PROGNOSIS OF TRANSIENT ISCHAEMIC ATTACK IN MODERN HEALTH CARE SETTINGS

Dr. Nashwa Najib

(MBBS)

Master of Philosophy (Medicine)

Faculty of Health and Medicine

School of Medicine and Public Health

The University of Newcastle

Australia

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Supervisors

Professor Christopher Levi
BMedSc, MB BS, FRACP

Senior Staff Neurologist, John Hunter Hospital
Director of Clinical Research and Translation, Research, Innovation and Partnerships
Hunter New England Local Health Districts
Conjoint Professor of Medicine (Neurology), University of Newcastle, Australia
Practitioner Fellow, NHMRC

Professor Parker Magin
MBBS, PhD, MFM(Clin), MGPP, GDipClinEpi, DPD, FRACGP

Conjoint Professor
Faculty of Health and Medicine
University of Newcastle, Australia

Associate Professor Daniel Lasserson
MA, MBBS, MD, MRCGP, FRCP

Associate Professor and Senior Clinical Researcher
Nuffield Department of Medicine
University of Oxford, United Kingdom

Declarations

Statement of Originality

*The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository**, subject to the provisions of the Copyright Act 1968.*

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Signature ……. Date ……..

Nashwa Najib

Dedication

I dedicate this thesis to my father.

Miss you.

Acknowledgements

In the name of Allah, the Most Gracious, the Most Merciful

I would like to begin by thanking God for helping me complete my thesis. I will further continue serving mankind and constantly contribute to the advancing field of health and medicine.

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Rationale for this M. Phil project

Transient ischaemic attacks (TIAs) are common (1) and place patients at risk of subsequent stroke. Analysis conducted by the Oxford Community Stroke Project (OCSP) (1981- 1986) reported high risk of stroke after TIA, with risks of 8.6% at 7- days and 12.0% at 30- days. (2) Similarly, the high risk of stroke following TIA was also appreciated following a study conducted in California (from March 1997 to February 1998), in which the 90- day risk of stroke was noted to be 10.5%. (3) Given the considerable potential for mortality and serious morbidity related to stroke, the risk of stroke following TIA is a major health issue. (4) High early post-TIA risk ('front-loaded risk') of stroke after a TIA was reported by the Oxford Vascular Study (OxVASC). This was published in 2009 and the risk of stroke was 5.1% at 24 hours. (5)

The Early Use of Existing Preventive Strategies for Stroke (EXPRESS) (6) study indicated that initiating early management of TIA or minor stroke can substantially reduce the risk of stroke. This study was conducted in two phases. In phase 1 (2002- 2004), patients generally were recommended aspirin and/or clopidogrel, simvastatin and antihypertensive commencement or intensification (and as required, anticoagulant). In phase 2 (2004- 2007), a more urgent non-appointment-based referral clinic was commenced. All patients were given aspirin to take in the clinic together with a prescription for a 4- week supply of any other medication (using the same treatment protocol as in phase 1) to start on the same day. In this study, the 90- day risk of recurrent stroke dropped from 10.3% in phase 1 to 2.1% in phase 2 (adjusted hazard ratio 0.20, 95%CI 0.08- 0.49; p= 0.0001). Thus, this study demonstrated an 80% relative risk reduction and 8.1% absolute risk reduction for stroke following a health system change to more urgent assessment and treatment. In 2009, the EXRESS study published the disability and hospital costs associated with urgent treatment of TIA and minor stroke. Hospital admissions (p= 0.001) for recurrent stroke, the 90- day risk of fatal or disabling stroke (p= 0.0005) and the overall number of bed- days (p= 0.017) were reduced in phase 2 as compared to phase 1. (7)

Similarly, the SOS-TIA study conducted in France found lower rates of stroke than expected on the basis of the $ABCD^2$ score (a prognostic score), when TIA patients were managed early. (8) The SOS- TIA clinic was a 24- hours access hospital clinic which could also be contacted via a toll- free telephone number. A stroke- prevention nurse was in charge of the call centre and during after- hours, all calls were automatically transferred to a senior vascular neurologist. Patients were admitted immediately after the telephone call from their respective family doctors if the patients had confirmed or suspected TIA. Initial standardised assessments were conducted by a vascular neurologist within 4- hours of admission. For suspected TIAs, further assessments such as brain imaging (MRI/CT scan), duplex ultrasonography, transcranial Dopler and ECG were conducted. Blood tests were done to test for lipid profile, Red Blood Cells (RBC), White Blood Cells (WBC), platelets, glycated haemoglobin (HbA1c), C-reactive protein (CRP) and creatinine. At the end of the assessments, patients were immediately discharged home unless admission criteria were met. All patients, or their GPs were instructed to immediately commence, received aspirin and blood pressure lowering. Lipid lowering drugs were either started or modified at the

time of discharge as required. Patients with atrial fibrillation (AF) were given an anticoagulant (low molecular weight heparin) until fully anticoagulated. A discharge summary was sent to the family doctor. The 90-day stroke rate for TIAs in this study was 1.24%, whereas the rate predicted from $ABCD^2$ scores of individual participants was 5.96%.

Results from these important studies for clinical practice were published in 2007 and demonstrated that early evaluation and commencement of early therapy of TIA and minor stroke markedly reduces the risk of a major stroke.

In contemporary practice, with emerging diagnostic techniques and with revised guidelines incorporating evidence for rapid management policies and use of risk stratification strategies, TIA can be diagnosed early and management initiated early. In the period following the publication of original studies alerting clinicians to the high risk of stroke following TIA, and especially following the landmark EXPRESS and SOS-TIA studies that demonstrated the efficacy of rapid assessment and initiation of treatment in TIAs, it may be expected that the prognosis of TIA in patients engaging with contemporary health care systems would be more favourable than in historical cohorts.

A better understanding of current contemporary prognosis of TIA rather than dependence on historical data will provide more refined approaches to the assessment of TIA. The aim of this M. Phil project was to conduct a systematic review and meta- analysis of studies reporting the prognosis of TIA in contemporary practice. Contemporary practice is defined as practice reported in studies published in the post- EXPRESS era (i.e. studies published after 2007).

Organisation of this thesis

This thesis is comprised of four chapters.

The first chapter is an introductory chapter, which provides an overview of the background and the natural history of TIA. In addition to the definitions of TIA, including both time-based and tissue-based; the pathophysiology and epidemiology of stroke and TIA are also discussed. Briefly, the signs and symptoms of TIA and its differential diagnosis are introduced in this section. This section also includes the risk factors of stroke and TIA, prognosis of TIA and the various risk stratification tools. The management of TIA is also discussed here, followed by the differing approaches of management of TIA among the health systems.

The second chapter is the methodology chapter; comprising the methods of the systematic review and meta-analysis, including the statistical methodology. The eligibility criteria of the studies, selection of studies and data collection process is included in this section.

The third chapter is the results chapter. The results of the systematic review and meta- analysis are presented here. This section also includes the table of characteristics of all the studies included in the systematic review and meta- analysis as well as the Preferred Reporting Items for Systematic Review and Meta- Analysis Protocols (PRISMA) checklist.

The fourth chapter is the discussion chapter. In this chapter, the results of the systematic review and meta-analysis are discussed briefly by comparison with previous pre- EXPRESS studies (studies published prior 2007). The strengths and limitations of the study are discussed and information provided on implications of the results for practice and policy and for further research. This chapter also summarises the results and concludes by emphasising the importance of this systematic review and meta-analysis for informing best practice.

Chapter 1

Background and Introduction

In this chapter, both stroke and TIA will be considered. Not only is stroke the major outcome relevant to TIA, stroke and TIA have similar clinical manifestations along with the same pathophysiological mechanisms. Studies of TIA often include minor stroke as well as TIA. There is a pathophysiological spectrum from TIA to minor ischaemic stroke to major ischaemic stroke.
The literature around the prognosis of TIAs is central to the topic of the systematic review conduced for this M. Phil thesis: Prognosis of transient ischaemic attack in modern health care settings.

The epidemiology, pathophysiology, clinical manifestations, differential diagnoses, risk stratification and management of TIAs, however, are also important in understanding the determinants and context of the prognosis of TIAs and in critically evaluating studies of the prognosis of TIAs. Thus, these will also be addressed in this chapter.

Definition of TIA

There are differing extant definitions of TIA. These reflect progressively more sophisticated means of ascertaining brain infarction via imaging modalities.

The 1988 World Health Organisation (WHO) definition for TIA, characterises TIA as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting less than 24 hours with no apparent cause other than that of vascular origin. (9) This is the long- established TIA definition and is entirely clinical.

With the implementation of advanced imaging studies such as CT perfusion, CT angiography and diffusion weighted MRI, it has become apparent that many ischaemic episodes with symptom resolution within 24 hours are associated with new infarction. (10, 11) Hence, a more refined tissue- based rather than a time- based definition was proposed in 2002, which defines transient ischaemic attack as a brief episode of neurologic dysfunction caused by focal ischaemia (brain or retinal) without acute infarction.(12) Advanced imaging is required to use this definition.

The 2009 American Stroke Association (ASA) definition of TIA, defines TIA as a brief episode of neurologic dysfunction resulting from focal cerebral ischaemia, which is not associated with permanent cerebral infarction. (13)

Importance of TIA

The principal importance of TIA lies in the fact that the risk of stroke following a TIA is very high. Historical cohorts suggest that 15% of stroke cases are preceded by a TIA. (14)

Stroke is one of the most common causes of life threatening illness. (15) (16) . According to The North East Melbourne Stroke Incidence Study (NEMESIS), the crude annual incidence rate of first ever strokes was 206 per 100, 000 per year. (15) Population- based stroke incidence studies conducted in the Hunter Region of New South Wales in Australia (17) show that, while there was a 0.85% reduction of stroke attack rate per year between 1996 and 2008, the case fatality rate remained constant during this period.

The importance of the link of TIA to stroke lies in the potentially devastating effects of stroke: in stroke mortality and stroke-related morbidity and in the economic consequences of stroke. Stroke is the third leading cause of death in Australia (after heart disease and cancer). (16) In Australia, stroke is the leading cause of disability. In the year 2003, disability among 146,400 Australians was attributed to stroke. (18) Stroke is one of the leading causes of health expenditure in Australia, followed by oral health, mental disorders, musculoskeletal conditions, injuries and neoplasms (cancers). (19) The NEMESIS estimated that in Australia, the total lifetime cost of first-ever stroke in 1997 was A$1.3 billion or A$44,000 per case. (20) Between 1997 and 2009, the cost of stroke care increased by roughly six per cent. (21) The existing burden of health cost is also contributed by treatment of various complications after stroke such as post-stroke dementia, depression, falls, fracture and epilepsy. (22)

Definition of stroke

According to the American Heart Association (AHA)/ American Stroke Association (ASA), the term "stroke" should broadly be used to include all of the following: (23)

Ischaemic stroke: An episode of neurological dysfunction caused by focal CNS infarction. CNS infarction is brain, spinal cord, or retinal cell death attributable to ischaemia, based on
1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischaemic injury in a defined vascular distribution; or
2. clinical evidence of cerebral, spinal cord, or retinal focal ischaemic injury based on symptoms persisting ≥24 hours or until death, and other aetiologies excluded.

Silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Stroke caused by intracerebral haemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Silent cerebral haemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.

Stroke caused by subarachnoid haemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Stroke caused by cerebral venous thrombosis: Infarction or haemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible oedema without infarction or haemorrhage do not qualify as stroke.

Stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

Definition of Minor stroke

Many observational studies report TIAs and minor strokes grouped together.

Minor stroke can be defined according to the National Institute of Health Stroke Scale (NIHSS) - where all patients with baseline NIHSS<=3 are categorised as minor stroke as these patients have better short- and medium- term outcomes than people with a higher NIHSS score. (24) The prognosis of minor stroke is similar to that of TIA. (6, 25-27)

(see Appendix III for the NIHSS)

Pathophysiology of stroke and TIA

The clinical manifestations and management of TIA are closely related to the pathophysiology of stroke and TIA. Hence, it is important to understand the underlying pathophysiology for diagnosis and implementing effective management. Changes in management in recent years underpinning the hypothesised improvement in TIA prognosis that this M. Phil project is investigating target specific aspects of stroke and TIA pathophysiology.

There are two main types of stroke: ischaemic stroke (also known as cerebral infarction) which is caused by blockage of a blood vessel due to a blood clot; and haemorrhagic stroke, which is caused by bleeding following a rupture of a blood vessel. The more common of these two, and the type relevant to this M.Phil project, are the ischaemic strokes, accounting for about 80% of strokes. Haemorrhagic strokes account for roughly 20%. (21)

A particular category of ischaemic stroke, constituting about 20- 25% of brain infarcts is lacunar strokes. Lacunar strokes result from occlusion of one of the small penetrating arteries supplying the deep structures of the brain. (28)

Ischaemic stroke results from a cascade of events that result in loss of neuronal function and cause irreversible ischaemia. The three major mechanisms that result in ischaemic stroke include

i) Occlusion of an intracranial vessel caused by an embolus arising at a distant location. The embolus is usually due to atrial fibrillation, emboli from carotid atherosclerotic plaque, or emboli from other sources such as aortic emboli
ii) In-situ thrombosis of an intracranial vessel typically affecting the small penetrating arteries arising from major intracranial arteries
iii) Hypoperfusion/ watershed ischaemia which is caused by flow- limiting stenosis of a major extracranial or intracranial vessel. (29)

Less commonly, but importantly, intracranial artery atherosclerosis can also cause ischaemic stroke. Within the large intracranial and the extracranial arteries of the brain, atherosclerosis is the most common cause of localised in-situ disease. Narrowing of the large intracranial arteries due to atherosclerosis can cause ischaemic stroke. In-situ thromboembolism leads to artery-to-artery embolism, resulting in haemodynamic insufficiency causing ischaemic stroke. (30)

Normally, the brain receives blood supply via three major arteries- the internal carotid arteries (supplying the anterior 2/3 of the brain) and the basilar artery (supplying the posterior 1/3 of the brain). These arteries branch throughout the brain supplying brain cells with a constant flow of oxygen, glucose and various nutrients required for their functions. The hallmark mechanism of ischaemic stroke is emboli lodged in a carotid artery plus existing stenosis and plaque, leading to impaired perfusion of the brain. In ischaemic stroke, the artery becomes narrowed or completely blocked, thus preventing the normal blood flow to the brain. The blockage may be caused by a blood clot (thrombus) which forms in an unhealthy artery of the brain as a result of atheroma/ stenosis. The lack of blood flow causes the brain tissue, which the artery supplies, to become ischaemic. Similarly, the blockage may be due to an embolus. This is a blood clot that is formed elsewhere in the body, such as the mural thrombus arising in the left ventricular due to myocardial infarction (MI) and emboli arising from the left atrial thrombus due to AF, or blood clot forming in large intracranial or extra- cranial arteries (artery- to- artery thrombo- embolism), which lodges in a narrowed artery obstructing blood flow to the brain.

A very important predictor of stroke is TIA, which unlike stroke, is a manifestation of reversible ischaemia. The pathophysiology of TIA is similar to ischaemic stroke, the difference being that the

neurological deficit is transient rather than persistent. The neurological deficit in a TIA is transient as the symptoms resolve within a few minutes or, by definition, within 24 hours. However, a major concern arises with clinical TIA when an infarct is identified on MRI imaging. According to the tissue- based definition of TIA, (12) TIA should be without acute infarction on imaging.

It is important to understand the vascular territories of the brain, as this knowledge enables recognition of the infarction occurring in arterial territories and in watershed regions. The brain is supplied with blood via two internal carotid arteries and the basilar artery (formed form the two vertebral arteries). These anastomose at the base of the brain forming the Circle of Willis.

Arterial territory of ischaemic strokes and TIAs

An understanding of arterial territories is of importance in interpreting the studies included in the systematic review, as territories will influence not only the prognosis of TIA and stroke but the clinical manifestations which influence diagnosis (including differentiation from TIA 'mimics').

The vascular territories of ischaemic stroke/ cerebral infarction can be classified according to the Oxford Stroke classification.

Oxford stroke classification or the Bamford classification system (31)

1. Total anterior circulation infarct (TACI)
2. Partial anterior circulation infarct (PACI)
3. Lacunar infarct (LACI)
4. Posterior circulation infarct (POCI)

This Oxford stroke classification provides information in regards to stroke prognosis.

Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (32)

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification contains arterial territory of the stroke (anterior or posterior), but also includes the pathophysiological mechanisms.

Five subtypes of ischaemic strokes are identified as follows by the TOAST classification:

1. Large- artery atherosclerosis
2. Cardio- embolism
3. Small- vessel occlusion
4. Stroke of other undetermined aetiology
5. Stroke of undetermined aetiology

The territories of deficit of strokes and TIAs can be diagnosed by looking for symptoms and with the help of radio- diagnostic techniques (such as CT, MRI, T2- FLAIR, arterial spin- labelling and MRA).

Symptoms of TIA and differential diagnosis with mimics

The relevance of considerations of symptoms and differential diagnoses of TIA is that, despite the contribution of advanced imaging techniques in recent years, the diagnosis of TIA is essentially a clinical one. It is also often a difficult diagnosis to make. Since, the clinical presentation of TIA is transient and may mimic the symptoms of many non- ischaemic transient focal neurological episodes such as in migraine, seizures and syncope; establishing a clear diagnosis of TIA may be difficult. The inter-observer reliability of TIA diagnosis is modest. (33, 34) The clinical manifestations are extremely varied and the range of potential differential diagnoses wide. (35) Even neurologists have been found to have only fair agreement on TIA diagnoses. (35, 36) The diagnosis of TIA is challenging, because there is no definitive diagnostic test and the rate of mimics is high. It is therefore important to make a diagnosis of TIA with sound clinical judgement and careful clinical assessments, so that the management can be initiated in a targeted manner. Critical evaluation of papers included in the systematic review conducted in this M. Phil study will include an evaluation of who has made the diagnosis and on what basis diagnosis was made.

The clinical symptoms and signs of a TIA are similar to focal symptoms of stroke. Most common presenting symptoms are as follows:

1. Hemiparesis
2. Paraesthesia
3. Amaurosis fugax
4. Aphasia
5. Impaired consciousness
6. Dysphagia
7. Headache
8. Dizziness
9. Vertigo

However, the symptoms vary in severity and are related to the territory involved.

Anterior cerebral artery ischaemia: This may include monoparesis, extrapyramidal symptoms such as tremor, apraxia, aphasia, sensory loss in same distribution as weakness, frontal lobe involvement (including mood and personality changes).

Middle cerebral artery ischaemia: This may include dysphasia (with involvement of left hemisphere), dyslexia, dysphagia, contralateral hemiparesis/ hemiplegia, contralateral hemisensory loss, rapidly declining level of consciousness, vomiting and homonymous hemianopia.

Posterior cerebral artery (central) ischaemia: With involvement of central thalamic or subthalamic nuclei; there is diffuse sensory loss, mild hemiparesis and intention tremor. With the involvement of cerebral peduncle; there is contralateral hemiplegia and oculomotor nerve deficit. With the involvement of brainstem; there is pupillary dysfunction, nystagmus and loss of conjugate gaze.

Posterior cerebral artery (peripheral) ischaemia: Where visual cortex is affected rather than optic pathway. This may include peripheral visual changes and may present with homonymous hemianopia, cortical blindness, lack of depth perception, failure to see objects not centered in visual field and pleasant visual hallucinations. Memory deficits, perseveration and dyslexia are also seen with this type of infarction.

Pure sensory TIAs: These are uncommon and can occur as a result of compromise of small vessels supplying blood to the postero- lateral part of the thalamus. This type is highly suggestive of the presence of PCA disease.

Many other diseases may mimic the signs and symptoms of TIA. Following are the differential diagnosis of TIA:

1. Migraine
2. Syncope
3. Seizure
4. Transient global amnesia (TGA)
5. Benign paroxysmal positional vertigo (BPPV)
6. Hypoglycaemia
7. CNS infection, such as meningitis and encephalitis
8. Brain tumour
9. Falls
10. Multiple sclerosis
11. Subarachnoid haemorrhage
12. Hypertensive encephalopathy
13. Demyelinating disease
14. Conversion disorder

In interpreting the prognoses of TIA cohorts, it should be noted that, not only can differentiation of TIA from mimic be difficult, but the prognoses of mimic conditions can range from the very benign to the very serious. Various reasons influence the differential diagnosis of TIA, such as, past medical/surgical history, presence/absence of risk factors, identification of neurological deficit symptom pattern at initial presentation (timing of symptoms, onset/progression and resolution, periodicity and presence/absence of non-specific symptoms).

Epidemiology of stroke and TIA

TIA

Incidence of TIA

The incidence of TIA has been evaluated by various studies worldwide. (33, 37, 38) Within these studies, increased incidence of TIA was recorded. According to a community study in Rochester, Minnesota in the United States (between 1955 and 1979), the average incidence for first TIA was 0.31/1000 person-years. (39) A study in Tartu, Estonia in USSR was conducted between 1970 and 1973, to establish the incidence of cerebrovascular events and reported the incidence of TIA was 0.33/1000 person-years. (40) In the Oxfordshire Community Stroke Project (OCSP), between 1981 and 1986, the crude incidence rate of TIA was 0.35/1000 person-years. Between 1985 and 1989, the incidence of TIA was calculated by the Rochester, Minnesota study in the United States. Between 1985 and 1989, the annual incidence of TIA was 68/100,000 population (adjusted for age and sex). (41) A prospective population-based study conducted in Belluno, Italy (between 1992 and 1993), reported the crude annual incidence of first TIAs was 0.80/1000 person-years. (42) The incidence of TIA was also evaluated in the Greater Cincinnati/Northern Kentucky population-based retrospective study of stroke and TIA between 1993 and 1994. Adjusted for age, race and gender, the annual incidence of TIA was 83 per 100,000. (37) Similarly, the incidence of TIA was evaluated in the population-based study of stroke and TIA, the Oxford Vascular Study (OxVASC). The OxVASC study population comprised 91,106 individuals. Between 2002 and 2005, this study ascertained 2024 acute vascular events among 1657 individuals, of which 300 incident cases of TIA were recorded.(43) In the Monash Transient Ischaemic Attack Triaging Treatment (M3T) between 2004 and 2007, 488 patients with suspected TIA were treated, of which 301 patients were identified as neurologist-confirmed TIA cases.(44) According to the Perth Community Stroke Study (PCSS) (between 1989 and 1990) 492/138708 patients were identified with acute stroke or TIA in Perth, Australia, of which 370 (75%, 95%CL, 71%, 79%) had an acute first-ever stroke.(45) In the North East Melbourne Stroke Incidence Study (NEMESIS) (between 1996 and 1997), of the total population of Melbourne in Australia (133816), 1371 patients with stroke were identified, of which 987 patients were excluded. It was found that of the excluded patients 12.7% had TIAs. (15)

Influence of age on TIA incidence

In the OCSP, the incidence of TIA markedly increased with age. (46) With age, acute vascular event and incidence rates increased in all arterial territories (all p- values < 0.0001). (43) In the Greater Cincinnati/Northern Kentucky study, the incidence of TIA increased markedly with age, regardless of race or gender. (37)

Thus, in studies reporting the influence of age on TIA incidence, it is shown that higher incidence of TIA was noted with increasing age.

Influence of gender on TIA incidence

In the OCSP, the incidence of TIA markedly increased with age; middle-aged men were 2.6 times more likely to suffer a TIA than middle-aged women. (46) In the OxVASC study, it was noted that the incidence of TIA was higher in men than in women, particularly among those aged younger than 65 years. (43) In the Rochester, Minnesota study, the incidence of TIA was higher in men (76/100,000; 95%CI 59.5-92.6) than in women (62/100,000; 95%CI 50.1-73.7). (41) Similarly, in the OCSP, the overall incidence of TIA was higher in men than in women (incidence ratio 1.3). (46) In the Greater Cincinnati/Northern Kentucky study, the incidence of TIA among males was 101.4/100,000 (95%CI 92.4, 110.4) and among females was 69.8/100,000 (95%CI 64.0, 75.8). (37) In Hisayama, Japan, a prospective community study of incidence of cerebrovascular events began in 1961. During a 20-year follow-up, it was found that the average incidence of first TIA was 0.78/1000 person-years in men and 0.38/1000 person-years in women. (47) Contrary to these results, in a study conducted in Italy, the incidence of TIA was higher in women (0.87/1000; 95%CI 0.70-1.06) than in men (0.73/1000; 95%CI 0.57-0.91). (42) However, the results from the Italian study were non-significant.

Thus, in studies reporting gender, results have generally shown a higher incidence of TIA among males than females.

Stroke

Stroke is the fourth leading cause of death in the United States and worldwide it is the number one cause of long-term disability. (48) In the US approximately 800,000 strokes occur each year, of which 87% are ischaemic infarctions, 10% are primary haemorrhages and 3% are subarachnoid haemorrhages.(49)

Studies from Belgium report a decreasing trend (from 1984-1999) in the incidence of stroke and TIA, however a weaker trend was reported for TIA than for stroke. (33) In recent decades, for high-income countries such as the US, the UK and Canada, the trends in stroke incidence and mortality have decreased.(50-53) However, this has not been the same for the low- to middle-income countries, (50) where increased stroke burden and mortality has been recorded.(54, 55) High stroke mortality rates were seen in eastern Europe, north Asia, central Africa and the south Pacific. (54) A systematic review and meta- analysis showed high stroke burden in Africa (between 2009- 2013). (56)

Stroke incidence and outcome varies greatly between different age groups and race/ethnicity.

Influence of age on stroke incidence

Studies have shown that incidence of stroke increases rapidly with age. (49, 57) Among adults aged between 35 to 44 years, the incidence of stroke is 30 to 120 of 100,000 per year and among adults aged

between 65 to 74 years, the incidence of stroke is 670 to 970 of 100,000 per year. (49) Many other studies have found that independent of stroke type, increased age is also associated with poorer outcome of stroke.(58, 59)

Influence of race/ethnicity on stroke incidence

Racial disparities in stroke incidence and outcomes have been well-described. In the US, the African Americans have higher stroke incidence and death rates as compared to non-Hispanic white people.(57) Mexican-Americans have a higher risk of stroke recurrence than non-Hispanic whites.(60) Australian Bureau of Statistics (ABS) has reported that the incidence of stroke is higher among Australian Aboriginal and Torres Strait Islander people as compared to other Australians. (61)

Incidence of stroke in Australia

The epidemiology of stroke has also been studied in Australia. Hunter stroke attack rate studies found that during 1996 to 2008, crude and age-standardised stroke attack rates have decreased. (17) However, in the Adelaide Stroke Incidence Study conducted from 2009 to 2010, first-ever strokes were reported to affect 161 per 100,000 persons per year. (62)

In 2007-2008, the prevalence of stroke in the lowest socio-economic group was 1.8 times higher as compared to highest socio-economic groups (1.7% compared with 0.9%). (21) In 2008, among Aboriginal and Torres Strait Islander individuals in Australia, the prevalence of cerebrovascular diseases was reported to be 1.7 times higher than that for the non-indigenous Australians (adjusted for age). (21)

Risk factors for stroke and TIA

The risk factors for TIA are those of ischaemic stroke. The most prominent risk factors for stroke include old age, carotid stenosis and cardiac sources of thromboembolism such as atrial fibrillation (AF) and recent myocardial infarction. Other prominent risk factors for stroke include hypertension, current smoking, abdominal obesity, diet, physical activity, diabetes mellitus, alcohol intake, psychological stress, depression, cardiac disease and ratios of apolipoproteins B to A1. (63)

Carotid stenosis is usually caused by carotid atherosclerosis. The risk of stroke is higher in people with 50%- 99% carotid stenosis. (64)

Several studies have reported that 13%-17% of all ischaemic strokes are caused by cardioembolic events. (65, 66) In a prospective study conducted from 1986- 1993, it was found that AF accounted for almost 57.1% of cardiac sources of emboli. (67) A more recent Australian study in a relatively older population found that 42% of all ischaemic strokes were cardioembolic strokes and AF accounted for 36% of all

ischaemic strokes. (62) Studies also show that there is a five- fold increased risk of stroke in patients with AF. (68)

Oral contraceptives and hormone replacement therapy are linked to increasing the risk of stroke as well. (69, 70) Rarely, certain inherited and acquired hypercoagulable states also predispose to this risk.

Prognosis of TIA

Risk models show substantial risk of stroke after a TIA and also identify that this risk is predictable. (3, 71) Stratifying the risk of stroke in a patient presenting with TIA allows for targeted management of those patients who are at greatest risk.

Following a TIA, patients are at increased risk of not only stroke but of other cardiovascular events (including myocardial infarction) and of death. In earlier cohort studies (prior to 2007), relatively high risk of stroke following a TIA have been noted. In the Oxfordshire Community Stroke Project (1981-1986), the risk of stroke during the first year after a TIA was 11.6% and the risk of death, stroke or MI was 8.4% per year within five years after a TIA. (72) A population-based study conducted in Alberta, Canada (1999-2000) reported the risk of stroke after TIA to be 14.5% (95%CI 12.8-16.2) at 1-year. (73) A systematic review of population health data was conducted to examine the trends from 1990 to 2001. It was found that there was a 10% risk of a recurrent stroke in the week following a TIA or a minor stroke. (74)

Over the years, with revised guidelines, (75) there have been major changes in the manner which the health care professionals manage TIA, such as with the implementation of urgent management in specialised clinics including immediate investigations, rapid treatment and implementation of urgent stroke prevention strategies. (76) This may reflect in the outcome of TIA. Studies have reported stroke risk at various time points- 2-days, 7-days, 30-days, 90-days, 1 year and 5 years after a TIA. However, most of the studies have reported stroke risk at 2-days, 7-days, 30-days and 90-days, which is summarised below:

2-days risk of stroke following a TIA

Year of publication	Sample size (N)	2-d stroke risk (%)
2000(3)	1707	5.3
2003(2)	209	4.3
2004(73)	2285	1.4
2004(77)	612	1.6
2004(78)	603	5.5
2005(37)	1023	3.9

2005(71)	190	6.8
2006(79)	141	9.9
2006(80)	117	1.7
2007(81)	98	3.1
2007(82)	201	2.0
2007(6)	160	0.6
2007(8)	629	0.0

7-days risk of stroke following a TIA

Year of publication	Sample size (N)	7-d stroke risk (%)
2000(3)	1707	6.0
2003(2)	209	8.6
2004(73)	2285	1.4
2005(83)	121	5.8
2005(37)	1023	7.0
2005(71)	190	10.5
2006(79)	141	12.8
2006(80)	117	1.7
2006(84)	226	8.0
2007(81)	98	4.1
2007(85)	345	6.4
2007(82)	201	2.5
2007(6)	160	0.6
2007(8)	629	0.3

30-days risk of stroke following a TIA

Year of publication	Sample size (N)	30-d stroke risk (%)
1973(86)	198	7.6
2003(2)	209	12.0
2004(77)	612	3.2
2004(73)	2285	6.7
2004(87)	87	11.5
2005(37)	1023	11.2
2006(79)	141	17.7

90-days risk of stroke following a TIA

Year of publication	Sample size (N)	90-d stroke risk (%)
1973(86)	198	10.1
1985(88)	62	8.1
2000(3)	1707	10.5
2003(2)	209	14.3
2004(73)	2285	9.5
2004(77)	612	4.0
2004(87)	87	17.3
2004(78)	603	20.1
2005(37)	1023	14.6
2005(71)	190	16.8
2006(79)	141	20.6
2006(80)	117	1.7
2007(81)	98	7.1
2007(82)	201	3.5
2007(6)	160	0.6
2007(8)	629	1.9

There has been a great variation in the sample size (N) for studies (in the above tables) which may have resulted in variability in stroke rates. For a study with a large sample size (n=2285), the stroke risk after a TIA was recorded to be 1.4% at 2 days and 7 days, 6.7% at 30 days and 9.5% at 90 days.(73) Similarly for another study with a large sample size (n=1707), the stroke risk after a TIA was recorded to be 5.3% at 2 days, 6.0% at 7 days and 10.5% at 90 days.(3) On the other hand, in a study with comparatively smaller sample size (n=141), the stroke risk after a TIA was recorded to be 9.9% at 2 days, 12.8% at 7 days, 17.7% at 30 days and 20.6% at 90 days.(79) It is seen that the heterogeneity of the studies might have contributed to the varied stroke rates.

The settings of the study population also varied (ranging from emergency departments (3), hospital in-patient and outpatient departments (89) to rural population(79)), contributing to the variability in stroke rates. It is also worth noting that with year of publication, no clear temporal trend is apparent.

Various systematic reviews and meta-analyses (including studies mentioned in tables above) have also been conducted to examine the risk of stroke at 2-days, 7-days, 30-days and 90-days. A systematic review and meta- analysis conducted on the historical observational studies (from 1980 to 2006) found the pooled early risk of stroke to be 3.5% at 2-days, 8.0% at 30-days and 9.2% at 90-days. (90) Another systematic review and meta- analysis conducted in 2007 predicted the 2-day risk of stroke following a TIA to be 3.1% and the 7-day risk to be 5.2%. (25)

From the results of these studies, it is evident that following a TIA, the risk of stroke was substantial during the pre-2008 era.

According to a study published in 2014, there has been an overall decline in the 90-days risk of stroke following hospital-presenting first TIAs during the period 2001-2011.(91) However, there are geographic disparities in stroke incidence with incidence varying between countries, different ethnic and socio-economic groups and between different age groups. Also, the stroke risk may not be completely precise because an unknown number of patients with TIA will never seek medical attention.

However, the prognosis of all TIAs is not the same. Lower risk of stroke is associated with amaurosis fugax, whereas carotid artery hemispheric TIAs carry a comparatively higher risk of stroke. (92, 93) However, according to the results published by the NASCET trial, patients who had severe stenosis of the internal carotid artery (>70% stenosis), did not have a greater risk of stroke as compared to patients with lesser degree of stenosis (adjusted hazard ratio 1.1; 95%CI 0.7-1.7). (78) Results published in 1977 by the Rochester, Minnesota study found that the survival rates were similar among patients with carotid TIA and vertebrobasilar TIA. (94) In a systematic review and meta-analysis, among studies including the acute phase (up to 7 days) after TIA and in presence of vertebrobasilar territory TIAs, higher relative risk of subsequent stroke was found (OR 1.47; 95%CI 1.1-2.0; *p*-value=0.014) as compared to carotid events. (95) Contrary to this, a lower risk of stroke (OR 0.74; 95%CI 0.7-0.8; *p*-value=0.00001) in patients with vertebrobasilar TIA than in patients with carotid territory TIAs was found in studies that recruited patients after the acute phase. (95)

Several factors such as carotid stenosis, atrial fibrillation, family history of stroke, older age, smoking, hyperlipidaemia, hypertension, male sex and prevalence of coexistent vascular diseases have been associated with higher risk in patients with TIA. Among hemispheric TIA patients, the risk of stroke is doubled in the presence of intracranial major-artery disease.(78) Various epidemiological studies (3, 96-99) have shown that older age, diabetes mellitus, hypertension, multiple recent TIAs are associated with a risk of stroke. Furthermore, clinical features such as motor weakness, speech disturbance and symptoms lasting more than or equal to 60 minutes were also associated with an increased risk of stroke. All these factors play a crucial role in predicting the prognosis of TIA.

It has also been noted that TIA patients have a high risk for various other adverse events such as death, MI and recurrent TIAs. High risk of myocardial infarction (MI) and non-stroke vascular death was reported in a systematic review and meta-analysis (1980-2005). The annual risk for MI was 2.2% (95%CI 1.7-2.7) and for non-stroke vascular death was 2.1% (95%CI 1.9-2.4). (100) Several studies suggest that following a TIA, the long-term risks of major vascular events remain high and emphasise the need and importance of continued treatments in patients thereby preventing vascular complications. (101-103)

As suggested here, the prognosis of presenting TIA is influenced by multiple factors. A consideration of these factors at the point of health care contact can inform decision- making in TIA management. Formal risk stratification decision- support tools for TIA have been developed.

Risk stratification

Patients with TIA who have a crescendo pattern of TIA (104) (two or more TIAs in one week) and/ or the presence of clinical features of carotid stenosis and atrial fibrillation have an increased risk for stroke. Other high- risk patients can be identified using risk scores, which were constructed to determine the risk of stroke following a TIA. Development of the initial risk stratification tools which have had a great impact on management algorithms and evidence- based guidelines was in California, USA and Oxfordshire, UK. These scores help to decide which patients need to be admitted and which would require an assessment within 24 hours. (99)

California Index

The California cohort study (3) was conducted to predict the 90- day risk of stroke among TIA patients presenting to the emergency department (ED). The California index score includes age (>60 years), diabetes mellitus, duration of episode (>10 minutes), weakness with episode and speech impairment with episode. In this cohort of 1707 TIA patients (who were identified as having had a TIA by an ED physician), 180 patients returned to ED with stroke. Factors associated with stroke were- age greater than 60 years (OR, 1.8; 95%CI, 1.1-2.7; *P* = .01), diabetes mellitus (OR, 2.0; 95% CI, 1.4-2.9; *P*<.001), symptom duration longer than 10 minutes (OR, 2.3; 95% CI, 1.3-4.2; *P* = .005), weakness (OR, 1.9; 95% CI, 1.4-2.6; *P*<.001), and speech impairment (OR, 1.5; 95% CI, 1.1-2.1; *P* = .01).

ABCD score

This is a 6- point score developed from the data of the OxVASC study conducted in Oxfordshire, UK.(71) It includes age (<60 years =0, >=60 years=1), blood pressure (systolic<=140 mmHg and diastolic<=90mmHg=0, systolic>140mmHg and/or diastolic>90mmHg=1), clinical features (unilateral weakness=2, speech disturbance without weakness=1, no symptom=0) and duration of symptoms (<10 minutes=0, 10- 59 minutes=1, >=60 minutes=2). This score predicts the 7- day risk of stroke.(71) The clinical use of this score has been validated in Oxfordshire (71) and Greek (84) cohorts. Among the OxVASC patients with TIA, this score was predictive of the 7- day risk of stroke. However, the clinical utility of this score in risk stratification after a TIA was found to be limited and studies concluded that the discriminatory capacity of the ABCD score was not optimal. (80, 105)

$ABCD^2$ score

The use of the ABCD score formed the basis of developing a more refined score (California+ ABCD score). Hence, the $ABCD^2$ score was developed that includes five parameters, namely age (>=60 years=1), blood pressure (>=140/90mmHg=1), clinical features (unilateral weakness=2, speech impairment without weakness=1), duration of TIA (>=60 minutes=2 or 10- 59 minutes=1) and diabetes (presence of diabetes=1). The score ranges between 0 and 7, where score>3 indicates high risk and score<4 indicates low risk of stroke. The validation of the $ABCD^2$ score was performed by Johnston,

Rothwell and colleagues (99) in Californian and Oxfordshire cohorts and this score was found to be more predictive of stroke than the California or ABCD scores.

The $ABCD^2$ score has become the most widely used clinical tool for predicting the risk of stroke after TIA. It has been used to help to decide which patients need to be admitted and which would require an assessment within 24 hours. (99) However, this does not replace careful clinical assessment and it may not be applicable for some sub- groups of patients such as younger age patients with non- atherosclerotic TIA or posterior circulation TIA.

To improve the risk prediction performance, further refinements have been made to the $ABCD^2$ score, which incorporates brain imaging and crescendo TIAs. Various scores such as $ABCD^2$- I, $ABCD^3$ and $ABCD^3$- I have been developed. (106, 107)

Acute management of TIA

Management strategies in TIA are of considerable importance to the context of this thesis. A hypothesised improvement in the prognosis of TIA is based on the implementation of management strategies from studies that suggest that urgent initiation of medical (and, in some cases, surgical) treatment can reduce the incidence of recurrent stroke after TIA.

Treating a TIA principally aims to prevent a recurrent stroke and may involve a number of medical and surgical interventions and life style modifications. TIA can be managed acutely by the use of antiplatelets (such as aspirin, clopidogrel, ticlopidine and dipyridamole), anticoagulants (such as warfarin and New Oral Anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban), antihypertensives (such as ACE inhibitors and diuretics) and statins (such as atorvastatin, rosuvastatin and simvastatin). The EXPRESS study found that with appropriate urgent management, 80% of recurrent strokes are preventable. (108) Long- term management of TIA, including lifestyle modifications will not be addressed in this thesis.

It is now well established that TIA or minor stroke are a medical emergency and that they should be treated urgently. Existing data show that the 'window of opportunity' is very short for prevention of stroke after a TIA (109) and hence this indicates the need for urgent evaluation and treatment. Current approaches to management are embodied in evidence- based guidelines including those of the National Stroke Foundation in Australia.

The National Stroke Foundation (110) recommends that all suspected TIAs should have full assessment and investigations (such as blood tests, carotid imaging and ECG) at the point of initial health care contact. 'High- risk' TIAs ($ABCD^2$ score>3 and/ or any one of AF, carotid territory symptoms or crescendo TIA) should undergo urgent brain imaging (preferably MRI with DWI) within 24 hours and urgent carotid imaging should also be undertaken in patients with anterior circulation symptoms, and should be admitted for further urgent management in a stroke unit or referred to a specialist TIA clinic.

'Low- risk' TIA patients (with $ABCD^2$ score<4 without AF or carotid territory symptoms or who present more than one week after symptoms) could be managed by the general practitioner and receive initial treatment (acute therapy initiated with aspirin and dipyridamole, ACE inhibitors and statin; which is also the recommended pharmacotherapy for high- risk TIAs), but it is recommended that they are referred to specialist care if possible (and seen within seven days); and should have brain and carotid imaging (where indicated) as soon as possible (within 48 hours).

The New Zealand guidelines (111) for TIA management recommend that the 'high- risk' patients (those with $ABCD^2$ score 4- 7 or those with any one of the following: atrial fibrillation, tight carotid stenosis, or crescendo TIA) should be transferred urgently to hospital (preferably admitted to a stroke unit or where possible referred to a specialist TIA clinic within 24 hours) to facilitate rapid assessment and treatment; and should have urgent brain and carotid imaging within 24 hours. 'Low- risk' patients (those with $ABCD^2$ score 0- 3) can be managed in the community by a general practitioner, private specialist or where possible referred to a specialist stroke/ TIA clinic and seen within seven days; and should have brain and carotid imaging within a week. In addition to this, it is also recommended low dose aspirin and dipyridamole, or clopidogrel alone, should be prescribed to patients with ischaemic stroke or TIA.

The UK NICE (104) clinical guidelines recommend that 'high- risk' patients (with $ABCD^2$ score >=4) should be immediately started on aspirin (300 mg) and that specialist assessment and investigations are done within 24 hours of symptom onset. 'Low- risk' patients (with $ABCD^2$ score<=3) should be immediately started on aspirin (300 mg) and specialist assessment and investigations done as soon as possible, preferably within one week of symptom onset.

Atrial fibrillation (AF) is associated with a higher mortality and more severe disability, hence management of AF with anticoagulant therapy is also recommended to prevent stroke. (112)

Procedures such as carotid endarterectomy (performed within two weeks of onset of symptoms of stroke or TIA (113)) can substantially benefit patients with symptomatic carotid artery stenosis (carotid stenosis 50- 99% according to the NASCET or 70- 99% according to the ECST Collaborative Group) and subsequently decrease the risk of stroke substantially. (114-116)

Health system approaches to TIA

In the early eras, the approaches to TIA management differed significantly across different countries and across different health care systems. In one comparison of stroke prevention practices between the United States and the United Kingdom (published in 1997), patients with TIA or minor stroke were more commonly referred to a neurologist by the physicians in the USA. (117)

In the EXPRESS (6) and the SOS- TIA study (8) , TIA patients were initially seen by the GP or at ED and then urgently referred to clinic; where they were seen by a neurologist and received specialised care and urgent management. Following the landmark results of the EXPRESS and the SOS-TIA studies,

many acute neurovascular clinics (ANVCs) were established, where TIA and stroke patients receive optimal care via specialised medical practitioners and specialists. In the pre-EXPRESS health settings, the use of antihypertensives, aspirin, warfarin and CEA were still an important part of TIA management. (118) Post-EXPRESS and SOS-TIA, however, the imperative (formalised in evidence-based guidelines) (104, 110, 111) has been for health systems organisations to deliver these treatments, along with appropriate investigation, more urgently than pre-EXPRESS. With modified guidelines, clinical practices have also changed in contemporary practice. A decrease in morbidity post-TIA in the post-EXPRESS era is noticed in clinical practice resulting improved clinical outcomes. (119)

Conclusion

The EXPRESS study conducted within the OxVASC study (109) and the SOS- TIA study (8), demonstrated that the high risk of recurrent stroke following a TIA can be markedly reduced if treatment is initiated promptly. These studies also indicated that the 'time window' for preventing stroke is relatively short and that urgent treatment is necessary. Furthermore, a 2007 systematic review and meta-analysis of observational studies has found lower risks of recurrent stroke among patients managed in health systems where the treatment was started immediately after the diagnosis of TIA than in systems where management was less urgent. (25)

These studies suggest that early identification and implementation of prompt management strategies for patients with TIA can reduce the risk of a potential stroke. The findings of the EXPRESS study and the SOS- TIA study have fundamentally changed the management of TIA and resulted in the modification of the guidelines for TIA management.

These findings and their uptake into practice marked a milestone in the field of stroke medicine. However, these studies are gold standard as they were conducted in highly specialised health care settings with availability of prompt diagnostic techniques, best practice methods and specialised staff. It is therefore important to look at the prognosis of TIA after the implementation of urgent care in modern era, including a wide range of health care settings. The EXPRESS and SOS-TIA studies aimed at providing urgent, specialised care to TIA patients. This has been widely implemented in various modern health care practices (though not always with the resources and expertise available in EXPRESS and SOS-TIA).

We hypothesised that in the post-EXPRESS era, TIA patients will receive urgent care and hence, the prognosis of such patients will be favourable compared to historical cohorts (i.e. prior EXPRESS study). To achieve this aim, a systematic review and meta- analysis were conducted in this M. Phil project to establish the risk of stroke following TIA in contemporary health care settings.

Chapter 2

Methodology

A systematic review was conducted of prospective and retrospective cohort studies (hospital- based and community- based cohorts) of TIA, plus placebo arms of Randomised Controlled Trials, that were published from the year 2008 to 2015. The primary outcomes of interest were stroke, recurrent TIA, myocardial infarction and mortality. Analysis of individual and composite outcomes was conducted.

Search strategy

The search was conducted using the electronic databases Ovid Medline, Cochrane Library and Embase. Search limits used were English language, human and 2005- current. The search terms used were: [TIA (OR) ischaemic attack, transient (OR) amaurosis fugax] AND [outcome (OR) prognosis (OR) follow-up (OR) cohort (OR) randomised control trial (OR) risk (OR) natural history].

After the database search was completed, the duplicate results of the search were removed and the abstracts were screened and assessed for eligibility to be included in the systematic review. Following the screening of abstracts, full- text copies of potentially eligible papers were retrieved and assessed for eligibility. The abstracts, the methods and the outcome rates for each study were assessed for eligibility separately by two researchers (NN and PM) and any cases of disagreement were adjudicated by a third researcher (CL). The last database search was conducted on 2nd June 2015.

As part of the assessment of eligibility, papers published prior to 2008 were excluded. The rationale was to only include in the review those papers published subsequent to the landmark EXPRESS and SOS-TIA studies' publication in 2007. While acknowledging that papers published later than 2007 would still often include patients recruited prior to 2007, this provided an identifiable marker of contemporary TIA practice.

Data collection process

The PRISMA 2009 criteria was followed. Full- text articles were obtained from online databases and library services. In studies including patients with both TIA and stroke, where the outcome of TIA patients was not reported separately, the respective corresponding authors were contacted via email and specific data on TIA was requested. Studies were excluded if authors were uncontactable, no response from authors was received or requested data was unavailable. If sufficient raw data was available to describe the cohort in each study, summary statistics were recorded. Otherwise it was not possible to define the cohort. Extracted information from each of the full- text articles included: title of the article, reason of exclusion (if excluded), first and second author, year of publication, journal, period of data collection, index event (TIA), diagnosis of TIA made by (eg. ED physician or neurologist), definition of TIA (standard WHO or time- based definition), country or countries where the study was conducted, study population (ED or hospital in-patient, study participant limitations such as gender, clinical aspect, carotid stenosis, AF), number of participants with TIA at baseline and number of participants with TIA analysed, study outcome (stroke), method of outcome ascertainment, type of study

(prospective/retrospective cohort, RCT), duration of follow- up, risk factors, treatment at discharge, results (stroke, mortality, TIA and MI) and comments. The studies that met inclusion criteria were then summarised and population characteristics, study design and outcome events rates tabulated. The full-text journal articles were screened separately by two researchers (NN and PM) and any cases of disagreement were adjudicated by a third researcher (CL).

Study selection: The studies were selected on the basis of inclusion/ exclusion criteria.

Inclusion criteria Prospective and retrospective cohort studies (hospital- based and community- based cohorts) of TIA were included. In addition to this, placebo- arms of randomised control trials were also included. The study factor was TIA and so studies of stroke *and* TIA were included only if TIA was reported separately. The primary outcome factor was stroke and secondary outcome factors were recurrent TIA, myocardial infarction and death. Studies reporting these outcomes were included. We included in the narrative systematic review all studies of TIA even if the entry criteria for the studies were restricted (eg. only TIA patients with AF or only TIA patients who went on to have carotid endarterectomy (CEA)). However, we restricted our meta- analysis to studies with no restriction on the type of TIA patients. Patients treated with medical therapy alone and carotid endarterectomy plus medical therapy were included.

Exclusion criteria Studies with outcomes only at time-points less than 48 hours post-TIA were not included in the systematic review. We excluded studies of both stroke and TIA, if the outcome of TIA patients were not reported separately.

For the meta- analysis, studies which included (on the basis of study population selection) only higher-risk or only lower-risk patient populations were excluded. These excluded studies were: those which defined TIA according to the tissue-based definition rather than the traditional World Health Organisation time-based definition, studies which excluded AF patients, studies which included only patients undergoing CEA and studies which had a restricted age group of patients.

TIA definition: The definition of TIA was by each individual study (either standard WHO definition or tissue-based definition) and was recorded on the data extraction form where stated.

Outcome definitions: The primary outcome of interest was stroke and we accepted the stroke definition as defined within each study. Similarly, the secondary outcomes were myocardial infarction and death.

The meta- analysis was performed only with stroke as the outcome factor.

Statistical Analysis

We present a meta-analysis of 40 studies (33 prospective studies, 7 retrospective studies) that investigated risk of stroke recurrence among those that had suffered a transient ischemic attack (TIA). The time-points of interest for cumulative risk of stroke recurrence are at 2, 7, 30 and 90 days post- TIA. The aim of this project was to estimate the pooled cumulative risk of stroke recurrence at each time point.

A standard meta- analysis of the risk at each time point is problematic since the same studies do not contribute data at each possible time-point; as such, estimates of the pooled cumulative risk at each time-point are not guaranteed to be non-decreasing since the within-study correlation of estimates are ignored. In this project we utilise the model proposed by Jackson et al. (120) for the multivariate (joint) analysis of all studies at every available time point. The benefits of this approach are that information is borrowed from studies that contribute to multiple time- points, improving the precision of the estimates, and the cumulative probabilities of stroke are explicitly constrained to be non- decreasing. Frequentist approaches to estimating parameters from multivariate (where each study contributes multiple time points) random-effects meta-analysis models can suffer from non-convergence and other computational issues, so we have utilised a Bayesian model, where parameters estimation is through Markov Chain Monte Carlo simulation methods and less prone to these computational problems. (121) The other advantage of the Bayesian approach is that parameter uncertainty is modelled through prior distributions, which when updated by the likelihood allow inference about the posterior distribution of the parameter.

General Statistical Methodology

The number of stroke events out of the number at risk at each site for each period is modelled as being drawn from a binomial distribution. The probability parameter for this distribution is the conditional probability of stroke occurring within the period from the last measured time- point, which is decomposed into the sum of the corresponding (conditional) probabilities of stroke within the comprising intervals. For example: the conditional probability of stroke between day 7 and day 90 is the probability of stroke at day 7 (conditional on surviving stroke-free to day 2), plus probability of stroke at day 30 (conditional on surviving stroke- free to day 7), plus the probability of stroke on day 90 (conditional on surviving stroke-free to day 30).

The probability of stroke for each study for each period is then modelled on the log- odds scale to be the sum of the unconditional log-odds of stroke at each time point (averaged across sites) and a study specific random effect (to model between study heterogeneity), assumed to follow a multivariate normal distribution. The unconditional probability of stroke at each time point (averaged across sites) is the parameter of interest, reflecting the pooled cumulative risk at each time- point. To complete the Bayesian model, uninformative prior distributions were placed on all model parameters; a Wishart prior was used for the covariance matrix of the random effect, and normal distributions (zero mean and variance of 1000) were used for the four time- specific unconditional log- odds parameters.

Bayesian inference was implemented using the WinBUGS software (122) where we took 500,000 simulations from the posteriors joint distribution, allowing for a burn- in period of 50,000 simulations.

Convergence was assessed using the Gelman- Rubin diagnostics. Cumulative risks are presented as the mean posterior distribution with 95% credible intervals given as the 2.5 and 97.5 percentiles.

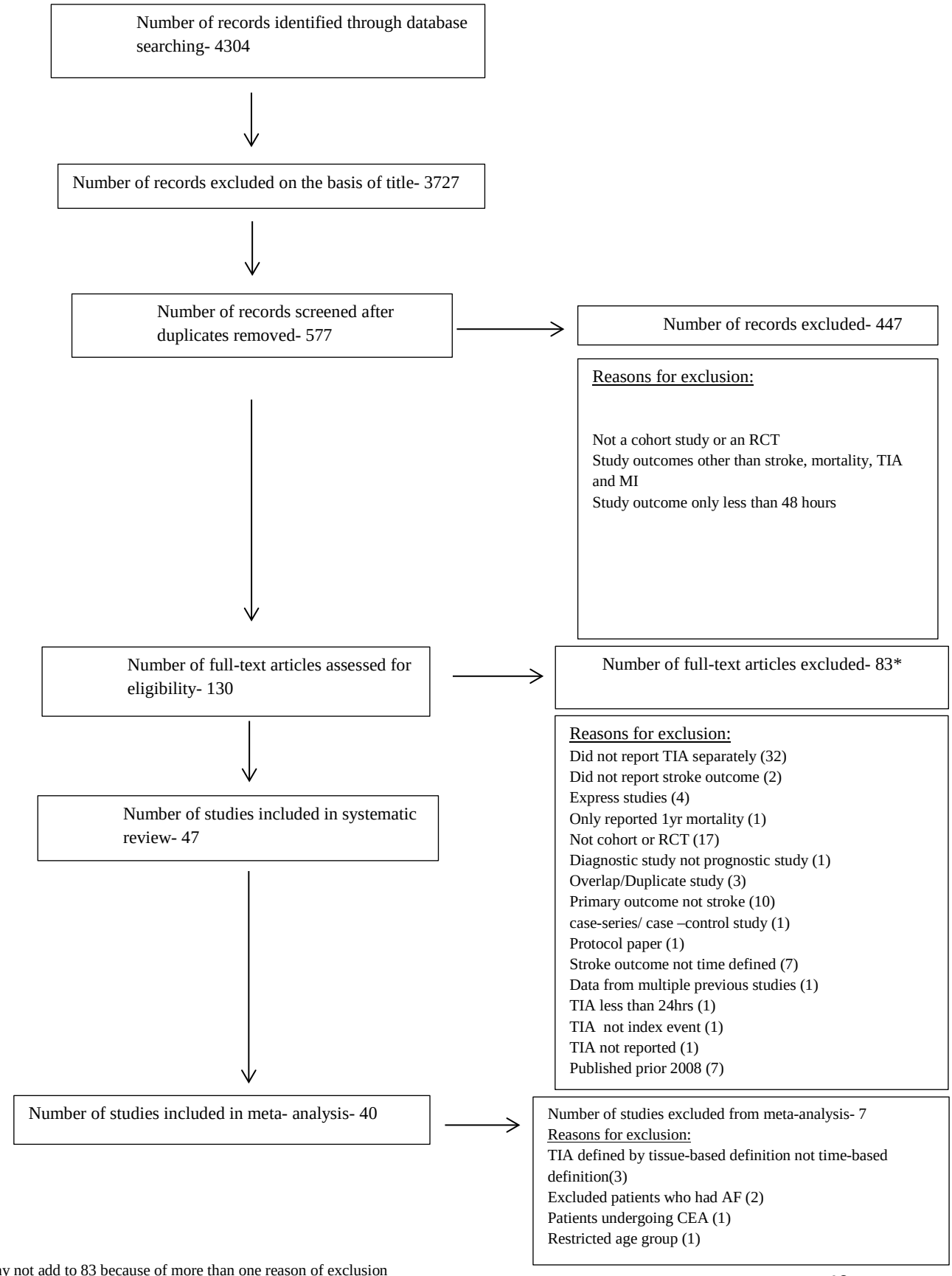
Chapter 3

Results

Study selection

The search of the databases yielded a total of 4304 publications. After excluding the duplicate records, 130 full- text articles were identified and screened against the inclusion criteria for eligibility to be included in the systematic review. A quasi-experimental study matched our inclusion criteria but was not included in the final analysis as the data received from the author was in German language. Five RCT arms also matched our inclusion criteria but were not included in the final analysis as the authors did not respond to our request of additional data. Among the studies which matched our inclusion criteria, but no response was obtained from contacted authors, the sample size of these studies ranged from 64 to 18980. Additionally, three RCTs were also identified but they did not match our inclusion criteria and hence were not included in our final analysis. Eighty- three (83) studies were excluded. The remaining forty seven (47) studies (N= 191, 202) met the inclusion criteria and were included in the systematic review. We included forty (40) studies (N= 68,563) in the meta- analysis. The sample size of the studies which were excluded from the meta-analysis ranged from 51 to 122063.

PRISMA 2009 Flow Diagram



*May not add to 83 because of more than one reason of exclusion

Characteristics of studies/data collected

Forty-seven (47) studies (N= 191,202 patients) were included in the systematic review. The study characteristics are summarised in table 1. In all of the 47 studies, the patients had a TIA as an index event at baseline. Stroke at 2- days was reported in 13/47 (27.7%), 20/47 (42.6%) reported stroke at 7- days, 12/47 (25.5%) at 30- days and 33/47 (70.2%) at 90- days.

The diagnostic criteria for TIA were either according to the standard WHO definition or tissue-based definition. The standard TIA definition was used in 32/47 (68.1%) of the studies and 3/47 (6.4%) of the studies used the tissue-based definition. However, in 12/47 (25.5%) of the studies the definition of TIA was not reported. It appeared likely that a standard TIA definition had been used in these studies. In 25/47 (53.2%) of studies, the diagnosis of TIA was made by a neurologist. However, ED physicians and stroke physicians made the diagnosis in 6/47 (12.8%) and 3/47 (6.4%) of the studies, respectively. In 1/47 (2.1%) of studies, physician made the diagnosis. Vascular neurologists made the diagnosis in 2/47 (4.3%) of the studies and in 10/47 (21.3%) of the studies it was not reported who made the diagnosis.

The admission criteria and patient population were also different among studies. In 19/47 (40.4%) of studies, the study population were non- selected ED care/ all comers. Hospital in- patient admission with a clear admission policy (study participant limitations such as age, gender, MRI/MRA on admission, carotid stenosis and admission within either 24 hours or 48 hours of symptom onset) accounted for 8/47 (17%) of studies, whereas 9/47 (19.1%) of studies included in-patient hospital admissions but without a clear admission policy or with admission policy not stated. In 2/47 (4.3%) of the studies, the patients referred to a stroke clinic were included in the study and 2/47 (4.3%) of the studies had patients from a TIA clinic. In 2/47 (4.3%) of studies, included patients from ED (attended by neurologist) and there were 2/47 (4.3%) community studies. In 2/47 (4.3%) of the studies, the location of the study population was not reported and in 1/47 (2.1%) of the studies had unclear study population

The median proportion of participants with the study outcome (stroke), across studies, at particular times post-TIA were 1% at 2-days, 2.8% at 7-days, 0.95% at 30-days and 2.95% at 90-days. The ranges of the proportion of participants with the study outcome (stroke), across studies, at particular times post-TIA were 0%-17.4% at 2-days, 0%-18.7% at 7-days, 0%-20.6% at 30-days and 0%-22.1% at 90-days (refer to table 1 for individual studies).

TIA was reported in 15/47 (31.9%) studies, mortality in 19/47 (40.4%) studies and MI in 9/47 (19.1%) studies. Unlike stroke, TIA, MI and mortality were not consistently reported at consistent time points (such as at 2- days, 7- days, 30-days and 90-days) , making calculation of summary statistics problematic.. The follow-up period varied between studies (from 72 hours to 13.8 years) and varied even within studies for different outcomes (refer to table 1 for individual studies).

Table 1: Table of Characteristics

Pub year	First author's name	Country	Period of data collection	TIA definition	No. of pts	Study Population	Study Type	Diagnosis made by	stroke day 2 (%)	stroke day 7 (%)	stroke day 30 (%)	stroke day 90 (%)	TIA^ (%)	MI^ (%)	Mortality^ (%)	Follow-up period
2008	Cem Koz (1)	Turkey	not stated	standard	95	not stated	Prospective	not stated	not stated	not stated	not stated	not stated	24.2	not stated	not stated	mean 14.2 +/- 4.6 (range 6-29 months)
2008	Rosella Sciolla*(2)	Italy	2006-2006	standard	274	ED (non selected)	Prospective	Neurologist	2.6	3.6	5.5	not stated	not stated	not stated	0.7	1 month
2008	Angel Ois*(3)	Spain	2004-2007	not stated	221	Hospital in-patient (hospital admission policy unclear)	Prospective	Neurologist	not stated	not stated	not stated	not stated	19	not stated	not stated	90 days
2008	Kenneth Geil*(4)	Puerto Rico	2006-2006	standard	53	ED (non selected)	Retrospective	not stated	0	not stated	not stated	not stated	not stated	not stated	not stated	72 hours
2008	Shelagh B Coutts*(5)	Canada	not stated	standard	87	Presented to ED - hospital (selective admission)	Prospective	Neurologist	not stated	not stated	not stated	1.1	not stated	not stated	not stated	90 days
2008	Hakan Ay*(6)	USA	2000-2006	not stated	477	Hospital in-patient (hospital admission policy not stated)	Retrospective	Neurologist	not stated	5.2	not stated	not stated	not stated	not stated	not stated	7 days
2008	David Calvet*(7)	France	2003-2007	not stated	343	Hospital in-patients (hospital admission policy unclear)	Prospective	not stated	1.2	1.5	not stated	2.9	4.1	not stated	0.6	3 months
2009	Christian Weimar*(8)	Germany	2002-2006	standard	1448	Admitted to acute stroke unit	Prospective	Neurologist	not stated	not stated	1	1.5	not stated	not stated	8.1	23.4 months (range 6-59 months)

2009	Judith H Lichtman(9)	USA	2002-2002	not stated	122063	Hospital discharged with dx TIA >=65yr, fee for service medicare	Prospective	not stated	not stated	not stated	1.5	not stated	5.2	not stated	13.6	1 year
2009	Brett L Cucchiara*(10)	USA	2002-2007	standard	164	not stated	Prospective	Neurologist	not stated	not stated	not stated	3	not stated	not stated	1.83	90 days
2010	Marcus Eng Hock Ong*(11)	Singapore	not stated	standard	470	ED (non selected)	Retrospective	Neurologist	17.4	18.7	20.6	22.1	not stated	not stated	not stated	90 days
2010	J.K. Harrison*(12)	UK	1992-2004	standard	795	Hospital	Retrospective	Stroke physician	not stated	not stated	not stated	3	not stated	not stated	not stated	13.8 years
2010	Katrin Holzer*(13)	Germany	2002-2004	standard	173	Hospital (selective admission)	Prospective	Neurologist	not stated	not stated	not stated	not stated	8.8	1.8	8.5	median 27 months (IQR 18-41 months)
2010	Jason Wasserman*(14)	Canada	2007-2009	not stated	982	ED (non selected)	Prospective	ED Physician	1	1.9	2.6	3.2	5.5	1	1.7	90 days
2010	G. Tsivgoulis*(15)	Greece, Singapore	2008-2009	standard	148	All TIA seen in ED and hospitalized	Prospective	Neurologist	not stated	8	not stated	16	not stated	not stated	0.7	3 months
2011	Domenico Marco Bonifati*(16)	Italy	not stated	standard	502	ED (non selected)	Retrospective	not stated	1.8	2.2	2.8	4	15.3	0.8	0	7-12 months (mean 11.4 months)
2011	E. Murat Arsava*(17)	USA	2003-2009	tissue-based	257	ED	Retrospective	not stated	not stated	9.3	not stated	not stated	not stated	not stated	not stated	7 days
2011	Iacopo Cancelli*(18)	Italy	2007-2009	standard	161	Community study	Prospective	Neurologist	2.5	5.6	6.2	11.2	not stated	not stated	3.1	90 days
2011	F. Purroy*(19)	Spain	2006-2009	standard	254	ED attended by neurologist	Prospective	Neurologist	not stated	2.8	not stated	4.7	3.9	2.4	not stated	90 days
2011	Latha G. Stead*(20)	USA	2001-2006	standard	637	ED (non selected)	Prospective	ED physician	not stated	0.94	not stated	2.4	not stated	not stated	not stated	90 days

2011	Lauren M. Sanders*(21)	Australia	2004-2007	standard	289	ED referred to acute stroke unit	Prospective	Stroke physician	1.4	1.4	not stated	2.4	not stated	not stated	not stated	90 days
2011	Pierre Amarenco*(22)	France	2003-2008	standard	1679	SOS-TIA registry; hospital in-patient after seen in TIA clinic	Prospective	Vascular neurologist	not stated	not stated	not stated	2.03	not stated	not stated	not stated	3 months
2011	Guy Leseche(23)	France	2003-2009	standard	64	Patients referred from TIA clinic to vascular surgery, operated CEA with 2 weeks of symptom onset, crescendo TIA (first ever), not amaurosis	Prospective	Vascular neurologist	0	0	0	0	0	0	0	1 year
2011	W. Dorigo(24)	Italy	2000-2008	not stated	51	Hospital in-patient (selective admission)	Prospective	Neurologist	0	0	0	0	1.96	0	4	34 months (SD 28.1)
2011	D Ghia*(25)	Australia	2004-2006	not stated	789	ED (non selected)	Prospective	ED physician	0.38	not stated	0.89	1.9	not stated	not stated	not stated	1 year
2012	Lauren M. Sanders*(26)	Australia	2004-2007	standard	296	ED (non selected)	Prospective	Neurologist	not stated	not stated	not stated	2.36	not stated	not stated	not stated	90 days
2012	Francisco Purroy*(27)	Spain	2007-2010	standard	283	ED attended by neurologist	Prospective	Neurologist	not stated	not stated	not stated	not stated	not stated	4.2	not stated	median 12.3 months (IQR 7.2-19.9 months)
2012	S. T. Engelter*(28)	Switzerland	2006-2008	standard	248	ED (non selected)	Prospective	Neurologist	not stated	not stated	not stated	5.2	8.1	not stated	not stated	3 months
2012	Jonathan M Raser*(29)	USA	not stated	standard	167	ED (all comers)	Prospective	ED physician	not stated	not stated	not stated	3	not stated	not stated	1.8	90 days

2012	Fadi Nahab(30)	USA	2008-2009	tissue-based	142	ED (non selected)	Retrospective	ED physician	not stated	not stated	not stated	0.7	4.2	not stated	not stated	90 days
2012	Pilar Delgado*(31)	Spain	not stated	standard	166	ED (non selected)	Prospective	Neurologist	not stated	4.8	not stated	7.2	4.8	not stated	not stated	30 days
2012	F Fluri*(32)	Switzerland	2006-2008	not stated	176	Unclear location	Prospective	not stated	not stated	not stated	not stated	4	not stated	not stated	not stated	3 months
2012	Nicola L. M. Paul*(33)	UK	2002-2011	standard	1000	Population-based community study	Prospective	Neurologist	not stated	9.4	not stated	not stated	not stated	not stated	not stated	7 days
2013	Ali Arhami Dolatabadi(34)	Iran	2010-2011	not stated	150	Hospital in-patient (hospital admission policy unclear)	Prospective	Neurologist	not stated	not stated	not stated	6	6	not stated	8	6 months
2013	Mohamed Al-Khaled*(35)	Germany	2005-2007	standard	878	Hospital in-patient (selective admission)	Prospective	Neurologist	not stated	not stated	not stated	1.9	not stated	not stated	1.9	3 months
2013	Jeffrey J. Perry*(36)	Canada	2006-2011	standard	3906	ED (non selected)	Prospective	ED physician or ED resident or neurologist	1.4	2.2	2.8	3.4	6.8	0.4	not stated	90 days
2013	S Gokhan*(37)	Turkey	2009-2011	not stated	90	Hospital in-patient (admission policy unclear)	Prospective	Neurologist	not stated	not stated	not stated	not stated	not stated	not stated	10.7	30 days
2013	Bo Song*(38)	China	2010-2011	standard	239	Hospital in-patient (hospital admission policy unclear)	Prospective	Neurologist	6.3	not stated	not stated	12.1	not stated	not stated	not stated	90 days

2013	Takuya Kiyohara*(39)	Japan	2007-2012	standard	693	Hospital in-patient (admission policy unclear)	Prospective	Neurologist	not stated	6.9	not stated	10.4	not stated	not stated	5.5	3 years
2014	D. Griffiths*(40)	Australia	2007-2010	not stated	189	ED (non selected)	Prospective	Stroke physician	not stated	not stated	not stated	1.5	not stated	not stated	not stated	90 days
2014	Mohamed Al-Khaled*(41)	Germany	2007-2010	standard	1335	Hospital in-patient (selective admission)	Prospective	Neurologist	not stated	not stated	2.8	not stated	not stated	not stated	1.4	3 months
2014	Takeshi Hayashi*(42)	Japan	2007-2010	tissue-based	74	Hospital (selective admission)	Retrospective	not stated	not stated	not stated	not stated	not stated	not stated	not stated	not stated	2 years
2014	Gian Marco De Marchis*(43)	Switzerland, Germany	2009-2011	standard	302	ED (non selected)	Prospective	not stated	not stated	not stated	not stated	3.6	not stated	not stated	9.8	3 months
2014	Vijaya Sundararajan*(44)	Australia	2001- 2011	not stated	46,971	ED presentation or hospital admission (hospital admission policy unclear)	Prospective	not stated	not stated	not stated	not stated	2.9	not stated	not stated	not stated	90 days
2014	Mariona Jove*(45)	Spain	2008-2012	standard	293	ED (non selected)	Prospective	Neurologist	not stated	3.8	not stated	5.1	not stated	not stated	not stated	6 months
2015	Vilanova MB*(46)	Spain	2006-2013	standard	628	ED (non selected)	Prospective	Neurologist	not stated	not stated	not stated	not stated	not stated	4.5	not stated	median 31.2 months
2015	Jae-Sung Lim*(47)	Republic of Korea	2010-2012	standard	500	Hospital in-patient (selective admission)	Prospective	Physician	not stated	2.8	not stated	5	not stated	not stated	not stated	90 days

Pub year= publication year

TIA= Transient Ischaemic Attack

Standard= Rapidly developing signs of focal (or global) disturbance of cerebral function, with symptoms lasting less than 24 hours with no apparent cause other than that of vascular origin.

Tissue- based= Brief episode of neurologic dysfunction caused by focal ischaemia (brain or retinal) without acute infarction on imaging

*= Studies included in meta-analysis

Hospital in-patient selective admission= Not all comers. Hospital admission policy varied from study-to-study.

ED (non-selected)= All comers

^= at the end of follow-up

Meta-Analysis

In Table 2, the study specific stroke risks at each time point are plotted together with estimates of the pooled risks with 95% credible intervals. In Figure 1, the pooled estimates at each time point are presented, where each coloured dot represents an individual study.

Table 2

Time point	Cumulative risk of stroke	95% credible interval	I^2
2 days	0.012	0.006,0.022	.87
7 days	0.034	0.02,0.055	.93
30days	0.05	0.029,0.082	.95
90 days	0.074	0.043,0.124	.96

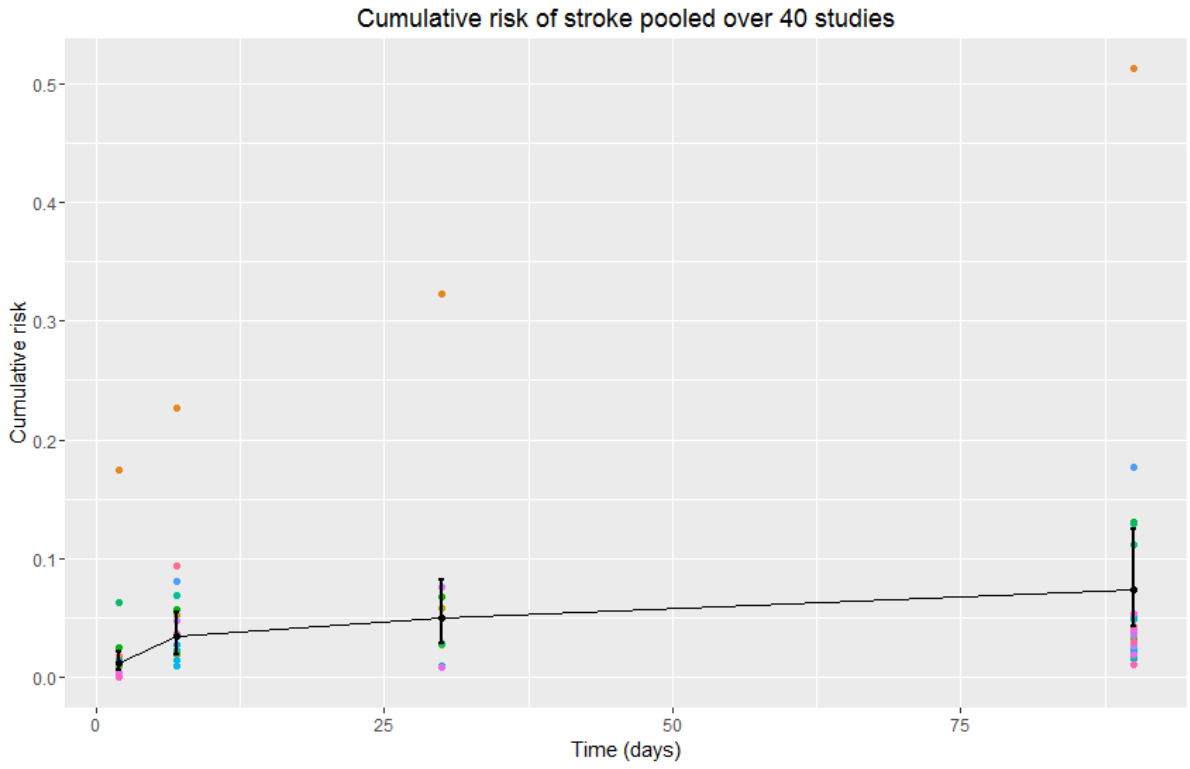


Figure 1

Chapter 4

Discussion

Brief summary of main findings

The 47 studies in the systematic review displayed variability in definition of TIA and the clinical status of a person who made the diagnosis of TIA. A few studies had markedly restricted study populations. While there were differences in study populations' location of care and service model between studies, the participants in these studies were almost all managed in secondary care rather than primary care. The meta-analysis of 40 included studies showed a cumulative risk of stroke of 1.2% (95% CI 0.6-2.2) at 2 days post-TIA, of 3.4% (95% CI 2.0-5.5) at 7 days post-TIA, of 5.0% (95% CI 2.9-8.9) at 30 days post-TIA and of 7.4% (95% CI 4.3-12.4) at 90 days post-TIA.

Comparison with previous studies

Historical studies prior 2007 (pre- EXPRESS)

The early Oxfordshire study (1981- 1986) reported a stroke risk of 8.6% at 7- days and 12.0% at 30- days after a TIA. (2) Results from the Greater Cincinnati/Northern Kentucky Stroke Study (1993-1994) reported a stroke risk of 14.6% after TIA. (89) Higher rates of stroke risk were similarly reported by various other studies. The California study (1997-1998), reported the 90-days risk of stroke of 10.5%. (3) A Canadian study (1999-2000) reported risk of stroke at 90 days to be 9.5% (95%CI 8.3 to 10.7). (73) In Northern Portugal (1998-2000), the risk of stroke was found to be 12.8% (95%CI 7.3 to 18.3) at 7 days. (79)

In one study, it was found that high short-term risk of stroke was noted among patients who were diagnosed with TIA in the emergency department. This study (2000), reported an overall 30-day risk of stroke of 5%. (123) Similar high risk of stroke was reported in a study conducted by Rothwell (2002-2005). There was a 0.4% (95%CI 0 to 1.1) risk of stroke at 7-days in 274 (73%) who had an ABCD score less than 5, 12.1% (95%CI 4.2 to 20.0) in 66 (18%) patients (with an ABCD score of 5) and 31.4% (95%CI 16.0 to 46.8) in 35 (95%) patients (with an ABCD score of 6). (71)

In another study (2003-2005) the risk of stroke at 1 week and 3 months was found to be 2.5% (95%CI 0.3 to 4.7) and 3.5% (95%CI 1.0 to 6.1), respectively. (82)

Thus, recurrent stroke in these 'pre-EXPRESS/pre-SOS-TIA' studies was generally less (often considerably less) than the stroke risk in our meta-analysis of studies reported 'post-EXPRESS/post-SOS-TIA'.

It should be noted, though, that the stroke risks in our meta-analysis were greater than in the SOS-TIA study and in the 'phase 2' of the EXPRESS study. In the SOS-TIA study (2003-2005), the risk of stroke was found to be 1.24% (95%CI 0.72 to 2.12) at 90-days. (8) In the EXPRESS study (2004-2007), the 90-day risk of recurrent stroke dropped from 10.3% in phase 1 to 2.1% in phase 2 (adjusted hazard ratio 0.20,

95%CI 0.08- 0.49; p= 0.0001). (6) Stroke risk in our meta-analysis was also greater than in a large study reported in a paper published subsequent to our review and meta-analysis. (119)

Interpretation of the findings

In our analysis, we included studies that not only have access to contemporary evidence- based best practice, diagnostic and intervention techniques but also some studies which had their patient recruitment commenced prior to the results of the EXPRESS study. The studies are heterogeneous as inconsistent application of management strategies is noted. This is because in this systematic review, there are some studies in which some patients were treated in the pre- EXPRESS era and some of the study settings are post- EXPRESS. In the post- EXPRESS studies, application of best practice evidence to practice may not have been universal due to resourcing issues. (124)

But despite these caveats, we note that when compared to pre-EXPRESS historical cohorts, our meta-analysis of studies in more contemporary health settings reported lower rates of stroke following a TIA.

In 'optimal' contemporary practice, Amarenco et al's recent multi-site study (2009- 2011) published in 2016 showed that stroke rates following a TIA or minor stroke at 2, 7, 30 and 90 days were 1.5%, 2.1%, 2.8% and 3.7%, respectively. (125) This study was published subsequent to our systematic review. It was conducted (like EXPRESS and SOS-TIA) in highly specialised settings where urgent evaluation and management of TIA was implemented via protocols in accordance with evidence- based best practice care. This study demonstrated lower risk of stroke than was found in our meta-analysis.

Thus, we have demonstrated a gradient of highest stroke risk post-TIA from 'historical' cohorts (highest risk), to the 'post-EXPRESS' cohorts included in our meta-analysis, to a 'contemporary best-practice' cohort (lowest risk).

The defining characteristics of this gradient were increasing expertise in diagnosis and management and, especially, decreasing time from incident event to initiation of management. Treatment modalities were largely unchanged. Hence, in preventing the occurrence of a potentially disabling stroke, emerges the importance of initiating early treatment and implementing preventive measures after a TIA.

Strengths and limitations

Strengths:

The strength of this systematic review and meta- analysis is that a large diverse number of studies were included from across the wide range of (secondary care) health care settings from around the world. Forty- seven studies (n= 191, 202) were included in the systematic review, of which forty studies (n= 68, 563) were included in the meta- analysis.

Limitations:

There are limitations in this study. Firstly, there is a time lag in introduction of system change in TIA care, data collection and publication. Our sample population of studies included some patients who received treatment before the EXPRESS study as well as those who received treatment after the results of the EXPRESS study were published (i.e. in 2007). This together with different patient population and different health systems' approaches, makes our sample population highly heterogeneous. There is some inconsistency of assessing and reporting TIA patients between studies and inconsistency of inclusion and exclusion criteria between studies. Not all the health settings in our study cohort were based on the phase 2 model of the EXPRESS study and hence, an appreciable proportion of patients in our study cohort would not have received what is now considered optimal specialised care. The relative availability of specific diagnostic, medical and surgical services, potentially leads to variation in management approaches across health care systems. This may have led to variability in stroke rates between studies (though noting that there is overlapping of 95% credible intervals in our meta-analysis).

Secondly, there is difference in ascertainment of study factor (TIA) acrossstudies. Case ascertainment method varied as different protocol of case ascertainment is followed across studies. Most of the studies identified TIA as per the standard WHO definition whereas some studies followed the tissue- based definition of TIA. Studies explicitly employing tissue-based definition of TIA were however, excluded from our meta-analysis.

The third limitation is the reliability of TIA diagnosis in each individual study. There is heterogeneity in clinicians who made the diagnosis of TIA. This ranged from stroke physicians to ED physicians to ED resident. (126) It is important to establish correct diagnosis of TIA by excluding TIA mimics. Since, several other conditions have a similar presentation as TIA and the interobserver reliability of TIA diagnosis is low, there is potential for differences in diagnostic accuracy between included studies. (33)

The last limitation is the inability to obtain further data from authors of some studies in the form that could be used in the meta- analysis.

Implications for practice and policy

Findings of our study suggest that TIA patients were treated less intensely in historical cohorts and such patients had worse prognosis. The results of the study conducted in expert tertiary stroke care centres and published in the New England Medical Journal in 2016, (125) suggest that with closer adherence to contemporary best practice, even better prognosis of TIA can be achieved. The results of this study shows better prognosis than our meta- analysis. This difference suggests that clinical expertise and stroke expert systems of care continue to be important factors influencing patients' outcomes in the modern era of TIA care.

The prompt implementation of best evidence medical management of patients with TIA requires, organised systems of care to be established. Although many Australian hospitals have stroke units (127) and acute neurovascular clinics, equipped with modern diagnostic facilities and specialist staff to provide optimal care to TIA patients. Delays in seeking medical help and delays in management will likely be continuing to have a negative impact on the outcome of TIA patients. (128) It is equally important that patients understand the symptoms of TIA and that health practices make a correct diagnosis and initiate treatment urgently.

Implications for further research

The processes of care and outcomes of TIA patients can be improved by having optimal infrastructure (having a stroke protocol including various baseline diagnostic tests such as brain CT/MRI, carotid Doppler, ECG, blood pressure measurement and routine bloods, availability of stroke specialty medical staff). It is important to note that in many settings establishment of such a highly specialised health care system with highly trained and specialised personnel with the availability of medical services, outside of a research setting is not highly feasible. (124)

Primary prevention of stroke and prehospital care after a TIA event plays an important role in primary health care settings. Managing TIA patients effectively in primary health care settings is of prime importance, as most of the patients seek initial help from their primary care physicians. Results from Newcastle, Australia show that the general practitioners (GPs) have a role in managing TIA or acute stroke. (129) Systems delays however can result in many patients not receiving appropriate care within guideline-benchmarked timeframes. (124, 130) The GPs also play an important role in patient education of the symptoms of TIA and stroke; and emphasising the need for seeking medical help urgently. (131, 132)

Our results hold significant implications for further future research. Urgent treatment and management of TIA as suggested by the results of our meta- analysis and very good prognosis seen in the Amarenco et al's recent multi-site 'optimal care' cohort (results published in 2016), indicate that further research needs to be conducted to investigate the prognosis of TIA in health care settings which do not have the state- of-

art medical services as seen in the Oxfordshire (EXPRESS), Paris (SOS-TIA) and other advanced research settings in Amarenco et al. Additional research is also required to explore the evidence of gap in management of TIA in primary health care systems, in particular to evaluate the prognosis of TIA in primary health care settings, where TIA patients are often managed without referral to secondary care.

Conclusion

We hypothesised that the prognosis of TIA patients in studies reported in the years post-2007 will be improved compared to studies reported prior to 2008. We found that the prognosis of TIA patients is more favourable in the modern health care settings. This may reflect differences in service models for TIA patients' care; possibly an improvement in service model and an example of evidence-based medicine being rapidly translated into clinical practice. With correct diagnosis and urgent management, the risk of stroke can be substantially reduced. Reducing the risk of stroke reduces the overall burden of stroke in the population and reduce the incidence of post- stroke complications, thereby reducing the mortality and morbidity as well as economic burden.

Appendix I

PRISMA checklist

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	✔
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	✔
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✔
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	✔
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	✔
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	✔
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	✔
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	✔
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✔
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	✔

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	✔
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	✔
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✔
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	✔
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✔
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✔
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix II

Supplementary table of study characteristics

Supplementary table of characteristics

Pub year	First author's name	Study outcome	Methods of outcome ascertainment	Risk factors	Treatment	Methodological considerations/comments
2008	Cem Koz (1)	TIA recurrence	Face-to-face interview	Male= 66.3%, hypertension= 68.4%, diabetes mellitus= 8.4%, coronary artery disease= 14.7%, smoking= 38.9%, hyperlipidaemia= 31.6%	not stated	This study had a small sample size (n=95) and only those patients who were referred from the Cardiology (outpatient departments)OPDs were included.
2008	Rosella Sciolla*(2)	Stroke and death	Telephone interview by study neurologist or by consultation with the recruiting neurologist. Brain imaging showing a new ischemic lesion in a vascular territory unaffected on the admission CT scan had to be present in all stroke cases. Strokes were then categorized on the basis of their ABCD and ABCDI scores and according to TOAST criteria.	Age, y Mean SD 71.5 10.5 Range 40–98 Age 60 y, n (%) 242 (88.3) Male, n (%) 169 (61.7) Blood pressure 140/90 mm Hg, n (%) 177 (64.6)	not stated	Only those patients who were evaluated by a neurologist were enrolled in this study.

2008	Angel Ois*(3)	TIA, stroke	Follow-up data were obtained from direct patient visit or else by telephone interview.	For n=689: Age, >70 years 435 (63.1) Symptoms, >1 hour 559 (81.1) Speech impairment 238 (34.5) Weakness 208 (30.2) Hypertension, 140/90 256 (37.2)) Minor stroke vs TIA 468 (67.9) Coronary artery disease 104 (15.1) Diabetes mellitus 203 (29.5) Prior stroke 94 (13.6) Heart failure 37 (5.4) Gender, male 376 (54.6) Hypertension 442 (64.2) Hyperlipidemia 322 (45.8) Current smoking 167 (24.2) Severe alcohol intake 46 (6.7) Peripheral arterial disease 69 (10) Atrial fibrillation 121 (17.6) Prior TIA 62 (9) Acute infarct in CT 55 (8) Vertebrobasilar event 80 (11.6) Severe arterial disease 111 (16.1)	Antiplatelet therapy except in patients with cardioembolic strokes, and in whom anticoagulation was initiated. An interventional procedure (5 patients angioplasty + stent; 45 patients endarterectomy) was performed in cases with symptomatic carotid stenosis >=70% without complete occlusion and in 2 patients with severe basilar stenosis.	
2008	Kenneth Geil*(4)	Stroke	not stated	not stated	not stated	This study had a small sample size (n=53).
2008	Shelagh B Coutts*(5)	Stroke	Clinical and imaging information reviewed by stroke neurologists.	not stated	All patients were treated acutely with aspirin. Patients with large artery disease were treated acutely with aspirin and clopidogrel (300 mg load and then 75 mg per day). This was before carotid intervention being performed. Patients with atrial fibrillation were treated with heparin while coumadin was commenced or simply started on coumadin. Most patients would be commenced on a statin before discharge.	This study had a small sample size (n=87).

2008	Hakan Ay*(6)	Stroke	The validation of a subsequent stroke from medical records was done without knowledge of clinical and imaging characteristics of index TIA and required a confirmatory note by a neurologist. One of the study investigators visually assessed the brain MRI in patients with clinical diagnosis of subsequent stroke to confirm the presence of a relevant acute infarction.	Age, mean +/- SD 67.7 +/- 14.7 years, Gender, female/male 246 (51.6%)/231 (48.4%), Age >=60 years 348 (73.0%), Admission blood pressure systolic >=140 mm Hg and/or diastolic>= 90 mm Hg 303 (63.5%), History of diabetes mellitus 95 (19.9%).	Antiplatelets 380 (79.7%), Anticoagulation 97 (20.3%), Statin 161 (33.8%).	
2008	David Calvet*(7)	Stroke Mortality and TIA	Patients assessed in person or by telephone intervews, otherwise data obtained from GP	Mean SD age, y 62.4 +/- 15.4 Male sex 212 (62) Hypertension 167 (49) Current smoking 86 (25) Coronary artery disease 46 (13) Peripheral vascular disease 12 (4) Previous stroke 30 (9) Previous TIA 42 (12) , AF 27 (8)	not stated	
2009	Christian Weimar*(8)	Stroke, mortality	Biannual interviews. Confirmation by treating GP/hospital and local death registry	For n=1448: Mean age (median), years 67.6 (69), Women, % 46.3, Previous cerebral ischemia, % 32.5, Previous stroke, % 19.1, Previous TIA only, % 13.4, Diabetes mellitus, % 22.8, Arterial hypertension, % 70.8, Hypercholesterolemia, % 33.8, Coronary artery disease or MI, % 20.3, Peripheral arterial disease, % 5.5, atrial fibrillation, % 13.8, Smoking during past five years, % 16.9, alcohol abuse 4.6	(Discharge treatment): Antiplatelets 81.4, Anticoagulation 15.0, None/unknown 3.7	

2009	Judith H Lichtman(9)	Rehospitalisation for recurrent TIA/ stroke/ coronary artey disease/mortality	Mortality was obtained from the Medicare Enrollment Database. Length of stay was determined for each index hospitalization and discharge disposition was categorized as home, skilled nursing facility, or other location.	Cancer 2.5 Dementia 9.9 Chronic obstructive pulmonary disease 18.4 Ischemic stroke 11.4 Diabetes 26.5 Smoking 6.2 Hypertension 65.4 Acute myocardial infarction 9.2 Congestive heart failure 10.3 Atrial fibrillation 15.8 Prior coronary artery bypass graft 7.3 Prior percutaneous transluminal coronary angioplasty 2.7 Age, years, mean SD 79 +/- 7.6	not stated	This study limited their study cohort to patients with at least 12 months of continuous fee-for-service Medicare beneficiaries.
2009	Brett L Cucchiara*(10)	Stroke, mortality	Clinical and radiographic information	Age, mean (SD) 62 +/- 14, Hypertension 107 (64%), Diabetes 36 (22%) Male sex 75 (45%) CAD/MI 21 (13%) Hyperlipidemia 68 (41%) Prior stroke 29 (17%) Peripheral vascular disease 8 (5%) Current smoker 27 (16%) Migraine 17 (10%)	not stated	In this study patients who were on warfarin with an INR>=1.5 were excluded. A limitation of this study is that the sample size was small (n=164).
2010	Marcus Eng Hock Ong*(11)	Stroke	The sensitivity, specificity, positive and negative predictive value (NPV) of the rule using different cut-off levels, and the associated admission rates for the rule.	Mean age (SD) 61.0 (13.2) Males (%) 293 (63.3) Diabetes (%) 209 (44.5) Hypertension (%) 267 (56.8) Dyslipidemia (%) 147 (31.3) Atrial fibrillation (%) 14 (3.0) Current cigarette smoke (%) 55 (11.7)	not stated	

2010	J.K. Harrison*(12)	Stroke	Stroke identification from hospital and death records, clinical audit data used.	Age Mean (SD) 67.0 (11.9) <60 years, n (%) 197 (24.8) 60 years, n (%) 598 (75.2) Blood pressure Systolic, mean (SD) 155.1 (26.4) Diastolic, mean (SD) 85.6 (13.5) SBP>140 or DBP 90, n (%) 232 (29.2) SBP 140 and DBP<90, n (%) 563 (70.8) Diabetes mellitus,b n (%) Yes 65 (8.2) No 724 (91.1) Sex, n (%) Male 342 (43.0) Female 453 (57.0)	not stated	
2010	Katrin Holzer*(13)	Stroke, TIA, MI	Patients contacted by telephone or mail. The data set was completed by information obtained from relatives, attending physicians and/or hospitals. The interviewer was blinded to the ABCD2 score.	not stated	not stated	A limitation of this study was a small sample size (n=173).
2010	Jason Wasserman*(14)	Stroke, mortality, TIA, MI	Validated, standardized telephone questionnaire and chart review by a neurologist. Other outcomes were adjudicated by a 3-physician committee, blinded to the initial data collection form and ABCD2 score (and its components).	Age, yr, mean (range) 67 (19 –97) Male 500 (50.9) Hypertension 571 (58.1) Coronary artery disease 163 (16.6) Atrial fibrillation 84 (8.6) Diabetes 195 (19.9) Prior stroke 115 (11.7) Smoking 131 (13.3) Hyperlipidemia 319 (32.5)	started in ED: Acetylsalicylic acid 429 (43.7) Clopidogrel 59 (6.0) Dipyridmole 172 (17.5) Statin 20 (2.0) Antihypertensive 16 (1.6) Ticlodipine 3 (0.3) Warfarin 7 (0.7)	

2010	G. Tsivgoulis*(15)	Stroke, mortality	Clinical review by neurologist (telephone interview if not attended in person). Assessment of hospital records, physicians' notes in private practice, necropsy findings or death certificates, and the patients' clinical presentation and telephone interviews by attending neurologist and brain imaging.	Age, mean (SD), y 60 (14) Age >60 y,%(n) 56 (83) Male sex,%(n) 55 (82) Hypertension,%(n) 64 (95) Diabetes mellitus,%(n) 26 (39) Hypercholesterolemia,%(n)) 54 (80) Current smoking,%(n) 31 (46) Coronary artery disease,%(n) 20 (29) Atrial fibrillation,%(n) 14 (21) Previous TIAs in the past month,%(n) 30 (43)	Antiplatelet agents 94 (139) Oral anticoagulants 21 (31) Antihypertensive medications 64 (95) Lipid-lowering medications 42 (62) Antidiabetic medications 29 (43) LMWH 10 (15)	Higher predictive values of 7- and 90- day risk of stroke were noted with increasing ABCD2 scores (p=0.0077 for 7-day risk and p<0.0001 for 90-day risk). No patients were lost to follow-up.
2011	Domenico Marco Bonifati*(16)	Death, stroke, further TIAs and other vascular events(retinal infarction)	Telephone interviews (by neurologist) and reviewing a centralised database for accesses to the Trenito Health Service (ED and hospitals).	Age, years Mean±SD (median; range) 68.7±17.1 (74.3; 20.1–99.9) Age>60 years, n (%) 365 (72.7%) Male, n (%) 233 (46.4%) Risk factors n (%) Blood pressure>140/90 mm Hg, n (%) 362 (73.1%) Mean systolic pressure 161.2 mm Hg (±29.4) Mean diastolic pressure 83.3 mm Hg (±13.7) Diabetes mellitus 82 (16.3%) Hypertension 404 (80.5%) Atrial fibrillation 51 (10.2%) Dyslipidemia 55 (11%) Previous TIA 37 (7.4%) Previous stroke 57 (10.6%) Cardiac disease 127 (25.3%) Current smoke 54 (10.8%)	Only 22 patients (4.4%) were discharged without any therapy. In almost all patients anti-platelet therapy was initiated in the first 24 h after the TIA, usually with ASA (100 mg). Ticlopidine, clopidogrel or ASA+dypiridamol was used if the patient was already taking ASA. Anticoagulation was introduced when indicated. Statins were introduced ex novo in 19 patients (3.8%). Nine patients underwent carotid endarterectomy for symptomatic stenosis during the admission.	

2011	E. Murat Arsava*(17)	Stroke	Information collected retrospectively by an investigator blinded to RRE scores; through inspection of inpatient medical record notes, as well as from routine 1- to 3-month outpatient assessment notes by the treating neurologist. Each clinically suspected recurrent event was adjudicated by a separate investigator using pertinent brain images without the knowledge of clinical and imaging characteristics of the index TSI.	Age= 52.9%, female= 48.2%, HTN= 66.5%, DM= 18.3%, AF= 15.6%, prior TIA/stroke= 35.4%.	Antiplatelet= 80.9%, anticoagulant= 49.4%	
2011	Iacopo Cancelli*(18)	Stroke, mortality	Face-to-face interview with a study neurologist. Hospital and outpatients records were reviewed to obtain a confirmation of the self-reported diagnosis and of the drug prescriptions. For patients who were dysphasic or died before assessment, information was obtained by relatives, GP and/or hospital records.	Age, y (11.7) Female (49), Hypertension 116 (72) Diabetes 28 (17) Hypercholesterolemia 55 (34) Symptomatic carotid stenosis > 50% 22 (14) Coronary heart disease 38 (24) Atrial fibrillation 42 (26) Current smoker 19 (12)	not stated	
2011	F. Purroy*(19)	Stroke, MI, TIA	Clinical visits performed by a stroke physician.	Age, years ± SD 69.3 ± 11.8, Male 156 (61.4), Hypertension 169 (66.5), Previous stroke 59 (23.2), Diabetes mellitus 72 (28.3), Coronary disease 30 (11.8), Smoking 43 (16.9), Hypercholesterolemia 85 (33.5), Atrial fibrillation 33 (13.0)	not stated	

2011	Latha G. Stead*(20)	Stroke	Telephone interviews, review of medical records	~~Age 23.1%,~~ Females 46.8%, Prior TIA 17.9, Prior ischemic stroke 18.2%, HTN 67.3%, DM 18.8%, Prior AF 18.5%	not stated	
2011	Lauren M. Sanders*(21)	Stroke	Outcome was determined from multiple sources, including specialist clinic reviews, outpatient and hospital records, and a validated telephone interview by independent personnel who were blinded to ABCD2 data or scores.	Male 58.1%, HTN 67.4%, Hyperlipidaemia 59.5%, DM 26.6%, Ever smoked 28.6%, AF 14.6%, Ipsilateral carotid stenosis >=70% 10%	not stated	
2011	Pierre Amarenco*(22)	Stroke	Face-to-face interviews by Neurologist or telephone calls by nurses. If the patient could not be contacted, a close relative or their family doctor was interviewed. Medical records were also obtained and the decision of whether an endpoint event had occurred was validated by consensus between two neurologists.	Men 52%, hypertension 68%, dyslipidaemia 41%, DM 11%, current smoker 21%	not stated	

2011	Guy Leseche(23)	Stroke, death, and major cardiac events	Follow-up and ultrasonography by vascular neurologist.	Median age (years) 72 (41-93) (Age 70, n 36; 80, n 11) Male gender 51 (79.5%) Hypercholesterolemia 46 (72%) Hypertension 45 (70%) Smokers (current or ex) 39 (61%) Diabetes 19 (30%) Previous stroke/TIA 14 (22%) Obesity 13 (20%) Chronic lung disease 13 (20%) Symptomatic peripheral arterial disease 13 (20%) Previous myocardial infarction 12 (19%) Coronary heart disease 12 (19%)	After discharge, only aspirin and/or clopidogrel was continued.	This study had a small sample size (n=64).
2011	W. Dorigo(24)	Stroke, death, MI, TIA	Clinical exam and duplex scan and telephone interviews.	Female sex 9 (17.5%) Median age (years) 73.5 Age > 79 yrs. 10 (25%) Hypercholesterolemia 11 (21.5%) Hypertrigliceridemia 7 (13.5%) Diabetes mellitus 8 (15.5%) Arterial hypertension 26 (51%) Coronary artery disease 7 (13.5%) Peripheral artery disease 7 (13.5%) Smoker or past smoker 29 (57%)	not stated	This study had a small sample size (n=51).
2011	D Ghia*(25)	Stroke	All available medical records were reviewed by either a consultant neurologist, stroke fellows or stroke database manager/biostatistician	Median age 73.0, Male 396 (50.2), Diabetes 173 (21.9), Hypertension 509 (64.5).	not stated	

2012	Lauren M. Sanders*(26)	Stroke	Face-to-face neurologist consultation for the majority of patients. A sensitive and validated telephone questionnaire in patients who declined consultation, or searched medical records if they were deceased or unable to be contacted.	Age, mean±SD 67.7±13.1, Male (%) 175 (58.1), Hypertension (%) 203 (67.4), Hyperlipidemia (%) 179 (59.5), Diabetes mellitus (%) 80 (26.6), Ever-smoker (%) 86 (28.6), Atrial fibrillation (%) 44 (14.6), Carotid stenosis >50% 39/372 (14.3).	not stated	
2012	Francisco Purroy*(27)	Stroke recurrence, MI	Face-to-face clinical interviews	Male 170 (60·1) Hypertension 188 (66·4) Previous stroke 63 (22·3) Diabetes mellitus 80 (28·3) Coronary disease 42 (14·8) Hypercholesterolemia 96 (33·9) Atrial fibrillation 36 (12·7) Smoking 39 (13·8) ABCD2, mean (SD) 4·41 (1·25)	Aspirin 149 (52·7) Clopidogrel 77 (27·2) Triflusal 4 (1·4) Anticoagulation 55 (19·4) Statins 120 (42·4) Renin-angiotensin system blockers 154 (54·4)	In this study, an association between an elevated common carotid artery intima-media thickness value and long-term risk of extracranial events was noted but no association was noted for stroke recurrence.
2012	S. T. Engelter*(28)	Stroke, TIA	Clinical visits by stroke neurologists, blinded to the ABCDE score, otherwise a telephone interview was performed using a standardized questionnaire to assess. All outcome events were adjudicated by a senior stroke neurologist.	Age, mean, years (±SD) 70 (±12.4), Male sex, % (number) 60% (149), Hypertension 71% (175), Smoking (current) 21% (53), Atrial fibrillation 15% (37), Hypercholesterolemia 39% (96), Diabetes mellitus 17% (41), Peripheral artery disease 9% (22), Coronary heart disease 19% (47)	not stated	

2012	Jonathan M Raser*(29)	Stroke, mortality, stenosis, or cardioembolic event for anticoagulatio n	Determination of outcome was blinded to ABCD2 score.	Age, mean (SD) 62 6 14 yrs Age >=60 yrs 34% Triage SBP >=140 or DBP >=90 68% Second SBP >=140 or DBP >=90 58% History of hypertension 64% Clinical features Unilateral weakness 36% Speech disturbance without weakness 24% Other 40% Duration of symptoms >=60 min 60% 10-59 min 25% <10 min 14% History of diabetes 22% Blood glucose, median 97 mg/dL Acute hyperglycemia (>120 mg/dL) 23%	not stated	
2012	Fadi Nahab(30)	Stroke	TIA workup in both groups compared	females= 62.7%, hypertension= 79.6%, DM= 28.9%, lipid idsorder= 83.1%, current tobacco use= 14.1%, coronary artery disease= 28.9%, AF= 17%, previous stroke/TIA= 22.5%.	Antithrombotic, statin, blood pressure, and diabetes therapies	A limitation of this study was a small sample size (n=142).
2012	Pilar Delgado*(31)	Stroke, TIA	Clinical interviews	Age, years 72 +/- 12 Males 86 (52%) Hypertension 88 (53%) Diabetes mellitus 41 (25%) Hyperlipidemia 44 (27%) Current smoking 25 (15%) Coronary artery disease 25 (15%) Peripheral artery disease 10 (6%)	After the index event, secondary prevention treatments were administered, which included antiplatelets, anticoagulants and lipid-lowering therapy, according to institutional protocol.	

2012	F Fluri*(32)	Stroke	not stated	Male= 83%, hypertension= 73.9%, AF= 56.9%, smoking 28.7%, hypercholesterolaemia= 70.6%, DM= 18.2%, coronary heart disease= 27.3%, family history of stroke= 21.25%	not stated	A limitation of this study was a small sample size (n=176) and so potential confounders couldn't be addressed.
2012	Nicola L. M. Paul*(33)	Stroke, TIA	All patients with recurrent events were assessed by senior neurologist.	Males= 47.3%, hypertension= 54.4%, diabetes mellitus= 13.4%, angina/MI= 18.1%, peripheral vascular disease= 4.7%, atrial fibrillation= 15.6%, current smoker= 12.6%, previous TIA= 12.9%, previous stroke= 9.4%.	not stated	
2013	Ali Arhami Dolatabadi(34)	Recurrent stroke and mortality	Patients interviewed prospectively at the outpatient clinic or contacted by telephone. Further stroke (or TIA) and death were diagnosed according to the hospital discharge record independent of the study team.	Age, years, mean +/- SD 68.9 (11.9) Male sex, n (%) 93 (62) Blood pressure, mean +/- SD Systolic BP, mm Hg 158 (32.4) Diastolic BP, mm Hg 86 (19.6) Diabetes 38 (25.3) Hypertension 87 (58.0) IHD 39 (26.0) Hyperlipidemia 54 (36.0) Peripheral vascular disease 5 (3.3) Current smoker 24 (16.0)	not stated	Definitive diagnosis of TIA was made by neurologist after the initial diagnosis was made by the ED physician.
2013	Mohamed Al-Khaled*(35)	Stroke and mortality	The patients were questioned by letter or telephone interview. When patients were unavailable, mortality was evaluated by a request in the registration office.	not stated	not stated	

2013	Jeffrey J. Perry*(36)	Stroke, TIA, MI	Telephone interviews, an Adjudication Committee blinded to the initial emergency department visit for TIA reviewed all of the possible events.	Mean age, y (SD) 68.0 (14.4) Female (%) 1976 (50.6),, Hypertension 2308 (59.1) High cholesterol 1295 (33.2) Diabetes mellitus 746 (19.1) Coronary artery disease 725 (18.6) Known prior stroke 509 (13.0) Current smoker 506 (13.0) Atrial fibrillation 349 (9.2) Carotid stenosis 154 (3.9) Peripheral vascular disease 155 (3.9)	Any antithrombotic 3595 (92.0) ASA 2511 (64.2) Antihypertensive 1918 (49.1) Statin 1330 (34.1) Clopidogrel 702 (18.0) Dipyridamole/ASA 494 (12.7) Warfarin 301 (7.7)	In this study, the emergency physicians enrolled the patients and hence reduced the classification bias. However, not all eligible patients were enrolled in the study.
2013	S Gokhan*(37)	Relationship between prognosis, stroke subtype, in- hopsital mortality and NLR	Comparison of neutrophil, lymphocyte and NLR levels	Age (mean ± SD; y) 67.87 ± 11.13 Male/Female 448/420 Hospital Stay (mean ± SD; day) 11.16 ± 5.57 Comorbidity Hypertension 568 (65.4%) Diabetes mellitus 376 (43.3%) Hyperlipidemia 284 (32.7%) Congestive heart failure 338 (38.9%)	not stated	This study had a small sample size (n=90).
2013	Bo Song*(38)	Stroke	Face-to-face assessments by 2 neurologists blinded to the scoring.	Women 96 (40.2) Age ≥60 y 113 (47.3) Blood pressure ≥140/90 mm Hg 127 (53.1) Diabetes mellitus 34 (14.2) Dual transient ischemic attack 146 (61.1) Ipsilateral ≥50% stenosis of ICA 38 (15.9) Hyperlipidemia 23 (9.6) Atrial fibrillation 4 (1.7) Coronary artery disease 23 (9.6) History of stroke 18 (7.5) Current smoker 73 (30.5)	not stated	

2013	Takuya Kiyohara*(39)	Stroke, mortality	Telephone interviews using a standardized interview form by reserach nurses blinded to the clinical data. All information was reviewed by the event committee members, who were masked to the clinical background. When the committee members could not be convinced of stroke event, detailed information on subsequent stroke was also sought from general practitioners or hospital records.	Age, y, mean±SD 69±13 Male, n/N (%) 431/693 (62.2) Risk factors, n/N (%) Hypertension 525/693 (75.8) Dyslipidemia 389/692 (56.2) Diabetes mellitus 163/693 (23.5) Atrial fibrillation 127/693 (18.3) Smoking 376/693 (54.3)	Antiplatelets At discharge 569/693 (82.1) Anticoagulants At discharge 164/693 (23.7) CEA or carotid artery stenting 27/693 (3.9)	
2014	D. Griffiths*(40)	Stroke	Follow-up by telephone and through an audit of hospital and neurologists' records. Local medical officers were contacted to fill in missing information. Cerebral imaging, initiation of antiplatelet therapy, and time to neurology follow-up was also examined.	Age Mean 68, range 28–93 years, Male sex 108 (54%)	On antiplatelet at discharge 191 (96%)	This study was conducted in a regional setting and a limitation of this study was a small sample size (n=189).
2014	Mohamed Al-Khaled*(41)	Stroke during hospitalisation and 3 months after discharge. Rates of readmission and mortality at 3 months.	A follow-up questionnaire was mailed to patients. In case of lack of information or clarity, a telephone interview with patients and/or caregivers was performed. When patients were unavailable, mortality was evaluated online by a request to the registration office.	Age= 6.4%, Male= 50.6%, previous stroke= 24.2%, hypertension= 79.1%, diabetes mellitus= 17.95%, hypercholesterolaemia= 54.3%, AF= 17.3%, antiplatelet therapy before TIA= 38.3%	rt-PA= 3%, oral anticoagulants= 18.9%, CEA/stenting= 3%, antiplatelet therapy within 48h of onset= 84%, antihypertensive= 77.7%, antidiabetic= 14.5%, statins= 61.4%.	Low retention rate of less than 50% was noted in this study. Comparatively lower rates of recurrent stroke at 90-days must take into account the low retention rate.

2014	Takeshi Hayashi*(42)	Stroke	Patients' profiles, risk factors for stroke, symptoms and symptom duration, presence of any old cerebral infarction and large-artery stenosis. Review subsequent use of antiplatelets, anticoagulants, statins, and stenting or bypass formation.	Age, mean +/- SD 66.6 +/- 11.0 Sex, male 44 (59.5%) Hypertension 51 (68.9%) Diabetes mellitus 9 (12.2%) Dyslipidemia 29 (39.2%) Current smoking 16 (21.6%) Atrial fibrillation 16 (21.6%)	Antiplatelets 59 (79.7%) Anticoagulants 16 (21.6%) Statins 17 (23.0%) Stent or bypass formation 7 (.9%)	A limitation of this study was a small sample size (n=74).
2014	Gian Marco De Marchis*(43)	TIA, stroke, mortality	Structured telephone interviews by trained stroke physicians blinded to copeptin levels. All reports of ischemic stroke were confirmed based on definitive, signed medical notes.	Age, median (IQR), y 69.0 (59.0–78.0). Women, n (%) 112 (37.1). Hypertension 208 (68.9). Atrial fibrillation 34 (11.3). Current smoking 63 (20.9). Diabetes mellitus 36 (11.9). Coronary heart disease 49 (16.2). Dyslipidemia 169 (56.0). Previous cerebrovascular event 25 (8.3).	not stated	
2014	Vijaya Sundararajan*(44)	Stroke	Fatal strokes were identified by a manual review of the primary cause of death by 2 stroke experts and then automated for complete capture.	Age <40 3.3 40–59 18.0 60–79 44.2 ≥80 34.5 Women 51.5 Married 33.0 Brain imaging 50.4	not stated	
2014	Mariona Jove*(45)	Stroke	A stroke physician performed clinical visits. Imaging data were required to confirm brain ischemia.	Age, y, mean (SD) 71.7 (10.8) Male 179 (61.1) Previous stroke 63 (21.5) Hypertension 201 (68.8) Coronary disease 39 (13.3) Diabetes mellitus 88 (30.0) Smoking 37 (12.6) Hypercholesterolemia 110 (37.5) Previous atrial fibrillation 34 (11.6)	not stated	

2015	Vilanova MB*(46)	Stroke and MI and vascular death	Face-to-face clinical interviews. All MI events were confirmed by a cardiologist.	Age, years (SD)70.6 (11.9), Hypertension 417 (66.4), Male 361 (57.6), Previous stroke 124 (19.8), Diabetes mellitus 188 (29.9), Coronary disease 90 (14.3), Smoking 90 (14.3), Alcoholism 19 (3.0), Hypercholesterolaemia 210 (33.4), Peripheral artery disease 22 (3.5), Previous Atrial fibrillation 73 (11.6)	(Discharge treatment): Antiaggregation 504 (80.3), Anticoagulation 127 (20.2), Statins 262 (41.7), Renin-angiotensin blockers 318 (50.6), Carotid endarterectomy or carotid angioplasty 20 (3.2)	
2015	Jae-Sung Lim*(47)	Stroke	Outpatient clinic or by telephone interview with a structured questionnaire. Medical records were also reviewed to confirm diagnosis.	Age, mean (SD), y 64.4 (11.8), Male sex 291 (58.2), Hypertension 333 (66.6) Diabetes mellitus 149 (29.8) Hyperlipidemia 157 (31.4) Atrial fibrillation 53 (10.6) Coronary artery disease 42 (8.4) Smoking 131 (26.2) History of stroke 87 (17.4) Family history of stroke 104 (20.8)	Antiplatelets 94.9%, anticoagulants 14.8%, statins 69.0%	A limitation of the study is **generalisability** of results to non-Asian population. This study had 100% follow-up.

TIA= Transient Ischaemic Attack
*= included in meta-analysis
GP= General Practitioner
TSI= Transient Symptoms of Infarction
RRE score= Recurrence Risk Estimator
NLR= Neutrophil Lymphocyte Ratio
MI= Myocardial Infarction
CEA= Carotid Endarterectomy

Appendix III

National Institutes of Health Stroke Scale (NIHSS)

Score	Stroke severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

The patients' performances in each of the following categories are recorded and score is given after each subscale exam.

Instructions	Scale definition
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.

the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).

quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed.

encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, “severe or total sensory loss,” should only be given when a	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.

severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can

words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain:_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the a	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

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