobserver variability. However, more advanced imaging (like MR with diffusion weighted imaging and CT or MR perfusion) can help in identifying those who are at risk of developing malignant MCA syndrome. In fact, a combination of perfusion and diffusion weighted MR scan has a high sensitivity and specificity to identify those at risk of malignant MCA syndrome as early as 6 hours[94]. In a recent study[95], it has been shown if the ASPECTS score is low, the risk of developing malignant MCA syndrome is quite high.

Gerriets et al[96] argue that transcranial colour coded sonography provides a non-invasive way of monitoring ill patients for the development of midline shift and it can be helpful in identifying those patients of risk of developing malignant MCA syndrome as early as 16 hours after stroke onset.

It is important to note that, in addition to the above arguments, it is worth noting that the presence of small vessel disease (which includes white matter lesions, silent/incidental infarctions and cerebral microbleeds) has a significant negative impact on functional outcome[97-99].

1.7.2.CT angiogram

Large vessel occlusion in CT angiogram is associated with poor functional outcome[100-102] – large vessel occlusion refers to internal carotid, middle cerebral (proximal) and basilar arteries. Rothwell et al[103] suggest that it is not just the large vessel occlusion has a poor functional outcome, it extends to the presence of internal carotid artery stenosis. In the prospective STOP-stroke study, Smith et al[104] showed that nearly 50% of patients who presented with stroke

to academic stroke centres had large vessel occlusion; the study suggested that demonstrating the presence of large vessel occlusion within 24 hours of onset of symptoms was associated with poor functional outcome at 6 months. Adding ASPECTS scoring to CT angiogram improved the outcome prediction. [105] It is also relevant to appreciate that recanalisation following intravenous thrombolysis predicts a better outcome as compared to those who had persistent occlusion. [106]

CT angiogram also has the advantage of giving an idea of how good the collateral circulation is and it appears that the presence of collateral circulation is closely related to a good functional outcome[107, 108] and a small volume of infarct[109]. In addition to collateral circulation, it appears that the total clot burden noted on CT angiogram may also be useful in predicting outcome[110].

CT perfusion studies have mainly concentrated on identifying patients who are appropriate for acute intervention, but there is no evidence that it has been used to predict functional outcome in the long term (of course, there may be indirect evidence where CT perfusion is used for interventions like mechanical thrombectomy).

1.7.3.Magnetic Resonance Imaging

Diffusion weighted imaging is particularly useful in early diagnosis of acute stroke. In 30 – 50% of patients who have symptoms lasting more than an hour have evidence of brain damage; this has led many to think that the definition of stroke needs to be based on the presence or absence of tissue damage, but this has not been endorsed (or for that matter rejected) by authoritative organisations. In a normal brain tissue, the water molecules move in a random fashion which is guarded by biologic barriers like cell membrane. When there is an ischaemic insult, there is a failure of sodium-potassium pump which leads to cytotoxic oedema; diffusion weighted imaging (DWI) is very sensitive to this and there is a drop in apparent diffusion coefficient (ADC) value and thus giving rise to a bright area in DWI but a darker area in ADC mapping.

MR imaging has been mainly looked at diagnosing acute stroke (or to evaluate stroke mimics). Diffusion weighted imaging is so sensitive that it can pick up very small lesions particularly in brain stem, but the lesion seen in scan can be disproportionately small compared to the clinical syndrome. There is very little literature on MR imaging findings and functional outcome in medium to long term.

Whilst one small study[111] suggested that the volume of lesion seen in DWI correlated with BI at the end of one month, another similar sized study[112] suggested that the volume of damage did not relate to the final outcome. Barrett et al[113] suggested that a growth in DWI by day 5 predicted a poor outcome on day 90, but this in those who had mild to moderate stroke at the onset.

Water molecular movement is 3 dimensional and it may be anisotropic (i.e. different physical property in different axis) in the brain parenchyma and is almost certainly the case in white matter. Diffusion tensor imaging (DTI) utilises this anisotropic nature of water molecule movement and provides extremely detailed images; when used appropriately, one can track the various tracts (e.g. corticospinal tract) – helping to determine whether the track is damaged or not. It is not hard to imagine that DTI when combined with functional MRI (fMRI) can give very detailed images of the corticospinal tract and help to predict prognosis. Studies have shown that DTI can predict prognosis of motor recovery both in anterior (corona radiata)[114] and posterior circulation[115] (pontine) infarcts by determining if the corticospinal tract is intact or not – the scans were done 1 – 12 weeks after the stroke onset in these studies. Lindenberg et al[116, 117] have suggested that the predictive power can

be improved by looking at both the corticospinal tract as well as alternative motor pathways and also one would be able to tailor the rehabilitation programme for individual patients. Thus, DTI done a few weeks after the stroke onset, would be very helpful in determining prognosis in severe stroke and in looking at rehabilitation potential in chronic stroke patient.

A very interesting study[118] showed that it is not necessarily the cortical damage, but it is the integrity of the tract which determines the recovery potential (this study looked at language function). Bigourdan et al[119] have shown that the initial (corticospinal) fibre number ratio (compared to the unaffected side) measured using early DTI (1 – 3 days after stroke) is very helpful in predicting motor recovery at 1 year, particularly in those with severe stroke at the onset.

Functional MR imaging (fMRI) measures changes in blood movement in the brain over time – blood oxygen level dependent (BOLD) signal. It reflects the amount of deoxyhaemoglobin in a tissue and hence an indirect measure of neural activity – the deoxyhaemoglobin levels will depend on the local metabolism of oxygen, cerebral blood flow

and volume. Hence the levels of deoxyhaemoglobin will increase when neural activity increases when neural activity increases as all the above 3 increases. fMRI may be done whilst the patient is undertaking activity or at rest. fMRI has been used mainly to help further our understanding of the neural connections and how the results differ in those who showed improvement and those who didn't, mainly looking at the site of lesion. But with advances in technology, it is possible to follow the tracts; however, the major problem with fMRI is the fact that even minimal head movement will render the images uninterpretable. As of date, the evidence of functional MR imaging being used to predict recovery is very sparse.

MR Spectroscopy allows non-invasive measurement of metabolites within a defined area of tissue. With a 3T MR scanner, we currently can reliably detect N-acetylaspartate, myo-inositol, choline, creatine, glutamate and lactate. We are yet to understand the roles of these metabolites and hence the applicability in predicting rehabilitation potential or functional recovery is very limited. Perhaps measuring N-acetylaspartate is the only one that appears to be useful as it is reduced in neuronal death and appears to be further reduced in the chronic state[120]. However, the usefulness of MR Spectroscopy has not moved further which is disappointing.

1.7.4.Transcranial Magnetic Stimulation (TMS)

Although TMS is not a form of neuro-imaging, it is included in this section as it can potentially give a correlation to the anatomical area of brain damage by testing the physiological integrity of the corticospinal tract. TMS activates neurons under the magnet and at high intensities, can depolarise the corticospinal neurons, which can be measured at the target muscle using surface electromyography. TMS can be excitatory or inhibitory and there have been attempts at using TMS both in the affected side and contralateral side. There are 2 types of TMS – single pulse and repetitive.

In the single pulse, the motor evoked potential (MEP) is calculated using the smallest threshold needed to evoke a motor response (akin to the voltage in temporary pacemaker). TMS assessment has shown altered brain activity and connectivity at various times after stroke (days, weeks and months). Some have suggested that a lack of elicitable MEP in the paralysed limb predicts poor prognosis[121] but others disagree with this view[122, 123]. It is possible that Stinear's[121]

data is a few years later and hence the technology might have progressed, but this result is yet to be reproduced.

Repetitive TMS (rTMS) can be applied in specific ways to modulate cortical activity. Some argue that the effect of rTMS persists long after the stimulation ceases[124, 125], which can be used to assess neuroplasticity and enhance rehabilitation potential[126, 127]. Although this sound very interesting and the potential for this in rehabilitation post stroke, unfortunately the results to date have been disappointing due to the inconsistent response to rTMS[128-131].

From what we currently know, TMS on its own, is unreliable in assessing neuroplasticity (and thus predictive potential) and in the rehabilitation process.

Table 1.7 (adapted and reproduced with permission)[132]

Methods	Benefits	Limitations	Used in which setting
CT scan – non contrast	Inexpensive Readily available Easy to interpret Excellent specificity in acute intracerebral haemorrhages	Poor in detecting early infarct	Clinical Rarely research setting these days
CT angiogram	Readily available Inexpensive	Harder to interpret Higher level of radiation exposure Risk of contrast nephropathy	Clinical and Research setting

CT perfusion	Detects penumbral tissue	Expensive Hard to interpret Significant level of radiation exposure	Mainly research setting Just coming into clinical practice
dw MRI	Quantification of brain volumes from basic structural scans Very sensitive and specific for acute stroke	Limited accuracy in individuals with lesions Not readily available worldwide (although available in Western world)	Clinical and research setting
Diffusion Tensor Imaging	Helps to identify tract integrity	Not easily available Needs expertise to capture images Difficult to interpret	Research setting only

fMRI	Identifies patterns of brain activation at high spatial resolution Detects neuronal connection	Poor resolution Limited to participants who can complete the task Not readily available Hard to interpret	Research setting only (in acute stroke)
Resting state fMRI	Not dependent on task completion	Movement renders it useless Not readily available Hard to interpret	Research setting only
MRS	Quantifies neurotransmitter in defined area	Requires technical expertise Expensive Not readily available	Research only (hardly ever in translational research at present)

TMS	Assessment and modulation of cortical excitability and plasticity Relatively inexpensive	Requires specialised equipment and trained personnel Not readily available	Research settings only

CT – Computerised Tomography

dw MRI – diffusion weighted sequence of Magnetic Resonance Imaging

fMRI – Functional Magnetic Resonance Imaging

MRS – Magnetic Resonance Spectroscopy

TMS – Transcranial Magnetic Stimulation

1.8. Other factors that predict functional outcome after Severe Stroke

It would be extremely helpful if one can predict the functional outcome after a severe stroke – to plan rehabilitation programme for the individual, to organise community care, to plan rehabilitation services, etc. Using Oxford classification of stroke subtypes and the routine use of one of the severity scales (e.g. NIHSS score) can be very helpful. However, a number of other variables can have a significant impact on the recovery potential.

1.8.1. Risk factors and post stroke complications

Advancing age is a major factor that affects mortality and morbidity[133-136]. Interestingly, this does not differ whether the individual has had a mild or a severe stroke. It also appears that those who have had a severe stroke over the age of 65 and being discharged to a nursing home facility have a higher risk of death within the first 2 – 3 months[137, 138]. One study found that age and

motor impairment were significant in predicting recovery after severe stroke but not vascular risk factors and gender[139].

A large number of co-morbid conditions, which may also be a risk factor for stroke, increase the risk of poor outcome. It may be related to the risk of having a large stroke – atrial fibrillation[37, 133, 140-142], heart failure[141], diabetes[141] or hyperglycaemia[143], dialysis[144], due to the underlying conditions which has a poor prognosis independent of the stroke - cancer[141, 145], dementia[37, 145, 146], dependency[141, 145] and poor nutritional status[147] or as yet poorly understood – low haemoglobin level[148]. Bizarrely, those who have low or normal body mass index have a worse prognosis in terms of mortality and functional outcome[149] compared those who are overweight or obese!

Some of the post stroke complications have been implicated in higher risk of mortality e.g. pneumonia[134] but there is very little literature on whether it predicts functional outcome after stroke.

1.8.2. Clinical Features

Severe aphasia tends to have a poorer prognosis[150, 151] and it appears that a year after stroke, fluent aphasics are more likely to be older than non-fluent aphasics[151].

Although dysphagia is common after stroke (>50% have dysphagia in the acute phase), there is very little literature on how it impacts on the prognosis. Recent Cochrane review[152] suggests that there is not enough evidence on what happens to the patients who are fed by Percutaneous Endoscopic Gastrostomy (PEG). FOOD trial[153] suggested that early tube feeding may improve survival but at the cost of more disability and it did not support the policy of early PEG tube feeding.

There is very little literature on the predictive potential of visuospatial neglect. One study suggested that those with visuospatial neglect, despite lower BI, had similar discharge destination as those with similarly severe stroke without neglect[154]. There is evidence, however, that those with significant neglect have poorer rehabilitation outcome[155].

Post stroke depression is common in the first few months after stroke and it has a significant negative impact on functional outcome[146].

1.9. Gaps in literature

SSS has been used in small number of studies in assessing non-motor symptoms and not been validated in large scale trials, OPS is not used routinely in clinical setting, CNS is poor predictor in those with posterior circulation stroke and FIM is very difficult to administer as well as the fact that is very dependent on the environment in which it is administered. SAFE score has neither been validated in different population nor has been reproduced in other trials and PREP2 algorithm uses complex and advanced imaging (although part of this is SAFE score) – in addition, these have been used only in those with ischaemic strokes and did not include those who had significant dysphasia and/or cognitive problems post stroke.

Presence of dense artery sign or low ASPECTS score suggests a poor outcome as well as large infarct volume (although it is not clear how

large the infarct needs to be) in non-contrast CT brain scan. There is very little evidence in literature if there are any other features in the non-contrast CT head scan that has prognostic implications in those with acute changes which is known to carry poor prognosis (as those acute changes are common in patients with severe stroke). Poor collateral circulation in the presence of large vessel occlusion in CT angiogram predicts a poor outcome. Advanced imaging may be very helpful in predicting outcome, but they are yet to be validated in large scale studies and their availability remains limited in most countries.

As of to date, there have been very little attempt to merge clinical and radiological findings to augment the predictive potential in those with severe stroke.

1.10. Aims and Hypothesis

I wanted to investigate if there was anything specific in the patient's clinical presentation and a wide range of (acute and background) radiological parameters that was available in the ENOS dataset that

could be used to identify those who do not recover well following a severe stroke.

The following hypotheses were tested in our study:

1. Poor score in the combined arm/hand score (as calculated from SSS) on day 0 is associated with poor 90-day clinical outcome in those with ischaemic stroke and ICH

2. Acute radiological changes in the baseline CT head scan is more frequent in those with severe stroke (in both ischaemic stroke and ICH)

3. Background radiological changes in the baseline CT head scan is more frequent in those whose arm/hand score did not improve by day 7 (in both ischaemic strokes and ICH)

4. Presence of background radiological changes in the baseline CT head scan is associated with a poor outcome in those whose

arm/hand score did not improve by day 7 (in both ischaemic strokes and ICH)

Chapter 2 – Ischaemic Stroke

2.1 Abstract

Introduction: Upper limb function is essential for regaining independence after stroke. I hypothesised that poor arm and hand function on day 0 and the presence of both acute and background parameters in baseline CT head scan are associated with a poor outcome in severe stroke.

Methods: I used patient data from the large ENOS trial and compared clinical and radiological outcomes between severe and mild/moderate stroke defined by the arm/hand scores in the Scandinavian Stroke Scale. The primary outcome was defined as a modified Rankin Score (mRS) of ≥ 3 on day-90. Secondary outcomes included death/institutionalisation, mRS (ordinal scale), Barthel Index, mood, cognition and quality of life on day-90 and length of hospital stay. Analyses were adjusted for age, baseline systolic BP and pre-stroke mRS and odds ratio (95% confidence intervals, CI) are given.

Results: Of the 3338 patients with an ischaemic stroke in ENOS trial, 1318 (39%) had an arm/hand score of ≤ 4 (out of 12 – derived from

the conversion of SSS to MRC grading) at the time of randomisation. Arm/hand score of ≤ 4 on day 0 was associated with a poor functional outcome at day-90: mRS>3 (OR 6.35. 95% CI 5.39-7.48); all secondary outcome measures were worse if the arm/hand score was ≤ 4 on day 0 ($p<0.001$). In those whose arm/hand score did not improve by day 7, the presence of acute neuroimaging markers of ischaemia was associated with poor day-90 recovery and the poor background brain health was associated with a prolonged length of stay (but not the other outcomes).

Conclusion: Poor arm/hand movement on day 0 and acute radiological parameters were associated with a day-90 poor outcome but not the background radiological parameters.

2.2 Introduction

Only 14% of stroke patients achieve full recovery of activities of daily living while 25 – 50% require some assistance and up to 50% are dependent in the long term. [156] Being able to predict outcome early after the stroke will be beneficial in the provision of health and social care, and in setting realistic rehabilitation goals.

Recovery of upper limb motor function is crucial to regaining independence after stroke. [15] Prospective cohort studies have shown that early recovery of finger extension in the first 7 days [58, 59] and shoulder shrug and abduction in the first 11 days [60] are important determinants of good functional upper limb outcome at 6 months after stroke. The EPOS study [61] suggested that the presence of finger extension and shoulder abduction within 72 hours of stroke predicted functional recovery of the hemiplegic arm at 6 months. Stinear et al [55, 56, 62] improved the shoulder abduction and finger extension (SAFE) prediction model by adding further investigations, including transmagnetic stimulation and magnetic resonance imaging to identify those who had a very poor recovery potential. Using this predicting recovery potential (PREP) algorithm, they not only showed that they could predict who was going to recover upper limb function (or functional independence) [55] at 3- and 6-months post stroke, but that this also allowed for modification of therapy with a reduction in length of stay in hospital.[56] Importantly, the SAFE and PREP algorithms involved only patients with mild-to-moderate ischaemic stroke and their development did not include patients with dysphasia or cognitive impairment post stroke.

Whilst MRI and TMS are used increasingly, CT scan remains the mainstay for acute stroke imaging. Some acute CT markers (e.g. hyperdense middle cerebral artery [90-92] and ASPECT scoring systems) [88, 89] may be helpful in predicting poor outcome. Further, pre-stroke brain changes, quantified as small vessel disease and brain frailty scores, are associated with poor outcome. [157, 158]

2.3 Methods

2.3.1 Participants

I used patient-level data from the ENOS trial, [159] an international multicentre randomised single-blind patient and outcome-assessor masked parallel group trial; ENOS recruited patients with both ischaemic stroke and intracerebral haemorrhage from July 2001 to Oct 2013. The full ENOS protocol has been published. [160] In brief, participants had to have motor weakness in the arm or leg and a diagnosis of ischaemic or haemorrhagic stroke; key exclusion criteria included pure sensory stroke, isolated dysphasia, premorbid dependency (mRS >2) or coma (Glasgow Coma Scale <9).

2.3.2 Measures

In this *post hoc* sub-study, patients with ischaemic stroke were analysed. Data included baseline demographics, Scandinavian Stroke scale [45] (SSS) on day 0 and 7, blood pressure, type of stroke (Oxford and TOAST subtypes), premorbid modified Rankin score (mRS) and baseline CT scan of head. 90-day clinical outcomes included mRS (primary outcome), death, disposition, telephone mini-mental state examination (t-MMSE), Zung depression scale, and quality of life (Euro-QoL-5 dimension-3 level, EQ-5D-3L; Euro-QoL-visual analogue scale, EQ-VAS) determined centrally by telephone (or post). Length of hospital stay was also collected.

I converted SSS motor scores to Medical Research Council (MRC) motor power grading, this giving a range of 0 to 12 (Appendix 8) – I used MRC grading as this was the measurement of weakness that was used in the PREP algorithm. I categorised patients into two groups based on the sum of arm and hand scores – those with severe weakness (MRC score of 0 – 4) and those with mild weakness (MRC 5 – 12). I also calculated the arm/hand scores on day 7 in those who presented with a baseline arm/hand score of 0–4; these were

categorised as ‘non-improvers’ if their score remained ≤ 4 on day 7 and ‘improvers’ if it was ≥ 5.

CT scan of head (baseline scan) were adjudicated for both acute (infarct size, Albert Stroke Programme Early CT Score [ASPECTS], hyperdense artery, mass effect and midline shift) and background (e.g. periventricular lucencies, old infarcts and atrophy) changes. [159] I also calculated a score for burden of small vessel disease (SVD) as sum of presence of acute lacunar infarct, established lacunes and periventricular lucencies, with range of 0 (none) to 3 (severe).[97, 99, 157, 161] Similarly, I calculated a score for brain frailty as sum of established lacunes, brain atrophy and periventricular lucencies, again having a range of 0 (none) to 3 (severe).

2.3.3 Outcomes

Poor outcome was defined as a stroke that led to a modified Rankin scale of >3 90 days after stroke. Secondary outcomes included death/institutionalisation, modified Rankin Scale, mRS (scores 0 = no residual disability to 6 = death), [63] cognition (as measured by modified telephone MMSE, [162] tMMSE – scores 0 = severe dementia

to 18 = normal), mood disorder (short Zung depression score [163] – scores 0 = normal to 100 = severe depression), activities of daily living (Barthel Index, [65] BI – scores 0 = severe disability to 100 = no disability), quality of life (European Quality of Life – 5 dimensions, [164] EQ-5D – scores 0 = dead to 1.0 = perfect; and European Quality of Life – Visual Analogue Scale, [164] EQ-VAS – scores 0 = very poor and 100 = excellent) and length of hospital stay.

I looked at the day-90 clinical outcome based on the arm/hand score at the time of randomisation. I also looked at the association between various acute and background radiological parameters in the non-improvers as identifying those with poor outcome would allow distribution of rehabilitation resources in a slightly different way i.e. targeting those who are more likely to respond. I did not look at the radiological association between clinical outcome at the time of randomisation as we know that having some of the acute radiological parameters like hyperdense middle cerebral artery is associated with poor outcome.

2.3.4 Analysis

I dichotomised patients by the arm/hand scores (≤ 4 and ≥ 5) on day 0, and by whether they had improved or not by day 7 (i.e. baseline arm/hand score of ≤ 4 on day 0 and remained ≤ 4 on day 7). SPSS version 24 was used for statistical analysis. Chi Square test and T test was used to look for any statistical difference in the baseline clinical and radiological categorical and continuous data respectively. I used binary logistic regression for categorical variables, ordinal logistic regression for mRS (shift analysis) and linear regression for continuous variables for analysis of the data. Data were analysed with adjustment for age, systolic blood pressure and premorbid mRS.

2.4 Results

2.4.1 Baseline outcomes

Of the 4011 patients recruited into ENOS, 3338 (83%) patients had a final diagnosis of ischaemic stroke. 1318 (39%) patients had an arm/hand score of ≤4 (severe weakness) and 2020 (61%) patients had a score of ≥ 5 (mild/moderate weakness) at randomisation

(Figure 1). Of the 1318 patients, the majority (n = 834, 62%) had no movement in arm and hand. Those who had an arm/hand score of ≤ 4 on presentation were more likely to be female and have a higher incidence of atrial fibrillation, hypertension, smoking and dysphasia, and more severe stroke (lower GCS, lower SSS/higher calculated NIHSS; Table 1); they were also more likely to have total anterior circulation syndrome (TACS) and cardioembolic or large vessel disease stroke (TOAST subtype). Conversely, those who had an arm/hand score of ≥ 5 were likely to have lacunar stroke or posterior circulation stroke (Table 1). There was no difference in the baseline pre-stroke function as assessed by modified Rankin Score. A lower arm/hand score (i.e. severe weakness) was associated with all acute stroke neuroimaging markers at baseline (hyperdense artery, larger infarct size, mass effect, midline shift, lower ASPECT score) and a lower SVD score (Table 2).

2.4.2 Clinical outcomes

An arm/hand score of ≤ 4 on day 0 (calculated using the MRC conversion of SSS score) was associated with a significantly poor primary (mRS > 3) and all of the secondary outcomes at day 90 compared to those who had an arm/hand score of ≥ 5 on day 0 (Table

3, Figure 6). Length of stay in hospital was 13 days longer with baseline arm/hand score ≤ 4 (Table 3).

Those with an arm/hand score of 0 on day 0 had a very poor chance of recovery on day 7 (Figure 2) and this was also associated with a poor primary outcome (Figure 3). Forest plots of various arm/hand score (Figure 5) revealed a significantly poor primary outcome in those who had an arm/hand score of ≤ 4, and it was significantly worse – odds ratio of a poor outcome was 6.91 (95% CI 5.787, 8.252) if the arm/hand score was 0 on day 0.

2.4.3 Non-improvers (arm/hand score ≤ 4 on day 0 and 7)

Of the 1318 patients who presented with an arm/hand score of ≤ 4 on day 0, 355 (27%) had improved with arm/hand score ≥ 5 on day 7, and 918 (70%) did not improve (45 had died – these were excluded from some of the analysis e.g. mood and cognition). Stroke was more severe and there was a higher incidence of TACS (Oxford classification) and cardioembolic and large vessel disease stroke (TOAST classification) in the non-improvers (Table 1). Acute, but not background radiological, features at baseline were more prevalent in those who had not improved by day 7 (Table 2).

Of the 834 patients who had no movement of arm and hand on day 0, 676 (81%) did not show any improvement on day 7. 62% of those who had an arm/hand score of ≤ 4 on day 0 were either dead or institutionalised (as opposed to 22% of those who had a score of ≥ 5 on day 0. The chance of recovery was poor if the sum of the arm/hand score was 0 (in SSS) on day 0 (odds ratio of poor recovery was 29) – Figure 5.

In the non-improvers (Table 5), the mean ASPECT score was 6.7 as compared to 8.4 in those who had improved on day 7, and infarct size (on an ordered 5-point ordinal scale of 1 being no infarct to 5 being an extensive infarct) was larger (2.54 vs 1.91, $p < 0.001$). Very few participants had a midline shift (n = 29, 3%). All of the acute markers were associated with those who did not improve in both the primary and secondary outcome measures apart from death/institutionalisation on day 90. In both groups (whole cohort as well as the non-improvers), forest plots suggest that the hand function is a better predictor of poor primary outcome than arm function – OR of 6.9 and 2.5 respectively (Figures 3, 4).

There was no difference in the mean SVD and Brain Frailty scores between the 2 groups (1.0 and 1.7 in those who did not improve on

day 7 vs. 1.0 and 1.8 in those who had improved, respectively). None of the background changes (old vascular lesions, periventricular lucencies, brain atrophy, brain frailty or SVD scores) were related to a poor outcome (Table 5).

2.5 Discussion

This study has shown that early hand and arm function (as measured by scores in SSS) may be helpful in predicting 90-day clinical outcome following an acute ischaemic stroke. Arm + hand scores show a high degree of predictability with regards 90-day outcome on various clinical parameters (i.e. if the arm + hand score was ≤ 4 on day 0), they had a poor clinical outcome in both the primary (mRS > 3) and secondary outcome measures (death/institutionalisation, quality of life, mood, cognition and length of stay). Our study highlights that poor hand function is perhaps a stronger predictor of poor outcome than arm function; it also suggests that a cut off value of arm/hand score of 4 is useful in predicting poor clinical outcome. Measuring hand function is easy to perform, and this, in addition to arm function, may provide clinically useful information regarding the 90-day outcome. NIHSS is the most commonly used scale in stroke research/clinical settings; however, it does not measure the hand

function. I believe a simple test of hand function (ability to grip and extend the fingers) may help better predict 90-day clinical outcomes when used in addition to NIHSS score.

All the acute radiological parameters were associated with a poor chance of recovery on day 90 in non-improvers (i.e. those whose arm/hand function was ≤ 4 on day 0 and day 7) – this is in keeping with the other literature which suggests that the presence of acute radiological markers like hyperdense artery [90, 91] and lower ASPECT score [88] carry a poor outcome.

One of the strengths of our study is the large cohort derived from a pragmatic acute randomised controlled trial. All patients had a baseline CT scan of the head which were adjudicated by neuroradiology experts which add strength to the quality of interpretation, allowing us to study the impact of both acute radiological parameters and background brain health.

The ENOS study was not designed to look at rehabilitation strategies; hence I am unable to comment what (and how much) rehabilitation

the patients received – this could potentially affect the clinical outcome i.e. creeping of unconscious bias – less rehabilitation for those with profound arm/hand weakness as they might have been believed to have a poor prognosis in any case. Over 99% of patients were independent at the time of randomisation (mean mRS of < 1), which makes it difficult to extrapolate our findings to a dependant population pre-stroke. One of the strongest prognostic factors is a high baseline stroke severity (as depicted by a low SSS score on admission) – but I could not adjust for this statistically as it was 2 of the components of SSS I was testing. Repeat neuroimaging was not mandatory in the ENOS study, thus potentially missing important changes like stroke progression, oedema or midline shift. I did not look at whether any of the patients had had a further cerebral event during the 90-day study period, which could potentially affect the 90-day outcomes. Finally, I converted the SSS score to MRC grading (to calculate the arm/hand score), an approach which has not been previously validated.

The PREP2 algorithm[62] measured the arm and hand function using SAFE score on day 3 but I used the day 7 scores as the ENOS study did not collect SSS on day 3 – so these studies are not directly comparable to each other; however, having the SSS done on day 7

might have allowed more time for our patients to improve, allowing us to predict outcome more accurately. In the PREP2 algorithm, they recruited all the patients in the 'comparison' group (those who did not have their PREP measured) before they recruited any patients to the 'implementation' group – i.e. sequential study and not a randomised design. The protocol was to use MRI scan in the PREP2 algorithm and although MRI scan gives better anatomy of brain parenchyma, our study is perhaps more applicable across the world as CT scan is much more readily available; it is also feasible that those with severe stroke may not be able to tolerate MRI scan. Also, in the PREP2 algorithm, the investigators did not look at the impact of any background changes in the brain scan.

Previous studies have shown that brain frailty[157] (a combination of lacunar infarct, leukoariosis and brain atrophy) and global small vessel disease burden[97, 99, 161] predicted poor recovery; our study suggests that in those with severe stroke, background brain changes were less important in predicting clinical outcome (as opposed to acute changes). Higher burden of small vessel disease or brain frailty predicted a longer length of hospital stay and this may reflect underlying comorbidity or inability to repair and reorganise. This is easy to measure and adds economic value (longer length of hospital

stay = higher cost), allowing one to modify the allocation of finite resources.

This study does not answer some of the questions including predictors of outcome after stroke in those who are disabled at the onset of stroke. I need to study those who have had repeat neuroimaging a few days after the event and how the development of complications (radiological changes) impacts on the clinical outcome. Further research is also needed in those who have had a cerebral haemorrhage as this study has looked only at those who have had a cerebral infarct (this aspect has been addressed later in this thesis).

In conclusion, I looked at early arm/hand function and found that a score of ≤ 4 on day 0 had a poor 90-day outcome. I found good correlation between the presence of acute radiological markers and poor 90-day clinical outcome. However, our study did not support the hypothesis that having pre-existing background changes in the brain (as detected in baseline CT scan) was associated with persistent weakness on day 7. Although the clinical outcome was

not any different, presence of pre-existing background changes prolonged the length of hospital stay in the non-improvers.

Table 2.1 – Baseline clinical characteristics

Clinical characteristic	Arm/Hand score, day 0		2p	Arm/Hand score of ≤ 4, day 0		2p
	≤ 4	≥ 5		Non-improvers (score ≤ 4 on day 7)	Improvers (score ≥ 5 on day 7)	
Patients, N (%)	1318 (39)	2020 (61)		918 (70)	355 (27)	
Male (%)	665 (50)	1198 (59)	< 0.001	454 (49)	185 (52)	0.39
Mean age (SD)	72 (12)	70 (12)	<0.001	72 (11)	71 (12)	0.19
Hypertension (%)	897 (68)	1284 (63)	0.008	634 (69)	234 (66)	0.28
Diabetes (%)	238 (18)	373 (18)	0.77	168 (18)	60 (17)	0.56
Atrial fibrillation (%)	254 (19)	259 (13)	<0.001	172 (19)	69 (19)	0.77
Previous Stroke (%)	184 (14)	324 (16)	0.10	127 (14)	54 (15)	0.53
IHD (%)	257 (19)	336 (17)	0.06	215 (23)	64 (18)	0.16
PAD (%)	106 (8)	159 (8)	0.22	74 (8)	28 (8)	0.98
Alcohol consumption** (%)	84 (6)	152 (7)	<0.001	65 (7)	16 (4)	0.28
Smoking - current or ex (%)	690 (52)	1035 (51)	< 0.001	492 (54)	177 (50)	0.56
Left sided weakness (%)	670 (51)	1047 (52)	0.31	475 50)	178 (50)	0.72

Dysphasia (%)	742 (56)	553 (27)	< 0.001	530 (58)	177 (50)	0.011
Oxford Classification [52]			<0.001			<0.001
TACS	665 (50)	297 (15)		514 (56)	113 (33)	
PACS	362 (27)	677 (33)		226 (25)	131 (37)	
LACS	289 (22)	911 (45)		178 (19)	110 (31)	
POCS	2 (0)	135 (7)		0 (0)	1 (0)	
TOAST classification [16]			<0.001			0.55
Cardioembolic	351 (27)	340 (17)		253 (28)	84 (24)	
Large vessel disease	379 (29)	346 (17)		291 (32)	73 (21)	
Small vessel disease	337 (25)	930 (46)		199 (22)	135 (38)	
Mean GCS (SD)	13.5 (2)	14.7 (1)	<0.001	13.3 (2)	14.1 (1)	<0.001
Mean systolic BP (SD)	167 (19)	166 (19)	0.48	167 (19)	166 (19)	0.66
Mean SSS (SD),	22.2 (10)	42.5 (8)	<0.001	20.6 (9)	27.2 (9)	<0.001
Mean calculated NIHSS (SD)	16.1 (4)	7.4 (3)	<0.001	16.8 (4)	14.0 (4)	<0.001
Mean baseline modified Rankin (SD)	0.4 (0.7)	0.4 (0.7)	0.567	0.4 (0.7)	0.4 (0.7)	0.42

SSS = Scandinavian Stroke Scale; SD = Standard deviation; IHD = ischaemic heart disease; PAD = peripheral arterial disease

** > 21 units in men or > 14 units in women

Table 2.2 – Baseline neuroimaging characteristics

Imaging characteristics	**Arm/Hand score on day 0**		**2p**	**Day 7 Arm/Hand score in those with a score of ≤ 4 on day 0**		**2p**
	≤ 4	≥ 5		≤ 4	≥ 5	
Patients, N (%)	1318 (39)	2020 (61)		918 (*)	355 (*)	
Acute						
Hyperdense MCA (%)	384 (29)	193 (9)	<0.001	302 (33)	62 (17)	<0.001
Mass effect (%)	621 (47)	483 (24)	<0.001	477 (52)	117 (33)	<0.001
Midline shift (%)	36 (2)	6 (0)	<0.001	29 (3)	2 (0)	0.007
Mean ASPECTS score (SD)	7.1 (3.3)	8.91 (1.8)	<0.001	6.73 (3.48)	8.38 (2.54)	<0.001
Mean Infarct size (SD)	2.21 (1.15)	1.79 (0.84)	<0.001	2.54 (1.21)	1.91 (1.04)	<0.001
Background						
Old vascular lesions (%)	761 (58)	1223 (60)	0.11	520 (57)	218 (61)	0.12
Brain tissue reduction (%)	1112 (84)	1675 (83)	0.27	774 (84)	303 (85)	0.64
Periventricular lucencies (%)	436 (33)	774 (38)	0.002	304 (33)	122 (34)	0.67
Mean Brain Frailty score (SD)	1.7 (0.9)	1.8 (0.9)	0.05	1.7 (0.9)	1.8 (0.9)	0.23
Mean Small Vessel Disease score (SD)	1.0 (0.8)	1.1 (0.8)	<0.001	0.9 (0.8)	1.0 (0.8)	0.08

Brain Frailty score = sum of old vascular lesions, brain tissue reduction and periventricular lucencies each getting 1 point; range 0 – 3

Small Vessel Disease score = sum of acute lacunes, periventricular lucencies and old vascular lesions each getting 1 point; range 0 – 3

Table 2.3 – Clinical outcomes based on baseline arm/hand score**.** Data re number (%) or mean (standard deviation).

CLINICAL OUTCOME	**Arm/Hand score on day 0**		**OR, 95% CI**	**2p value**	**Arm/Hand score on day 7**		**OR, 95% CI**	**2p value**
	≤ 4	**≥ 5**			**≤ 4**	**≥ 5**		
Patients, N (%)	1318 (39)	2020 (61)			1448 (42)	1814 (53)		
mRS > 3 (%)	850 (64)	493 (24)	6.35 (5.388, 7.484)	<0.001	928 (69)	365 (21)	8.22 (6.927, 9.767)	<0.001
Dead/Institutionalised (%)	816 (62)	436 (22)	1.43 (1.233, 1.652)	< 0.001	621 (53)	577 (6)	1.58 (1.363, 1.821)	<0.001
mRS (/6)	4.0 (1.5)	3.4 (1.6)	1.80 (1.666, 1.937)	< 0.001	4.3 (1.4)	2.4 (1.5)	2.12 (1.976, 2.257)	<0.001
Barthel Index (/100)	43.6 (39.3)	79.6 (30.6)	-34.3 (-36.52, -32.08)	< 0.001	35.9 (36.53)	80.9 (28.69)	-37.5 (-39.56, -35.41)	<0.001

t-MMSE (/22)	7.5 (8.3)	13.5 (5.9)	-5.4 (-6.05, -4.78)	< 0.001	6.47 (8.25)	13.78 (5.61)	-5.7 (-6.32, -5.11)	<0.001
EQ-5D (/1.0)	0.2 (0.4)	0.6 (0.3)	-0.3 (-0.37, -0.32)	< 0.001	0.18 (0.35)	0.62 (0.34)	-0.4 (-0.41, -0.37)	<0.001
EqVAS (/100)	42.9 (33.3)	64.5 (26.5)	-20.8 (-22.90, -19.63)	< 0.001	38.74 (32.35)	65.46 (25.67)	-23.0 (-25.05, -21.01)	<0.001
Zung (/102.5)	68.3 (26.2)	52.3 (20.4)	15.2 (13.52, 16.97)	< 0.001	71.49 (25.53)	51.57 (19.82)	15.6 (13.95, 17.25)	<0.001
Length of stay	28.2 (27.1)	15.0 (17.8)	12.7 (11.19, 14.20)	< 0.001	30.9 (28.14)	15.5 (17.93)	15.1 (13.58, 16.53)	<0.001

Dead/institutionalised and mRS > 3 – analysed using Chi Square test; rest analysed using T-Test. *Adjusted for age, baseline modified Rankin score and systolic BP on day 0

OR – odds ratio, MD – mean difference. Analysed using binary logistic or multiple linear regression.

Table 2.4 – Radiological predictors of 90-day outcome in those whose arm/hand score did not improve (i.e. ≤ 4 on day 0 and day 7 (n = 918)

(adjusted for age, sex, baseline modified Rankin scale score and systolic blood pressure on day 0)

	HDA	ASPECTS score	Ischaemic size	Mass effect	Midline shift	Old vascular lesion	Atrophy	PVL	Brain Frailty	SVD score
Patients, N (%)	302 (33)			477 (52)	29 (3%)	520 (57)	744 (84)	304 (33)		
mRS > 3	2.11 (1.436, 3.091), <0.001	0.16 (0.105, 0.215), <0.001	1.43 (1.232, 1.657), <0.001	1.99 (1.424, 2.793), <0.001	7.69 (1.605, 36.810), 0.011	1.00 (0.713, 1.408), 0.99	1.05 (0.680, 1.631), 0.82	0.92 (0.623, 1.365), 0.69	-0.01 (-0.198, 0.181), 0.93	0.04 (-0.180, 0.269), 0.70
Dead/institutionalised (n = 433), 47%	0.88 (0.665,	1.02 (0.984,	0.93 (0.835,	1.25 (0.963,	0.75 (0.347,	1.15 (0.879,	1.09 (0.747,	0.96 (0.711,	0.95 (0.820,	0.98 (0.822,

	1.167), 0.38	1.061), 0.26	1.045), 0.23	1.635), 0.09	1.603), 0.45	1.514), 0.30	1.593), 0.65	1.283), 0.76	1.111), 0.55	1.172), 0.84
mRS (ordinal)	0.73 (0.479, 0.989), <0.001	0.12 (0.090, 0.159), <0.001	1.34 (1.216, 1.487), <0.001	0.62 (0.387, 0.863), <0.001	0.85 (0.178, 1.521), 0.013	-0.14 (-0.376, 0.105), 0.27	-0.18 (-0.513, 0.155), 0.29	0.02 (-0.242, 0.287), 0.87	-0.07 (-0.203, 0.069), 0.33	0.01 (-0.145, 0.168), 0.88
Barthel index	13.1 (8.94, 17.31), <0.001	2.4 (1.88, 2.99), <0.001	5.82 (4.159, 7.479), <0.001	11.7 (7.74, 15.64), <0.001	21.8 (10.47, 33.22), <0.001	0.1 (-3.99, 4.29), 0.94	-1.0 (-6.73, 4.72), 0.73	-0.4, (-4.88, 4.12), 0.87	-0.2 (-2.54, 2.10), 0.85	0.9 (-1.78, 3.62), 0.50
tMMSE	2.47 (1.094, 3.841),	0.57 (0.385, 0.746), <0.001	1.56 (1.018, 2.094), <0.001	2.55 (1.245, 3.861),	7.43 (3.177, 11.689), 0.001	0.77 (-0.639, 2.177), 0.28	1.47 (-0.747, 3.698), 0.19	-2.20 (-3.716, -0.688)	-0.17 (-0.988, 0.644), 0.68	-0.43 (-1.360, 0.500), 0.36

	<0.001			<0.001				, 0.004		
Eq5d	0.10 (0.059, 0.1470, <0.001	0.02 (0.014, 0.0260, <0.001	0.05 (0.030, 0.065), <0.001	0.11 (0.068, 0.151), <0.001	0.19 (0.066, 0.307), 0.002	0.00 (-0.041, 0.045), 0.93	-0.02 (-0.083, 0.037), 0.45	0.02 (-0.025, 0.069), 0.36	0.00 (-0.022, 0.027), 0.83	0.02 (-0.008, 0.049), 0.15
EQ-VAS	-8.87 (-13.450, -4.299), <0.001	-1.95 (-2.574, -1.332), <0.001	-4.30 (-6.157, -2.448), <0.001	-8.39 (-12.681, -4.075), <0.001	-14.71 (-27.834, -0.322), 0.045	0.41 (-4.059, 4.880), 0.86	-0.20 (-6.267, 5.867), 0.95	-2.08 (-6.998, 2.836), 0.41	-0.44 (-2.923, 2.047), 0.73	-0.20 (-3.140, 2.734), 0.89
Zung	-8.8 (-12.54, -5.00),	-1.4 (-1.96, -	-3.83 (-5.340, -	-6.5 (-10.01, -3.01),	-14.5 (-25.90, -	0.6 (-3.03,	-0.9 (-5.65,	0.2 (-3.83,	0.1 (-1.93,	-0.4 (-2.75,

	<0.001	0.94), <0.001	2.316), <0.001	<0.001	3.02), 0.013	4.25), 0.74	3.93), 0.72	4.14), 0.94	2.08), 0.94	1.99), 0.75
Length of hospital stay	6.1 (2.56, 10.36), 0.001	1.0 (0.49, 1.51), <0.001	1.82 (0.246, 3.400), 0.023	3.3 (-0.37, 6.99), 0.08	0.6 (-9.92, 11.15), 0.91	5.2 (1.40, 8.97), 0.007	4.0 (-1.18, 9.27), 0.13	3.5 (-0.64, 7.60), 0.10	3.2 (1.09, 5.33), 0.003	3.6 (1.15, 6.09), 0.004

Data analysed using logistic, ordinal or linear regression methods. Adjusted for age, baseline mRS and systolic blood pressure

Data shows odds ratio, 95% CI and p values for Death; and mean difference, 95% CI and p values for mRS, independent living, Barthel index, EQ-5D, EQ-VAS, tMMSE and Zung depression scores

Figure 2.1: Patient population included in this trial

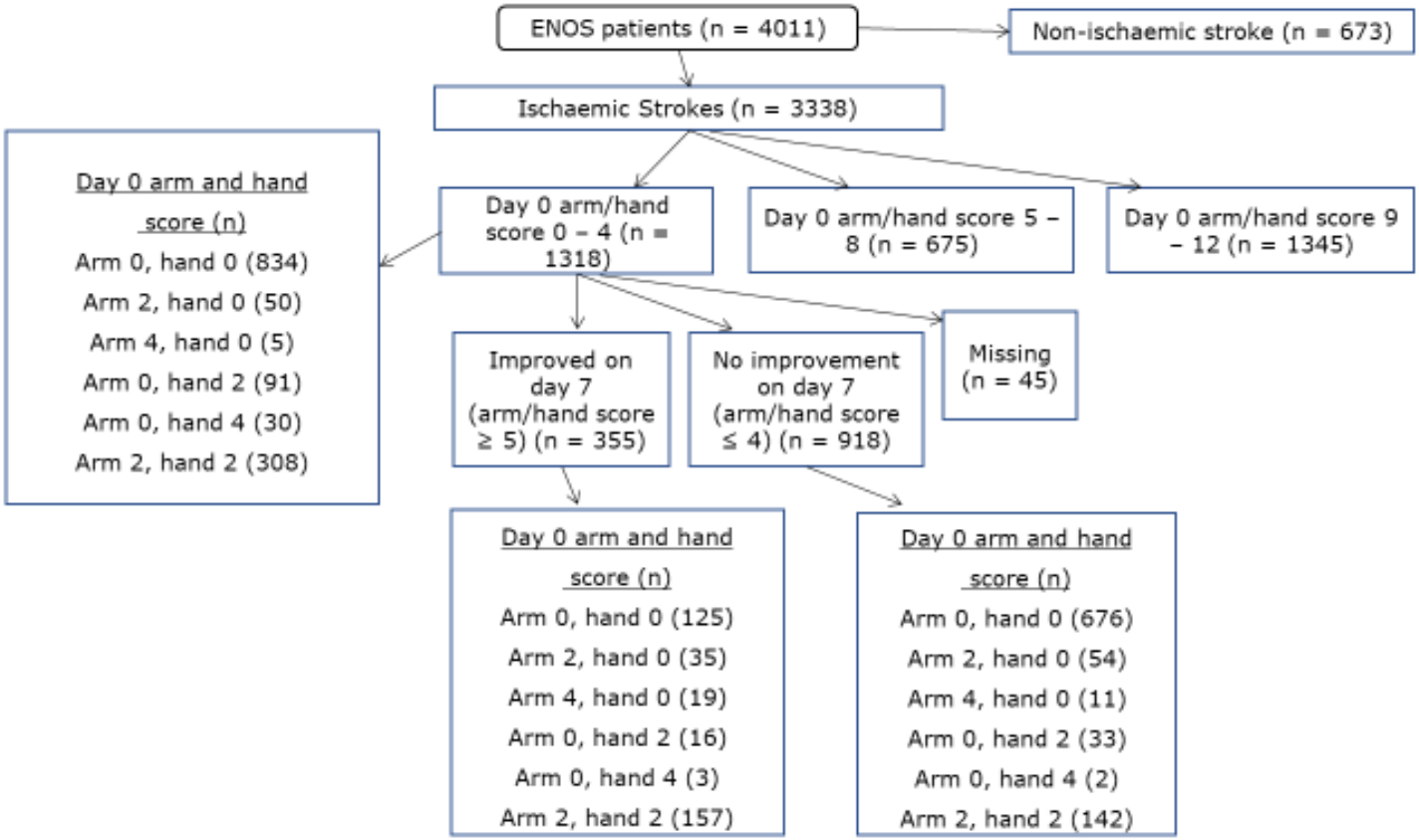

ENOS patients (n = 4011)
Non-ischaemic stroke (n = 673)
Ischaemic Strokes (n = 3338)
Day 0 arm and hand score (n)
Arm 0, hand 0 (834)
Arm 2, hand 0 (50)
Arm 4, hand 0 (5)
Arm 0, hand 2 (91)
Arm 0, hand 4 (30)
Arm 2, hand 2 (308)
Day 0 arm/hand score 0 – 4 (n = 1318)
Day 0 arm/hand score 5 – 8 (n = 675)
Day 0 arm/hand score 9 – 12 (n = 1345)
Improved on day 7 (arm/hand score ≥ 5) (n = 355)
No improvement on day 7 (arm/hand score ≤ 4) (n = 918)
Missing (n = 45)
Day 0 arm and hand score (n)
Arm 0, hand 0 (125)
Arm 2, hand 0 (35)
Arm 4, hand 0 (19)
Arm 0, hand 2 (16)
Arm 0, hand 4 (3)
Arm 2, hand 2 (157)
Day 0 arm and hand score (n)
Arm 0, hand 0 (676)
Arm 2, hand 0 (54)
Arm 4, hand 0 (11)
Arm 0, hand 2 (33)
Arm 0, hand 4 (2)
Arm 2, hand 2 (142)

Figure 2.2 Probability of arm/hand score not improving in those presenting with arm/hand score of ≤ 4 on day 0

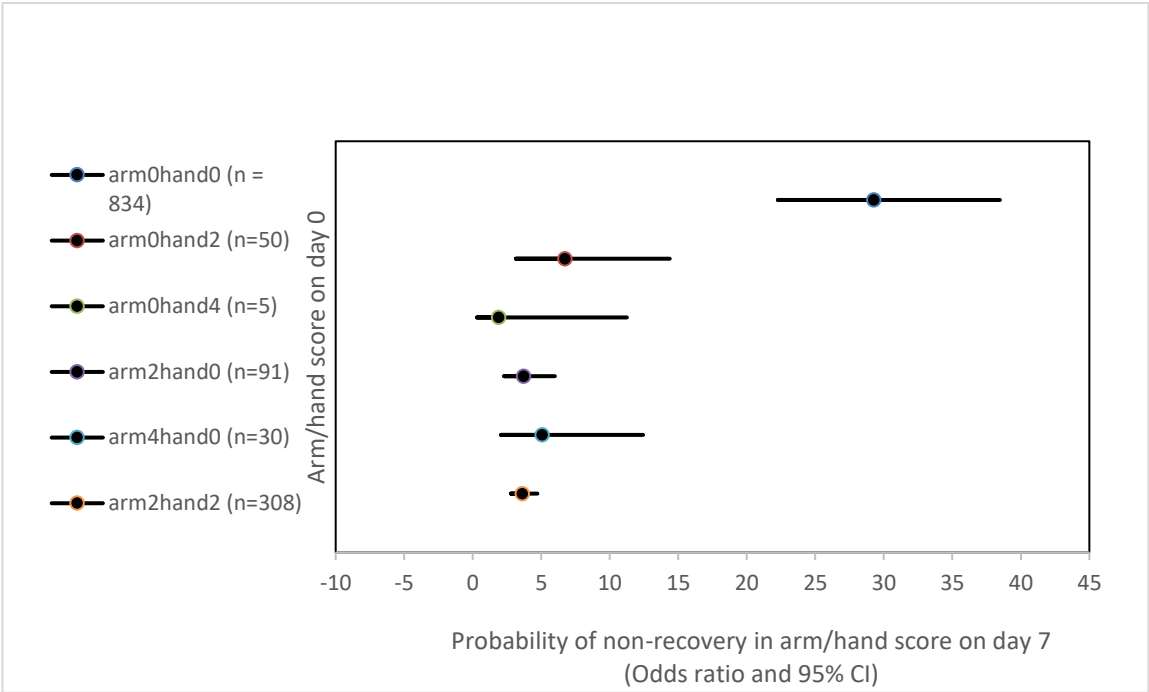


Figure 2.3 – Probability of mRS > 3 on day 90 in those presenting with arm/hand score ≤ 4 on day 0

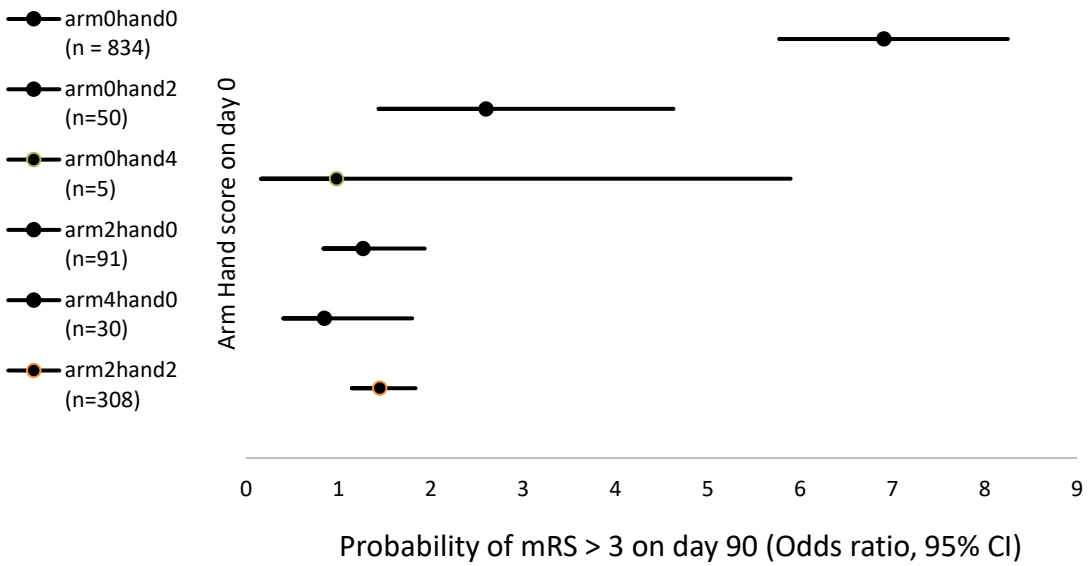
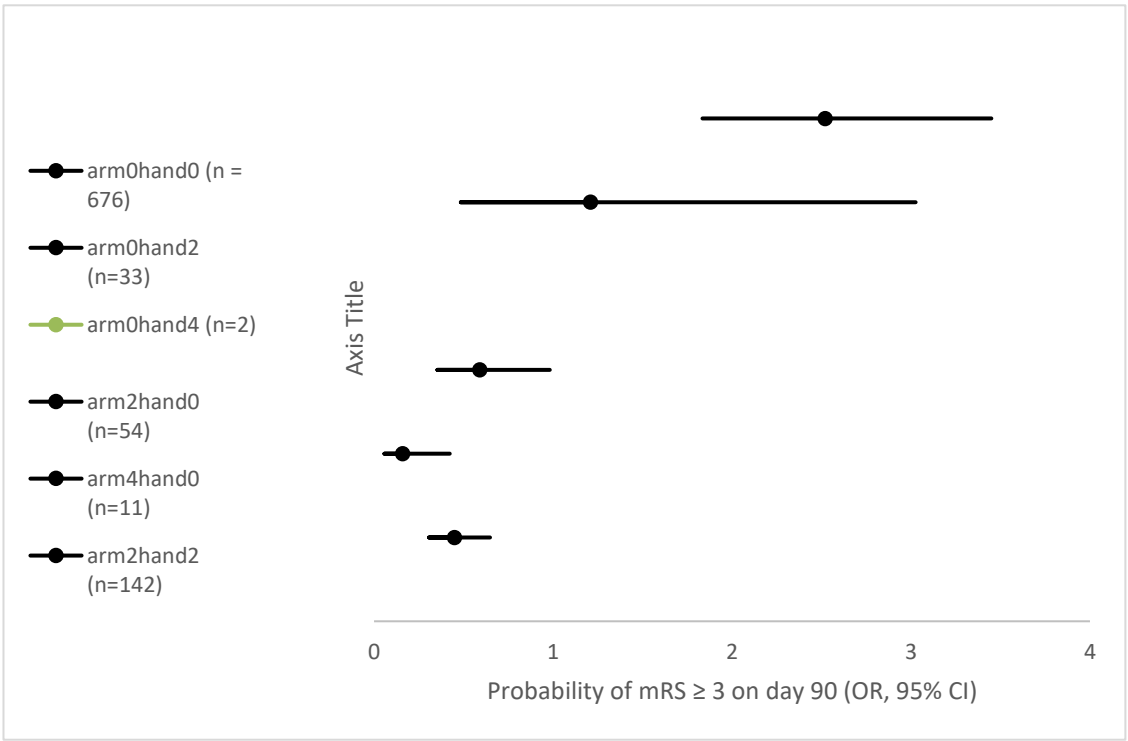


Figure 2.4 Probability of mRS > 3 on day 90 in those whose arm/hand score did not improve on day 7 (i.e. score of ≤ 4 on day 0 and 7)*



*there were only 2 patients who had arm0hand4 – hence they were not analysed.

Figure 2.5 Probability of having a mRS of > on day 90 vs. arm/hand score on day 0

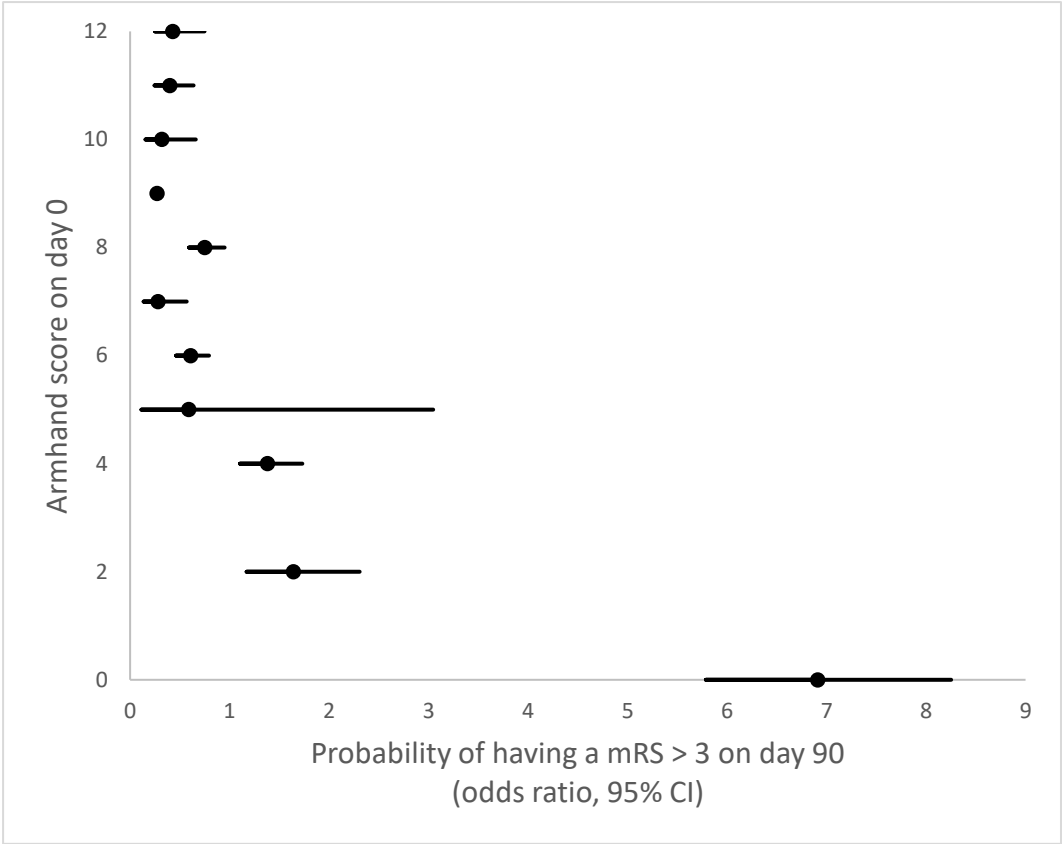
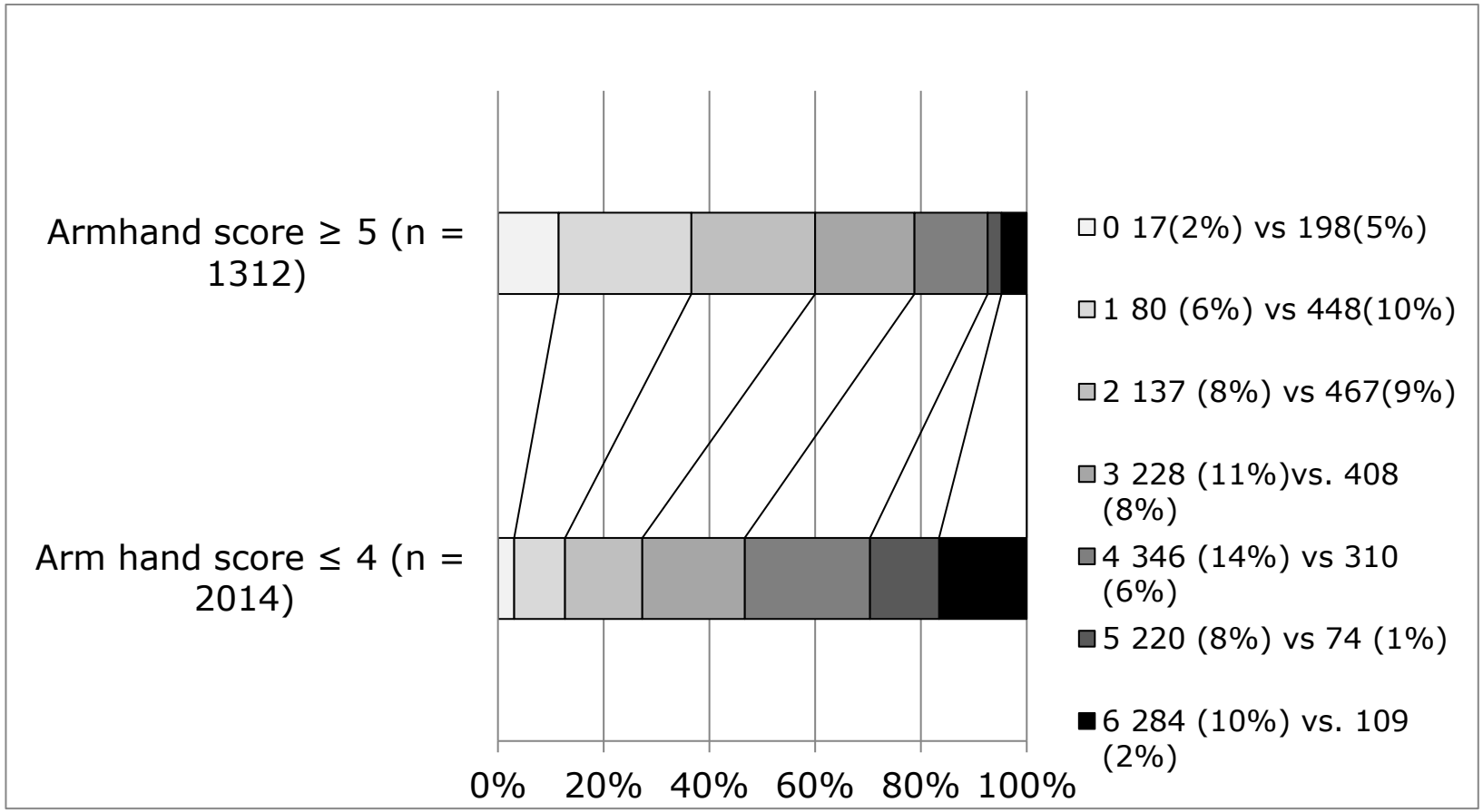


Figure 2.6 – day 90 mRS outcome in patients with arm/hand score of ≤ 4 vs. ≥ 5 on day 0



Chapter 3 – Intracerebral Haemorrhage (ICH)

3.1 Abstract

Introduction: Upper limb function is essential for regaining independence after stroke. I hypothesised that poor arm and hand function on day 0 and day 7 and the presence of acute and background parameters in baseline CT head scan is associated with a poor outcome in severe stroke following ICH.

Methods: I used patient data from the ENOS trial and compared clinical and radiological outcomes between severe and mild/moderate stroke defined by the arm/hand scores in the Scandinavian Stroke Scale. The primary outcome was defined as a modified Rankin Score (mRS) of >3 on day-90. Secondary outcomes included death/institutionalisation, mRS (ordinal), Barthel Index, mood, cognition and quality of life and length of hospital stay. Analyses were adjusted for age, baseline systolic BP and mRS; odds ratio (95% confidence intervals, CI) are given.

Results: Of the 629 patients with an ICH (in ENOS trial), 343 (54%) had an arm/hand score of ≤4 at the time of randomisation. Arm/hand score of ≤4 (out of 12 – derived from the conversion of SSS to MRC grading) on day 7 was associated more strongly with a poor primary outcome than day 0 – OR 11.49 (7.49-17.63) and 7.40, (4.93-11.09) respectively; all secondary outcome measures were worse if the arm/hand score was ≤4 on either day ($p<0.001$). In those whose arm/hand score did not improve by day 7, haematoma length (≥5 cm), shape and density, midline shift, brain frailty and SVD scores were associated with poor outcome.

Conclusion: Poor arm/hand movement on days 0 and 7 and some acute and background radiological parameters were associated with poor day-90 outcome.

3.2 Introduction

Intracerebral haemorrhage (ICH) causes 10 – 15% of strokes and the incidence is rising rapidly[165] and is associated with significant mortality and morbidity. Haematoma volume has been the most

important predictor of clinical outcome after ICH. [26, 166] In addition, haematoma expansion also plays a very important role in early neurological deterioration. [167]

Various studies have shown that recovery of finger extension by 7 days[58, 59] and shoulder movement[60] were very good determinants of good functional outcome at 6 months after stroke. EPOS study[61] showed that the presence of finger extension and shoulder abduction in the first 72 hours predicted upper limb function at 6 months after ischaemic stroke. Stinear[55, 56, 62] improved this model by adding further investigations (magnetic resonance imaging and transmagnetic stimulation) and our own study[168] showed that measuring arm and hand function on day 0 and day 7 using Scandinavian stroke scale[45] (SSS) can predict the functional outcome (90-day) in those with severe ischaemic stroke.

In this study, I hypothesised that severe arm and hand weakness on day of randomisation and day 7 (as measured in Scandinavian Stroke Scale) predicted a poor 90-day clinical outcome after an ICH. I also assessed the association of acute and background parameters in CT head scan and poor outcome in the 'non-improvers'.

3.3 Methods

3.3.1 Participants

I used patient data from the Efficacy of Nitric Oxide in Stroke (ENOS) trial, [159] an international multicentre randomised placebo-controlled, patient and outcome-assessor masked parallel group trial, which recruited from July 2001 to Oct 2013. The full ENOS protocol is available online. [160] To be included in the trial, the patient had to have motor weakness in the arm or leg or both and a diagnosis of ischaemic or haemorrhagic stroke had to be confirmed by CT or MRI scan done before or by 7 days after enrolment; key exclusion criteria included pure sensory stroke, isolated dysphasia, premorbid dependency (mRS of 3 – 5) or coma (Glasgow Coma Scale of 8 or less).

3.3.2 Measures

In addition to baseline demographics, data collected included Scandinavian Stroke scale (on day of randomisation – will be referred to as day 0 from now onwards – and day 7), blood pressure,

type of stroke (Oxford and TOAST subtypes), premorbid modified Rankin score and baseline CT scan of head. 90-day clinical outcomes included modified Rankin Score (primary outcome), death, disposition, telephone mini-mental state examination (t-MMSE), Zung depression scale, and quality of life (Euro-QoL-5 dimension-3 level, EQ-5D-3L; Euro-QoL-visual analogue scale, EQ-VAS) determined centrally by telephone (or post). Length of hospital stay was also collected.

I converted SSS motor scores to Medical Research Council (MRC) motor power grading, this giving a range of 0 to 12 (Appendix 1). I categorised patients into two groups based on the sum of arm and hand scores – those with severe weakness (MRC score of 0 – 4) and those with mild weakness (MRC 5 – 12). I also calculated the arm/hand scores on day 7 in those who presented with a baseline arm/hand score of 0–4; these were categorised as 'non-improvers' if their score remained ≤ 4 on day 7 and 'improvers' if it was ≥ 5.

CT scan of head (baseline scan) was used to measure both acute (e.g. presence of site and size of intracerebral haemorrhage, haematoma shape and density (in an ordered 5-point categorical scale), [169] mass effect and midline shift and Intraventricular

haemorrhage) and background parameters (e.g. periventricular lucencies, old infarcts and atrophy). Haematoma volume was measured using ABC/2 formula and the intraventricular and subarachnoid haemorrhages were measured using Graeb and modified Graeb scores – Krishnan[170] has described this in more detail. Site of haematoma were divided in to lobar (border zone regions, anterior cerebral artery, middle cerebral artery – excluding striato-capsular region and posterior cerebral artery), deep (lacunar, striato-capsular region and brainstem) and Cerebellar. I also calculated 'brain frailty' scores (a sum of established lacunes, brain atrophy and periventricular lucencies) – range of 0 – 3)[97, 99, 157, 161] and small vessel disease scores (a sum of acute lacunes, established lacunes and periventricular lucencies). [158]

3.3.3 Outcomes

I dichotomised the patients with intracerebral haemorrhage using the arm/hand scores (≤ 4 severe weakness and ≥ 5 mild weakness) on day 0 and day 7 and assessed if either score was associated with poor outcome. Poor outcome was defined as a stroke that led to a modified Rankin scale of > 3. The secondary outcomes included cognition (as measured by telephone MMSE), mood disorder (Zung

depression score), functional outcome (Barthel Index), quality of life (EQ5D and EQVas) and length of hospital stay.

I did not look at the radiological association between clinical outcome at the time of randomisation as we know that having some of the acute radiological parameters like large haematoma volume is associated with poor outcome.

3.3.4 Analysis

SPSS version 24 was used for statistical analysis. Chi Square test and T test was used to look for any statistical difference in the baseline clinical and radiological categorical and continuous data respectively. I used binary logistic regression for categorical variables, ordinal logistic regression for mRS (shift analysis) and linear regression for continuous variables for analysis of the data. Data was analysed using SPSS version 24 after adjusting for age, baseline systolic blood pressure and mRS. [159]

3.4 Results

3.4.1 Baseline characteristics

Of the 4011 patients recruited into ENOS, 629 patients had a final diagnosis of intracerebral haemorrhage. 343 (54%) of patients had an arm/hand score of ≤ 4 and 286 (45%) had a score of ≥ 5 at randomisation – data on 9 (3%) were missing (Figure 1). In those who presented with an arm/hand score of ≤ 4 at the time of randomisation, 234 (68%) of patients did not have any movement in either arm or hand. There was a higher incidence of dysphasia and more severe stroke (lower GCS, baseline SSS and calculated NIHSS scores) in those with severe arm/hand weakness (Table 1). Those with severe arm/hand weakness also had a higher baseline systolic BP (173.49 vs. 170.34). All the acute radiological markers apart from the site of ICH were associated with severe arm/hand weakness (arm/hand score of ≤ 4) – haematoma volume, size, intraventricular haemorrhage and volume, mass effect, midline shift, shape and density) but there was no difference in the background parameters (Table 2).

3.4.2 Arm/hand score vs. clinical outcome

Both the primary and secondary outcomes at day 90 were significantly worse in those who had an arm/hand score of ≤ 4 at randomisation and day 7 (Table 3). Arm/hand score of ≤ 4 on day 7 was a stronger predictor of poor outcome than that on day 0 (Table 3). Length of hospital stay was 10 days longer if the arm/hand score was ≤ 4 (both on day 0 and day 7). Shift analysis of mRS showed a significant association between poor arm/hand score and poor outcome on day 90 (Figure 4).

3.4.3 Non-improvers (arm/hand score ≤ 4 on day 0 and day 7)

3.4.3.1 Baseline characteristics

Of the 343 patients who presented with an arm/hand score of ≤ 4 on day 0, 265 (77%) patients had not improved on day 7, 69 (20%) had improved and 9 (3%) had died (by day 7) – those who had died would have excluded from some of the analysis e.g. mood and cognition. Although they had had more severe stroke (lower GCS, lower SSS and higher calculated NIHSS), the baseline systolic blood pressure was the same in improvers and non-improvers. Off the 234 who had no movement of arm and hand (i.e. sum of arm/hand score of 0) on day 0, 202 (86%) did not show any improvement on day 7. Of the acute radiological parameters, haematoma volume, length,

shape and density of ICH were significantly worse in those with severe arm/hand weakness.

3.4.3.2 Non-Improvers and its association with radiological parameters

A number of acute radiological parameters including the haematoma length (> 5 cm), haematoma shape and density and midline shift were associated with a poor outcome in the non-improvers (Table 4).

Presence of IVH, volume of IVH, Graeb and modified Graeb scores were not associated with a poor outcome on day-90 (Table 4). Those with higher SVD and brain frailty scores were associated with poor day-90 outcomes (Table 4). There was no correlation between the radiological parameters and length of hospital stay in the non-improvers (Table 4).

3.5 Discussion

This study has shown that early (both day 0 and 7) hand and arm function as measured by SSS is strongly associated with a poor 90-

day clinical outcome following an intracerebral haemorrhage. This study has also shown that if the arm + hand score is ≤ 4, the length of hospital stay and the probability of death/institutionalisation is considerably higher (by day 90). It also appears that a poor arm + hand score on day 7 is a stronger predictor of outcome than day 0 – there could be a number of reasons which might explain this including haematoma growth, perilesonal oedema and development of midline shift. As in ischaemic stroke (see Chapter 2), hand function, which is easy to measure, may provide an important additional information on top of NIHSS score regarding 90 day outcome. Most patients who had an arm/hand score of ≤ 4 had no movement in either arm or hand.

Whilst it is known that a number of acute parameters like haematoma volume and midline shift are known to be associated with poor outcome after ICH, [26] our study has shown a number of other acute parameters like haemorrhage length, shape and density are also associated a poor outcome in non-improvers. In addition, background parameters like SVD and brain frailty scores were also associated with poor outcome in the non-improvers following a severe stroke following ICH. In the non-improvers, I did not show any association between the location of ICH (lobar vs. deep) and

clinical outcome – this is consistent with the literature (some suggest better outcome [171] following a lobar ICH, but others contradict that). [172-174]

Previous research [168] by the same authors has shown that the lack of hand function compared to arm weakness was a better predictor of poor outcome on day 90 in those with ischaemic stroke. In this cohort (those with ICH), there were very few who had either specific arm or hand weakness – majority of them had a combination of severe hand and arm weakness. Hence, I am unable to comment which one of those is a better predictor of poor recovery. The non-improvers in this group (ICH) had a poor outcome if they had a poor background brain health.

This analysis has several strengths – large number of patients (629) was derived from a pragmatic randomised trial from multiple ethnic groups, patients had baseline CT head scan which were adjudicated by expert neuroradiologists. However, the patients were enrolled a few years ago and the guidelines for management of hypertension post ICH have changed since. [31] I did not look how soon after the stroke onset was the initial scan done as the ENOS study protocol

did not specify that – the inclusion criteria was that the patient should have been randomised within 48 hrs of stroke onset – resulting in a potential selection bias (i.e. those with very large haematoma (or posterior fossa haematoma) at the time of presentation may have been excluded from the trial. Repeat neuroimaging was not done routinely – this might have found new changes (e.g. haematoma expansion, perilesional oedema, etc.). Although our study shows that the haematoma length, shape and density reveal a useful association with clinical outcome, these are rarely measured in clinical practice. Length of haematoma in the longest axis is easy to measure and would be helpful to use in clinical practice. Finally, I am unable to comment on the cerebral amyloid angiopathy status as the adjudication of CT head scan did not include features recently suggested by Rodrigues et al[175] and the patients did not undergo MRI brain scan (Boston [176] or Modified Boston [177] criteria).

In conclusion,mlooked at day 0 and day 7 arm/hand function and found severe arm/hand weakness was associated with a poor outcome – the arm/hand score on day 7 was even more strongly associated with a poor outcome than day 0 after ICH. This study not only shows that the presence of acute radiological parameters, but

also poor background brain health is associated with a poor 90-day outcome in non-improvers after ICH.

Table 3.1 – Baseline clinical characteristics

Clinical characteristics	Arm/Hand score on day 0		2p value	Non improvers	Improvers	2p value
	≤ 4	≥ 5				
Patients, N (%)	343 (54)	286 (46)		265 (77)	69 (20)	
Male (%)	220 (65)	195 (68)	0.29	169 (64)	46 (67)	0.65
Age	67.59 (12)	66.34 (13)	0.21	67.75 (12)	66.88 (12)	0.56
Hypertension (%)	218 (64)	183 (64)	0.98	163 (61)	50 (72)	0.09
Diabetes (%)	46 (13)	35 (12)	0.66	39 (15)	6 (9)	0.19
Atrial fibrillation (%)	15 (4)	20 (7)	0.15	13 (5)	2 (3)	0.47
Previous Stroke (%)	40 (12)	39 (14)	0.46	34 (13)	3 (4)	0.046
IHD (%)	35 (10)	23 (8)	0.35	13 (5)	2 (3)	0.71
PAD (%)	25 (7)	13 (4)	0.35	18 (7)	3 (4)	0.021
Alcohol consumption (%)	24 (7)	33 (11)	0.028	17 (6)	7 (10)	0.61

Smoking - current or ex (%)	158 (46)	150 (52)	0.44	120 (45)	34 (49)	0.14
Left sided weakness (%)	198 (58)	150 (52)	0.34	149 (56)	41 (59)	0.79
Dysphasia (%)[168]	198 (58)	87 (30)	<0.001	158 (60)	34 (49)	0.12
Oxford Classification			<0.001			0.031
TACS	165 (48)	52 (18)		137 (51)	22 (32)	
PACS	100 (29)	96 (34)		73 (27)	25 (36)	
LACS	75 (22)	125 (44)		53 (20)	21 (30)	
POCS	3 (1)	13 (4)		2 (1)	1 (1)	
GCS	13.6 (1.8)	14.6 (1.0)	<0.001	13.4 (1.9)	14.3 (1.4)	0.001
Systolic BP	173.49 (19.69)	170.34 (18.86)	0.042	173.00 (19.66)	175.78 (20.24)	0.30
SSS	21.91 (8.62)	40.80 (7.24)	<0.001	20.65 (8.48)	26.97 (7.18)	<0.001
Calculated NIHSS	16.26 (3.71)	8.13 (3.19)	<0.001	16.8 (3.65)	14.08 (3.09)	<0.001

Baseline modified Rankin	0.37 (0.7)	0.34 (0.7)	0.57	0.35 (0.7)	0.36 (0.7)	0.91

SSS = Scandinavian Stroke Scale; IHD = ischaemic heart disease; PAD = peripheral arterial disease. Continuous data expressed as mean. Continuous variables are expressed as mean (standard deviation)

Table 3.2 – Baseline neuroimaging characteristics

Imaging characteristics	**Arm/Hand score on day 0**		**2p value**	**Non improvers**	**Improvers**	**2p value**
	≤ 4	**≥ 5**				
Patients, N (%)	343 (54)	286 (46)		265 (77)	69 (20)	
ACUTE PARAMETERS						
Haematoma volume	16.9 (19.6)	9.5 (13.0)	0.001	18.4 (21.1)	11.3 (12.6)	0.009
Site of parenchymal haemorrhage						
Lobar	103 (30)	74 (26)	0.25	22 (32)	79 (30)	0.83
Deep	236 (69)	210 (73)	0.20	46 (67)	183 (69)	0.70
Cerebellar	4 (1)	2 (1)	0.55	1 (1)	3 (1)	0.74
Size of parenchymal haemorrhage						
< 5 cm	253 (74)	234 (82)	0.016	61 (88)	188 (71)	0.003

≥ 5 cm	68 (11)	24 (4)	<0.001	60 (23)	5 (7)	0.004
Intraventricular haemorrhage (%)	108 (36)	46 (16)	<0.001	9 (13)	97 (37)	<0.001
Intraventricular haemorrhage volume	1.51 (4.23)	0.78 (4.06)	0.03	0.48 (1.83)	1.78 (4.63)	0.027
Mass effect (%)	185 (54)	113 (39)	0.001	33 (48)	148 (56)	0.20
Midline shift (%)	56 (16)	14 (5)	<0.001	6 (9)	48 (18)	0.05
Graeb	1.12 (2.13)	0.52 (1.47)	<0.001	0.55 (1.82)	1.23 (2.150	0.018
Modified Graeb	1.60 (3.55)	0.79 (2.46)	<0.001	0.94 (3.66)	1.71 (3.400	0.110
Haemorrhage shape	3.6 (1.4)	3.0 (1.3)	<0.001	3.8 (1.4)	2.85 (1.4)	<0.001
Haemorrhage Density	2.8 (1.3)	2.4 (1.3)	<0.001	2.9 (1.3)	2.9 (1.2)	0.008
Subarachnoid haemorrhage (%)	59 (17)	35 (12)	0.05	6 (9)	50 (19)	0.13
BACKGROUND						

Old vascular lesions (%)	151 (44)	140 (49)	0.22	30 (43)	119 (45)	0.83
Brain tissue reduction (%)	203 (29)	166(58)	0.77	38 (55)	161 (61)	0.39
Periventricular lucencies (%)	214 (62)	177 (62)	0.90	44 (64)	164 (62)	0.77
Brain Frailty score	1.66 (1.11)	1.69 (1.15)	0.42	1.62 (1.10)	1.68 (1.12)	0.73
Small vessel disease score	1.17 (0.84)	1.21 (0.83)	0.54	1.06 (0.90)	1.22 (0.83)	0.17

Haematoma volume – measured manually by ABC/2 formula

Lobar haematoma included border zone regions, anterior cerebral artery, middle cerebral artery – excluding striato-capsular region and posterior cerebral artery)

Deep haematoma included lacunar, striato-capsular region and brainstem

Size of haemorrhage – measured in the longest axis

Shape and Density – measured on an ordered 5-point ordinal scale

Graeb and Modified Graeb – used to measure the amount of blood in the subarachnoid space and ventricles

Brain Frailty score = sum of old vascular lesions, brain tissue reduction and periventricular lucencies each getting 1 point; range 0 – 3.

Small vessel disease score = sum of old vascular lesions, brain tissue reduction and acute lacunar infarct, each getting 1 point; range 0 = 3.

All continuous data are expressed as Mean (SD)

Table 3.3 – Clinical outcomes based on arm/hand score on day 0 and day 7

CLINICAL OUTCOME	Arm/Hand score on day 0		OR, 95% CI	2p value	Arm/Hand score on day 7		OR, 95% CI	2p value
	≤ 4	≥ 5			≤ 4	≥ 5		
Patients, N (%)	343 (54)	286 (46)			277 (42)	335 (53)		
mRS > 3 (%)	211 (61)	62 (22)	7.40 (4.932, 11.092)	<0.001	192 (69)	71 (21)	11.49 (7.487, 17.629)	<0.001
Dead/Institutionalised (%)	178 (20)	9 (3)	2.09 (1.496, 2.934)	<0.001	147 (53)	22 (6)	2.55 (1.817, 3.587)	<0.001
mRS (/6)	3.8 (1.5)	2.55 (1.5)	1.57 (1.263, 1.873)	<0.001	4.1 (1.5)	2.5 (1.5)	2.03 (1.705, 2.350)	<0.001
Barthel Index (/100)	47.5 (38.6)	79.0 (31.6)	-29.5 (-34.60, -24.46)	<0.001	41.9 (38.02)	79.9 (29.09)	-35.8 (-40.54, -30.99)	<0.001

t-MMSE (/22)	7.91 (8.06)	12.74 (6.71)	-4.53 (-6.042, -3.016)	<0.001	6.85 (8.13)	13.48 (5.91)	-5.74 (-7.215, -4.272)	<0.001
EQ-5D (/1.0)	0.28 (0.37)	0.60 (0.32)	-0.31 (-0.358, -0.251)	<0.001	0.23 (0.36)	0.60 (0.32)	-0.35 (-0.404, -0.302)	<0.001
EqVAS (/100)	46.64 (31.91)	64.63 (27.83)	-16.63 (-21.387, -11.875)	<0.001	43.99 (33.05)	65.33 (25.39)	-19.33 (-23.985, -14.672)	<0.001
Zung (/102.5)	65.80 (25.88)	53.47 (20.51)	10.86 (7.064, 14.666)	<0.001	68.24 (26.72)	52.38 (18.82)	14.12 (10.362, 17.870)	<0.001
Length of stay	28.0 (29.63)	17.7 (19.95)	9.4 (5.45, 13.37)	<0.001	29.0 (29.12)	19.1 (22.70)	8.9 (4.94, 12.96)	<0.001

Dead/institutionalised and mRS > 3 – analysed using Chi Square test; rest analysed using T-Test. Adjusted for age, baseline modified Rankin score and systolic BP on day 0

OR – odds ratio, MD – mean difference. Analysed using binary logistic or multiple linear regression.

Table 3.4 – Radiological predictors of 90-day outcome in the non-improvers (whose arm/hand score was ≤ 4 on day 0 and remained ≤ 4 on day 7 (n = 265)

(adjusted for age, baseline modified Rankin scale score and systolic blood pressure on day 0)

Radiological Features	Clinical Outcomes								
	mRS > 3	**Dead/Institutionalised**	**mRS (ordinal)**	**Barthel index**	**tMMSE**	**Eq5d**	**EqVas**	**Zung**	**Length of hospital stay**
Haematoma volume	1.00 (0.987, 1.023), 0.59	0.99 (0.977, 1.007), 0.29	-0.01 (-0.024, 0.001), 0.06	-0.2 (-0.36, 0.02), 0.07	-0.02 (-0.073, 0.023), 0.30	-0.00 (-0.003, 0.001), 0.36	-0.18 (-0.372, 0.004), 0.05	0.15 (0.002, 0.305), 0.05	-0.1 (-0.24, 0.12), 0.51
Haematoma site									
Deep	0.84 (0.437, 1.065), 0.59	1.34 (0.770, 2.364), 0.29	-0.37 (-0.854, 0.113), 0.13	-2.4 (-10.81, 0.59), 0.57	-.65 (-1.863, 3.157), 0.61	-0.07 (-0.153, 0.021), 0.14	-4.63 (-13.111, 3.844), 0.28	-5.89 (-13.026, 1.248), 0.11	5.5 (-2.18, 13.11), 0.16
Lobar									

	1.28 (0.664, 2.481), 0.46	0.80 (0.455, 1.409), 0.44	0.48 (-0.011, 0.971), 0.05	3.9 (-4.54, 12.42), 0.36	-0.65 (-3.157, 1.863), 0.61	0.08 (-0.009, 0.166), 0.08	4.42 (-4.100, 12.494), 0.31	6.10 (-1.074, 13.284), 0.10	--4.0 (-11.72, 3.76), 0.31
Haematoma length ≥5 cm	2.31 (1.064, 4.995), 0.034	2.14 (1.121, 4.075), 0.021	-1.09 (-1.662, -0.522), <0.001	-16.8 (-25.78, -7.77). <0.001	3.18 (0.638, 5.728), 0.014	0.15 (0.058, 0.245), 0.002	-10.78 (-19.840, -1.727), 0.020	-10.18 (-17.672, -2.686), 0.008	3.1 (-5.38, 11.57), 0.47
IVH	1.70 (0.891, 3.228), 0.11	0.72 (0.420, 1.242), 0.24	0.24 (-0.215, 0.705), 0.30	-6.1 (-14.19, 1.89), 0.13	0.83 (-1.505, 3.160), 0.49	0.09 (0.010, 0.176), 0.027	-2.42 (-10.491, 5.653), 0.56	0.03 (-6.687, 6.783), 0.99	5.2 (-2.18, 12.61), 0.167
IVH volume	1.04 (0.961, 1.137), 0.31	0.97 (0.911, 1.037), 0.39	-0.05 (-0.106, 0.002), 0.06	-0.6 (-1.50, 0.24), 0.15	-0.08 (-0.284, 0.126), 0.451	-0.00 (-0.013, 0.005), 0.38	-0.38 (-1.201, 0.446), 0.37	0.33 (-0.331, 0.985), 0.33	-0.5 (-1.27, 0.34), 0.260

Graeb	1.14 (0.971, 1.340), 0.11	0.97 (0.852, 1.098), 0.61	-0.08 (-0.180, 0.026), 0.14	-1.0 (-2.90, 0.86), 0.29	0.06 (-0.420, 0.550), 0.79	-0.02 (-0.040, -0.001), 0.039	-0.09 (-1.882, 1.700), 0.92	0.18 (-1.278, 1.648), 0.80	-0.8 (-2.53, 0.96), 0.38
Modified Graeb	1.08 (0.972, 1.198), 0.15	0.98 (0.904, 1.062), 0.62	-0.05 (-0.117, 0.012), 0.11	-0.6 (-1.74, 0.62), 0.35	0.03 (-0.264, 0.333), 0.82	-0.01 (-0.024, 0.000), 0.06	0.02 (-1.099, 1.141), 0.97	-0.01 (-0.914, 0.903), 0.99	-0.5 (-1.60, 0.59), 0.37
Haemorrhage shape	0.68 (0.545, 0.852), 0.001	0.84 (0.695, 1.018), 0.08	-0.27 (-0.444, -0.105), 0.002	-5.1 (-7.98, -2.24), <0.001	-1.13 (-2.197, -0.463), 0.003	-0.03 (-0.064, -0.004), 0.027	-2.02 (-4.921, 0.879), 0.17	1.84 (-0.606, 4.289), 0.14	0.7 (-1.97, 3.40), 0.60
Haemorrhage density	0.60 (0.462, 0.785), <0.001	0.82 (0.668, 1.013), 0.07	-0.40 (-0.590, -0.218), <0.001	-6.1 (-9.09, -3.04), <0.001	-0.96 (-1.934, 0.006), 0.05	-0.06 (-0.090, -0.027), <0.001	-4.87 (-7.979, -1.764), 0.002	0.21 (1.268, 6.467), 0.004	1.8 (-1.13, 4.65), 0.23
Mass effect	0.88 (0.475, 1.646), 0.70	1.69 (0.986, 2.913), 0.06	-0.27 (-0.731, 0.192), 0.25	6.0 (-2.07, 14.08), 0.14	0.28 (-2.106, 2.671), 0.82	-0.07 (-0.0149, 0.019), 0.12	1.49 (-6.608, 9.589), 0.72	0.12 (-6.700, 6.933), 0.97	1.2 (-6.24, 8.69), 0.75

	4.09 (1.591, 10.502), 0.003	2.49 (1.207, 5.119), 0.013	-1.10 (-1.708, -0.501), <0.001	-19.9 (-29.74, -10.04), <0.001	3.51 (0.748, 6.272), 0.013	0.14 (-0.033, 0.240), 0.009	-11.37 (-21.175, -1.574), 0.023	-9.10 (-17.221, -0.916), 0.029	-0.1 (-9.50, 9.28), 0.98
PV lucencies	1.37 (0.333, 5.669), 0.66	0.88 (0.481, 1.600), 0.67	0.29 (-0.225, 0.797), 0.27	-2.3 (-22.14, 17.58), 0.82	-1.97 (-8.771, 4.825), 0.59	0.05 (-0.038, 0.148), 0.24	-4.34 (-23.934, 15.248), 0.66	-3.87 (-11.318, 3.574), 0.31	8.4 (-0.18, 16.62), 0.045
Old vascular lesions	1.70 (0.412, 6.995), 0.46	0.65 (0.377, 1.128), 0.13	0.05 (-0.412, 0.520), 0.82	-5.5 (-25.07, 14.05), 0.58	-1.54 (-2.058, 2.733), 0.79	0.01 (-0.074, 0.093), 0.82	-4.17 (-23.413, 15.080), 0.67	-0.73 (-7.567, 6.107), 0.83	7.1 (-0.27, 14.49), 0.06
Brain tissue reduction	1.12 (0.278, 4.503), 0.87	0.82 (0.445, 1.499), 0.51	0.39 (-0.147, 0.927), 0.15	-1.4 (-21.12, 18.40), 0.89	1.83 (-0.926, 4.595), 0.19	0.06 (-0.030, 0.160), 0.18	-3.15 (-22.665, 16.368), 0.75	-2.24 (-9.862, 5.372), 0.56	2.9 (-5.55, 11.33), 0.50
Brain Frailty	1.36 (1.015,	1.14 (0.879,	-0.18 (-0.408,	-4.7 (-8.52, -	-0.20 (-1.354,	-0.03 (-0.073	-0.41 (-4.250,	1.50 (-1.694,	-3.1 (-6.65,

	1.816), 0.040	1.471), 0.33	0.038), 0.10	0.869), 0.019	0.957), 0.74	0.007), 0.97	3.438), 0.84	4.703), 0.36	0.39), 0.08
Small Vessel Disease score	0.59 (0.437, 0.802), 0.001	0.98 (0.743, 1.284), 0.87	0.32 (0.078, 0.560), 0.009	-6.21 (-10.694, -1.737), 0.007	-1.25 (-2.526, 0.032), 0.06	-0.04 (-0.090, 0.002), 0.06	-2.45 (-6.669, 1.772), 0.25	1.48 (-2.088, 5.057), 0.41	0.31 (-3.561, 4.180), 0.87

Data analysed using logistic, ordinal or linear regression methods. Adjusted for age, baseline mRS and systolic blood pressure

Data shows odds ratio, 95% CI and p values for Death; and mean difference, 95% CI and p values for mRS, independent living, Barthel index, Eq5d, EqVas, tMMSE and Zung depression score

Figure 3.1: Patient population included in this trial

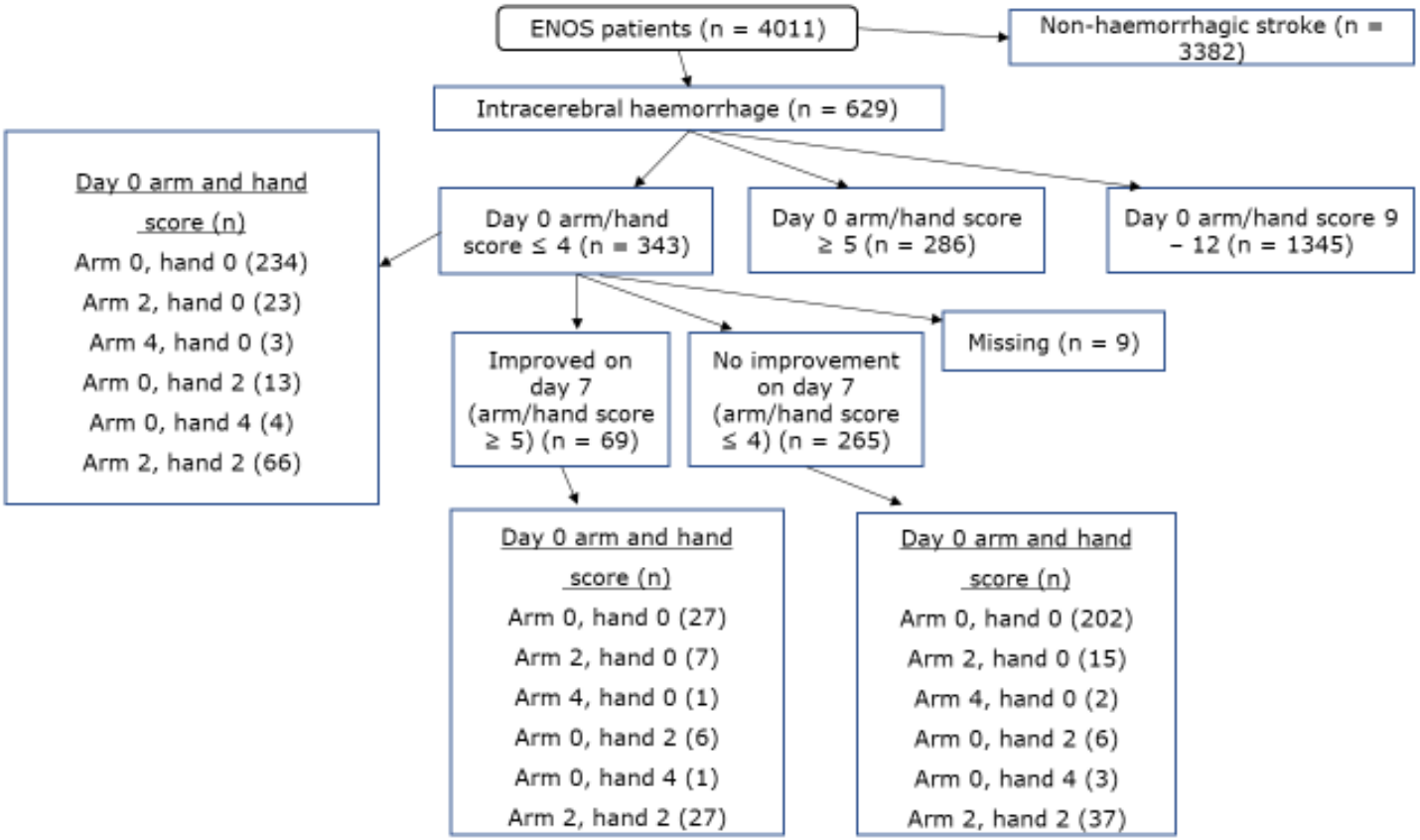

ENOS patients (n = 4011)
Non-haemorrhagic stroke (n = 3382)
Intracerebral haemorrhage (n = 629)
Day 0 arm and hand score (n)
Arm 0, hand 0 (234)
Arm 2, hand 0 (23)
Arm 4, hand 0 (3)
Arm 0, hand 2 (13)
Arm 0, hand 4 (4)
Arm 2, hand 2 (66)
Day 0 arm/hand score ≤ 4 (n = 343)
Day 0 arm/hand score ≥ 5 (n = 286)
Day 0 arm/hand score 9 – 12 (n = 1345)
Missing (n = 9)
Improved on day 7 (arm/hand score ≥ 5) (n = 69)
No improvement on day 7 (arm/hand score ≤ 4) (n = 265)
Day 0 arm and hand score (n)
Arm 0, hand 0 (27)
Arm 2, hand 0 (7)
Arm 4, hand 0 (1)
Arm 0, hand 2 (6)
Arm 0, hand 4 (1)
Arm 2, hand 2 (27)
Day 0 arm and hand score (n)
Arm 0, hand 0 (202)
Arm 2, hand 0 (15)
Arm 4, hand 0 (2)
Arm 0, hand 2 (6)
Arm 0, hand 4 (3)
Arm 2, hand 2 (37)

Figure 3.2 Probability of arm/hand score not improving by day 7 in those presenting with arm/hand score of ≤ 4 on day 0

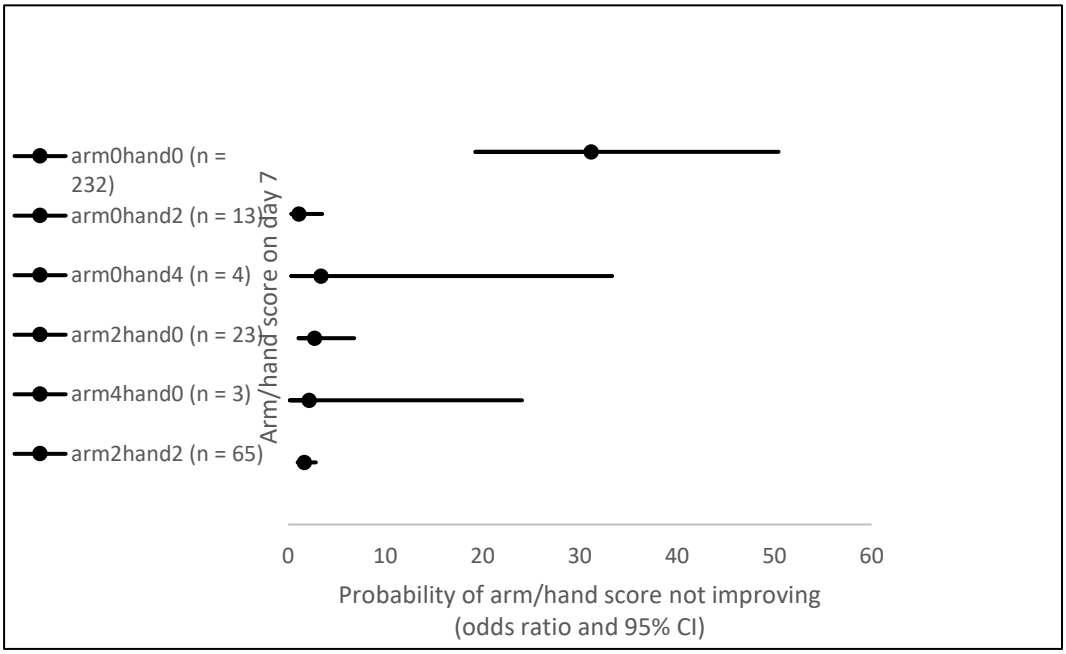


Figure 3.3 Probability of mRS > 3 on day 90 in those presenting with arm/hand score of ≤ 4 on day 0

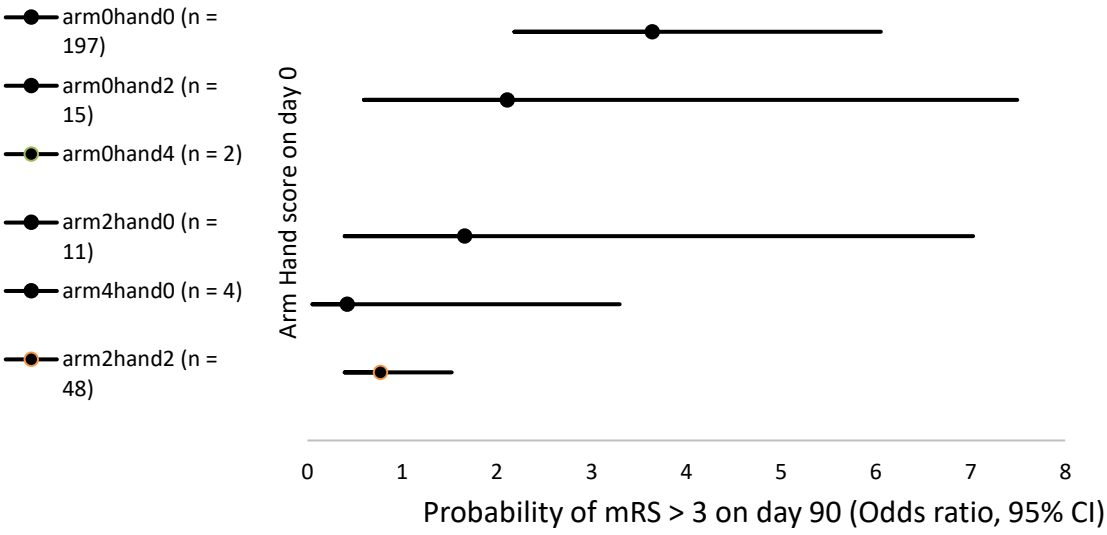


Figure 3.4 Probability of mRS > 3 on day 90 in those presenting with arm/hand score of ≤ 4 on day 7

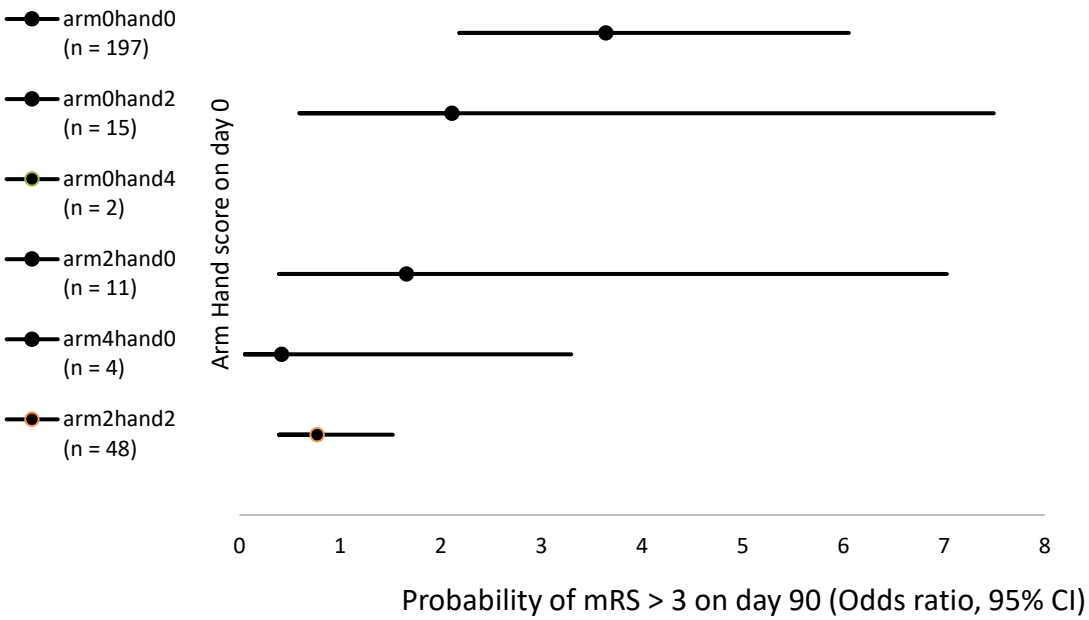


Figure 3.5 Probability of mRS > 3 on day 90 in those with various arm/hand scores on day 7

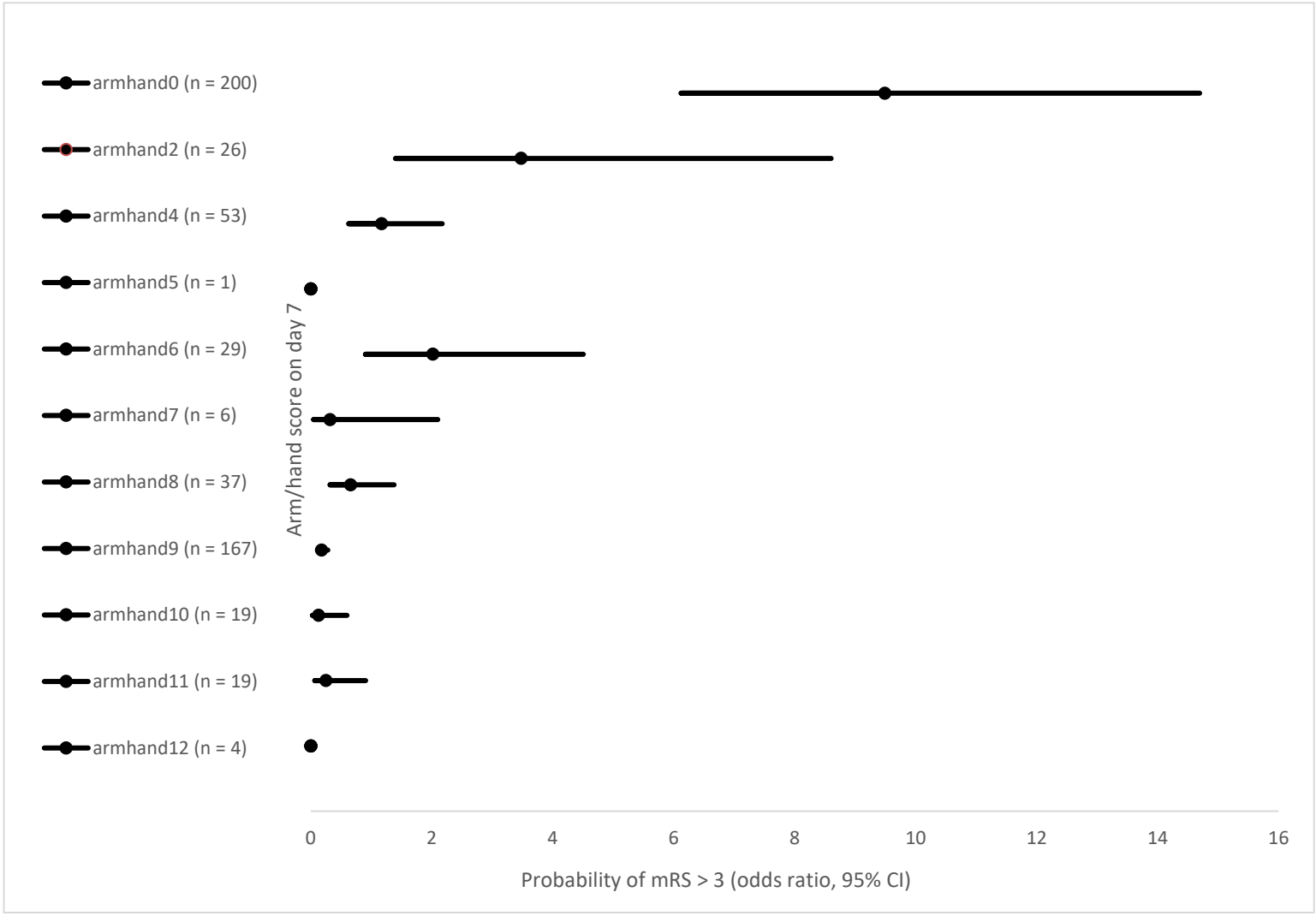
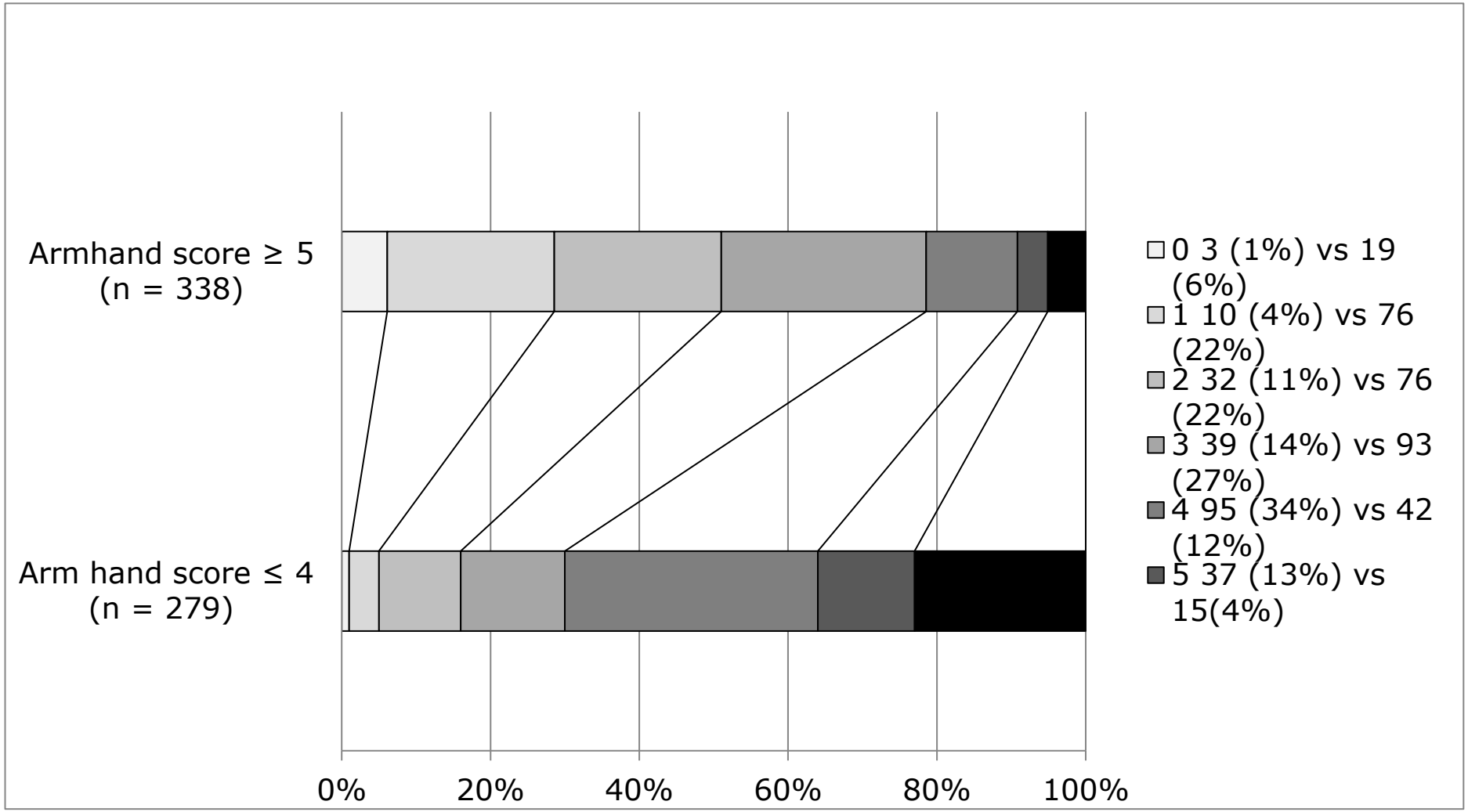

armhand0 (n = 200)
armhand2 (n = 26)
armhand4 (n = 53)
armhand5 (n = 1)
armhand6 (n = 29)
armhand7 (n = 6)
armhand8 (n = 37)
armhand9 (n = 167)
armhand10 (n = 19)
armhand11 (n = 19)
armhand12 (n = 4)
Arm/hand score on day 7
0
2
4
6
8
10
12
14
16
Probability of mRS > 3 (odds ratio, 95% CI)

Figure 3.6 Day 90 mRS outcome in patients with arm/hand score of ≤ 4 vs. ≥ 5 on day 7



Chapter 4 – Discussion

I hypothesised that a poor arm/hand function at baseline would predict a poor 90 day outcome after stroke; I also hypothesised that acute and background radiological markers would be more frequent in those with severe strokes and poor background brain health (as measured by small vessel disease and brain frailty scores) would be associated with poor outcome in those whose arm/hand score did not improve in the first week after stroke.

These analysis showed that a poor arm/hand score (as measured by Scandinavian Stroke Scale) on day 0 and day 7 is associated with a poor clinical outcome (both primary – mRS > 3) and secondary (death/institutionalisation, mRS on an ordinal scale, cognition, mood, Barthel Index and length of hospital stay) outcomes. Even though a poor baseline arm/hand score was associated with a poor 90 day outcome thus confirming our hypothesis, day 7 arm/hand score showed a better association – this was particularly helpful in predicting a poor outcome in those with ICH (more so than those with ischaemic stroke). In both groups (ischaemic stroke and ICH), the chance of arm/hand score recovery was very poor (on day 90) if

the sum of arm/hand score was 0 at the time of randomisation. A poor hand score on day 0 was strongly associated with a poor outcome in those with ischaemic strokes; although this was not the case in those with ICH, it is possible that it is due to the fact that the number of patients with ischaemic stroke was much larger than those with ICH. It is also known that the outcomes and predictors vary in ischaemic stroke and ICH. [178] It is easy to measure hand function in clinical practice and it can be done by all member of the multidisciplinary team – this might help in early identification of those who are less likely to progress with rehabilitation.

In both groups, there were a number of acute radiological parameters (hyperdense artery, lower ASPECT score, mass effect, size of ischaemia in those with ischaemic stroke and haematoma length, shape and density in those with ICH) that were associated with poor clinical outcome in non-improvers (i.e. those in whom the arm/hand score remained ≤ 4 on day 0 and day 7). Although these are known to be markers of severe stroke, this is the first time (to the best of our knowledge) that these have been shown to be of prognostic value within a purely severe stroke population. In those with ICH, it is difficult to measure shape, density and volume without additional software; however, haematoma length is very easy to measure, it is rarely if ever used in clinical practice in United

Kingdom – I believe it has good clinical utility to help in prognosticating outcome after a severe stroke.

In our group of patients with severe stroke, in particular the non-improvers, there was no correlation between the background radiological parameters and the clinical outcomes in those with ischaemic strokes. This patient cohort (both ischaemic strokes and ICH) had suffered a severe stroke as evidenced by lower GCS, higher NIHSS score (derived from SSS score) and poor arm/hand score; however poor background brain health was associated with a poor clinical outcome only in those who did not improve in the first week after stroke following an ICH, but not in ischaemic stroke – the severity of stroke as measured by SSS, GCS and calculated NIHSS score were similar in both groups; this makes it difficult for me to provide a rationale to explain the difference. I did not look at those with milder strokes where the background brain health might be more important as a predictor of outcome. [179] Subgroup analysis of IST-3 trial [157] showed that the presence of poor background brain health predicted poor outcome (as measured by Oxford Handicap Score), but this included patients of all stroke severity (mild, moderate and severe).

Our studies demonstrated 2 different clinically important outcomes in the non-improvers; firstly, in those with a severe stroke due to cerebral infarction, a combination of poor functioning arm and hand along with a poor background brain health (SVD and Brain Frailty scores) predicts a prolonged length of stay in hospital and thus has significant impact on financial resources and service organisation. It is possible that the length of hospital stay was prolonged due to poor ability to repair and reorganisation of brain tissue in those with severe stroke or may be related to associated comorbidities. Secondly, a combination of poor functioning arm and hand in association with a poor background brain health predicts a poor 90 day outcome in those with severe stroke due to ICH.

Our studies include a large number of patients and tested clinic-radiological associations and outcome in those with severe ischaemic strokes. Earlier study by Stinear [62] included just over 200 patients with ischaemic strokes and it excluded patients with severe stroke and those with dysphasia. Literature search did not reveal any such attempts been made in the past in those with intracerebral haemorrhages – making our study in those with ICH a novel concept.

It is already known that some of the acute radiological parameters (e.g. ASPECT score[88] and hyperdense artery[90-92] in ischaemic strokes

and haematoma volume[23-25] and location in posterior fossa[22] in ICH) are associated with poor outcome. There is very little literature on the effect of background brain health and clinical outcome in those with severe stroke. In addition, I wanted to mirror the PREP2 algorithm as much as possible but specifically looking at the non-improvers instead of the improvers.

Whilst I acknowledge that the PREP2 algorithm has its limitations (sequential study), so does this study as it was a retrospective analysis. Our study is different in the fact that every patient who was recruited to the ENOS study was included (i.e. there were no 'comparison' group). In PREP2 algorithm, once they were established into different groups for prognostic purposes (Figure 1.1), the physiotherapists were able to modify the therapy provided for the patients. Whereas in ENOS trial, not only that this was not the case as per the protocol, I am also unable to ascertain how much rehabilitation the patients received; in addition, with improvements in stroke care, the rehabilitation received by patients would have changed over time with the establishment of SSNAP database (e.g. minimum time with therapist from each discipline for 45 minutes per day or as long as possible if they cannot tolerate 45 minutes). PREP2 algorithm included only those with ischaemic strokes and excluded those who had significant aphasia or cognitive problem post stroke.

Stinear et al used advanced imaging to look for both anatomical and physiological integrity of corticospinal tract (MRI and TMS respectively). Whilst I appreciate that MRI scan is much more sensitive in detecting acute changes, I believe our study is perhaps more universally applicable as CT scan of head is more readily available in developing countries than MRI scan. In this cohort, it is also feasible that patients with severe stroke may not tolerate MRI scan. Whilst Stinear et al used TMS to identify those that are likely to improve (and hence alter the focus of rehabilitation), I used poor background brain health as a surrogate marker of poor rehabilitation potential (i.e. unlikely to improve).

Our study differs from the PREP2 algorithm in that I endeavoured to identify those with severe stroke who did not improve - thus allowing us not only to change the focus and the type of rehabilitation from improvement to maintenance/safe discharge, but more importantly help in expectation management of the patient and their family – whereas Stinear's group tried to identify the improvers so that they could channel more resources to improve the functionality of the patients. In addition, using our model in those with severe strokes, the healthcare professional can have an honest discussion with patients and their family regarding what is an acceptable 'quality of

life' for that particular individual and tailor the rehabilitation on the individual patient needs.

ENOS study recruited between 2001 and 2013 and management of stroke has progressed since. In 2001, very few patients were admitted to hyperacute or acute stroke unit in United Kingdom as only a few hospitals had such a facility; however the SSNAP data[180] from 2013 – 18 suggests that 53% of the patients were scanned within 1 hour of arrival to hospital, 57% of patients were admitted to the stroke unit within 4 hours of arrival to hospital – this is substantially different to the care received by stroke patients in 2001. More importantly, 95% of patients received physiotherapy assessment within 72 hours of hospital admission (if necessary). From the acute management perspective, intravenous thrombolysis is routinely provided to eligible patients and the number of patients undergoing intra-arterial intervention (e.g. mechanical thrombectomy) is increasing. Our patients had a non-contrast CT head scan before randomisation and hence the presence of large vessel occlusion may have been missed in those with severe stroke – we now know that this carries a poor prognosis. [104] In those with ICH, maintaining a blood pressure of 140 mmHg has been shown to be effective in improving outcome. [31] All these interventions may have a significant impact on the outcome of patients with stroke now

compared to those of the ENOS population. An important limitation of our study pertains to those with ICH – I did not look at the timing of CT scan following symptom onset. Even a short delay might have missed important feature like haematoma expansion, which potentially could have affected the outcome. [181]

Whilst the acute radiological parameters were more frequently observed in those with severe strokes, the background parameters were not significantly different between the 2 groups (i.e. mild – moderate vs. severe strokes). This may be different (background brain health i.e. SVD and Brain Frailty scores) in those who are dependent preceding the stroke; I did not measure the comorbidity as I did not have that information – frailty/comorbidity can potentially affect the outcome and this needs to be included in future studies. I propose that future studies should include patients who are dependent premorbid and should include measures of comorbidity (e.g. Charlson index) [182] and frailty (e.g. Rockwood Frailty score) [183] whilst looking for radiological predictors following severe stroke.

As this is a post-hoc analysis, I had to work with the dataset that was available both in terms of clinical and radiological data. Ideally, I would have liked to assess the association of clinical outcome with

data (preferably SSS and neuroimaging) from day 3 and 7 – this would have mirrored the timing of assessments with PREP2 study. There is scope to improve our study in the future by including CT angiogram (in those with ischaemic strokes at the time of randomisation) and adjudication methods identifying features suggestive of cerebral amyloid angiopathy as per the Edinburgh criteria [175] in those with ICH.

The number of patients with significant midline shift was very small, particularly in those with ischaemic strokes (2%) – this was slightly better in those with ICH (21%); hence I was unable to evaluate the effect of other radiological changes like background brain health. This may represent a selection bias as those who had significant midline shift within the first 24 – 48 hours were not included in the ENOS study. The treatment of increased intracranial pressure (in those with ischaemic stroke) has also changed during the ENOS recruitment phase and subsequently (e.g. surgical intervention like hemicraniectomy), which improves survival in those with severe stroke – future studies need to take this into consideration.

Most of the patients had a very good premorbid function (mean mRS was < 1 in both groups of patients – ischaemic strokes and ICH). So, further research is warranted to look at the clinico-radiological

predictors of outcome following a severe stroke in those who are disabled pre-stroke. I need to recruit them in the hyperacute stages of the stroke journey (to avoid potential selection bias) and consider further imaging to look for large vessel occlusion in ischaemic strokes and features of cerebral amyloid angiopathy in those with ICH. Our method of converting SSS scores into MRC grading needs validating in future.

Conclusion

I have shown that both day 0 and day 7 arm/hand function (as assessed by SSS) is associated with poor clinical outcome on day 90 in both ischaemic strokes and ICH. In those with no improvement after 7 days, although acute radiological markers were associated with poor outcome in both ischaemic stroke and ICH, background changes were only relevant in those with ICH in our cohort of severe stroke as defined by an arm/hand score of ≤ 4 at baseline. More research is needed to statistically test whether the addition of hand function to NIHSS score can help to identify those who are likely to have a poor outcome compared to NIHSS score alone.

Appendices

Appendix 1 – Oxford Classification of stroke [51]

Total Anterior Circulation Stroke	Motor &/or sensory loss of face, arm and leg Visual field deficit Higher cortical dysfunction (e.g. aphasia, apraxia, altered sensorium or astereognosis) (Could be all 3 or even just visual deficit and higher cortical dysfunction)
Partial Anterior Circulation Stroke	Any 2 of the following 3 Motor &/or sensory loss of face, arm and leg Visual field deficit Higher cortical dysfunction (e.g. aphasia, apraxia, altered sensorium or astereognosis) Or higher cortical dysfunction alone

Lacunar Stroke	Pure motor (face, arm and leg weakness) Pure sensory (face, arm or leg sensory loss) Sensory-motor Ataxic hemiparesis
Posterior Circulation Stroke	Cerebellar signs Isolated hemianopia Brain stem signs

Appendix 2 – NIHSS Score [40]

Category	Score/Description		Date/Time Initials
1a. **Level of Consciousness** (Alert, drowsy, etc.)	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma		
1b. **LOC Questions** (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect		
1c. **LOC Commands** (Open/close eyes, make fist/let go)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect		
2. **Best Gaze** (Eyes open - patient follows examiner's finger or face)	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation		
3. **Visual Fields** (Introduce visual stimulus/threat to pt's visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)		
4. **Facial Paresis** (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete		
5a. **Motor Arm - Left** 5b. **Motor Arm - Right** (Elevate arm to 90° if patient is sitting, 45° if supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left Right	
6a. **Motor Leg - Left** 6b. **Motor Leg - Right** (Elevate leg 30° with patient supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left Right	
7. **Limb Ataxia** (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs		
8. **Sensory** (Pin prick to face, arm, trunk, and leg - compare side to side)	0 = Normal 1 = Partial loss 2 = Severe loss		
9. **Best Language** (Name item, describe a picture and read sentences)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute		
10. **Dysarthria** (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near to unintelligable or worse X = Intubated or other physical barrier		
11. **Extinction and Inattention** (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect		
	TOTAL SCORE		

Appendix 3 – Scandinavian Stroke Scale [45]

Function Score	Prognostic Score	Long Term	Score
Consciousness:			
fully conscious 6	_____		
somnolent, can be awaked to full consciousness 4			
reacts to verbal command, but is not fully conscious 2			
Eye movement:			
no gaze palsy 4	_____		
gaze palsy present 2			
conjugate eye deviation 0			
Arm, motor power *:			
raises arm with normal strength 6	_____		_____
raises arm with reduced strength 5			
raises arm with flexion in elbow 4			
can move, but not against gravity 2			

paralysis 0

Hand, motor power *:

normal strength 6 _____

reduced strength in full range 4

some movement, fingertips do not reach palm 2

paralysis 0

Leg, motor power *:

normal strength 6 _____ _____

raises straight leg with reduced strength 5

raises leg with flexion of knee 4

can move, but not against gravity 2

paralysis 0

Orientation:

correct for time, place and person 6 _____

two of these 4

one of these 2

completely disorientated 0

Speech:

no aphasia 10 _____

limited vocabulary or incoherent speech 6

more than yes/no, but not longer sentences 3

only yes/no or less 0

Facial palsy:

none/dubious 2 _____

present 0

Gait:

walks 5 m without aids 12 _____

walks with aids 9

walks with help of another person 6

sits without support 3

bedridden/wheelchair 0

Maximal Score	22	48

* Motor power is assessed only on the affected side.

Appendix 4 – Orpington Prognostic Score [53]

Clinical Features	Score
Motor deficit in arm	
Medical Research Council grade	
5	0
4	0.4
3	0.8
1-2	1.2
0	1.6
Proprioception (eyes closed)	
Locates affected thumb	
Accurately	0
Slight difficulty	0.4
Finds thumb via arm	0.8
Unable to find thumb	1.2
Balance	
Walks 10 feet without help	0
Maintains standing position	0.4
Maintains sitting position	0.8
No sitting balance	1.2
Cognition	
Mental test score	
10	0
8-9	0.4
5-7	0.8
0-4	1.2

Total score= 1.6+motor+proprioception+balance+cognition

Appendix 5 – Canadian Neurological Scale [49]

				Date Time		
Mentation		Level of Consciousness	Alert	3		
			Drowsy	1.5		
		Orientation	Oriented	1		
			Disoriented or Nonapplicable	0		
		Speech	Normal	1		
			Expressive Aphasia	0.5		
			Receptive Aphasia	0		
Section A1	No Comprehensive Deficit	**Motor Functions:**	Weakness:			
		Face:	None	0.5		
			Present	0		
		Arm: Proximal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Arm: Distal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Leg: Proximal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Leg: Distal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
Section A2	Comprehensive Deficit	Face:	Symmetrical	0.5		
			Asymmetrical	0		
		Arms:	Equal	1.5		
			Unequal	0		
		Legs:	Equal	1.5		
			Unequal	0		
			Total Score			

Appendix 5 – Functional Independence Measure [69]

FIM™ instrument

LEVELS		
	7 Complete Independence (Timely, Safely) 6 Modified Independence (Device)	**NO HELPER**
	Modified Dependence 5 Supervision (Subject = 100%+) 4 Minimal Assist (Subject = 75%+) 3 Moderate Assist (Subject = 50%+) **Complete Dependence** 2 Maximal Assist (Subject =25%+) 1 Total Assist (Subject = less than 25%)	**HELPER**

	ADMISSION	DISCHARGE	FOLLOW-UP
Self-Care			
A. Eating	☐	☐	☐
B Grooming	☐	☐	☐
C. Bathing	☐	☐	☐
D. Dressing - Upper Body	☐	☐	☐
E. Dressing - Lower Body	☐	☐	☐
F. Toileting	☐	☐	☐
Sphincter Control			
G. Bladder Management	☐	☐	☐
H. Bowel Management	☐	☐	☐
Transfers			
I. Bed, Chair, Wheelchair	☐	☐	☐
J. Toilet	☐	☐	☐
K. Tub, Shower	☐	☐	☐
Locomotion			
L. Walk/Wheelchair	☐ W Walk C Wheelchair B Both	☐ W Walk C Wheelchair B Both	☐ W Walk C Wheelchair B Both
M. Stairs	☐	☐	☐
Motor Subtotal Score	☐	☐	☐
Communication			
N. Comprehension	☐ A Auditory V Visual B Both	☐ A Auditory V Visual B Both	☐ A Auditory V Visual B Both
O. Expression	☐ V Vocal N Nonvocal B Both	☐ V Vocal N Nonvocal B Both	☐ V Vocal N Nonvocal B Both
Social Cognition			
P. Social Interaction	☐	☐	☐
Q. Problem Solving	☐	☐	☐
R. Memory	☐	☐	☐
Cognitive Subtotal Score	☐	☐	☐
TOTAL FIM Score	☐	☐	☐

NOTE: Leave no blanks. Enter 1 if patient not testable due to risk

Appendix 6 – Barthel Index [65]

Barthel Index Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	
BATHING 0 = dependent 5 = independent (or in shower)	
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	

Appendix 7 – Modified Rankin Scale [63]

Score	Description
0	Independent, no symptoms
1	No significant disability despite some symptoms; able to perform all activities
2	Slight disability. Unable to perform all activities but able to manage their own affairs
3	Moderate disability. Needs help with activities of daily living but able to walk without assistance
4	Moderately severe disability. Needs assistance to walk and with activities of daily living
5	Severe disability. Bedbound, incontinent and needs 24-hour care
6	Dead

Appendix 8 – Conversion of SSS into Medical Research Council (MRC) grading

Scandinavian Stroke Scale	SSS score	MRC equivalent
Raises arm with normal strength	6	5
Raises arm with reduced strength	5	4
Raises arm with flexion in elbow	4	3
Can move arm but not against gravity	2	2
Paralysis	0	0
Hand, normal strength	6	5
Hand, reduced strength in full range	4	4
Some movement in hand	2	2
Paralysis	0	0

Reference

1. The world health organization monica project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. Who monica project principal investigators. *J Clin Epidemiol*. 1988;41:105-114
2. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (oxford vascular study). *Lancet*. 2005;366:1773-1783
3. Paley L, Williamson E, Bray BD, Hoffman A, James MA, Rudd AG, et al. Associations between 30-day mortality, specialist nursing, and daily physician ward rounds in a national stroke registry. *Stroke*. 2018;49:2155-2162
4. Newton JN, Briggs AD, Murray CJ, Dicker D, Foreman KJ, Wang H, et al. Changes in health in england, with analysis by english regions and areas of deprivation, 1990-2013: A systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;386:2257-2274
5. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. *Stroke*. 2011;42:1489-1494
6. 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
7. Williams GR, Jiang JG, Matchar DB, Samsa GP. Incidence and occurrence of total (first-ever and recurrent) stroke. *Stroke*. 1999;30:2523-2528
8. 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
9. 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
10. 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
11. Warlow CP. Epidemiology of stroke. *Lancet*. 1998;352 Suppl 3:SIII1-4
12. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, et al. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient a scientific statement from the american heart association. *Stroke*. 2010;41:2402-2448
13. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: Results of a follow-up study. *Disabil Rehabil*. 1999;21:357-364
14. Bailey RR, Klaesner JW, Lang CE. Quantifying real-world upper-limb activity in nondisabled adults and adults with chronic stroke. *Neurorehabil Neural Repair*. 2015;29:969-978
15. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: A systematic review. *Lancet Neurol*. 2009;8:741-754
16. Adams HP, Jr., 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. Toast. Trial of org 10172 in acute stroke treatment. *Stroke*. 1993;24:35-41
17. Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline nih stroke scale score strongly predicts outcome after stroke: A report of the trial of org 10172 in acute stroke treatment (toast). *Neurology*. 1999;53:126-131
18. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929-1935
19. Goyal M, Menon BK, van Zwam WH, Dippel DW, 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
20. Stroke Unit Trialists C. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013:CD000197
21. Back L, Nagaraja V, Kapur A, Eslick GD. Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: A meta-analysis of randomised trials. *Intern Med J*. 2015;45:711-717
22. 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
23. 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
24. 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; discussion 773-764
25. 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
26. 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
27. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28:2370-2375
28. 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
29. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ich score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897
30. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033-1043
31. 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

32. Sprigg N, Flaherty K, Appleton JP, Al-Shahi Salman R, Bereczki D, Beridze M, et al. Tranexamic acid for hyperacute primary intracerebral haemorrhage (tich-2): An international randomised, placebo-controlled, phase 3 superiority trial. *Lancet*. 2018;391:2107-2115
33. Chai-Adisaksopha C, Hillis C, Siegal DM, Movilla R, Heddle N, Iorio A, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thromb Haemost*. 2016;116:879-890
34. Pollack CV, Jr., Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511-520
35. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with factor xa inhibitors. *N Engl J Med*. 2019;380:1326-1335
36. . *Stroke: National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (tia)*. London; 2008.
37. Appelros P, Nydevik I, Seiger A, Terent A. Predictors of severe stroke: Influence of preexisting dementia and cardiac disorders. *Stroke*. 2002;33:2357-2362
38. Nolfe G, D'Aniello AM, Muschera R, Giaquinto S. The aftermath of rehabilitation for patients with severe stroke. *Acta Neurol Scand*. 2003;107:281-284
39. Quinn TJ, Singh S, Lees KR, Bath PM, Myint PK, Collaborators V. Validating and comparing stroke prognosis scales. *Neurology*. 2017;89:997-1002
40. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*. 1989;20:864-870
41. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the nih stroke scale. *Arch Neurol*. 1989;46:660-662
42. Glymour MM, Berkman LF, Ertel KA, Fay ME, Glass TA, Furie KL. Lesion characteristics, nih stroke scale, and functional recovery after stroke. *Am J Phys Med Rehabil*. 2007;86:725-733
43. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, et al. Endovascular therapy for acute ischaemic stroke: The pragmatic ischaemic stroke thrombectomy evaluation (piste) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88:38-44
44. Racosta JM, Di Guglielmo F, Klein FR, Riccio PM, Giacomelli FM, Gonzalez Toledo ME, et al. Stroke severity score based on six signs and symptoms the 6s score: A simple tool for assessing stroke severity and in-hospital mortality. *J Stroke*. 2014;16:178-183
45. Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian stroke study group. *Stroke*. 1985;16:885-890
46. Gray LJ, Ali M, Lyden PD, Bath PM, Virtual International Stroke Trials Archive C. Interconversion of the national institutes of health stroke scale and scandinavian stroke scale in acute stroke. *J Stroke Cerebrovasc Dis*. 2009;18:466-468
47. Askim T, Bernhardt J, Churilov L, Indredavik B. The scandinavian stroke scale is equally as good as the national institutes of health stroke scale in identifying 3-month outcome. *J Rehabil Med*. 2016;48:909-912
48. Christensen H, Boysen G, Truelsen T. The scandinavian stroke scale predicts outcome in patients with mild ischemic stroke. *Cerebrovasc Dis*. 2005;20:46-48
49. Cote R, Hachinski VC, Shurvell BL, Norris JW, Wolfson C. The canadian neurological scale: A preliminary study in acute stroke. *Stroke*. 1986;17:731-737

50. Nilanont Y, Komoltri C, Saposnik G, Cote R, Di Legge S, Jin Y, et al. The canadian neurological scale and the nihss: Development and validation of a simple conversion model. *Cerebrovasc Dis*. 2010;30:120-126
51. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521-1526
52. Lindley RI, Warlow CP, Wardlaw JM, Dennis MS, Slattery J, Sandercock PA. Interobserver reliability of a clinical classification of acute cerebral infarction. *Stroke*. 1993;24:1801-1804
53. Kalra L, Dale P, Crome P. Improving stroke rehabilitation. A controlled study. *Stroke*. 1993;24:1462-1467
54. Rieck M, Moreland J. The orpington prognostic scale for patients with stroke: Reliability and pilot predictive data for discharge destination and therapeutic services. *Disabil Rehabil*. 2005;27:1425-1433
55. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The prep algorithm predicts potential for upper limb recovery after stroke. *Brain*. 2012;135:2527-2535
56. Stinear CM, Byblow WD, Ackerley SJ, Barber PA, Smith MC. Predicting recovery potential for individual stroke patients increases rehabilitation efficiency. *Stroke*. 2017;48:1011-1019
57. Thirumala P, Hier DB, Patel P. Motor recovery after stroke: Lessons from functional brain imaging. *Neurol Res*. 2002;24:453-458
58. Smania N, Paolucci S, Tinazzi M, Borghero A, Manganotti P, Fiaschi A, et al. Active finger extension: A simple movement predicting recovery of arm function in patients with acute stroke. *Stroke*. 2007;38:1088-1090
59. Fritz SL, Light KE, Patterson TS, Behrman AL, Davis SB. Active finger extension predicts outcomes after constraint-induced movement therapy for individuals with hemiparesis after stroke. *Stroke*. 2005;36:1172-1177
60. Katrak P, Bowring G, Conroy P, Chilvers M, Poulos R, McNeil D. Predicting upper limb recovery after stroke: The place of early shoulder and hand movement. *Arch Phys Med Rehabil*. 1998;79:758-761
61. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, Investigators E. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: Early prediction of functional outcome after stroke: The epos cohort study. *Stroke*. 2010;41:745-750
62. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. Prep2: A biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol*. 2017;4:811-820
63. Rankin J. Cerebral vascular accidents in patients over the age of 60. Ii. Prognosis. *Scott Med J*. 1957;2:200-215
64. Jeng JS, Huang SJ, Tang SC, Yip PK. Predictors of survival and functional outcome in acute stroke patients admitted to the stroke intensive care unit. *J Neurol Sci*. 2008;270:60-66
65. Mahoney FI, Barthel DW. Functional evaluation: The barthel index. *Md State Med J*. 1965;14:61-65
66. Della Pietra GL, Savio K, Oddone E, Reggiani M, Monaco F, Leone MA. Validity and reliability of the barthel index administered by telephone. *Stroke*. 2011;42:2077-2079

67. Ronning OM, Guldvog B. Outcome of subacute stroke rehabilitation: A randomized controlled trial. *Stroke*. 1998;29:779-784
68. Fagerberg B, Claesson L, Gosman-Hedstrom G, Blomstrand C. Effect of acute stroke unit care integrated with care continuum versus conventional treatment: A randomized 1-year study of elderly patients: The goteborg 70+ stroke study. *Stroke*. 2000;31:2578-2584
69. Linacre JM, Heinemann AW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the functional independence measure. *Arch Phys Med Rehabil*. 1994;75:127-132
70. Alexander MP. Stroke rehabilitation outcome. A potential use of predictive variables to establish levels of care. *Stroke*. 1994;25:128-134
71. Sandstrom R, Mokler PJ, Hoppe KM. Discharge destination and motor function outcome in severe stroke as measured by the functional independence measure/function-related group classification system. *Arch Phys Med Rehabil*. 1998;79:762-765
72. Stineman MG, Granger CV. Outcome, efficiency, and time-trend pattern analyses for stroke rehabilitation. *Am J Phys Med Rehabil*. 1998;77:193-201
73. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med*. 1975;7:13-31
74. Gladstone DJ, Danells CJ, Black SE. The fugl-meyer assessment of motor recovery after stroke: A critical review of its measurement properties. *Neurorehabil Neural Repair*. 2002;16:232-240
75. Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A, et al. Fugl-meyer assessment of sensorimotor function after stroke: Standardized training procedure for clinical practice and clinical trials. *Stroke*. 2011;42:427-432
76. Mao HF, Hsueh IP, Tang PF, Sheu CF, Hsieh CL. Analysis and comparison of the psychometric properties of three balance measures for stroke patients. *Stroke*. 2002;33:1022-1027
77. Shelton FD, Volpe BT, Reding M. Motor impairment as a predictor of functional recovery and guide to rehabilitation treatment after stroke. *Neurorehabil Neural Repair*. 2001;15:229-237
78. Hsieh YW, Wu CY, Lin KC, Chang YF, Chen CL, Liu JS. Responsiveness and validity of three outcome measures of motor function after stroke rehabilitation. *Stroke*. 2009;40:1386-1391
79. Vogt G, Laage R, Shuaib A, Schneider A, Collaboration V. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: An analysis of the virtual international stroke trials archive (vista) database. *Stroke*. 2012;43:1266-1272
80. Schiemanck SK, Kwakkel G, Post MW, Prevo AJ. Predictive value of ischemic lesion volume assessed with magnetic resonance imaging for neurological deficits and functional outcome poststroke: A critical review of the literature. *Neurorehabil Neural Repair*. 2006;20:492-502
81. Beloosesky Y, Streifler JY, Burstin A, Grinblat J. The importance of brain infarct size and location in predicting outcome after stroke. *Age Ageing*. 1995;24:515-518
82. Saver JL, Johnston KC, Homer D, Wityk R, Koroshetz W, Truskowski LL, et al. Infarct volume as a surrogate or auxiliary outcome measure in ischemic stroke clinical trials. The ranttas investigators. *Stroke*. 1999;30:293-298

83. Yoo AJ, Chaudhry ZA, Nogueira RG, Lev MH, Schaefer PW, Schwamm LH, et al. Infarct volume is a pivotal biomarker after intra-arterial stroke therapy. *Stroke*. 2012;43:1323-1330
84. Walcott BP, Miller JC, Kwon CS, Sheth SA, Hiller M, Cronin CA, et al. Outcomes in severe middle cerebral artery ischemic stroke. *Neurocrit Care*. 2014;21:20-26
85. Nazzal ME, Saadah MA, Saadah LM, Trebinjac SM. Acute ischemic stroke: Relationship of brain lesion location & functional outcome. *Disabil Rehabil*. 2009;31:1501-1506
86. Cheng B, Forkert ND, Zavaglia M, Hilgetag CC, Golsari A, Siemonsen S, et al. Influence of stroke infarct location on functional outcome measured by the modified rankin scale. *Stroke*. 2014;45:1695-1702
87. Ois A, Cuadrado-Godia E, Solano A, Perich-Alsina X, Roquer J. Acute ischemic stroke in anterior choroidal artery territory. *J Neurol Sci*. 2009;281:80-84
88. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Aspects study group. Alberta stroke programme early ct score. *Lancet*. 2000;355:1670-1674
89. Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, et al. Alberta stroke program early ct scoring of ct perfusion in early stroke visualization and assessment. *AJNR Am J Neuroradiol*. 2007;28:1975-1980
90. Launes J, Ketonen L. Dense middle cerebral artery sign: An indicator of poor outcome in middle cerebral artery area infarction. *J Neurol Neurosurg Psychiatry*. 1987;50:1550-1552
91. Zorzon M, Mase G, Pozzi-Mucelli F, Biasutti E, Antonutti L, Iona L, et al. Increased density in the middle cerebral artery by nonenhanced computed tomography. Prognostic value in acute cerebral infarction. *Eur Neurol*. 1993;33:256-259
92. Goldmakher GV, Camargo EC, Furie KL, Singhal AB, Roccatagliata L, Halpern EF, et al. Hyperdense basilar artery sign on unenhanced ct predicts thrombus and outcome in acute posterior circulation stroke. *Stroke*. 2009;40:134-139
93. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: Clinical course and prognostic signs. *Arch Neurol*. 1996;53:309-315
94. Oppenheim C, Samson Y, Manai R, Lalam T, Vandamme X, Crozier S, et al. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. *Stroke*. 2000;31:2175-2181
95. MacCallum C, Churilov L, Mitchell P, Dowling R, Yan B. Low alberta stroke program early ct score (aspects) associated with malignant middle cerebral artery infarction. *Cerebrovasc Dis*. 2014;38:39-45
96. Gerriets T, Stolz E, Konig S, Babacan S, Fiss I, Jauss M, et al. Sonographic monitoring of midline shift in space-occupying stroke: An early outcome predictor. *Stroke*. 2001;32:442-447
97. Kissela B, Lindsell CJ, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, et al. Clinical prediction of functional outcome after ischemic stroke: The surprising importance of periventricular white matter disease and race. *Stroke*. 2009;40:530-536
98. Held V, Szabo K, Bazner H, Hennerici MG. Chronic small vessel disease affects clinical outcome in patients with acute striatocapsular stroke. *Cerebrovasc Dis*. 2012;33:86-91

99. Leonards CO, Ipsen N, Malzahn U, Fiebach JB, Endres M, Ebinger M. White matter lesion severity in mild acute ischemic stroke patients and functional outcome after 1 year. *Stroke*. 2012;43:3046-3051
100. Puetz V, Sylaja PN, Coutts SB, Hill MD, Dzialowski I, Mueller P, et al. Extent of hypoattenuation on ct angiography source images predicts functional outcome in patients with basilar artery occlusion. *Stroke*. 2008;39:2485-2490
101. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, et al. Prediction of outcome in patients with suspected acute ischaemic stroke with ct perfusion and ct angiography: The dutch acute stroke trial (dust) study protocol. *BMC Neurol*. 2014;14:37
102. Fischer U, Arnold M, Nedeltchev K, Brekenfeld C, Ballinari P, Remonda L, et al. Nihss score and arteriographic findings in acute ischemic stroke. *Stroke*. 2005;36:2121-2125
103. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107-116
104. Smith WS, Lev MH, English JD, Camargo EC, Chou M, Johnston SC, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and tia. *Stroke*. 2009;40:3834-3840
105. Gonzalez RG, Lev MH, Goldmacher GV, Smith WS, Payabvash S, Harris GJ, et al. Improved outcome prediction using ct angiography in addition to standard ischemic stroke assessment: Results from the stopstroke study. *PLoS One*. 2012;7:e30352
106. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: Real-world experience and a call for action. *Stroke*. 2010;41:2254-2258
107. Bang OY, Saver JL, Kim SJ, Kim GM, Chung CS, Ovbiagele B, et al. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. *Stroke*. 2011;42:693-699
108. Kucinski T, Koch C, Eckert B, Becker V, Kromer H, Heesen C, et al. Collateral circulation is an independent radiological predictor of outcome after thrombolysis in acute ischaemic stroke. *Neuroradiology*. 2003;45:11-18
109. Bozzao L, Fantozzi LM, Bastianello S, Bozzao A, Fieschi C. Early collateral blood supply and late parenchymal brain damage in patients with middle cerebral artery occlusion. *Stroke*. 1989;20:735-740
110. Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. Ct angiography clot burden score and collateral score: Correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30:525-531
111. Thijs VN, Lansberg MG, Beaulieu C, Marks MP, Moseley ME, Albers GW. Is early ischemic lesion volume on diffusion-weighted imaging an independent predictor of stroke outcome? A multivariable analysis. *Stroke*. 2000;31:2597-2602
112. Hand PJ, Wardlaw JM, Rivers CS, Armitage PA, Bastin ME, Lindley RI, et al. Mr diffusion-weighted imaging and outcome prediction after ischemic stroke. *Neurology*. 2006;66:1159-1163
113. Barrett KM, Ding YH, Wagner DP, Kallmes DF, Johnston KC, Investigators A. Change in diffusion-weighted imaging infarct volume predicts neurologic outcome at 90

days: Results of the acute stroke accurate prediction (asap) trial serial imaging substudy. *Stroke*. 2009;40:2422-2427
114. Cho SH, Kim DG, Kim DS, Kim YH, Lee CH, Jang SH. Motor outcome according to the integrity of the corticospinal tract determined by diffusion tensor tractography in the early stage of corona radiata infarct. *Neurosci Lett*. 2007;426:123-127
115. Radlinska B, Ghinani S, Leppert IR, Minuk J, Pike GB, Thiel A. Diffusion tensor imaging, permanent pyramidal tract damage, and outcome in subcortical stroke. *Neurology*. 2010;75:1048-1054
116. Lindenberg R, Renga V, Zhu LL, Betzler F, Alsop D, Schlaug G. Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke. *Neurology*. 2010;74:280-287
117. Lindenberg R, Zhu LL, Ruber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. *Hum Brain Mapp*. 2012;33:1040-1051
118. Breier JI, Hasan KM, Zhang W, Men D, Papanicolaou AC. Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. *AJNR Am J Neuroradiol*. 2008;29:483-487
119. Bigourdan A, Munsch F, Coupe P, Guttmann CRG, Sagnier S, Renou P, et al. Early fiber number ratio is a surrogate of corticospinal tract integrity and predicts motor recovery after stroke. *Stroke*. 2016;47:1053-1059
120. Gideon P, Sperling B, Arlien-Soborg P, Olsen TS, Henriksen O. Long-term follow-up of cerebral infarction patients with proton magnetic resonance spectroscopy. *Stroke*. 1994;25:967-973
121. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain*. 2007;130:170-180
122. Delvaux V, Alagona G, Gerard P, De Pasqua V, Pennisi G, de Noordhout AM. Post-stroke reorganization of hand motor area: A 1-year prospective follow-up with focal transcranial magnetic stimulation. *Clin Neurophysiol*. 2003;114:1217-1225
123. Pennisi G, Alagona G, Rapisarda G, Nicoletti F, Costanzo E, Ferri R, et al. Transcranial magnetic stimulation after pure motor stroke. *Clin Neurophysiol*. 2002;113:1536-1543
124. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45:201-206
125. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain*. 1994;117 (Pt 4):847-858
126. Brodie SM, Meehan S, Borich MR, Boyd LA. 5 hz repetitive transcranial magnetic stimulation over the ipsilesional sensory cortex enhances motor learning after stroke. *Front Hum Neurosci*. 2014;8:143
127. Meehan SK, Linsdell MA, Handy TC, Boyd LA. Interhemispheric enhancement of somatosensory cortical excitability through contralateral repetitive transcranial magnetic stimulation. *Clin Neurophysiol*. 2011;122:1637-1644
128. Carey JR, Deng H, Gillick BT, Cassidy JM, Anderson DC, Zhang L, et al. Serial treatments of primed low-frequency rtms in stroke: Characteristics of responders vs. Nonresponders. *Restor Neurol Neurosci*. 2014;32:323-335

129. Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke*. 2006;37:2115-2122
130. Seniow J, Bilik M, Lesniak M, Waldowski K, Iwanski S, Czlonkowska A. Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: A randomized, double-blind, placebo-controlled study. *Neurorehabil Neural Repair*. 2012;26:1072-1079
131. Talelli P, Wallace A, Dileone M, Hoad D, Cheeran B, Oliver R, et al. Theta burst stimulation in the rehabilitation of the upper limb: A semirandomized, placebo-controlled trial in chronic stroke patients. *Neurorehabil Neural Repair*. 2012;26:976-987
132. Auriat AM, Neva JL, Peters S, Ferris JK, Boyd LA. A review of transcranial magnetic stimulation and multimodal neuroimaging to characterize post-stroke neuroplasticity. *Front Neurol*. 2015;6:226
133. Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide danish study of 26,818 patients with first-ever ischemic stroke. *Stroke*. 2011;42:2806-2812
134. Koennecke HC, Belz W, Berfelde D, Endres M, Fitzek S, Hamilton F, et al. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. *Neurology*. 2011;77:965-972
135. Konig IR, Ziegler A, Bluhmki E, Hacke W, Bath PM, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke: A simple index works in patients from controlled clinical trials. *Stroke*. 2008;39:1821-1826
136. Heuschmann PU, Wiedmann S, Wellwood I, Rudd A, Di Carlo A, Bejot Y, et al. Three-month stroke outcome: The european registers of stroke (eros) investigators. *Neurology*. 2011;76:159-165
137. Kammersgaard LP, Jorgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS, et al. Short- and long-term prognosis for very old stroke patients. The copenhagen stroke study. *Age Ageing*. 2004;33:149-154
138. Steiner T, Mendoza G, De Georgia M, Schellinger P, Holle R, Hacke W. Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit. *Stroke*. 1997;28:711-715
139. Veerbeek JM, Kwakkel G, van Wegen EE, Ket JC, Heymans MW. Early prediction of outcome of activities of daily living after stroke: A systematic review. *Stroke*. 2011;42:1482-1488
140. McGrath ER, Kapral MK, Fang J, Eikelboom JW, Conghaile A, Canavan M, et al. Association of atrial fibrillation with mortality and disability after ischemic stroke. *Neurology*. 2013;81:825-832
141. O'Donnell MJ, Fang J, D'Uva C, Saposnik G, Gould L, McGrath E, et al. The plan score: A bedside prediction rule for death and severe disability following acute ischemic stroke. *Arch Intern Med*. 2012;172:1548-1556
142. Kimura K, Minematsu K, Yamaguchi T, Japan Multicenter Stroke Investigators C. Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2005;76:679-683
143. Desilles JP, Meseguer E, Labreuche J, Lapergue B, Sirimarco G, Gonzalez-Valcarcel J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: A registry and systematic review. *Stroke*. 2013;44:1915-1923

144. Toyoda K, Fujii K, Fujimi S, Kumai Y, Tsuchimochi H, Ibayashi S, et al. Stroke in patients on maintenance hemodialysis: A 22-year single-center study. *Am J Kidney Dis*. 2005;45:1058-1066
145. Saposnik G, Kapral MK, Liu Y, Hall R, O'Donnell M, Raptis S, et al. Iscore: A risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation*. 2011;123:739-749
146. Pohjasvaara T, Vataja R, Leppavuori A, Kaste M, Erkinjuntti T. Cognitive functions and depression as predictors of poor outcome 15 months after stroke. *Cerebrovasc Dis*. 2002;14:228-233
147. Collaboration FT. Poor nutritional status on admission predicts poor outcomes after stroke: Observational data from the food trial. *Stroke*. 2003;34:1450-1456
148. Barlas RS, Honney K, Loke YK, McCall SJ, Bettencourt-Silva JH, Clark AB, et al. Impact of hemoglobin levels and anemia on mortality in acute stroke: Analysis of uk regional registry data, systematic review, and meta-analysis. *J Am Heart Assoc*. 2016;5
149. Doehner W, Schenkel J, Anker SD, Springer J, Audebert HJ. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: Observations from the tempis trial. *Eur Heart J*. 2013;34:268-277
150. Plowman E, Hentz B, Ellis C, Jr. Post-stroke aphasia prognosis: A review of patient-related and stroke-related factors. *J Eval Clin Pract*. 2012;18:689-694
151. Pedersen PM, Vinter K, Olsen TS. Aphasia after stroke: Type, severity and prognosis. The copenhagen aphasia study. *Cerebrovasc Dis*. 2004;17:35-43
152. Geeganage C, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev*. 2012;10:CD000323
153. Dennis MS, Lewis SC, Warlow C, Collaboration FT. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (food): A multicentre randomised controlled trial. *Lancet*. 2005;365:764-772
154. Kalra L, Perez I, Gupta S, Wittink M. The influence of visual neglect on stroke rehabilitation. *Stroke*. 1997;28:1386-1391
155. Katz N, Hartman-Maeir A, Ring H, Soroker N. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. *Arch Phys Med Rehabil*. 1999;80:379-384
156. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, et al. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: A scientific statement from the american heart association. *Stroke*. 2010;41:2402-2448
157. group ISTc. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third international stroke trial (ist-3): Secondary analysis of a randomised controlled trial. *Lancet Neurol*. 2015;14:485-496
158. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total mri brain small-vessel disease burden. *Neurology*. 2014;83:1228-1234
159. Investigators ET. 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
160. Investigators ET. 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). *Int J Stroke*. 2006;1:245-249
161. Arba F, Inzitari D, Ali M, Warach SJ, Luby M, Lees KR, et al. Small vessel disease and clinical outcomes after iv rt-pa treatment. *Acta Neurol Scand*. 2017;136:72-77
162. Roccaforte WH, Burke WJ, Bayer BL, Wengel SP. Validation of a telephone version of the mini-mental state examination. *J Am Geriatr Soc*. 1992;40:697-702
163. Zung WW. A self-rating depression scale. *Arch Gen Psychiatry*. 1965;12:63-70
164. Whynes DK, Sprigg N, Selby J, Berge E, Bath PM, Investigators E. Testing for differential item functioning within the eq-5d. *Med Decis Making*. 2013;33:252-260
165. Gaist D, Wallander MA, Gonzalez-Perez A, Garcia-Rodriguez LA. Incidence of hemorrhagic stroke in the general population: Validation of data from the health improvement network. *Pharmacoepidemiol Drug Saf*. 2013;22:176-182
166. LoPresti MA, Bruce SS, Camacho E, Kunchala S, Dubois BG, Bruce E, et al. Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. *J Neurol Sci*. 2014;345:3-7
167. 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
168. Subramanian G KK, et al. Can we predict clinical outcomes after a moderate/severe stroke? 2018
169. 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
170. Krishnan K, Scutt P, Woodhouse L, Adami A, Becker JL, Berge E, et al. Glyceryl trinitrate for acute intracerebral hemorrhage: Results from the efficacy of nitric oxide in stroke (enos) trial, a subgroup analysis. *Stroke*. 2016;47:44-52
171. Zia E, Engstrom G, Svensson PJ, Norrving B, Pessah-Rasmussen H. Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. *Stroke*. 2009;40:3567-3573
172. Nilsson OG, Lindgren A, Brandt L, Saveland H. Prediction of death in patients with primary intracerebral hemorrhage: A prospective study of a defined population. *J Neurosurg*. 2002;97:531-536
173. Inagawa T, Ohbayashi N, Takechi A, Shibukawa M, Yahara K. Primary intracerebral hemorrhage in izumo city, japan: Incidence rates and outcome in relation to the site of hemorrhage. *Neurosurgery*. 2003;53:1283-1297; discussion 1297-1288
174. Palm F, Henschke N, Wolf J, Zimmer K, Safer A, Schroder RJ, et al. Intracerebral haemorrhage in a population-based stroke registry (lusst): Incidence, aetiology, functional outcome and mortality. *J Neurol*. 2013;260:2541-2550
175. Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, et al. The edinburgh ct and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: Model development and diagnostic test accuracy study. *Lancet Neurol*. 2018;17:232-240
176. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein e epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. *Ann Neurol*. 1995;38:254-259
177. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74:1346-1350

178. Bhalla A, Wang Y, Rudd A, Wolfe CD. Differences in outcome and predictors between ischemic and intracerebral hemorrhage: The south london stroke register. *Stroke*. 2013;44:2174-2181
179. Onteddu SR, Goddeau RP, Jr., Minaeian A, Henninger N. Clinical impact of leukoaraiosis burden and chronological age on neurological deficit recovery and 90-day outcome after minor ischemic stroke. *J Neurol Sci*. 2015;359:418-423
180. SSNAP. Https://www.Strokeaudit.Org/documents/national/clinical/apr2017mar2018/apr2017mar2018-annualreport.Aspx. 2019
181. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: A systematic review and meta-analysis of individual patient data. *Lancet Neurol*. 2018;17:885-894
182. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40:373-383
183. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489-495