Transient Ischaemic Attack (TIA) Management Study

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Submitted in fulfillment of the requirements of the degree of
Master of Philosophy

December 2010
ABSTRACT

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BACKGROUND:
There is increasing evidence of a high early risk of stroke following TIA. Patients presenting after a TIA offer a unique opportunity for the urgent initiation of proven secondary preventive measures known to reduce the risk of a subsequent stroke. Despite this many TIA patients remain under-investigated and under-treated.

OBJECTIVE:
The aim of this study was to assess whether a structured treatment pathway would improve patient management and outcomes. The clinical pathway categorizes patients with TIA into high or low-risk for stroke according to the ABCD² prognostic scoring system so as to guide their treatment accordingly. It was hoped that the use of the clinical pathway would result in improved medical management and investigation for patients with TIA and ultimately reduce their risk of subsequent stroke and other adverse events at 90 days.

METHODS:
A retrospective pre-pathway audit of consecutive patients presenting with TIA to the Emergency Department (ED) of the Royal Brisbane & Women’s Hospital from 1 July 2006 – 31 Dec 2006 was conducted to determine the standard of TIA management practices prior to pathway implementation.

A TIA clinical pathway was developed based on current national TIA/stroke care guidelines, which stratified patients into high or low-risk for stroke using a dichotomised version of the ABCD² prognostic scoring system (high-risk 4 – 7 points, low-risk 0 – 3 points). The pathway included guidance on decisions regarding investigations, medical management, and the need for hospital admission. All high-risk patients were to be admitted. Low-risk patients without co-morbidities were deemed suitable for discharge. The pathway advised appropriate timeframes for investigations and follow-up for those patients discharged from the ED.
Following an introductory pathway education and familiarisation period, a post-pathway retrospective chart review was conducted for patients presenting from 12 June 2007 – 12 Dec 2007. The primary outcome was stroke occurring within 90 days of first presentation. The combined secondary outcome comprised first presentation with any of the following: stroke, recurrent TIA, other vascular event (angina, myocardial infarction, congestive cardiac failure, limb ischaemia, admission for other cardiac cause), or death due to any cause within 90 days of presentation with the index TIA. The impact of the pathway on processes of care, including the use and timeliness of investigations and prescription of appropriate secondary prevention strategies, was also assessed.

RESULTS:
The pre-pathway cohort comprised 104 patients (median age 65 years; interquartile range 29 years; 48.1% male), and the post-pathway cohort 134 patients (median age 67 years; interquartile range 30 years, 47.8% male).

The percentages of patients prescribed secondary preventive medications at discharge rose following pathway implementation: antithrombotic agents 73/104 (70.2%) pre-pathway, 120/134 (89.6%) post-pathway (p < 0.001); antihypertensive agents 52/104 (50%) pre-pathway, 76/134 (56.7%) post-pathway (p = 0.30); statins 40/104 (38.5%) pre-pathway, (80/134) 59.7% post-pathway (p = 0.001).

No significant changes were seen in the rates of CT/MRI brain or ECG use. There was no significant increase in the use of carotid duplex and echocardiogram in the overall post-pathway cohort, except for the subgroup of pathway-enrolled patients. The median number of days to carotid duplex decreased from 11 days pre-pathway (interquartile range 29 days) to 6 days post-pathway (interquartile range 11 days) (p = 0.001). No significant improvement in the timeliness of echocardiography was seen. There was a statistically significant increase in the proportion of patients tested for fasting lipids, 41/104 (39.4%) pre-pathway, 88/134 (65.7%) post-pathway (p < 0.001) and fasting glucose, 33/104 (31.7%) pre-pathway, 64/134 (47.8%) post-pathway (p = 0.01).

For patients discharged from the ED, who comprised 58/104 (55.8%) of the pre-pathway cohort and 60/134 (44.8%) of the post-pathway cohort, the median number of
days to hospital clinic follow-up fell from 13.5 days pre-pathway (interquartile range 24 days) to 8 days post-pathway (interquartile range 10 days) (p = 0.02).

Follow-up data at 90 days after index TIA was available for 218/234 (93.2%) patients. There was no significant improvement in outcome events. The primary endpoint of stroke occurred in 3/95 (3.2%) patients in the pre-pathway cohort and 1/123 (0.8%) patients in the post-pathway cohort, p = 0.22. All 4 patients who suffered a stroke were deemed to be high-risk as per their ABCD² score. The combined secondary endpoint occurred in 10/95 (10.5%) patients in the pre-pathway cohort and 17/123 (13.8%) patients in the post-pathway cohort (p = 0.46). Of the patients with a secondary outcome event 9/10 (90%) in the pre-pathway cohort and 13/17 (76.5%) in the post-pathway cohort were deemed to be high-risk as per their ABCD² score.

CONCLUSION:
Significant improvements in the process of care were demonstrated following implementation of the TIA clinical pathway, but this did not translate into a statistically significant change in outcome events within 90 days due to an unexpectedly low rate of primary outcome events in both cohorts. The study has highlighted local issues within our hospital regarding access to investigations within an appropriate time-frame, and other areas where there is still room for improvement. This study supports the role of clinical pathways as a potential mechanism of effectively implementing evidence-based guidelines for the management of patients with TIA.
Statement of Originality

This thesis comprises only my original work. This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person except where due reference has been made in the thesis itself.

Signed____________________________________________

Helen Brown

Date ________________________________________________
Acknowledgements

First and foremost I offer my sincerest gratitude to my supervisors, Professor Simon Broadley, Dr Stephen Read, and Dr Robert Henderson. In particular, I wish to thank both Professor Broadley and Dr Read, both of whom have supported me throughout my thesis with knowledge and patience. Without their advice, encouragement, effort, and understanding I would not have been able to complete this thesis. One simply could not wish for better supervisors.

I would like to thank Professor Mervyn Eadie who was instrumental in encouraging me to pursue a career in neurology, undertake this master’s degree, and point out that one of the main aims of undertaking a master’s degree is to complete it.

I would like to acknowledge the financial support that I received from The Royal Brisbane and Women’s Hospital Research Foundation which enabled me to devote all my time and effort towards this study during the initial study development and implementation phases and afforded me the necessary time to carry out all the chart reviews in this retrospective study.

I would also like to thank both project officers from the Clinical Practice Improvement Centre at The Royal Brisbane and Women’s Hospital. In particular, Caroline Ford who was of great help with the regular education sessions we carried out in phase 2 of the study and in ensuring that the clinical pathway met all the necessary hospital requirements to enable it to be used.

Finally, I thank my husband, Dr Jason Brown, for all his love, support, computer prowess, and most of all, patience whilst I endeavoured to complete this thesis.
# Table of Contents

ABSTRACT .......................................................................................................................... II

STATEMENT OF ORIGINALITY ......................................................................................... V

ACKNOWLEDGEMENTS ...................................................................................................... VI

LIST OF TABLES .................................................................................................................. X

LIST OF FIGURES ............................................................................................................... XIII

SECTION I: LITERATURE REVIEW ...................................................................................... 0

1.1 INTRODUCTION ........................................................................................................ 1

1.2 THE CHANGING DEFINITION OF A TRANSIENT ISCHAEMIC ATTACK (TIA) .......... 4

1.3 DIAGNOSIS OF TIA ................................................................................................... 8

1.4 EPIDEMIOLOGY OF TIA .............................................................................................. 15

1.5 RISK OF SUBSEQUENT STROKE .............................................................................. 22

1.6 PROGNOSTIC SCORING SYSTEMS TO PREDICT RISK OF SUBSEQUENT STROKE .... 24

1.7 VALIDATION OF THE “ABCD” AND “ABCD2” PROGNOSTIC SCORING SYSTEMS. 26

1.8 INPATIENT VERSUS OUTPATIENT MANAGEMENT OF TIA ................................. 32

1.8.1 THE UNITED STATES (US) .................................................................................. 34

1.8.2 THE UNITED KINGDOM (UK) .......................................................................... 35

1.8.3 AUSTRALIA ......................................................................................................... 36

1.9 COMPARISON OF INPATIENT AND OUTPATIENT MODELS OF CARE ............. 38

1.10 EVIDENCE-BASED RECOMMENDATIONS FOR MEDICAL MANAGEMENT OF TIA. 46

1.11 DO CLINICIANS MANAGE PATIENTS ACCORDING TO THE GUIDELINES? .......... 54

1.12 IMPLEMENTATION OF EVIDENCE-BASED GUIDELINES – THE ROLE OF CLINICAL PATHWAYS ...................................................................................................................... 58

1.13 CLINICAL PATHWAYS OF CARE FOR STROKE AND TIA PATIENTS .............. 61

1.13 CONCLUSION .......................................................................................................... 64

SECTION II METHODOLOGY .............................................................................................. 67

2.1 HYPOTHESIS ............................................................................................................. 68

2.2 OBJECTIVES ............................................................................................................. 68

2.3 STUDY DESIGN ......................................................................................................... 68
4.2 OUTCOME EVENT FINDINGS ................................................................. 118
4.2.1 PRIMARY OUTCOME EVENTS ...................................................... 118
4.2.2 SECONDARY OUTCOME EVENTS ................................................. 120
4.3 IMPACT OF PATHWAY ON PROCESSES OF CARE ......................... 120
4.3.1 UTILISATION OF INVESTIGATIONS ............................................. 120
4.3.2 NEUROIMAGING ........................................................................ 120
4.3.3 CAROTID DUPLEX ...................................................................... 123
4.3.4 CARDIAC INVESTIGATIONS ........................................................ 124
4.3.5 ANTITHROMBOTIC AGENTS ....................................................... 127
4.3.6 ANTIHYPERTENSIVE AGENTS ..................................................... 129
4.3.7 LIPID LOWERING AGENTS ......................................................... 132
4.4 UTILISATION AND EFFECT OF THE TIA/STROKE CLINICAL PATHWAY .... 134
4.5 VALIDITY OF THE ABCD² SCORE AND EFFICACY OF DICHOTOMISING THE ABCD² SCORE ........................................................................................................ 136
4.6 DECISION MAKING REGARDING INPATIENT VERSUS OUTPATIENT MANAGEMENT .................................................................................................................. 140
4.7 IMPACT OF INCLUDING STROKE PATIENTS IN THE ANALYSIS .......... 143
4.8 STRENGTHS AND WEAKNESSES OF THIS STUDY .............................. 144
4.9 CONCLUSIONS AND FUTURE DIRECTIONS ..................................... 147

SECTION V: BIBLIOGRAPHY .................................................................... 150
List of Tables

SECTION I: LITERATURE REVIEW .................................................................

Table 1.1 Duration of TIA Symptoms..........................................................6
Table 1.2 DWI Abnormalities in Patients with TIA.......................................8
Table 1.3 Differential Diagnosis of TIA Adapted from Albucher et al (2005)......12
Table 1.4 Focal Neurological and Ocular Symptoms (Hankey 2002).............13
Table 1.5 Non-Focal Neurological Symptoms (Hankey 2002)..........................14
Table 1.6 Inter-Observer Differences in Diagnosis of TIA..............................16
Table 1.7 Comparisons of Incidence Rates of TIAs around the World............18
Table 1.8 Risk of Stroke Following TIA at Selected Time Intervals.................23
Table 1.9 ABCD Score to Predict 7 Day Risk of Stroke Following TIA (Rothwell, Giles et al. 2005)...................................................25
Table 1.10 ABCD² Score and Risk of Stroke Following TIA (Johnston, Rothwell et al. 2007)..........................................................26
Table 1.11 Validation Studies for ABCD Prognostic Scoring System to Identify those at High-Risk of Stroke Following TIA..............................................27
Table 1.12 Relationship between ABCD² Score and Hazard Ratio for Subsequent Stroke (Selvarajah, Smith et al. 2008).................................31
Table 1.13 Recommended Treatment Protocol for all TIA and Minor Stroke Patients in the EXPRESS Study (Rothwell, Giles et al. 2007).........................44
Table 1.14 Comparisons of International Guidelines for the Acute Management of TIA..................................................................................48

SECTION II METHODOLOGY ......................................................................

Table 2.1 Clinical Pathway Recommendations for Choice of Antiplatelet Agent...71
Table 2.2 ABCD² Prognostic Score (Johnston, Rothwell et al. 2007)...............74
Table 2.3 The Modified Rankin Scale..........................................................78
SECTION III: RESULTS

Table 3.1 Comparisons of Diagnoses in the Pathway-Enrolled Subgroup Compared to those Not Enrolled on the Pathway.................................88
Table 3.2 Baseline Patient Characteristics in the Pre-Pathway and Post-Pathway Cohorts..................................................................89
Table 3.3 Medical Management Pre- and Post-TIA/Stroke Pathway Implementation..90
Table 3.4 Medical Management for those Admitted versus Discharged from ED……91
Table 3.5 Reasons why Patients were not Commenced on an Antihypertensive Agent in the Post-Pathway Cohort..............................................91
Table 3.6 Details of Patients Deemed Unsuitable for Warfarin..........................93
Table 3.7 Investigations Pre- and Post- TIA/Stroke Pathway Implementation……..94
Table 3.8 Investigations for those Admitted versus Discharged from ED...........96
Table 3.9 Patients who did not have a Carotid Duplex....................................97
Table 3.10 Timeframe to Investigations Pre and Post TIA/Stroke Pathway Implementation............................................................................97
Table 3.11 Risk Stratification of Patients..........................................................98
Table 3.12 Details of Patients with a Primary Outcome Event (Subsequent Stroke) within 90 Days.................................................................101
Table 3.13 Details of Pre-Pathway Patients with Secondary Outcome Event within 90 Days.................................................................................102
Table 3.14 Details of Post-Pathway Patients with a Secondary Outcome Event within 90 Days.................................................................................103
Table 3.15 Outcome events for those Admitted versus Discharged from ED........105
Table 3.16 Most Common Diagnoses among TIA Mimics in this Study..............106
Table 3.17 Percentage of Patients with TIA/Stroke versus TIA Mimic in each Risk Category..............................................................................107
Table 3.18 Frequency of each ABCD² Score in TIA/Stroke Group compared to TIA Mimic Group.................................................................108
Table 3.19 Frequency of ABCD² Scores and Outcome Events..........................109
Table 3.20 Medical Management Pre and Post-TIA/Stroke Pathway Implementation According to Patient Risk Stratification.................................110
Table 3.21 Investigations Performed Pre and Post-TIA/Stroke Pathway Implementation According to Patient Risk Stratification.................................111
Table 3.22 Number of Patients in the Overall Cohort and the TIA Subgroup........112
SECTION IV: DISCUSSION AND CONCLUSION

Table 4.1 Definition of Normal Blood Pressure as Defined by the Stroke and TIA Guidelines……………………………………………………………………………….133
Table 4.2 Effect of Admission versus Discharge on the Rate of Subsequent Stroke or Recurrent TIA (Kehdi, Cordato et al. 2008)………………………………………..143
List of Figures

Figure 1.1 Variations in Management of TIA in Hospital-Based Studies ..........................56
Figure 2.1 TIA/Stroke clinical pathway .................................................................76-77
Figure 3.1 Cases Eligible for Inclusion .................................................................87
Figure 3.2 Median ABCD² score and Interquartile Range for TIA/Minor Stroke and TIA Mimics ........................................................................................................106
Figure 3.3 Median ABCD² Score and Interquartile Range for TIA Subgroup and Stroke Subgroup ........................................................................................................115
Figure 4.1 Comparison of Rates of Utilisation of Investigations in Retrospective Hospital-Based Studies of patients with TIA .................................................................121
Figure 4.2 Availability of MRI in Australia by State, Stroke Unit Status, and Rurality (National Stroke Foundation 2009) .................................................................123
Figure 4.3 Availability of Carotid Doppler in Australia by State, Stroke Unit Status, and Rurality (National Stroke Foundation 2009) .................................................................125
Figure 4.4 Comparisons of Rates of Utilisation of Antithrombotic Agents at Time of Discharge from ED in Retrospective Hospital-Based Studies of Patients with TIA ....128
1.1 Introduction

Each year 15 million people worldwide suffer a stroke. Of these, 5 million die as a direct consequence of their stroke and another 5 million are left permanently disabled (Mackay and Mensah 2004). Despite better understanding of underlying risk factors, availability of drug therapy options and widespread availability of published practice guidelines for secondary prevention (Sacco, Adams et al. 2006; National Stroke Foundation 2007; Royal College of Physicians London and Party 2007), it remains the second leading cause of death above the age of 60 years, and the fifth leading cause in people aged 15 to 59 years (Mackay and Mensah 2004).

Hospital and population based studies over the past 10 years have shown that a TIA is a significant risk factor for subsequent stroke, carrying a 90 day risk of stroke following TIA ranging from 6 – 15% (Johnston, Gress et al. 2000; Coull, Lovett et al. 2004; Gladstone, Kapral et al. 2004; Kleindorfer, Panagos et al. 2005; Bray, Coughlan et al. 2007). The first 48 hours following TIA has also been shown to be a critical period, with up to 50% of post-TIA strokes occurring within this time (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004; Sciolla and Melis 2008). These findings highlight the importance of rapid implementation of evidence-based secondary preventative measures to reduce the risk of subsequent stroke and its associated morbidity and mortality.

Despite this growing evidence base, the management of suspected TIA patients is problematic for physicians at the coal-face, and poses three main questions: what should be done, where should this be done, and when (or how urgently) should management take place.

With regard to what investigations and management should be implemented, the main issues are to ensure all evidence-based treatment measures are implemented and all necessary investigations are performed. Unfortunately, despite a convincing evidence base supporting a range of secondary preventive measures to reduce the risk of subsequent stroke, these measures are inconsistently applied or ignored in everyday practice. A number
of hospital- and community-based studies have shown under-investigation and under-treatment of patients with TIA (Johnston, Gress et al. 2000; Chang, Holroyd et al. 2002; Duffy, Phillips et al. 2003; Gladstone, Kapral et al. 2004; Read and Levy 2005; Edlow, Kim et al. 2006; Obviagele, Hills et al. 2006; Selvarajah, Smith et al. 2008), despite widely available evidence-based guidelines for best practice in the management of patients with suspected TIA, such as those compiled by the National Stroke Foundation in Australia (National Stroke Foundation 2007) and their equivalent in other countries (Intercollegiate stroke working party 2004; National Pre-hospital Guidelines Group 2006; Sacco, Adams et al. 2006). Methods to bridge this knowledge-to-practice gap, such as clinical pathways of care, have been studied in stroke and other areas of healthcare, such as management of patients presenting with chest pain, with promising results (Fonarow, Gawlinski et al. 2001; LaBresh, Ellrodt et al. 2004; Obviagele, Saver et al. 2004; Read and Levy 2006). Thus, there is potential for a clinical pathway to assist with the effective utilisation of appropriate investigations and implementation of evidence-based secondary preventative measures in the acute management of TIA patients.

Where the investigation and management of patients with TIA should take place also poses a challenge for clinicians. Marked variation exists in the rate of hospitalization of patients with TIA. This largely relates to restrictions faced by each healthcare service with regard to the availability of hospital beds for inpatient care, and/or urgent access to the necessary investigations and appropriate specialists for outpatient management. The option of outpatient management of patients with TIA is attractive, given the hospital bed shortages faced by many healthcare systems (NHS Executive 2000; Australian Government Department of Health and Ageing 2007), but the main concern is whether or not outpatient management is rapid enough. There is considerable variation in the number of and access to outpatient neurovascular (TIA) clinics; 5% of Australian hospitals when surveyed in 2007 had a TIA clinic (National Stroke Foundation 2007) compared to 78% of hospitals in the United Kingdom (UK) when surveyed in 2006 (Royal College of Physicians of London Clinical effectiveness and Evaluation Unit and Intercollegiate stroke working party 2007). Systems with poorly developed outpatient services will inherently incur delays in outpatient management for TIA patients. In contrast, a 10 year national study on ED visits for TIA in the United States showed that 54% of all TIA patients were admitted to hospital for acute
management and this figure remained constant over the 10 year period of the study and was regardless of age, gender, ethnicity, urban status or type of insurance (Edlow, Kim et al. 2006). This variation in approach to where a patient with TIA should be investigated and managed may be a reflection of the proportion of people who hold private insurance in each country; 67.5% of US citizens held private health insurance in 2007 (De Navas-Walt, Proctor et al. 2008), compared to approximately 10% of the UK population (Smee 2000). In Australia the percentage of people who hold private insurance varies from 24% of Australians living in households with incomes below $25,000 per year to 69% of those living in households with incomes greater than $100,000 per year (Denniss 2005).

There are a number of advantages to admitting patients with TIA to hospital, including: greater opportunity for risk factor modification; commencement of medical management at a time when patients are motivated to begin and maintain these interventions to lower their future risk of cerebrovascular disease; expedited performance of all necessary investigations; facilitation of early carotid revascularization if necessary; and immediate access to thrombolysis if the patient suffers a subsequent stroke. However, these advantages have to be weighed up against the disadvantages, including: the inconvenience posed to a patient with no residual symptoms; exposure of asymptomatic patients to iatrogenic complications of hospital admission (such as deep vein thrombosis and nosocomial infection); hospital bed shortages; and the cost of hospital admission. Unfortunately there is no hard evidence to resolve this uncertainty, and this lack of evidence is reflected in a lack of consensus amongst the various published TIA and stroke guidelines as to where TIA management should take place.

There is also the question of when the investigation and management of patients with TIA should occur. Performing all necessary investigations and implementing appropriate therapy at the time of presentation would be ideal and 2 studies have shown this to be very effective (Lavallée, Meseguer et al. 2007; Rothwell, Giles et al. 2007). However, outside of a study setting, this is unlikely to occur due to issues with access to appropriate investigations and specialist follow-up (Widjaja, Salam et al. 2005; Goode, Altaf et al. 2007; Royal College of Physicians London and Party 2007). Given that this is the case, methods to help determine those patients with TIA at highest risk of subsequent stroke and
who are, therefore, most in need of urgent assessment and management have been
developed. One such method is the use of a prognostic scoring system, the ABCD² score
(Johnston, Rothwell et al. 2007), which enables risk stratification of patients into high and
low-risk groups based on a score derived from the patient’s Age, Blood pressure, Clinical
signs, Duration of symptoms, and whether or not they have a history of Diabetes; all of
which can be rapidly assessed at the patient’s bedside and thus is quick and easy to use. The
score can then assist with the decision making process regarding which patients require
immediate, same-day, assessment and investigation versus those who could potentially be
discharged home and have their investigations performed over the subsequent week.

In the following sections I will address the problems faced by the physician across the
entire TIA management process; from the initial difficulty in the correct identification of
those patients with a TIA, the changing definition of TIA, the decision making process of
inpatient versus outpatient management, what investigations to perform and how urgently,
and the appropriate implementation of medical management. I will review the
epidemiology of TIA so as to gain better insight as to the number of patients with TIA,
compare current international guidelines for management of patients with TIA, and provide
an overview of the studies looking at the current management of TIA to highlight the
problem of both under-investigation and under-treatment of patients with TIA. I will also
review potential methods to address these issues, such as, the utilisation of the ABCD²
prognostic scoring system (Johnston, Rothwell et al. 2007) and the use of clinical pathways
of care to ensure the delivery and implementation of all appropriate evidence-based
investigations and secondary preventive measures in the acute management of patients with
TIA, with the aim of ensuring that the window of opportunity that exists following a TIA to
prevent the devastating consequences of stroke is not missed.

1.2 The Changing Definition of a Transient Ischaemic Attack (TIA)

The classic definition of a Transient Ischaemic Attack is the rapid development of clinical
signs of focal or global disturbance of cerebral function lasting less than 24 hours, with no
apparent non-vascular cause (WHO MONICA Project Principal Investigators 1988).
However, it has been suggested that TIA is a “Treacherously Inaccurate Acronym” (Fred 2002), with the main problem being that the 24 hour time-frame may be too long. The 24 hour criterion is based on the assumption that a transient clinical deficit is not associated with permanent brain injury or infarction, but if the deficit persists longer than 24 hours the damage to brain parenchyma should be permanent and detectable by microscopy. This definition was created at a time when there was no acute treatment for stroke; therefore, the need to distinguish between TIA and stroke was not a matter of urgency. However, with the advent of thrombolysis for the treatment of acute ischaemic stroke within 3 hours of symptom onset, the need to redefine the time frame for duration of a TIA has become a priority in order to prevent unnecessary delay in the treatment of acute stroke patients. This had led to Albers et al to propose a new definition for TIA as a brief episode of neurological dysfunction caused by focal brain or retinal ischaemia, with clinical symptoms lasting typically less than one hour, and without evidence of acute infarction (Albers, Caplan et al. 2002). There are a number of studies which support this much shorter time-frame of symptoms for TIA which I will now discuss.

In Levy’s study of 1,343 patients with a final diagnosis of TIA, Reversible Ischaemic Neurologic Deficit (RIND), or stroke (Levy 1988), 382 had a final diagnosis of TIA as per the 24 hour timeframe definition for symptom resolution in TIA. Of these 382 classically defined TIA patients, 191 (50%) had complete resolution of their symptoms within 30 minutes and 228 (60%) had complete resolution of symptoms within 60 minutes. Of the 1,115 patients with a deficit persisting for at least 60 minutes only 13.8% had complete resolution of symptoms within 24 hours (Levy 1988). This suggests that patients with a deficit persisting at least 60 minutes have a less than 2% chance of resolving spontaneously during any subsequent 1 hour period up to 24 hours (Levy 1988).

Another study which showed a low likelihood of symptom resolution for patients with symptoms persisting more than 1 hour is the National Institute of Neurological Disorders and Stroke trial of tissue plasminogen activator for acute ischaemic stroke (The National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator (r-tpa) stroke study group 1995). All patients with rapidly improving symptoms were excluded, such that the duration of symptoms for all participants was greater than or equal
to 1 hour. Within the placebo cohort only 2% of patients had complete resolution of their neurological deficit at 24 hours post symptom onset.

Other studies which also support a shorter time-frame of symptomatology for TIA patients have shown complete resolution of symptoms within the first hour in 50 – 73% of patients with TIA (see Table 1.1) (Harrison, Marshall et al. 1978; Bogousslavsky, Hachinski et al. 1986; Werdelin and Juhler 1988; Kimura, Minematsu et al. 1999). A National Institute of Neurological and Communicative Diseases and Stroke supported multi-centre study of 1,307 patients with TIA symptoms, which separated patients into anterior circulation versus posterior circulation TIAs, showed an even shorter median TIA symptom duration of 14 minutes for an anterior circulation TIA and 8 minutes for a posterior circulation TIA (Dyken, Conneally et al. 1977). Overall, these studies show that from a clinical perspective the 24 hour time criterion for the definition of TIA is too long.

Table 1.1 Duration of TIA Symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients with TIA</th>
<th>Resolution of symptoms ≤ 1 hour Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Harrison, Marshall et al. 1978)</td>
<td>116</td>
<td>65/116 (56%)</td>
</tr>
<tr>
<td>(Bogousslavsky, Hachinski et al. 1986)</td>
<td>205</td>
<td>150/205 (73%)</td>
</tr>
<tr>
<td>(Levy 1988)</td>
<td>382</td>
<td>228/382 (60%)</td>
</tr>
<tr>
<td>(Werdelin and Juhler 1988)</td>
<td>20</td>
<td>10/20 (50%)</td>
</tr>
<tr>
<td>(Kimura, Minematsu et al. 1999)</td>
<td>81</td>
<td>41/81 (51%)</td>
</tr>
</tbody>
</table>

Strengthening the case to redefine TIA is evidence from neuroimaging studies of patients with TIA which have shown evidence of infarction on computed tomography (CT) in 8 –
30% (Ladurner, Sager et al. 1979; Calandre, Gomara et al. 1984; Bogousslavsky and Regli 1985; Bogousslavsky, Hachinski et al. 1986; Dennis, Bamford et al. 1990; Koudstaal, van Gijn et al. 1992; Sempere, Duarte et al. 1996; Kimura, Minematsu et al. 1999).

The advent of magnetic resonance imaging (MRI) techniques, such as Diffusion-Weighted Imaging (DWI), allow earlier identification of acute brain infarction (Warach, Gaa et al. 1995; González, Schaefer et al. 1999; Thijs and Albers 2000; Chalela, Kidwell et al. 2007). MRI based studies have shown evidence of infarction on DWI in 21 – 67% of patients who have been diagnosed with TIA (Kidwell, Alger et al. 1999; Rovira, Rovira-Gols et al. 2002; Crisostomo, Garcia et al. 2003; Inatomi, Kimura et al. 2004; Ay, Koroshetz et al. 2005; Coutts, Simon et al. 2005; Lamy, Oppenheim et al. 2006; Prabhakaran, Chong et al. 2007; Calvet, Touze et al. 2009).

MRI studies have also shown that there is an increased likelihood of evidence of infarction on DWI with increasing symptom duration (Crisostomo, Garcia et al. 2003; Lamy, Oppenheim et al. 2006; Prabhakaran, Chong et al. 2007; Calvet, Touze et al. 2009) (see Table 1.2). One study showed in their cohort of 58 TIA patients that 100% of their patients with an attack lasting greater than 6 hours had evidence of infarction on DWI (Rovira, Rovira-Gols et al. 2002).

In summary, TIAs commonly last less than 30 minutes and are rapid in onset (no symptoms to maximal symptoms in less than 5 minutes and usually less than 2 minutes) (Whisnant, Basford et al. 1990), and the longer the episode the greater the likelihood of finding evidence of infarction on cerebral Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) (Kimura, Minematsu et al. 1999; Rovira, Rovira-Gols et al. 2002; Crisostomo, Garcia et al. 2003; Lamy, Oppenheim et al. 2006; Prabhakaran, Chong et al. 2007; Calvet, Touze et al. 2009). With this evidence from imaging studies of an increased likelihood of infarction with increasing symptom duration, events ≥ 1 hour in duration should no longer be considered transient or benign. Unfortunately, other than when imaging positively identifies evidence of acute cerebral ischaemia, this knowledge does not help the clinician correctly make the sometimes difficult diagnosis of TIA nor confidently distinguish TIA/stroke mimics, as will be discussed in the next section.
Table 1.2 DWI Abnormalities in Patients with TIA

<table>
<thead>
<tr>
<th>Study</th>
<th>Total number of patients with TIA</th>
<th>TIA symptoms &lt; 1 hour</th>
<th>TIA symptoms ≥ 1 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>DWI positive n (%)</td>
<td>Total n</td>
</tr>
<tr>
<td>Crisostomo, Garcia et al. 2003</td>
<td>77</td>
<td>3/40 (7.5%)</td>
<td>37</td>
</tr>
<tr>
<td>Lamy, Oppenheim et al. 2006</td>
<td>98</td>
<td>NR</td>
<td>39</td>
</tr>
<tr>
<td>Prabhakaran, Chong et al. 2007</td>
<td>146</td>
<td>15/95 (15.8%)</td>
<td>51</td>
</tr>
<tr>
<td>Calvet, Touzé et al. 2009.</td>
<td>339</td>
<td>57/184 (31.0%)</td>
<td>155</td>
</tr>
</tbody>
</table>

1.3 Diagnosis of TIA

The main difficulty with diagnosing a TIA is that it is a purely clinical diagnosis, often based upon the recollection of symptoms by a patient who was neurologically impaired at the time of the event but has since recovered, for which there is no blood test or neuroimaging study that can confirm the diagnosis. In addition, if the patient is not reviewed promptly, the historical details can get blurred with the passage of time. This makes diagnosing a TIA much more difficult than diagnosing a stroke.

In stroke there are objective clinical signs upon which the diagnosis can be based and the diagnosis can be confirmed by showing evidence of infarction on neuro-imaging. Thus, stroke is an objective diagnosis. In comparison, the diagnosis of TIA is entirely subjective and dependent upon the interpretation of the history by the treating doctor.
Given that the distinguishing feature between a TIA and a stroke is the duration of symptoms, the current 24 hour definition for TIA makes it difficult to distinguish between TIA and stroke if the patient presents with ongoing symptoms within 24 hours of onset. That said, persisting symptoms or signs should perhaps always lead to a provisional diagnosis of stroke, rather than TIA, until they resolve, even in the patient who has exhibited improvement from an initially more severe deficit.

The interpretation of the history by the treating doctor is also problematic in the diagnosis of TIA as the concept of a TIA is understood differently by neurologists and non-neurologists. This is important, as the first point of contact for a patient with acute stroke or TIA is almost never a neurologist (Morgenstern, Lisabeth et al. 2004). For the majority of patients the first point of contact is either a General Practitioner (GP) or an Emergency Physician, amongst whom diagnostic accuracy is variable. Studies looking at the diagnostic accuracy of cases deemed to be a TIA by GPs show that this varies from 19 – 38% (Dennis, Bamford et al. 1989; Ferro, Falcao et al. 1996; Whitehead, Mc Manus et al. 2005). A Portuguese study (Ferro, Falcao et al. 1996) showed accurate GP diagnosis of a TIA in only 19% of cases referred to a neurologist, with 50% being due to a stroke, and 31% due to a non-cerebrovascular event. In the Oxford Community Stroke Project (Dennis, Bamford et al. 1989) of the 512 patients referred to the study as a TIA by GPs in Oxford, the diagnosis was correct in only 38% of cases. A rapid access TIA clinic in East Scotland reviewed their GP referrals to the clinic over a 6 month period (Whitehead, Mc Manus et al. 2005) and found only 32.5% of cases were correctly diagnosed as a TIA, 22.5% were due to a minor stroke, and 35% were due to non-cerebrovascular disease. This low rate of correct TIA diagnosis amongst GPs may be somewhat artificial, as the GP may realize that the diagnosis is unlikely to be a TIA, but if unsure regarding the correct diagnosis for the patient’s transient neurological symptoms, referral to a rapid access TIA service where the patient is reviewed by a neurologist is an attractive option so as to clarify the diagnosis. This is reflected in the higher rates of diagnostic accuracy for TIA by GPs seen in postal surveys using case vignettes of TIA cases which have been used in both the Netherlands and Poland. The study in the Netherlands surveyed 375 GPs (Quik-van Milligen, Kuyvenhoven et al. 1992) and showed that TIA was correctly diagnosed in 80% of cases,
with the correct diagnosis most often made in cases with transient hemispheric ischaemia, longer attacks, recurrent attacks, and age under 60 years. In a Polish survey of 89 GPs (Tomasik, Windak et al. 2003) a correct diagnosis of a TIA was made in 46 – 78% of cases due to hemispheric ischaemia, but in only 20 – 44% of cases where transient monocular blindness was the presenting symptom. This study also found that patients with their first attack and no history of non-specific symptoms had a higher percentage of correct diagnoses in comparison to those with recurrent attacks and a history of non-specific symptoms (Tomasik, Windak et al. 2003).

Studies which have looked at the diagnostic accuracy of TIA cases by Emergency Physicians show that this varies from 4/31 cases (13%) in a Portuguese study (Ferro, Falcao et al. 1996), to 1,604 /1,707 cases (94%) in a multi-centre study in California (Johnston, Gress et al. 2000). One retrospective review carried out in an urban teaching hospital in Cincinnati (Kothari, Brott et al. 1995) reviewed 351 cases diagnosed as either TIA or stroke by an Emergency Physician and showed that the diagnosis was correct in 346 cases, which gives a 98.6% sensitivity and 94.8% positive predictive value for Emergency Physician diagnosis of stroke and TIA. The Brain Attack Surveillance in Corpus Christi (BASIC) project also performed a multi-centre, retrospective audit in seven acute care hospitals in Texas County of cases diagnosed as TIA or stroke by Emergency Physicians (Lisabeth, Ireland et al. 2004). Of the 2,059 cases that met study criteria, 1,800 were validated by the study neurologist as a correct diagnosis of TIA or stroke. This results in a sensitivity of Emergency Physician diagnosis of 92% and a positive predictive value of 89%. Overall, these studies show greater diagnostic accuracy amongst Emergency Physicians compared to GPs.

It is not just among General Practitioners and Emergency Physicians that inter-observer diagnostic variability exists. Even amongst senior neurologists with stroke expertise there is still inter-observer diagnostic variability (Kraaijeveld, Van Gijn et al. 1984), with one study showing a kappa index of true agreement between two neurologists of only 0.65, which means that in as many as 35% of all possible TIA diagnoses, the diagnostic agreement may be due to chance (Tomasello, Mariani et al. 1982). This variation can be reduced through the use of check lists written in lay terms rather than medical nomenclature and utilization
of national guidelines for the diagnosis of TIA (Koudstaal, van Gijn et al. 1986; Maasland, Koudstaal et al. 2007).

The early distinction between TIAs, stroke, and other nonvascular transient neurological disturbances has important consequences, with patients potentially being denied appropriate investigation and treatment or, conversely, receiving inappropriate investigation and exposure to the risk of iatrogenic injury from unnecessary treatment. This is particularly pertinent given the availability of intravenous thrombolysis for the treatment of acute stroke, which can result in symptomatic intracranial haemorrhage in 1.7% to 8.6% of those treated (Wahlgren, Ahmed et al. 2007). Hence, it is important that all non-ischaemic causes of focal neurologic symptoms, so-called “TIA mimics,” are excluded. The differential diagnosis for TIA is summarized in Table 1.3.

Physicians have now begun to envisage TIA and stroke in the same way as cardiologists think about unstable angina and myocardial infarction, as different parts of a spectrum of the same disease (Edlow, Kim et al. 2006), as they share the same symptoms and signs. The distinguishing factor between the two is merely the duration of the focal neurological symptoms, with TIA lasting less than 24 hours (and usually less than 1 hour) and stroke having a persistent deficit. They both cause sudden onset of focal neurological symptoms that allow clinico-anatomical correlation; such as, focal motor and/or sensory deficits, speech disturbances, visual disturbances, and reduced co-ordination and imbalance. These symptoms are outlined in greater detail in Table 1.4.
Table 1.3 Differential Diagnosis of TIA Adapted from Albucher et al. (2005)

<table>
<thead>
<tr>
<th>Neurological Disorders</th>
<th>Non-Neurological Disorders</th>
<th>Transient monocular blindness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine with aura</td>
<td>CNS infections</td>
<td>Detached retina</td>
</tr>
<tr>
<td>Seizure with Todd’s Paresis</td>
<td>Encephalitis/brain abscess</td>
<td>Amaurosis related to malignant hypertension</td>
</tr>
<tr>
<td>Structural abnormalities</td>
<td>Metabolic disorders</td>
<td>Central retinal vein thrombosis</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>(particularly hypoglycaemia)</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Cerebrovascular malformation</td>
<td>Peripheral vertigo</td>
<td>Acute glaucoma</td>
</tr>
<tr>
<td>Subdural haematoma</td>
<td>Ménière’s disease</td>
<td>Intracranial hypertension</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Benign positional vertigo</td>
<td></td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>Vestibular neuritis</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Mononeuropathy/Radiculopathy</td>
<td>Hyperventilation syndrome</td>
<td></td>
</tr>
<tr>
<td>Periodic paralysis</td>
<td>Hysteria.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychosomatic disorders</td>
<td></td>
</tr>
</tbody>
</table>
Table 1.4 Focal Neurological and Ocular Symptoms (Hankey 2002)

Motor symptoms
- Weakness or clumsiness of one side of the body, in whole or in part (Hemiparesis)
- Simultaneous bilateral weakness (Paraparesis, Quadriparesis)
- Difficulty swallowing (Dysphagia)
- Imbalance (Ataxia)

Speech or language disturbance
- Difficulty understanding or expressing spoken language (Dysphasia)
- Difficulty reading (Dyslexia) or writing (Dysgraphia)
- Difficulty calculating (Dyscalculia)
- Slurred speech (Dysarthria)

Sensory symptoms
- Altered feeling on one side of the body, in whole or in part (Hemisensory disturbance)

Visual symptoms
- Loss of vision in one eye, in whole or in part (Transient monocular blindness or Amarosis fugax)
- Loss of vision in the left or the right half or quarter of the visual field (Hemianopia, quadrantanopia)
- Bilateral blindness
- Double vision (Diplopia)

Vestibular symptoms
- A spinning sensation (Vertigo)

Consideration also needs to be given to common, non-specific, neurological complaints such as dizziness, isolated vertigo, pre-syncope, syncope, and confusion. These symptoms should not be deemed to be a TIA without other substantiating evidence (Flaherty and Brown Jr 2004). For example, one population based study in Texas reviewed 1,297 patients over the age of 44 years that presented with isolated dizziness. They found only 0.7% of cases were due to TIA/stroke (Kerber, Brown et al. 2006). Their multivariate logistic regression analysis showed a negative association between isolated dizziness and
TIA/stroke (odds ratio (OR) 0.05, 95% CI 0.02 – 0.11). Other non-focal neurological signs which are not neuro-anatomically localizing are outlined in more detail in Table 1.5.

**Table 1.5 Non Focal Neurological Symptoms (Hankey 2002)**

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised weakness</td>
</tr>
<tr>
<td>Light-headedness</td>
</tr>
<tr>
<td>Faintness</td>
</tr>
<tr>
<td>“Blackouts” with altered or loss of consciousness or fainting, with or without impaired vision in both eyes</td>
</tr>
<tr>
<td>Incontinence of urine or faeces</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Any of the following if isolated*</td>
</tr>
<tr>
<td>- A spinning sensation (Vertigo)</td>
</tr>
<tr>
<td>- Ringing in the ears (Tinnitus)</td>
</tr>
<tr>
<td>- Difficulty swallowing (Dysphagia)</td>
</tr>
<tr>
<td>- Slurred speech (Dysarthria)</td>
</tr>
<tr>
<td>- Double vision (Diplopia)</td>
</tr>
<tr>
<td>- Loss of balance (Ataxia)</td>
</tr>
</tbody>
</table>

*If these symptoms occur in combination, or with focal neurological symptoms they may indicate focal cerebral ischaemia.

There is a vast array of neurological symptoms that can occur as a result of a TIA, some of these symptoms are clear cut and allow clinico-anatomical correlation with the affected region of brain (see Table 1.4). Other non-specific symptoms may be of clinical relevance depending on the clinical scenario (see Table 1.5). It is up to the treating doctor to piece together the jigsaw puzzle of patient symptoms in order to see the overall picture and correctly diagnose a TIA, which is not always an easy task. This issue of difficulty in trying to correctly diagnose patients with TIA can also cause problems when trying to determine the incidence of TIA.
1.4 Epidemiology of TIA

There are many obstacles in the path of determining the true incidence of TIAs. The first is that the diagnosis of TIA is purely clinical, based upon the patient’s recollection of events and the treating doctor’s interpretation of those events. This results in inter-observer diagnostic variability as seen in both community-based cohorts where the diagnosis of TIA was found to be correct in only 19 – 38% of patients (Dennis, Bamford et al. 1989; Ferro, Falcao et al. 1996; Whitehead, Mc Manus et al. 2005) and in 13 – 94% of ED referrals in hospital-based cohorts (Ferro, Falcao et al. 1996; Johnston, Gress et al. 2000) (see Table 1.6).

Another difficulty carrying out TIA incidence studies is distinguishing between patients with TIA and stroke. This is due to the fact that both present with the same symptoms and signs, with the distinguishing factor being simply the duration of the focal neurological symptoms. Studies have shown that 5 – 50% of patients referred to TIA studies are ultimately diagnosed as a stroke (see Table 1.6) (Ferro, Falcao et al. 1996; Sempere, Duarte et al. 1996; Martin, Young et al. 1997; Whitehead, Mc Manus et al. 2005; Lavallée, Meseguer et al. 2007).

The lack of public awareness of the symptoms and signs of TIA also hinders TIA incidence studies, as shown in a nationwide telephone survey of adults in the USA in which over 90% of the population could not correctly identify any symptoms of a TIA (Johnston, Fayad et al. 2003). This appears to be a global phenomenon as 15 – 20% of both the Australian and Northwest Indian population cannot name any signs of stroke (Pandian, Jaison et al. 2005; National Stroke Foundation 2006). Similarly, in a UK survey which asked people what they would do if they experienced “Numbness or paralysis in one arm or leg, perhaps blurred vision and confusion, and maybe slurring of your speech, lasting possibly a few hours but gone away completely and feeling normal the next day;” 60% said they would go to or call their GP, 30% replied they would call an ambulance or go to hospital, and 10% replied they would ignore it or phone a friend (National Audit Office 2004). Although these proportions did not vary by ethnicity or region, men were more likely to ignore symptoms than women, and older people were less likely to say they would call an ambulance than younger people.
### Table 1.6 Inter-observer Differences in Diagnosis of TIA

<table>
<thead>
<tr>
<th>Study</th>
<th>Referral source</th>
<th>No of patients referred</th>
<th>Confirmed TIA n (%)</th>
<th>Confirmed stroke n (%)</th>
<th>Other diagnosis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Dennis, Bamford et al. 1989)</td>
<td>GP</td>
<td>512</td>
<td>195 (38%)</td>
<td>0</td>
<td>317 (62%)</td>
</tr>
<tr>
<td>(Whitehead, Mc Manus et al. 2005)</td>
<td>GP</td>
<td>372</td>
<td>121 (32.5%)</td>
<td>84 (22.5%)</td>
<td>130 (35%)</td>
</tr>
<tr>
<td>(Sempere, Duarte et al. 1996)</td>
<td>GP &amp; ED</td>
<td>325</td>
<td>103 (32%)</td>
<td>132 (40%)</td>
<td>90 (28%)</td>
</tr>
<tr>
<td>(Martin, Young et al. 1997)</td>
<td>GP &amp; ED</td>
<td>508</td>
<td>200 (39%)</td>
<td>136 (27%)</td>
<td>172 (34%)</td>
</tr>
<tr>
<td>(Correia, Silva et al. 2006)</td>
<td>GP &amp; ED</td>
<td>1,229</td>
<td>130 (11%)</td>
<td>0</td>
<td>1,099 (89%)</td>
</tr>
<tr>
<td>(Lavallée, Meseguer et al. 2007)</td>
<td>GP, ED &amp; other non-stroke specialists</td>
<td>1,085</td>
<td>787 (73%)</td>
<td>58 (5%)</td>
<td>240 (22%)</td>
</tr>
<tr>
<td>(Ferro, Falcao et al. 1996)</td>
<td>GP</td>
<td>52</td>
<td>10 (19%)</td>
<td>26 (50%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>31</td>
<td>4 (13%)</td>
<td>10 (32%)</td>
<td>17 (55%)</td>
</tr>
<tr>
<td>(Johnston, Gress et al. 2000)</td>
<td>ED</td>
<td>1,707</td>
<td>1,611 (94%)</td>
<td>0</td>
<td>96 (6%)</td>
</tr>
</tbody>
</table>

Worryingly, lack of recognition of the serious nature of stroke symptoms has been shown in one study to be the most common cause for delay in seeking medical evaluation, even amongst patients with a personal history of stroke (Williams, Bruno et al. 1997). This shows the ongoing, important role that public education has to play in this area, given that some patients may not seek any medical attention as they may not recognise the importance of
having these transient symptoms investigated and treated, so as to reduce their risk of future stroke.

Despite these obstacles, one of the earlier TIA incidence studies carried out in Rochester, Minnesota from 1955 – 1969 found the age and sex adjusted incidence for TIA to be 33/100,000 population and that the incidence increased sharply with age (Whisnant, Matsumoto et al. 1973). A more recent study from the same site from 1985 – 1989 showed a much higher age and sex matched incidence of 68/100,000 population (Brown Jr, Petty et al. 1998), which is in keeping with incidence rates shown in other studies around the World which vary from 18 – 110/100,000 population as shown in Table 1.7 (Whisnant, Matsumoto et al. 1973; Zupping and Roose 1976; Ueda, Kiyohara et al. 1987; Terént 1988; Dennis, Bamford et al. 1989; Ricci, Celani et al. 1991; Sempere, Duarte et al. 1996; Brown Jr, Petty et al. 1998; Lemesle, Madinier et al. 1998; Feigin, Shishkin et al. 2000; Somerford P and Gawthorne G 2002; Kleindorfer, Panagos et al. 2005; Rothwell, Coull et al. 2005; Correia, Silva et al. 2006; Edlow, Kim et al. 2006).

The incidence figures obtained in the earlier Rochester study were later shown to have underestimated the true incidence of TIA from as little as 23% to as much as 131% (Whisnant, Melton et al. 1990; Brown Jr, Petty et al. 1998). This was due to methodological issues regarding case ascertainment as a result of the diagnosis coding system that was used at that time, the Berkson code, which allowed non-specific diagnoses to be used for TIA, such as “spasms” and “insufficiency.” After 1961 most patients with TIA were coded as “ischaemic brain disease or attack,” but the more general terms still had to be screened for. The coding system was changed to the International Classification of Diseases in 1975 which enabled more specific diagnostic coding of TIA. Given that TIA is a clinical diagnosis, the diagnostic accuracy is dependant upon both the experience and skill of the person interpreting the patient’s symptoms and the patient’s ability to recall the episode in detail, consequently, it is likely that some cases were missed or coded with a general term, not specifically indicative of ischaemia, e.g. paraesthesia of the extremities. In addition, patients who presented with a stroke with a history of a preceding TIA (where the TIA was not recorded as a separate diagnosis) were also missed.
<table>
<thead>
<tr>
<th>Location</th>
<th>Time Period</th>
<th>Mean Age</th>
<th>Study Type</th>
<th>Case No.</th>
<th>Incidence rate (crude unadjusted by age/100,000 population)</th>
<th>Age/sex adjusted Incidence rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester, Minnesota</td>
<td>1955-1969</td>
<td>NR</td>
<td>Population Based Registry</td>
<td>198</td>
<td>31 31 31</td>
<td>33**</td>
</tr>
<tr>
<td>Rochester Minnesota (Brown et al.)</td>
<td>1985-1989</td>
<td>NR</td>
<td>Population Based Registry</td>
<td>202</td>
<td>68 54 61</td>
<td>68**</td>
</tr>
<tr>
<td>Estonia, USSR (Zupping and Roose)</td>
<td>1970-1973</td>
<td>NR</td>
<td>Population Based Registry</td>
<td>119</td>
<td>36 33 33</td>
<td>37**</td>
</tr>
<tr>
<td>Hishiya, Japan (Ueda et al.)</td>
<td>1961-1981</td>
<td>71.6+/-8.5</td>
<td>Population Based Registry</td>
<td>18</td>
<td>78 38 56</td>
<td>22**</td>
</tr>
<tr>
<td>Söderham, Sweden (Terent)</td>
<td>1975-1978</td>
<td>♂67.7, ♀66.7</td>
<td>Population Based Registry</td>
<td>44</td>
<td>43 48 NR</td>
<td>33**</td>
</tr>
<tr>
<td></td>
<td>1983-1986</td>
<td>♂71.2, ♀75.0</td>
<td>Population Based Registry</td>
<td>53</td>
<td>56 45 NR</td>
<td>38**</td>
</tr>
<tr>
<td>Oxfordshire, England (Dennis)</td>
<td>1981-1986</td>
<td>69.4 Range; 20-100</td>
<td>Population Based Registry</td>
<td>184</td>
<td>39 31 35</td>
<td>36**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbria, Italy (Ricci)</td>
<td>1986-1989</td>
<td>69.4+/-10. Range: 46-91</td>
<td>Population Based Registry</td>
<td>94</td>
<td>63 65 64</td>
<td>42***</td>
</tr>
<tr>
<td>Segovia, Spain (Sempere)</td>
<td>1992-1994</td>
<td>71.8</td>
<td>Population Based Registry</td>
<td>103</td>
<td>42 29 35</td>
<td>21***</td>
</tr>
<tr>
<td>Location</td>
<td>Time Period</td>
<td>Mean Age (Years)</td>
<td>Study Type</td>
<td>Case No.</td>
<td>Incidence rate (crude unadjusted by age/100,000 population)</td>
<td>Age/sex adjusted Incidence rate/100,000</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------</td>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------</td>
<td>-------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Dijon, France (Lemesle, Madinier et al. 1998)</td>
<td>1990-1994</td>
<td>♂ 70.35 ♀ 71.75</td>
<td>Population Based Prospective Registry</td>
<td>258</td>
<td>38.6 32.7 36</td>
<td>NR</td>
</tr>
<tr>
<td>Novosibirsk, Russia (Feigin, Shishkin et al. 2000)</td>
<td>1987-1988</td>
<td>♂ 62.3+/-11.4</td>
<td>Population Based</td>
<td>122</td>
<td>17 15 16</td>
<td>18*</td>
</tr>
<tr>
<td></td>
<td>1996-1997</td>
<td>♀ 66.5+/-11.2</td>
<td>Prospective Registry</td>
<td>89</td>
<td>25 32 29</td>
<td>31*</td>
</tr>
<tr>
<td>Western Australia (Somerford and Gawthorne 2002)</td>
<td>1989-1998</td>
<td>NR</td>
<td>Hospital-based Retrospective Registry</td>
<td>6,689</td>
<td>50 36 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Oxford Vascular Study (Rothwell, Coull et al. 2005)</td>
<td>2002-2004</td>
<td>Population Based Prospective Registry</td>
<td>181</td>
<td>45 89 66</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Cincinnati/ Northern Kentucky (Kleindorfer, Panagos et al. 2005)</td>
<td>1993-1994</td>
<td>70.4+/-12.6</td>
<td>Population Based Prospective Registry</td>
<td>927</td>
<td>NR NR NR</td>
<td>83†</td>
</tr>
<tr>
<td>Rural &amp; Urban Northern Portugal (Correia, Silva et al. 2006)</td>
<td>1998-2000</td>
<td>69.9</td>
<td>Population Based Prospective Registry</td>
<td>141</td>
<td>66 69 67</td>
<td>67***</td>
</tr>
<tr>
<td>American National Hospital Ambulatory care Survey. (Edlow, Kim et al. 2006)</td>
<td>1992-2001</td>
<td>NR</td>
<td>Hospital-based Retrospective Registry</td>
<td>769†</td>
<td>130 90 110</td>
<td>NR</td>
</tr>
</tbody>
</table>

† 769 cases were representative of 2,969,000 ED visits for TIA during the 10 year period. * Age and sex adjusted to 1980 US white population, per 100,000 population. **Age and sex adjusted to the 1981 population of England and Wales. ***Age and sex adjusted to European population. †Age, race and sex adjusted to 1990 US population, per 100,000 population. NR = Not reported
A cohort study in Rochester from a similar time frame, 1960 – 1972, without these methodological issues showed incidence rates comparable to that of more recent data (Whisnant, Melton et al. 1990).

The lowest reported incidence was found in a population-based, prospective, registry study performed in Russia during 2 separate time periods over a decade (Feigin, Shishkin et al. 2000). This showed an age and sex adjusted (using 1980 US white population) incidence of TIA of 18/100,000 population in their 1987 – 1988 cohort, which increased to 31/100,000 population in their 1996 – 1997 cohort. This increase did not reach statistical significance and was most prominent in the ≥ 75 year old age group. The authors attributed the low incidence found in their study to the small proportion of patients ≥ 65 years (7.5%). Given that the incidence of TIA increases sharply with age this would seem to be a likely explanation.

One of the highest overall age, race, and sex adjusted incidence rate for TIA of 83/100,000 was found by Kleindorfer et al in the Greater Cincinnati/Northern Kentucky Stroke Study carried out from July 1993 – June 1994 (Kleindorfer, Panagos et al. 2005). This increased incidence rate is likely due to two factors. The first is the inclusion of a much higher proportion of blacks in this study, comprising 15.2% of the study population. They found that blacks had a significantly higher overall incidence of TIA compared to whites, with the highest incidence of TIA of any group seen in elderly black males (≥ 85 years of age), at 1,558 events per 100,000 population, compared to 719 events per 100,000 population in the same age group for white males. The second factor is that unlike the other incidence studies, they included both first ever TIAs and recurrent TIAs (where the previous TIA occurred outside the study time period). Other than during the second study period of the Swedish incidence study (Terent 1988), all other incidence studies included only first ever TIAs, thus potentially explaining the higher incidence rate of TIA found in the Kleindorfer study.

The highest incidence rate was found by Edlow et al in their hospital-based, retrospective study carried out over a 10 year period from 1992 – 2001 (Edlow, Kim et al. 2006). They conducted a secondary analysis of the National Hospital Ambulatory Medical Care Survey
(NHAMCS) looking at the incidence and management of TIA patients in this cohort. The NHAMCS database is a cross-sectional survey representing estimates for 974 million ED visits during the 10 year period. It surveyed non-institutional, general, and short stay hospitals across the US (excluding federal, military, and Veteran Affairs hospitals). Data with regard to all ED visits was collected for a randomly assigned 4 week period each year for 10 years in each of the selected hospitals. During this time data was collected on 769 actual TIA cases representative of 2,969,000 ED visits for TIA over the 10 year period. They found an overall incidence rate for TIA of 110/100,000 US population. The study also showed a statistically significant increase in the incidence of TIA with age, with an incidence of 10/100,000 for those aged less than 50 years, and an incidence of 1,170/100,000 for those aged ≥ 80 years. A potential explanation for the higher TIA incidence is the hospital-based setting of this study as TIAs account for 0.3% of all ED visits (Edlow, Kim et al. 2006) compared to 0.1% of all visits in a general practice setting (Senes and Britt 2001). The higher TIA incidence found in this study may be a more accurate prediction of the true incidence of TIA.

The only Australian data on TIA incidence is from a 10 year study in Western Australia which looked at the first ever hospitalisation incidence for acute cerebrovascular disease from 1989 to 1998 (Sommerford, Gawthorne et al. 2002). In this study there was an annual rate of first ever hospitalisation for TIA of 50/100,000 for males and 36/100,000 for females. In both sexes the rate increased with age from 1.9/100,000 for males under the age of 45 years to 556/100,000 for males over the age of 75 years. Similarly in females the incidence increased from 1.8/100,000 under the age of 45 years to 431/100,000 for females over the age of 75 years. These figures likely underestimate the true incidence of TIA as this study reviewed rates of hospitalization only, whereas many patients may present to their GP instead of to a hospital or may not seek any medical attention at all, leaving themselves at increased risk of a subsequent stroke.
1.5 Risk of Subsequent Stroke

It has long been recognized that a TIA can be an early warning of a potential stroke in the near future. This was noted as early as 1884 in the writings of RJ Graves where he describes: “Attacks of hemiplegia, in every respect complete, and depriving him of the use of his speech. Some of these attacks lasted only fifteen minutes, while the longest continued about an hour and a half: they ceased as suddenly as they commenced, and left no traces of hemiplegia behind them. I have carefully watched the progress of several cases, which after months and years have finally terminated in hemiplegia” (Graves 1884).

Until recently it has been presumed that the risk of stroke following TIA is reasonably low, with the percentage risk being quoted as 1 – 2% at 7 days and 2 – 4% at 1 month (Hankey 1996). However, more recent studies have shown that this risk is much higher than previously anticipated, with the 90 day stroke risk following TIA ranging from 6 – 15% (Whisnant, Matsumoto et al. 1973; Johnston, Gress et al. 2000; Coull, Lovett et al. 2004; Gladstone, Kapral et al. 2004; Hill, Yiannakoulias et al. 2004; Kleindorfer, Panagos et al. 2005; Bray, Coughlan et al. 2007). Given this much higher risk of stroke following TIA and evidence which shows that this risk is heavily time dependent, with up to 50% of subsequent strokes occurring within the first 48 hours following TIA (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004; Sciolla and Melis 2008) (see Table 1.8), urgent investigation and management of all patients with TIA is very important. In an ideal situation all patients with TIA would undergo all necessary investigations at the time of their presentation. However, in many clinical settings this is difficult to achieve, largely due to restrictions faced within the relevant healthcare system limiting urgent access to the necessary investigations and appropriate specialists for outpatient management. Consequently, methods to identify those at highest risk of subsequent stroke are of benefit to try and identify those patients at highest risk so they can be urgently investigated versus those at lower risk who could afford to wait to have their investigations performed over the following week. One such method to risk stratify patients with TIA is the use of a prognostic scoring system.
Table 1.8 Risk of Stroke Following TIA at Selected Time Intervals

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with TIA at follow-up</th>
<th>2 days n (%)</th>
<th>7 days n (%)</th>
<th>30 days n (%)</th>
<th>90 days n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population Based Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Whisnant et al 1973</td>
<td>198</td>
<td>NR</td>
<td>NR</td>
<td>15(7.6%)</td>
<td>20(10%)</td>
</tr>
<tr>
<td>• Dennis et al (OCSP) 1990*</td>
<td>184</td>
<td>NR</td>
<td>NR</td>
<td>8(4.4%)</td>
<td>NR</td>
</tr>
<tr>
<td>• Coull et al (Oxford Vascular Study) 2004</td>
<td>82</td>
<td>NR</td>
<td>6(7.2%)</td>
<td>7(8.4%)</td>
<td>10(13%)</td>
</tr>
<tr>
<td>• Hill et al 2004 **</td>
<td>2,285</td>
<td>32(1.4%)</td>
<td>NR</td>
<td>153(6.7%)</td>
<td>217(9.5%)</td>
</tr>
<tr>
<td>• Kleindorfer et al 2005</td>
<td>927</td>
<td>36(3.9%)</td>
<td>65(7%)</td>
<td>104(11%)</td>
<td>135(14.6%)</td>
</tr>
<tr>
<td>• Correia et al 2006***</td>
<td>141</td>
<td>14(9.9%)</td>
<td>18(12.8%)</td>
<td>25(17.7%)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Hospital-based Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Johnston et al 2000</td>
<td>1,707</td>
<td>91(5%)</td>
<td>NR</td>
<td>NR</td>
<td>180(10.5%)</td>
</tr>
<tr>
<td>• Gladstone et al 2004</td>
<td>265</td>
<td>7(3%)</td>
<td>10(4%)</td>
<td>13(5%)</td>
<td>17(6%)</td>
</tr>
<tr>
<td>• Tsivgoulis et al 2006</td>
<td>226</td>
<td>NR</td>
<td>18(8%)</td>
<td>22(9.7%)</td>
<td>NR</td>
</tr>
<tr>
<td>• Bray et al 2007</td>
<td>98</td>
<td>3(3.1%)</td>
<td>4(4.1%)</td>
<td>NR</td>
<td>7(7.1%)</td>
</tr>
<tr>
<td>• Purroy et al 2007</td>
<td>345</td>
<td>NR</td>
<td>17(4.9%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>• Sciolla et al 2008</td>
<td>274</td>
<td>2.55%</td>
<td>3.6%</td>
<td>5.5%</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: Not Reported

*OCSP: Oxfordshire Community Stroke Project. There was an average 3 day interval between index TIA and enrollment, thus potentially missing early events (Dennis, Bamford et al. 1990).

**Day 1 events excluded from analysis

***Higher risk of early subsequent stroke may be partially explained by the inclusion of 4 retrospectively identified cases of TIA (2.8%), having subsequently presented with a stroke shortly following the TIA. The other studies excluded TIA cases identified in this manner.
1.6 Prognostic Scoring Systems to Predict Risk of Subsequent Stroke

Patients with TIA are a highly heterogeneous group in terms of risk factors, underlying pathology, and prognosis. As a result, models to stratify risk of subsequent stroke have been developed to try and identify those patients at highest risk.

Johnston and his group identified 5 factors that were independently associated with 90 day risk of stroke within their hospital-based cohort of TIA patients: age greater than 60 years (OR, 1.8; 95% CI 1.4 – 2.9%), motor weakness (OR 1.9; 95% CI 1.4 – 2.6%), speech impairment (OR 1.5; 95% CI 1.1 – 2.1%), symptom duration greater than 10 minutes (OR 2.3; 95% CI 1.3 – 4.2%) and diabetes mellitus (OR 2.1; 95% CI 1.1 – 2.7%) (Johnston, Gress et al. 2000). When used in combination, these 5 factors allowed identification of subgroups with a spectrum of 90 day risk of subsequent stroke ranging from 0% (in those who had no risk factors) to 34% (if all 5 risk factors were present).

This prognostic model was expanded upon by Rothwell and colleagues to create the “ABCD” score to predict the risk of stroke during the first 7 days following TIA (Rothwell, Giles et al. 2005). The score was derived using their Oxford Community Stroke Project cohort and included hypertension, as this had been found predictive of 90 day risk of stroke in a population based study in Alberta, Canada (Hill, Yiannakoulia et al. 2004). The score was subsequently validated in 2 independent cohorts: 2 cohorts from the Oxford Vascular Study and a cohort of non-study patients in Oxfordshire that were referred to a hospital-based TIA clinic (Rothwell, Giles et al. 2005). They found neither a history of diabetes mellitus nor hypertension were predictive of 7 day risk of subsequent stroke, but hypertension on presentation was predictive of subsequent stroke (p value = 0.002). The resultant “ABCD” score, with a maximum score of 6, is outlined in Table 1.9. The study showed an overall 7 day risk of subsequent stroke of approximately 5%. However, this varied according to the ABCD score: 0.4% (95% CI 0 – 1.1%) for an ABCD score < 5; 12.1% (95% CI 4.2 – 20%) for an ABCD score of 5; and 31.4% (95% CI 16.0 – 46.8%) for an ABCD score of 6 (Rothwell, Giles et al. 2005).
**Table 1.9 ABCD Score to Predict 7 Day Risk of Stroke Following TIA**  
(Rothwell, Giles et al. 2005)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥ 60 years</strong></td>
<td>1</td>
<td>2.57 (0.75 – 8.81%)</td>
<td>0.133</td>
</tr>
<tr>
<td><strong>BP at presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥ 140mmHg and/or Diastolic BP ≥ 90mmHg</td>
<td>1</td>
<td>9.67 (2.23 – 41.94%)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2</td>
<td>6.61 (1.53 – 28.5%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Speech disturbance without weakness</td>
<td>1</td>
<td>2.59 (0.50 – 13.56%)</td>
<td></td>
</tr>
<tr>
<td>Other symptoms</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60 minutes</td>
<td>2</td>
<td>6.17 (1.43 – 26.62%)</td>
<td>0.019</td>
</tr>
<tr>
<td>10-59 minutes</td>
<td>1</td>
<td>3.08 (0.640 – 14.77%)</td>
<td></td>
</tr>
<tr>
<td>&lt;10 minutes</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

By combining these 2 scoring systems a unified “ABCD²” score was created, which has the same components as the ABCD score, with an additional point for diabetes mellitus (Johnston, Rothwell et al. 2007). This refined 7 point score proved to be a more accurate predictor than either of the previous scores in both derivation groups, performed better in the validation groups, and allowed the prediction of subsequent stroke risk at 2 days, 7 days, and 90 days post TIA (see Table 1.10).
Table 1.10 ABCD² Score and Risk of Stroke Following TIA (Johnston, Rothwell et al. 2007)

<table>
<thead>
<tr>
<th>ABCD² Score</th>
<th>2 day risk</th>
<th>7 day risk</th>
<th>90 day risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>8.1%</td>
<td>11.7%</td>
<td>17.8%</td>
</tr>
<tr>
<td>4-5</td>
<td>4.1%</td>
<td>5.9%</td>
<td>9.8%</td>
</tr>
<tr>
<td>0-3</td>
<td>1.0%</td>
<td>1.2%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

These scores have the potential to assist front-line physicians to identify those at highest risk of subsequent stroke, so as to enable urgent assessment. One of the benefits of the ABCD or ABCD² prognostic scoring systems is their simplicity; they do not require any specialised training to use, and are based on patient history and clinical features which can be quickly assessed at the bedside to calculate a score. They are primarily aimed to be used by those who are the first point of contact for patients with TIA, which is usually an emergency physician or GP, but almost never a neurologist (Morgenstern, Lisabeth et al. 2004). However, independent validation studies of both the ABCD and ABCD² prognostic scoring systems have shown mixed results (see Table 1.11).

1.7 Validation of the “ABCD” and “ABCD²” Prognostic Scoring Systems

Both the ABCD and ABCD² scores have received criticism as being sub-optimal at predicting the risk of subsequent stroke in some studies. One hospital-based, prospective study in North America of 117 patients with TIA found the predictive value of the ABCD score to be sub-optimal for predicting their primary outcome event, in particular for those in the low to moderate risk groups (Cucchiara, Messe et al. 2006). However, the outcome measure chosen by Cucchiara et al was the dichotomization of patients into high and low-risk categories rather than solely looking at the risk of subsequent stroke, which is what the score aims to predict (Rothwell, Giles et al. 2005). This study defined high-risk patients as not only those with stroke or death within 90 days, but also those with ≥ 50% stenosis in a vessel referable to symptoms, or cardio-embolic source warranting anticoagulation.
Table 1.11 Validation Studies for ABCD Prognostic Scoring System to Identify those at High-risk of Stroke Following TIA

<table>
<thead>
<tr>
<th>Study</th>
<th>Found ABCD useful</th>
<th>Days post-TIA</th>
<th>No of Subsequent stroke for each ABCD score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Tsivgoulis, Spengos et al. 2006)</td>
<td>Yes</td>
<td>7</td>
<td>0/5  0/12  0/22  1/58  2/58  2/21  0/15  3/28  0/19  1/20  4/98  22/226</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>0/5  0/12  0/22  1/58  2/58  2/21  0/15  3/28  0/19  1/20  4/98  22/226</td>
<td></td>
</tr>
<tr>
<td>(Bray, Coughlan et al. 2007)</td>
<td>Yes</td>
<td>7</td>
<td>0/1  0/6  0/7  0/21  0/15  3/28  1/11  5/20  4/20  7/98</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>0/1  0/6  1/7  14.3%  0/21  0/15  3/28  1/11  5/20  4/20  7/98</td>
<td></td>
</tr>
<tr>
<td>(Sciolla and Melis 2008)</td>
<td>Yes</td>
<td>7</td>
<td>0/0  0/8  0/27  0/41  2/84  4/74  2.4%  5.4%  4/40  10/274</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>0/0  0/0  0/0  0/0  3/84  0/674  0/3.6%  8.1%  6/40  15/274</td>
<td></td>
</tr>
<tr>
<td>(Cucchiara, Messe et al. 2006)*</td>
<td>No</td>
<td>90</td>
<td>0/0  0/8  0/13  1/23  0/44  0/19  1/10  1/10  2/117</td>
<td></td>
</tr>
<tr>
<td>(Purroy, Molina et al. 2007)</td>
<td>No</td>
<td>7</td>
<td>0/0  1/15  3/49  3/55  3/103  5/90  6.7%  6%  5.5%  2/33  17/345</td>
<td></td>
</tr>
</tbody>
</table>

*Median time to enrollment was > 24 hours post TIA, thus potentially missing TIA patients with a subsequent stroke within the first 24 hours.
Additionally, they had a low number of strokes in their study 2/117 (1.7%), which may be attributable to their study design. The median time to enrolment was > 24 hours, which potentially missed any strokes that may have occurred during the first 24 hours post-TIA. Thus, if this study were to look at the ABCD score in its primary role of aiming to predict risk of stroke following TIA, the small number of strokes in this study does not lend itself to a statistically meaningful result, and neither supports nor refutes the usefulness of the ABCD score.

Interestingly, following this study Rothwell and colleagues reviewed the data from the Oxford Vascular Study cohort, and found that whilst there was no clear relationship between either the ABCD or ABCD² scores and the prevalence of Atrial Fibrillation or ≥ 50% carotid artery stenosis, that both prognostic scoring systems appeared to identify patients with these risk factors at high-risk of stroke, but due to the small numbers in these subgroups further validation was required (Koton and Rothwell 2007).

A hospital-based study from Spain, without the methodological issues of the previous study and with a higher proportion of the primary outcome event of subsequent stroke (17/345, 4.9%), found the ABCD score to have poor predictive value (Purroy, Molina et al. 2007). They prospectively assessed 345 consecutive TIA patients who presented to ED and found 17/345 (4.9%) patients suffered a stroke within 7 days of their index TIA, of which 7 patients had an ABCD score ≥ 5 giving a 7 day risk of subsequent stroke of 5.7%. The other 10 patients had an ABCD score < 5, thus making them low-moderate risk according to the ABCD score, yet their actual 7 day risk of subsequent stroke turned out to be quite high at 4.5%.

Another hospital-based, retrospective study in Canada also found the ABCD score predicted risk of subsequent stroke relatively poorly in their cohort of 525 patients with TIA (Sylaja, Choi et al. 2007). However, details regarding the ABCD scores of those patients who suffered a subsequent stroke were not provided by the authors. Interestingly, 75% of this cohort was managed as inpatients, with the remaining 25% managed as outpatients. Inpatients were more likely to have weakness, carotid disease, baseline National Institute of Health Stroke Score (NIHSS) > 1, lower glucose and a higher ABCD.
score. The 90 day risk of stroke was lower for those managed as an inpatient (5.6%) compared to those managed as an outpatient (6.8%); however, this did not reach statistical significance (p = 0.666).

There have also been a number of studies which have found in favour of the predictive value of the ABCD and ABCD² scores. The validation study with the highest number of strokes following TIA was a hospital-based, retrospective review over a 4 year period from 2000 to 2004 of 226 consecutive patients with TIA in Greece, which found the ABCD score highly predictive of the risk of subsequent stroke (Tsivgoulis, Spengos et al. 2006). They found that after adjustment for stroke risk factors, history of previous TIAs, medication use before the index TIA, and secondary prevention strategies, an ABCD score of 5 to 6 was independently associated with an 8-fold increase in 30 day risk of stroke (hazard ratio 8.01, 95% CI 3.21 – 19.98). On their multivariate analysis an ABCD score of 5 – 6, hyper-cholesterolaemia, and diabetes mellitus were independent predictors of 30 day stroke risk.

Following the introduction of the ABCD² score, they calculated the ABCD² score for each of the 226 patients from their original cohort (Tsivgoulis, Vassilopoulou et al. 2007). They found the c-statistics (areas under receiver operator curves) were higher than for the ABCD score, although the confidence intervals overlapped; c statistics for the ABCD² score were 0.80 (95% CI 0.72 – 0.88%) and 0.81 (95% CI 0.73 – 0.89%) for risk of stroke at 7 days and 30 days respectively, compared to 0.77 (95% CI 0.68 – 0.86%) and 0.78 (95% CI 0.69 – 0.87%) for the same periods using the ABCD score. This study speaks to the slight superiority of ABCD² over ABCD.

An Australian, hospital-based, retrospective, validation study supported the prognostic scoring ability of the ABCD score (Bray, Coughlan et al. 2007). The authors dichotomised the ABCD score into high-risk (ABCD score ≥ 5) and low-risk (ABCD score ≤ 4). For their cohort of 98 consecutive patients with TIA during a 6 month period in 2004. The high-risk group contained all 4 strokes that occurred within 7 days of the incident TIA (see Table 1.11). In this study the ABCD score had 100% sensitivity (95% CI 40 – 100%), but the test specificity of 53% (95% CI 43 – 63%) and positive predictive value of only 8% (95% CI 3
– 21%) were less impressive, showing that the score was overly inclusive. However, over-
inclusion is preferable to under-inclusion, and a negative predictive value of 100% (95% CI
91 – 100%) is reassuring that the score does not have problems with false negatives. The
high-risk group also contained 6 of the 7 strokes that occurred during the 90 day follow-up
period. This study showed that dichotomising the ABCD score into high- and low-risk was
safe and effective.

A hospital-based, prospective, observational study in Northern Italy which found in favor
of the prognostic value of the ABCD score in predicting risk of subsequent stroke at 2, 7,
and 30 days post-TIA (Sciolla and Melis 2008), see Table 1.11. The diagnosis of TIA was
confirmed by the attending neurologist prior to enrolment. The study showed that the
higher the ABCD score the greater the risk of subsequent stroke, with ABCD scores of 4 to
6 being associated with a 4-fold increase in stroke risk at 7 and 30 days, and ABCD scores
of 5 to 6 being associated with a 6-fold increase in stroke risk at the same time intervals.
All of the 15/274 (5.5%) of patients in this study who suffered a subsequent stroke within
30 days of the index TIA had an ABCD score of ≥ 4, thus supporting the fact that scores of
< 4 carry a low-risk of subsequent stroke.

Two studies which utilised the ABCD² score found it to be of prognostic value. The first
study was a multicentre study (Selvarajah, Smith et al. 2008) involving five hospitals in
Greater Manchester and Liverpool. This study aimed to determine if the ABCD² score
maintained prognostic value when used within a more representative sample of NHS TIA
services, where delayed presentation of both TIA and minor stroke are common, rather than
under study conditions at Oxfordshire. Four of the hospitals had a weekly TIA clinic; the
fifth hospital had a twice weekly clinic. The low 90 day risk of subsequent stroke of 4% (n
= 29/709) found in this study is a likely reflection of the median delay between index TIA
or minor stroke and study entry of 15 days (range 0 – 42 days). This delay would result in
exclusion of any patients with a moderate-severe subsequent stroke within this time period
and is likely an underestimation of the true risk of subsequent stroke. They found the
ABCD² score useful in predicting risk of subsequent stroke as outlined in Table 1.12.
Table 1.12 Relationship Between ABCD² Score and Hazard Ratio for Subsequent Stroke (Selvarajah, Smith et al. 2008)

<table>
<thead>
<tr>
<th>ABCD² Score</th>
<th>No of Patients</th>
<th>Hazard Ratio for Subsequent Stroke (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>210</td>
<td>1.0</td>
</tr>
<tr>
<td>4-5</td>
<td>356</td>
<td>3.4 (1.0 – 12%)</td>
</tr>
<tr>
<td>6-7</td>
<td>145</td>
<td>4.8 (1.3 – 18%)</td>
</tr>
</tbody>
</table>

The second study was carried out in a French, hospital-based, specialist stroke service unit (Calvet, Touze et al. 2009). In their cohort of 339 consecutive patients with TIA patients they found the ABCD² score to be of benefit to predict those at risk of subsequent stroke at 90 days, with 9/10 (90%) of all strokes that occurred in the study at 90 days having an ABCD² score ≥ 4, of whom 8/9 (88.9%) had evidence of acute infarction on DWI.

The absolute risk of stroke found in this study for patients with an ABCD² score ≥ 4 was 2.5% (95% CI 0.4 – 4.7%) at 7 days and 4.4% (95% CI 1.7 – 7.1%) at 90 days. When a patient had an ABCD² score ≥ 4 and evidence of acute infarction on DWI the absolute risk of subsequent stroke increased to 5.4% (95% CI 0.9 – 9.9%) at 7 days and 9.7% (95% CI 3.6 – 15.8%) at 90 days, thus showing the ability of DWI to help identify those at high early risk of stroke post-TIA when added to the ABCD² score.

They also found that large artery atherosclerosis was an independent predictor of early risk of subsequent stroke. They defined large artery atherosclerosis as ≥ 50% stenosis or occlusion, presumably due to atherosclerosis, in the clinically relevant extra-cranial or intra-cranial artery. They found that patients with an ABCD² score ≥ 4, evidence of acute infarction on DWI, and large artery atherosclerosis were at highest risk of subsequent stroke, with a 7 day risk of subsequent stroke of 9.3% (95% CI 2.1 – 34.1%) and 90 day risk of subsequent stroke of 18.2% (95% CI 2.1 – 34.1%).

Overall, there have been more positive than negative validation studies for the ABCD and ABCD² prognostic scoring systems. In the study by Cucchiara et al (Cucchiara, Messe et al.
2006) the main reasons that the ABCD score performed poorly was because of the study’s definition of what they deemed to be high-risk (those whose outcomes included stroke or death within 90 days, ≥ 50% stenosis in a vessel referable to symptoms, or cardio-embolic source warranting anticoagulation). Yet the score was not designed to pre-empt the results of these investigations, but rather for use in primary care and ED settings to triage those who require immediate investigation versus investigation over the subsequent week in situations where access to these investigations is limited. The results of these investigations should then be used in conjunction with the ABCD/ABCD² score which may change patients previously deemed to be “low-risk” on the basis of their ABCD/ABCD² score into “high-risk patients” on the basis of this additional clinical data and treated accordingly.

The second study which found the ABCD prognostic score as suboptimal did keep with the original definition of high-risk as being that of a subsequent stroke following TIA (Purroy, Molina et al. 2007). However, given the positive results found in the other studies, with the majority of subsequent strokes occurring in patients with a higher ABCD/ABCD² score (as shown in Table 1.11), the ABCD score remains a reliable prognostic scoring system to predict those at high-risk of subsequent stroke post TIA. Whether these high-risk patients require inpatient versus outpatient management remains unclear.

1.8 Inpatient versus Outpatient Management of TIA

There is a lack of evidence to guide clinicians in deciding whether it is best to manage patients after a TIA as an inpatient or as an outpatient. Indeed the American Stroke Association guidelines for prevention of stroke in patients with ischaemic stroke and TIA are notable for the absence of guidance regarding when, if ever, admission is indicated for patients with TIA (Sacco, Adams et al. 2006). The UK guidelines (National Pre-hospital Guidelines Group 2006) recommend patients first seen in the community that have made a good recovery should be assessed and investigated in a specialist service as soon as possible and certainly within 7 days of the event or immediate hospital admission to a specialist stroke service for those with a greater than 20% risk of developing a completed stroke. The Australian guidelines (National Stroke Foundation 2007) recommend the use of the ABCD² prognostic scoring system to categorise patients into high- and low-risk
groups. They advise high-risk patients ($\text{ABCD}^2 \geq 4$) should be assessed within 24 – 48 hours either as an inpatient or outpatient, depending on local resources, and low-risk patients ($\text{ABCD}^2 < 4$) may be managed as an outpatient and reviewed within 7 – 10 days.

Given the high-risk of stroke following TIA of 6% to 15% (Whisnant, Matsumoto et al. 1973; Johnston, Gress et al. 2000; Coull, Lovett et al. 2004; Gladstone, Kapral et al. 2004; Hill, Yiannakoulas et al. 2004; Kleindorfer, Panagos et al. 2005; Bray, Coughlan et al. 2007) patients require urgent evaluation, in particular given this risk of subsequent stroke is heavily time dependent, with up to 50% of subsequent strokes occurring within the first 48 hours following TIA (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004; Sciolla and Melis 2008). If all patients with TIA could undergo all the necessary investigations at their time of presentation, the question of inpatient versus outpatient management would perhaps be redundant. An outpatient model of care that offers same day investigation has been shown to be effective at reducing the risk of stroke following TIA (Lavallée, Meseguer et al. 2007; Rothwell, Giles et al. 2007). However, this requires the organization and availability of all necessary resources and personnel to offer such timely service and in many clinical settings this is difficult to achieve, largely due to restrictions faced within the relevant healthcare system limiting urgent access to the necessary investigations and appropriate specialists for outpatient management.

Conversely, the limited availability of hospital beds may make admission to expedite investigation and management similarly difficult. Admission practices also vary depending upon the speed of outpatient access to investigations and specialist follow-up in each healthcare system and the treating clinician’s impression of stroke risk in each case. This variation in practice is reflected in the international guidelines as I will now outline.
1.8.1 The United States (US)

The United States (US) is the only wealthy, industrialized nation that does not have a universal health-care system (De Navas-Walt, Proctor et al. 2008). In 2007 the US government directly covered only 27.8% of the population through health-care programs for the elderly, disabled, military service families and veterans, children, and the poor (De Navas-Walt, Proctor et al. 2008). Federal law ensures public access to emergency services regardless of ability to pay. In 2007 67.5% of US citizens held private health insurance, this was either provided through an employer, a union, or purchased individually from a private company (De Navas-Walt, Proctor et al. 2008). It is interesting given this high proportion of the US population that hold private medical insurance that inpatient management for TIA patients seems to be more common in the US, as shown in a 10 year National US study on ED visits for TIA (Edlow, Kim et al. 2006). This study showed that 54% of all TIA patients were admitted to hospital for acute assessment and management. The authors found that this percentage remained constant over the 10 year duration of the study period, and was not affected by age, gender, race ethnicity, urban status or type of insurance. The only socio-demographic factor that played a role was geographical region with the highest rates of admission being 68% in the Northeast and the lowest being 41% in the West. This geographical variation may partly explain the much lower percentage of TIA patients that were admitted in the California based study of ED presentations with TIA (Johnston, Gress et al. 2000), where only 243/1,707 (14%) of patients with TIA were admitted.

The National Stroke Association selected a panel of 15 stroke experts from around the World to review the current available guidelines for the treatment of TIA, from which they compiled a unified set of guidelines for the management of TIAs (Johnston, Nguyen-Huynh et al. 2006). They give a broad spectrum of advice regarding whether a patient with TIA should be managed as an inpatient or an outpatient:

- Consider hospitalization in the first 24 to 48 hours to facilitate early deployment of lytic therapy and other medical management and to expedite institution of definitive secondary prevention.
- A timely hospital referral of recent (within 1 week) TIA is advisable and hospital admission is generally advised in the following scenarios:
- Crescendo TIAs
- Duration of symptoms greater than one hour
- Symptomatic carotid stenosis greater than 50%
- Known cardiac source of embolus such as atrial fibrillation
- Known hypercoagulable state
- Appropriate California score or ABCD score (however, there was no guidance with regard to what was deemed to be an appropriate California or ABCD score)

- A local admission policy should be developed to determine which patients should be admitted.
- A specialised clinic for the rapid assessment of TIA within 24 – 48 hours of diagnosis should be available.

1.8.2 The United Kingdom (UK)

The National Health Service (NHS) is the publicly funded healthcare system in the United Kingdom (UK). It was born in 1948 out of a long-held ideal that good healthcare should be available to all regardless of wealth. The NHS provides healthcare to anyone normally resident in the UK with most services free at the point of use for the patient. It provides a wide range of health services to the entire population including primary care, inpatient care, ophthalmology and dentistry (National Health Service 2010). The NHS is largely funded from national taxation and does not bill its services to either its patients or an insurance fund. Only approximately 10% of the UK population hold private health insurance (Smee 2000). Private care is usually for specialist referrals, with most people retaining their NHS GP as point of first contact (Association of British Insurers 2008). In the UK the number of general (mainly older patients) and acute patients admitted to hospital has increased steadily in recent years, whereas, the total number of general and acute hospital beds has fallen (NHS Executive 2000). This resulted in nearly 57,000 National Health System patients having their operations cancelled between Sept 1998 and 1999 due to bed shortages (NHS Executive 2000). Thus, outpatient management for patients with TIA is preferable, unless deemed to be at high-risk (National Pre-hospital Guidelines Group 2006).
The Royal College of Physicians National Pre-hospital Stroke Guidelines group published new guidelines on treating Stroke and TIAs in 2006 (National Pre-hospital Guidelines Group 2006), which is supplementary to the existing Royal College of Physicians National Clinical Guidelines for Stroke published in 2004 as compiled by the Intercollegiate Stroke Working Party. They recommend patients first seen in the community with TIA or stroke that have made a good recovery should be assessed and investigated in a specialist service (e.g. neurovascular clinic) as soon as possible and certainly within 7 days of the event. Patients are advised to return to hospital immediately if the symptoms return. Immediate admission to a specialist stroke service is recommended for those with a greater than 20% risk of developing a completed stroke (any one of the following categories):

- more than 1 TIA in 7 days
- ≥ 3 of the following characteristics; Blood pressure > 140/90 mmHg, unilateral weakness or speech disturbance, symptoms lasting 60 minutes or longer.
- History of diabetes

1.8.3 Australia

Australia has a combination of public and private health-care systems. Medicare is Australia’s public health-care system which, similar to the National Health Service (NHS) in the United Kingdom, provides a wide range of free health services to the entire population. It is nominally funded by an income tax surcharge called the Medicare levy, which is currently set at 1.5%, with exemption for low income earners. There is an additional Medicare levy surcharge of 1% for those on high annual incomes who do not have adequate levels of private hospital insurance coverage (Australian Taxation Office 2010), which is an effort by the Federal Government in Australia to encourage people towards private health insurance. Data collected from a survey of 56,344 people aged 14 and over across Australia during the period from Oct 2003 to Sept 2004 showed that the number of people who hold private insurance in Australia increases based upon income, with 24% of Australians living in households with incomes below $25,000 per year holding private insurance, compared to greater than 80% of individuals earning $130,000 or more per year (Denniss 2005). Public and private hospitals have different roles in the Australian
health-system, with public hospitals providing the majority of emergency services and private hospitals playing a larger role in elective admissions (Australian Government Department of Health and Ageing 2007). Public hospitals in Australia face a similar problem to the NHS with a reducing number of available beds across Australia and an increasing number of public-patient admissions (Australian Government Department of Health and Ageing 2007). In 2005 – 2006 people aged 65 years and over represented 13.2% of Australia’s population. This proportion is expected to increase to 25% by 2047. Given that 36% of all hospital admissions and 47% of occupied bed days were for people aged 65 and over in 2005 – 2006 (Australian Government Department of Health and Ageing 2007) the current bed shortages are likely to worsen. In Queensland alone it is anticipated that the number of hospital admissions will double over the next 15 years, due to the growing and ageing population and the increasing incidence of chronic disease (Australian Government Department of Health and Ageing 2007). Consequently, it is not surprising that outpatient management of low-risk patients with TIA and inpatient management of high-risk patients is preferable (National Stroke Foundation 2007).

The 2007 edition of the clinical guidelines for acute stroke management published by the National Stroke Foundation (NSF) of Australia (2007) acknowledges 3 separate models of acute assessment and their potential benefits and drawbacks:

1. Hospital admission.
   - Allows immediate access to thrombolysis should the patient deteriorate.
   - Increased likelihood of necessary diagnostic tests being carried out (e.g. carotid duplex).
   - Higher adherence to protocols and processes of care consistent with best practice stroke care, in particular if admitted to a stroke unit, rather than a conventional hospital ward (Cadilhac, Ibrahim et al. 2004).

2. Rapid TIA clinic.


Overall it was concluded that there is little evidence to suggest which method is most appropriate for the acute assessment of patients with TIA and given the geographical barriers posed by providing an optimal stroke service in a country the size of Australia, the
focus should be on rapid assessment and management of these patients in a manner tailored to match local resources. As a result they advise;

- All patients with suspected TIA require assessment and management within 24 – 48 hours of symptom onset.

- Utilization of the ABCD² prognostic scoring system allows categorization of patients into high- and low-risk groups.
  
  - High-risk patients (ABCD² > 4) should be admitted to a stroke unit (or referred to a specialist TIA clinic within 24 – 48 hours, if available) to facilitate rapid assessment and treatment.
  
  - Low-risk patients (ABCD² < 4) may be managed in the community by a general practitioner, private specialist, or referred to a specialist TIA clinic for review within 7 – 10 days.

1.9 Comparison of Inpatient and Outpatient Models of Care

Given the variation in practice and guideline recommendations as outlined above, best practice might be determined by considering the potential patient benefits and cost-effectiveness of inpatient versus outpatient management.

The benefits of hospital admission for TIA patients include:

1. *Expedited diagnostic evaluation:* When access to urgent outpatient services is limited and time is of the essence, as is the case with TIA, sometimes the only way to ensure the necessary investigations get done as soon as possible is to admit the patient to hospital. The UK guidelines recommend that all patients be assessed and investigated in a specialist service (e.g. a neurovascular clinic) as soon as possible and certainly within 7 days of the event. However, the 2006 National Sentinel Stroke Audit found that 22% of hospitals which treat stroke patients did not offer a TIA clinic and that the average waiting time was 12 days (range 7 – 17 days). Only 35% of UK hospitals were able to achieve the target of seeing, assessing, and managing patients within 7 days (Royal College of Physicians and Intercollegiate Stroke Working Party. 2007). Whilst there is no Australian data on waiting times
for clinic review of patients with TIA, given only 5% of Australian hospitals offered a clinic for rapid assessment of patients with TIA when surveyed in 2007 (National Stroke Foundation 2007) the wait is likely to be a lot longer than that found in the UK.

2. **Immediate access to thrombolysis if the patient has a subsequent stroke:** Studies have shown that the earlier intra-venous thrombolysis is administered for the treatment of acute ischaemic stroke the better, with the number needed to treat for a favourable outcome increasing from 4.5 (if treated within 90 minutes) to 21.4 (if treated between 271 – 360 minutes) (Kennedy, Erich et al. 2010). Given the initial 48 hours following TIA is a period of high-risk of subsequent stroke (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004; Sciolla and Melis 2008), inpatient management of patients with TIA means they have immediate access to thrombolysis should they suffer a subsequent stroke. One cost utility analysis of 24 hour hospital admission for patients with TIA showed that it is borderline cost-effective solely on the basis of increased ability to use tissue-Plasminogen Activator (tPA) in the event of a subsequent stroke and of definite cost-effectiveness in patients with TIA with a high 24 hour stroke risk (> 5% risk within 24 hours) (Nguyen-Huynh and Johnston 2005).

3. **Facilitation of early carotid revascularization:** The sooner a carotid endarterectomy can be performed for symptomatic carotid artery stenosis the better. An analysis of the pooled data of 5,893 patients in the European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial showed that for patients with ≥ 50% carotid artery stenosis the number needed to treat to prevent one ipsi-lateral stroke in 5 years increased from 5 (for those randomised within 2 weeks after their last ischaemic event) to 125 (for patients randomised after more than 12 weeks) (Rothwell, Eliasziw et al. 2004). Thus, if patients are waiting 12 days, on average, to be reviewed in a specialist outpatient TIA clinic and then have to await urgent referral to a vascular surgeon, the 2 week time window of greatest benefit from carotid revascularisation is well and truly closed.
4. **Greater opportunity for risk factor modification:** Whilst an inpatient there is greater accessibility to services such as diabetes educators, dieticians, and direct liaison with stroke specialty nurses and doctors (Ovbiagele, Saver et al. 2004). This allows a valuable opportunity for risk factor modification and the initiation of medical management at a time when patients are motivated to begin and maintain interventions that lower their risk and strengthens the patient’s perception that the therapy is an essential part of this process (Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults 2001; LaBresh, Ellrodt et al. 2004). They also have access to the expertise of inpatient pharmacists and other healthcare professionals to facilitate patient education, which can help alleviate patient concerns regarding medication tolerability and side effects (Fonarow 2003). This is advantageous as failure to initiate therapy early is believed to be one of the causes of a large “treatment gap” because outpatient follow-up may be less consistent and more fragmented (Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults 2001). Early commencement of medication and education regarding the role the medication plays in the secondary prevention of future TIA and stroke also improves long term medication adherence (Fonarow, Gawlinski et al. 2001; Ovbiagele, Saver et al. 2004; Ovbiagele, Kidwell et al. 2005; Sanossian, Saver et al. 2006).

The disadvantages to inpatient management of TIA patients include;

1. **Cost of hospital admission:** If all patients with TIA were managed as an outpatient the cost of hospital admission could be avoided. Whilst all those who are eligible for Medicare in Australia are entitled to hospital admission at no cost to the patient themselves, healthcare is never “free” and the actual cost of hospital admission is probably better reflected by the amount charged for a public-hospital admission in Queensland for those ineligible for Medicare which ranges from $820 – $951 per day (Princess Alexandra Hospital 2007). Depending on the services available in each hospital, this may be additional cost with very little gain, as some hospitals may not have immediate access to brain and vascular imaging facilities, particularly after hours (Lavallée, Meseguer et al. 2007).
2. **Hospital bed shortages:** Public hospitals in many countries face similar problems; with a reducing number of available hospital beds and a steadily increasing number of public-patient admissions (NHS Executive 2000; Australian Government Department of Health and Ageing 2007).

3. **Inconvenience to patients:** Normally hospital admission is reserved for patients who are unwell to the extent that their medical care requirements exceed the services that can be provided on an outpatient basis. By definition, a patient with TIA has no residual neurological symptoms, yet they may be admitted to hospital for urgent investigation simply because the outpatient access to these services is often limited.

4. **Iatrogenic complications of hospital admissions:** Exposure of asymptomatic patients with TIA to iatrogenic complications of hospital admission, such as deep vein thrombosis and nosocomial infection. Whilst the risk of deep vein thrombosis is highest amongst patients with hip fracture (40% to 70%) or total hip or knee replacement (40% to 70%), it can also occur in up to 15% of general medical patients (Hyers, Agnelli et al. 2001). The incidence of health-care-associated MRSA varies in Australia from 0.6/100,000 in Tasmania to 13.3/100,000 in Darwin. In Queensland the incidence is 3.4/100,000 (Ferguson 2007).

As a result, the option of outpatient management of patients with TIA is quite attractive. The main concern, however, is that outpatient assessment and investigation may not be rapid enough. This problem has been shown in one of the independent validation studies of the “ABCD” score in Oxfordshire, where patients were referred to a weekly hospital-based TIA clinic (Rothwell, Giles et al. 2005). In this study 14/206 (6.7%) patients, all of whom had an ABCD score ≥ 4, suffered a stroke before their scheduled clinic appointment; the median (IQR) time from referral to clinic appointment being 9 (4 – 16) days. Supporting this study is a review from a rapid assessment stroke clinic in Sheffield which showed that of 1,460 referrals with TIA and minor ischaemic stroke to the clinic over a 2 year period 39 (2.7%) patients failed to attend as they had suffered a subsequent stroke requiring admission to hospital prior to their clinic appointment (mean waiting time from referral to clinic appointment was 17 days, range 0 – 96 days). Of these 39 subsequent strokes, 27 (69%) occurred during the first 3 days after referral and 13 (33%) were fatal (Widjaja, Salam et al. 2005).
UK guidelines recommend specialist review within 7 days of symptom onset (Intercollegiate stroke working party 2004), but this is currently achieved in only 35% of UK centers, and the average waiting time for a TIA clinic appointment in the UK in 2006 was 12 days (Royal College of Physicians of London Clinical Effectiveness and Evaluation Unit 2007). However, depending on how the clinic is structured (for example, if the clinic is run weekly rather than daily), this wait can be up to 66 days (Goode, Altaf et al. 2007). The main reason for this delay is that there is potentially a 7-fold underestimation of the true demand for TIA clinics in the UK (Giles and Rothwell 2007).

A multi-centre, prospective study in the Netherlands (Scholte Op Reimer, Dippel et al. 2006), showed that the management of TIA and minor stroke patients in the Netherlands is predominantly carried out on an outpatient basis (only 10% of those admitted were due to TIA, the remaining 90% of cases that were admitted were due to stroke). Overall, it was found on comparing the inpatient and outpatient groups that the assessment and management received by outpatients was less rapid and rigorous compared to those managed as inpatients. Whilst less rapid assessment depends on the structure of outpatient care available in that system, the type of treatment received should be the same irrespective of whether the patient is an inpatient or an outpatient, providing evidence-based guidelines are followed. However, this study shows that this is not always the case.

Recent studies have shown that if rapid access clinics are appropriately organised, they are an effective method of implementing necessary secondary preventive measures, reducing risk of subsequent stroke, and provide the additional benefit of avoiding hospital admission. Two such studies are the EXPRESS (Rothwell, Giles et al. 2007) and SOS –TIA studies (Lavallée, Meseguer et al. 2007).

The Early use of Existing Preventive Strategies for Stroke (EXPRESS) study (Rothwell, Giles et al. 2007) compared usual UK practice of delayed clinic assessment and treatment of 310 patients with TIA or minor stroke in phase 1 of the trial, to more urgent clinic assessment and immediate treatment of 281 TIA or minor stroke patients in phase 2. In the first phase of the study GPs referred all TIA and minor stroke patients who did not require hospital admission to the daily TIA clinic. Inherent delays occurred due to receiving
referrals and organising appointments for patients. A CT brain and ECG was performed the same day as clinic, or shortly thereafter. A carotid duplex was arranged for the following week for all patients and echocardiogram for those patients where it was clinically indicated. A letter was subsequently faxed to the GP within 24 hours of the clinic appointment, outlining the clinical assessment and treatment recommendations as outlined in Table 1.13. No treatment was given in the study clinic and no prescriptions were issued. Patients were instructed to contact their GPs as soon as possible in order to obtain prescriptions for recommended treatment.

In the second phase of the study no appointments were necessary for the TIA clinic. GPs were able to directly send all TIA or minor stroke patients to the weekday afternoon clinic. A CT brain was organized in the clinic for all patients with incomplete resolution of symptoms at the time of assessment to exclude intra-cerebral haemorrhage before giving aspirin, clopidogrel, or anti-coagulants. Otherwise patients were assessed in the same manner as in phase 1. All those who were considered to have had a TIA or stroke were given aspirin 300mg to take in the clinic, together with a 4 week supply of any other necessary medication, so as to enable same day commencement of recommended therapy. This resulted in a statistically significant reduction in wait for clinic appointment from 3 days (range 2 – 5 days) to less than 1 day in phase 2 (range 1 – 3 days) p < 0.0001. Whilst this is a significant improvement, a wait of 3 days for a clinic appointment in phase 1 of the study is “rapid” compared to the UK average of a 12 day wait for a TIA clinic appointment when surveyed in 2006 (Royal College of Physicians London and Intercollegiate Stroke Working Party 2007). Median delay to first prescription of recommended treatment fell from 20 days in phase 1 (range 8 – 53 days) to 1 day in phase 2 (range 0 – 3 days) p < 0.0001. The 90 day risk of subsequent stroke reduced from 10.3% (32/310) in phase 1 to 2.1% (6/281) in phase 2.
Table 1.13 Recommended Treatment Protocol for all TIA and Minor Stroke Patients in the EXPRESS Study (Rothwell, Giles et al. 2007). (To be tailored to each individual patient)

- Antiplatelet therapy
  - Aspirin 75mg daily, if not previously taking an anti-platelet agent
  - Clopidogrel if aspirin contra-indicated
- Simvastatin 40mg daily
- Blood pressure lowering agent (unless systolic blood pressure was below 130mmHg on repeated measure)
- Anticoagulation as required
- Clopidogrel 75mg daily for 30 days in addition to aspirin for patients seen within 48 hours of symptom onset or within 7 days who were deemed to be at high early risk of subsequent stroke

The French SOS-TIA study (Lavallée, Meseguer et al. 2007) also looked at the effects of rapid assessment of TIA patients with complete resolution of their symptoms in their 24 hour hospital-based TIA clinic. An educational leaflet was sent to 15,000 physicians in Paris explaining that TIA is an emergency and inviting referrals to their 24 hour TIA clinic that was contactable via a toll-free telephone number. The only stipulation being that the referred patients had to have complete resolution of their symptoms. If the symptoms were persistent they were advised to refer the patient to their local ED. The clinic provided immediate CT brain or MRI brain, carotid duplex, and transcranial doppler. Urgent trans-thoracic or trans-oesophageal echocardiography was also organised if the vascular neurologist reviewing the patient suspected a high risk of recurrent cardiac embolism; which included, cases with suspected endocarditis, suspected aortic dissection, mitral stenosis, prosthetic heart valve with suspicion of thrombus, or acute myocardial infarction. Blood testing was also performed in the clinic, including fasting glucose and lipid profile if the patient was in a fasting state. Overall the study assessed 1,085 patients with suspected TIA; of which 643 (76%) were diagnosed as definite TIAs, 144 (17%) possible TIAs, 58 (7%) minor strokes, and 240 (22%) were deemed to have an alternate diagnosis. Eight
hundred and eight patients (75%) were discharged home. Of the 845 with a TIA or minor stroke, antithrombotics were commenced in 824 (98%). Of the 58 patients with atrial fibrillation, 44 (76%) were given a prescription for oral anticoagulants. Among the 701 patients with definite TIA or minor stroke, antihypertensives were commenced or modified in 199 (28%). Advice was given to GPs for the remaining 502 (72%) of patients in this group regarding optimal blood pressure targets (140/90 mm Hg in non-diabetic patients and 130/85 mm Hg in diabetic patients). Similarly, a lipid lowering agent was either commenced or modified in 315 (45%) patients with definite TIA or minor stroke. Advice was given to GPs for the remaining 386 patients in this group to aim for a target Low Density lipoprotein of ≤ 2.56mmol/L. An antihypertensive agent was not commenced in any patients on the basis of a single elevated blood pressure reading at the clinic without a prior history of hypertension, nor was a lipid lowering agent commenced in any patient without first obtaining a fasting lipid profile. However, evidence from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study (Amarenco, Bogousslavsky et al. 2006), which was subsequently published, supports the use of high dose atorvastatin in all patients with TIA or stroke.

There were 13 subsequent strokes at 90 days amongst the 1,052 patients (97% of the total study population) referred to the clinic that were available for follow-up. This gives an overall 90 day stroke risk of 1.24% (95% CI 0.72 – 2.12%). The expected 90 day stroke risk for this group based on their ABCD² score was 5.96%. Twelve (92%) of these subsequent strokes occurred in patients with definite TIA and 1 (8%) occurred in a patient with a possible TIA. There were no subsequent strokes in the group of patients deemed to have an alternate diagnosis. Given the high risk of subsequent stroke within the first 48 hours (Johnston, Gress et al. 2000; Hill, Yiannakoulis et al. 2004; Sciolla and Melis 2008) the SOS-TIA authors assessed the 90 day stroke risk of the 552/1,052 (52.5%) patients that were seen within 24 hours their symptom onset. This group had a 90 day risk of subsequent stroke of 1.63% (95% CI 0.85 – 3.12%), whereas the risk predicted for this group according to their ABCD² score was 6.49%, showing a 75% reduction in their 90 day risk of stroke. One possible explanation for this lower 90 day stroke risk, other than the rapid assessment and management of patients with TIA provided in this study, is selection bias; as physicians may have preferentially only selected low-risk patients to be referred to the clinic, whilst
continuing to refer high-risk patients to ED. Another possible explanation is that of recall bias for minor events as the median delay to interview was 16 months. In addition, follow-up was carried out with relatives in 88/1,085 (8%) cases and with the patients doctor in 103/1,085 (9.5%) cases.

On exclusion of those patients who were ultimately found to have an alternate diagnosis, the authors did find that the 90 day risk of stroke was higher amongst the 434/552 (79%) patients seen within 24 hours of symptom onset who were deemed to have suffered a definite or possible TIA or minor stroke, with their 90 day risk of stroke being 2.08% (95% CI 1.09 – 3.96%). They also showed that the 90 day stroke risk amongst this group of definite or possible TIAs or minor stroke that were seen within 24 hours of symptom onset increased with higher ABCD² scores; the 90 day stroke risk for the 396/434 (91.2%) of patients with an ABCD² score of ≥ 4 was 2.01% (95% CI 1.05 – 4.15%) which increased to 3.18% (95% CI 1.44 – 6.95%) for the 198/434 (45.6%) patients with an ABCD² score of ≥ 5.

Overall, these studies show that outpatient assessment and management of patients with TIA is effective and enables a significant reduction in the 90 day risk of subsequent stroke providing it is performed rapidly. Whilst this is possible in a study setting is it a viable option in the real world?

1.10 Evidence-based Recommendations for Medical Management of TIA

Aside from the question of whether patients with TIA should be managed as an inpatient or as an outpatient, there is broad consensus between published international management guidelines regarding the medical management and timing of investigations after TIA. The main management recommendations from each of the main sets of guidelines are summarized in Table 1.14. As the American Stroke Association (ASA) does not have a dedicated set of guidelines for the acute management of TIA, for the purposes of this review the ASA guidelines for the acute management of stroke (Adams, del Zoppo et al.
2007) were reviewed in conjunction with the guidelines for prevention of stroke in patients with ischaemic stroke or TIA (Sacco, Adams et al. 2006).
### Table 1.14 Comparisons of International Guidelines for the Management of TIA

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<td><strong>CT Brain</strong></td>
<td>High-risk patient; ABCD² &gt; 4</td>
<td>All patients on initial assessment</td>
<td>Within 24 hours</td>
<td>As soon as possible or Outpatients with resolution of symptoms; within 7 days. High-risk patients* within 24 hours</td>
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<td>Low-risk patient; ABCD² &lt; 4</td>
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<td>• Within 48–72 hours</td>
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<td><strong>Carotid Duplex</strong></td>
<td>All patients with carotid territory symptoms AND are candidates for carotid re-vascularisation High-risk patient; ABCD² &gt; 4</td>
<td>Carotid duplex recommended, but no advice regarding timing of carotid duplex.</td>
<td>Within 24–48 hours, for those with carotid territory TIAs.</td>
<td>For those seen in the community, with resolution of symptoms; within 7 days.</td>
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<td>High-risk patient; ABCD² &gt; 4</td>
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<td></td>
<td>• Within 24 hours</td>
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<td></td>
<td>Low-risk patient; ABCD² &lt; 4</td>
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<td></td>
<td>• Within 48–72 hours</td>
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<tr>
<td><strong>Echo</strong></td>
<td>All patients with a potential cardiac source:</td>
<td>Echo recommended, but no advice regarding which patients should undergo echocardiogram and when this should be performed.</td>
<td>• All patients where a cardio-embolic mechanism is suspected.</td>
<td>No recommendation regarding which patients should undergo echocardiogram or when this should be performed.</td>
</tr>
<tr>
<td></td>
<td>• Hx of cardiac abnormalities.</td>
<td></td>
<td>• Patients under 45 where investigation of the brain and neck provide no clue to the cause of the TIA (No time frame given).</td>
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<td></td>
<td>• Abnormal ECG</td>
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<tr>
<td></td>
<td>• Stroke of unknown origin after standard diagnostic workup (No time frame given).</td>
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</table>
| **ECG** | **Australian Guidelines**  
(National Stroke Foundation 2007) | **American Stroke Association Guidelines**  
(Sacco, Adams et al. 2006)  
(Adams, del Zoppo et al. 2007) | **National Stroke Association Guidelines**  
(Johnson, Nguyen-Huynh et al. 2006) | **United Kingdom Guidelines**  
(Intercollegiate stroke working party 2004; National Pre-hospital Guidelines Group 2006) |
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<tr>
<td>All patients on initial assessment</td>
<td>All patients on initial assessment</td>
<td>Within 24 hours</td>
<td>For those seen in the community, with resolution of symptoms; within 7 days. High-risk Patients* within 24 hours</td>
<td></td>
</tr>
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</table>

| **Blood tests** | **Australian Guidelines**  
(National Stroke Foundation 2007) | **American Stroke Association Guidelines**  
(Sacco, Adams et al. 2006)  
(Adams, del Zoppo et al. 2007) | **National Stroke Association Guidelines**  
(Johnson, Nguyen-Huynh et al. 2006) | **United Kingdom Guidelines**  
(Intercollegiate stroke working party 2004; National Pre-hospital Guidelines Group 2006) |
|---|---|---|---|---|
| All patients on initial assessment:  
- Full blood count  
- Electrolytes/Renal Function  
- Cholesterol level  
- Glucose Level  
Selected patients on initial assessment:  
- Hepatic function tests  
- Blood alcohol level  
- Arterial blood gas (if hypoxia is suspected) | All patients on initial assessment:  
- Full blood count  
- Electrolytes/Renal Function  
- Blood glucose  
- Coagulation profile | Blood work to be performed on all patients within 24-48 hours | No recommendation regarding timing of blood tests or what tests should be ordered for low-risk patients. High-risk Patients* within 24 hours: No recommendations re what tests to perform other than blood glucose. |
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<tr>
<td><strong>Anti-platelets</strong></td>
<td>All TIA patients due to a non cardio-embolic cause.</td>
<td>All TIA patients due to a non cardio-embolic cause.</td>
<td>One of the following for TIA patients due to a non cardio-embolic cause:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Aspirin 50-325mg /day</td>
</tr>
<tr>
<td></td>
<td>Acute Setting:</td>
<td>Daily long term anti-platelet therapy:</td>
<td>• Aspirin/ Dipyridamole SR 50/200mg is a reasonable option as first line therapy</td>
</tr>
<tr>
<td></td>
<td>• Aspirin 160-300mg as soon as possible (within 48 hours)</td>
<td></td>
<td>• Clopidogrel may be slightly more effective than aspirin.</td>
</tr>
<tr>
<td></td>
<td>Long term treatment:</td>
<td></td>
<td>• Clopidogrel may be prescribed as first choice where aspirin or aspirin in combination with dipyridamole is not tolerated</td>
</tr>
<tr>
<td></td>
<td>• Aspirin and modified release dipyridamole is more effective than aspirin alone.</td>
<td></td>
<td>For patients intolerant of aspirin:</td>
</tr>
<tr>
<td></td>
<td>• Aspirin alone or clopidogrel alone for those who do not tolerate combination. Aspirin/dipyridamole therapy.</td>
<td></td>
<td>• Clopidogrel75mg/day or</td>
</tr>
<tr>
<td></td>
<td>• Clopidogrel alone for those who do not tolerate aspirin or where aspirin is contra-indicated.</td>
<td></td>
<td>• Dipyridamole modified release twice daily.</td>
</tr>
<tr>
<td></td>
<td>• The combination of aspirin and clopidogrel is not recommended in the patients who do not have acute coronary disease or recent coronary stent.</td>
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Patients with an ischaemic cerebrovascular event whilst taking aspirin → no evidence of additional benefit by increasing aspirin dose. Alternate anti-platelet agents considered, no single or combination agent well studied in this group.
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<tbody>
<tr>
<td>All following patients (unless contra-indicated):</td>
<td></td>
<td>All following patients (unless contra-indicated):</td>
<td>All cardioembolic TIA (unless contra-indicated) due to:</td>
<td>All following patients (unless contra-indicated):</td>
</tr>
<tr>
<td></td>
<td>• Atrial Fibrillation (persistent or paroxysmal)</td>
<td>• Atrial Fibrillation (persistent or paroxysmal)</td>
<td>• Persistent or paroxysmal atrial fibrillation</td>
<td>• Atrial Fibrillation (persistent or paroxysmal)</td>
</tr>
<tr>
<td></td>
<td>• Cardioembolic stroke from valvular heart disease or post myocardial infarction</td>
<td>• Left ventricular mural thrombus post myocardial infarction.</td>
<td>• Recent myocardial infarction</td>
<td>• Sinus Rhythm with major source of cardiac embolism.</td>
</tr>
<tr>
<td></td>
<td>• Dilated cardiomyopathy (anticoagulation or antiplatelet therapy)</td>
<td>• Dilated cardiomyopathy (anticoagulation or antiplatelet therapy)</td>
<td>• Mechanical heart valve prosthesis</td>
<td>• Severe dilated cardiomyopathy (Ejection fraction &lt; 20%)</td>
</tr>
<tr>
<td></td>
<td>• Prosthetic heart valves</td>
<td></td>
<td>• Mitral stenosis</td>
<td>For those patients where anticoagulation is contra-indicated aspirin is advised (clopidogrel if aspirin intolerant).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intra-cardiac clot</td>
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| All TIA patients, whether normotensive or hypertensive should receive an antihypertensive, unless contra-indicated by symptomatic hypotension. Normal BP defined as:  
• Non diabetics < 140/90mmHg  
• Diabetics < 130/85mmHg | All TIA patients should receive antihypertensive treatment, even those without a history of hypertension. Target BP level should be individualized. Normal BP defined as < 120/80mmHg. Specific drug choice should be individualised | Start a BP lowering medication 7-14 days post TIA in all patients unless symptomatic hypotension. Target BP  
• Non diabetics < 140/90 mmHg  
• Diabetics: < 130/80 mmHg Use an ACE inhibitor alone, or in combination with a diuretic. In normotensive patients aim to lower BP by 9/4mmHg providing there is no high grade internal carotid stenosis | High Blood pressure persisting over 2 weeks should be treated. Optimal BP defined as;  
• Non diabetics; < 140/85mmHg  
• Diabetics < 130/80mmHg Advised antihypertensives; Thiazide diuretic or an ACE inhibitor, or preferably a combination of both, unless contra-indicated. |
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<tr>
<td></td>
<td>All patients commenced on a statin.</td>
<td>All patients with elevated cholesterol, co-morbid coronary artery disease, or evidence of atherosclerotic origin should be managed according to NCEP guidelines, which include lifestyle modification, dietary guidelines and medication recommendations. Reasonable to consider statins for stroke and TIA patients presumed to be of atherosclerotic origin, without pre-existing indication for statins (normal cholesterol levels, no coronary artery disease). Those with low HDL – cholesterol can be considered for treatment with niacin or gemfibrozil.</td>
<td>Treatment with a statin is recommended for most atheroembolic TIAs Dietary modification and regular physical activity is advised. However if fasting cholesterol remains increased (LDL cholesterol &gt; 3.3mmol/L), then a lipid lowering agent should be commenced, aiming for an LDL level &lt; 2.6mmol/L</td>
<td>All patients with a total cholesterol &gt; 3.5mmol/L should be commenced on a statin (unless contra-indicated).</td>
</tr>
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*High-risk patients are deemed to be those with more than 1 TIA within 7 days or ≥ 3 of the following; BP > 140/90mmHg, Unilateral weakness or speech disturbance, symptoms lasting more than 60 minutes, or those who have diabetes.*
The Australian National Stroke Foundation guidelines for the management of TIA are different to the other three sets of guidelines with respect to advising a statin for all patients with TIA regardless of their baseline fasting lipid profile. The UK guidelines recommend a statin for all patients with a total cholesterol > 3.5mmol/L (Intercollegiate stroke working party 2004). This reflects the fact that the Australian guidelines were the only set of guidelines published following the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study (Amarenco, Bogousslavsky et al. 2006). Other than this, it is apparent from Table 1.15 that there are few significant differences between these guidelines.

1.11 Do clinicians manage patients according to the guidelines?

Due to the high risk of subsequent stroke following a TIA (Dennis, Bamford et al. 1990; Johnston, Gress et al. 2000; Hill, Yiannakoulia et al. 2004; Kleindorfer, Panagos et al. 2005) patients with TIA have a unique window of opportunity for initiation of secondary preventive measures. It would, therefore, seem imperative that all necessary investigations are performed and all proven secondary preventative measures are appropriately initiated as recommended by the TIA and stroke guidelines. Unfortunately this does not appear to always be the case, with a large knowledge-to-practice gap that leaves patients with TIA under-investigated and under-treated.

Under-investigation has been shown in hospital-based studies in the US and Canada where the percentage of patients with TIA presenting to an ED received neuroimaging in 60 – 81% (Chang, Holroyd et al. 2002; Douglas, Johnston et al. 2003; Gladstone, Kapral et al. 2004; Edlow, Kim et al. 2006). One multi-centre study, involving four regional stroke centres in Ontario (Gladstone, Kapral et al. 2004), showed that same day neuroimaging was only carried out in 45% of TIA patients following presentation to the ED, despite a median time from onset of symptoms to arrival at the ED of 120 minutes. A US national study on ED visits for TIA (Edlow, Kim et al. 2006), showed that over a 10 year period the percentage of patients receiving neuroimaging doubled, from 35% in 1992 – 1993 to over 70% in 2000 – 2001, yet still failed to meet guideline recommendations that all TIA patients should receive neuroimaging (Sacco, Adams et al. 2006; National Stroke Foundation 2007). There were no statistically significant differences by age (p = 0.32), gender (p = 0.38), insurance type (p = 0.61), or region (p
In population-based studies the percentage of patients that received neuroimaging varied from 23% in an Eastern United States study carried out in 1992 – 1994 (Goldstein, Bian et al. 2000), 62% in the Italian SEPIVAC study carried out in 1986 – 1989 (Ricci, Celani et al. 1991), 72% in the Oxford Community Stroke Project carried out in 1981 – 1986 (Dennis, Bamford et al. 1990), 94.7% in the Southeast Texas County Brain Attack Surveillance in Corpus Christi (BASIC) project carried out in 2000 – 2002 (Lisabeth, Ireland et al. 2004), and 100% in a Spanish study carried out in 1992 – 1994 (Sempere, Duarte et al. 1996).

Carotid doppler was performed in 42 – 92% of patients with TIA in hospital-based studies (Chang, Holroyd et al. 2002; Gladstone, Kapral et al. 2004; Selvarajah, Smith et al. 2008), and in 40 – 70% of TIA patients in population based studies (Ricci, Celani et al. 1991; Goldstein, Bian et al. 2000; Lisabeth, Ireland et al. 2004).

An electrocardiograph (ECG) was carried out in 73 – 85% of patients with TIA in hospital-based studies (Chang, Holroyd et al. 2002; Gladstone, Kapral et al. 2004; Edlow, Kim et al. 2006) and in 18 – 97% of patients with TIA patients in population-based studies (Ricci, Celani et al. 1991; Goldstein, Bian et al. 2000; Lisabeth, Ireland et al. 2004).

One community-based retrospective audit carried out in 27 primary-care practices in 2 geographically separate communities in the Eastern United States (Goldstein, Bian et al. 2000) looked at the management of incident TIA and stroke patients by primary-care physicians. Amongst the cohort of patients with TIA, almost one third had no investigation whatsoever within 30 days.

Under-treatment of patients with TIA is also evident in both hospital-based and community-based studies. Despite recommendations by all guidelines that all patients with TIA should receive either an antiplatelet agent or anticoagulant (if deemed to be cardio-embolic in origin), hospital-based studies have shown that the percentage of patients discharged home on no antithrombotic agent varies from 0% – 42% (Johnston,
Gress et al. 2000; Chang, Holroyd et al. 2002; Gladstone, Kapral et al. 2004; Edlow, Kim et al. 2006; Selvarajah, Smith et al. 2008). However, in the two hospital-based studies that showed the highest percentage of patients discharged home without any antithrombotics (Gladstone, Kapral et al. 2004; Edlow, Kim et al. 2006), this may be an over-estimation, as both studies had similar methodological issues: patients may have been advised to commence aspirin on discharge, or antiplatelet agents may have been contra-indicated, but unless this was documented in their notes, they were recorded as having been discharged without an antiplatelet agent. A summary of some of the studies showing variations in management of patients with TIA is shown in figure 1.1.

**Figure 1.1 Variations in Management of TIA in Hospital-Based Studies**

The most important modifiable cause of stroke is high blood pressure; for every ten people who die of stroke, four could have been saved if their blood pressure had been regulated (Mackay and Mensah 2004). Antihypertensive agents have been shown to be under-utilised. The likelihood of a patient with TIA receiving a new prescription for an antihypertensive agent on discharge from ED in Ontario was shown to be as low as 8% (Gladstone, Kapral et al. 2004). An Australian multi-centre, retrospective audit of
consecutive TIA and stroke admissions to eight metropolitan tertiary referral hospitals from five Australian states (Duffy, Phillips et al. 2003) showed that of the 2,383 TIA and stroke patient cases that were reviewed, 41% (range 31 – 51%) had sub-optimal systolic blood pressure control at their time of discharge (systolic BP > 140mmHg). The authors did not provide data indicating if the percentage of those discharged with sub-optimal blood pressure control were patients with TIA or stroke. Nonetheless, given that TIA and stroke are spectrums of the same disease (Edlow, Kim et al. 2006) these studies show that there is room for improvement in the utilisation of antihypertensive agents in order to meet guideline recommendations.

Despite recommendations from all the guidelines regarding utilisation of lipid-lowering agents in TIA patients, studies of combined populations of stroke and TIA patients looking at the frequency of lipid-profile testing and utilisation of lipid-lowering agents have shown that both are under-utilised. Only 10 – 50% of TIA and stroke patients underwent lipid-profile assessment and only 13 – 50% of patients were commenced on a lipid-lowering drug (Duffy, Phillips et al. 2003; Gladstone, Kapral et al. 2004; Read and Levy 2005; Reeves, Arora et al. 2005; Ovbiagele, Hills et al. 2006). A lower rate of testing and treatment amongst patients with TIA compared to patients with stroke and marked variation amongst hospitals has also been observed (Duffy, Phillips et al. 2003; Gladstone, Kapral et al. 2004; Read and Levy 2005; Reeves, Arora et al. 2005; Ovbiagele, Hills et al. 2006).

Despite the known benefits of anticoagulation for the secondary prevention of stroke in patients with atrial fibrillation, the REACH registry, an international, observational registry shows that less than two-thirds of patients with a history of past stroke and/or TIA are anticoagulated (Hill, Roether et al. 2007). An Australian multi-centre, retrospective audit showed that 116/363 (32%) patients with stroke and atrial fibrillation in their cohort were anticoagulated (Duffy, Phillips et al. 2003). Given that patients with TIA generally receive less rigorous investigation and management compared to patients with stroke (Scholte Op Reimer, Dippel et al. 2006), the percentage of patients with TIA due to a cardio-embolic source that are anticoagulated is probably even lower than this.

Given this evidence of under-investigation and under-treatment of patients with TIA, effective methods to bridge this evidence-to-practice gap are needed to ensure all
evidence-based treatment measures are implemented and all necessary investigations are performed.

1.12 Implementation of Evidence-based Guidelines – the Role of Clinical Pathways

Most of the time there are several obstacles that have to be overcome in the transition from best evidence to best practice. These obstacles occur at a number of levels, including at the level of the individual healthcare professional, the multi-disciplinary healthcare team, and the healthcare organization. These obstacles include ensuring appropriate levels of knowledge by individual healthcare professionals, organisation of team members to deliver best practice care, and the availability of the necessary equipment and resources to permit the timely delivery of care.

A review of 235 studies that examined guideline dissemination and implementation strategies found that these interventions result in no more than a 10% median improvement in healthcare provider behavior (Grimshaw, Thomas et al. 2004). The ideal method to bridge this knowledge-to-practice gap should be one which reminds physicians of key relevant actions in both the diagnostic and therapeutic realms that are supported by an existing evidence base (Lang, Wyer et al. 2007).

One potential method to improve utilisation of guidelines in everyday practice is through translation of the guidelines into protocols/clinical pathways which are designed to assist clinical decision making regarding diagnosis, investigation, and acute treatment in a standardised, efficient manner, based on the best available research evidence and clinical guidelines in order to optimize and streamline patient care and improve outcomes (Baker, Miller et al. 1998; Lanska 1998). Clinical pathways in health-care were first researched in the early 1970s, but the environment for implementation was not receptive (Coffey, Richards et al. 1992). Clinical pathways were introduced in the early 1990s in the UK and USA (Open Clinical 2003) and are being increasingly used throughout the developed World, with pathways existing for a wide range of conditions and procedures (Campbell, Hotchkiss et al. 1998).
Articles which have reviewed care pathways have concluded that there is a weak evidence base to support the use of a care pathway over standard medical care, despite their widespread acceptance, but acknowledge the need for further high quality research in this area (Campbell, Hotchkiss et al. 1998; Kwan and Sandercock 2005; Hunter and Segrott 2008). One of the biggest problems in trying to evaluate the potential benefit of a care pathway is the difficulty posed by trying to carry out a blinded randomised control trial to assess their benefit. Thus, many of the studies are non-randomised.

Clinical pathways are generally developed for high-volume, high-risk, and high-cost diagnoses and procedures, in particular for those conditions where inefficient variation in the process of care is thought to exist (Coffey, Richards et al. 1992). Ischaemic heart disease is one such condition that lends itself well to successful implementation of a clinical pathway. Non-randomised studies looking at the use of clinical pathways for the management of patients with chest pain have shown that they enable risk stratification of patients allowing early identification and treatment of high-risk patients, and early, safe discharge of low-risk patients (Aroney, Dunlevie et al. 2003; Boufous and Kelleher 2003). Care pathways for chest pain have also been shown to reduce lengths of stay, which ultimately means reduced costs (Roberts, Zalenski et al. 1997), and have been shown to significantly improve the utilization of proven secondary preventive therapies (Fonarow, Gawlinski et al. 2001; Mehta, Montoye et al. 2002; Wolff, Taylor et al. 2004) and their longer term adherence (Fonarow, Gawlinski et al. 2001).

The Cardiovascular Hospitalization Atherosclerosis Management Plan (CHAMP) (Fonarow, Gawlinski et al. 2001) successfully implemented a clinical pathway, with retrospective data collection and quarterly feedback to clinicians, for patients hospitalized with coronary artery disease at a university associated teaching hospital in Los Angeles. They focused on in-hospital initiation of proven secondary preventive measures and showed substantial and statistically significant (p < 0.01) improvements in each when comparing the 2 year periods before and after implementation of CHAMP: aspirin use increased from 200/256 (78%) to 278/302 (92%), statin use 15/256 (6%) to 260/302 (86%), beta-blocker use 31/256 (12%) to 184/302 (61%), and ACE inhibitor use 10/256 (4%) to 169/302 (56%). This resulted in improved rate of achievement of target LDL cholesterol of less than 2.6 mmol/L during the 6 – 18 month follow-up (6% to 58%), statistically significant reductions (p < 0.05) in recurrent
myocardial infarction from 20/256 (7.8%) to 10/302 (3.3%) and total mortality from 18/256 (7%) to 10/302 (3.3%).

The Cooperative Cardiovascular Project Pilot (Marciniak, Ellerbeck et al. 1998) aimed to improve quality of care for Medicare patients with acute myocardial infarction in the United States by providing performance feedback to 379 hospitals across four states in America. This project looked at acute management, implementation of secondary preventive measures, and mortality at each hospital. Results were presented in a positive manner and emphasized approaches for improvement. These improvements were implemented using various methods including the creation, or revision, of management pathways and standing orders as well as educational efforts. This produced statistically significant ($p < 0.001$) increases in utilisation of secondary preventive measures. Use of aspirin increased from 6,226/7,447 (84%) to 3,984/4,412 (90.3%) and beta blocker use increased from 745/1,569 (47.5%) to 683/999 (68.4%). Smoking cessation counseling increased from 360/1,257 (28.6%) to 320/780 (41%) and there was a 2.7% reduction in 1 year mortality from 3,002/9,294 (32.3%) to 1,709/5,773 (29.6%).

The demonstration of the ability to implement system change to increase rates of in-hospital implementation of guideline derived secondary preventive measures, resulting in improved patient outcomes, formed the basis of the American Heart Association’s “Get With the Guidelines” (GWTG) program (LaBresh, Ellrodt et al. 2004). This pilot trial was carried out in 24 hospitals in Massachusetts from July 1, 2000 – June 30, 2001. It focused on the American Heart Association/American College of Cardiology guidelines, to ensure that patients were discharged home on a regimen of appropriate medications and received adequate counseling for risk factor modification. This was achieved through the utilisation of educational measures (interactive multi-disciplinary team workshops, didactic presentations, and best practices sharing), pre-printed orders, discharge forms, and the implementation of a web based interactive program (Patient Management Tool, PMT). The PMT served as a computerized clinical pathway, providing reminders of appropriate guidelines if a specific measure or intervention was omitted prior to discharge. The web-based program also enabled data collection of all enrolled patients. This showed significant improvements in utilisation of secondary preventive measures at the time of hospital discharge across all 24 hospitals within a 1 year period. Amongst the cohort of 1,738 patients the following improvements were seen: LDL-cholesterol measurement increased from 1,025 (59%) to 1,408 (81%), use of
a lipid lowering agent increased from 939 (54%) to 1,373 (79%), cardiac rehabilitation referral increased from 591 (34%) to 1,269 (73%), smoking cessation counseling increased from 834 (48%) to 1,512 (87%), and adequate blood pressure control increased from 1,043 (60%) to 1,182 (68%). Baseline use of 82 – 87% was maintained for the use of aspirin, beta-blockers, and ACE inhibitors at the time of discharge. Following the success of the “Get With The Guidelines” pilot study, the program was adopted by the AHA as a national program (LaBresh, Gliklich et al. 2003).

1.13 Clinical Pathways of Care for Stroke and TIA Patients

A TIA could be considered the neurological equivalent of cardiac angina, where some patients are very high risk and warrant urgent investigation and management, whereas others can be categorized as low risk. Similar problems exist in both conditions with respect to under-utilisation of secondary preventive medical therapies in patients with established coronary artery disease (Ellerbeck, Jencks et al. 1995; Frolkis, Zyzanski et al. 1998; Miller, Byington et al. 2000; Fonarow, Gawlinski et al. 2001) and the need to identify non-cardiac causes of chest pain (for example, musculoskeletal pain, gastro-oesophageal or anxiety syndromes) so as to enable appropriate treatment and avoid unnecessary testing or prolonged hospital admission. Given the success seen in the aforementioned studies of clinical pathways in the management of patients with ischaemic heart disease, TIA management should also be amenable to, and could potentially benefit from, the implementation of a clinical pathway.

One systematic review of studies using a clinical pathway to guide the management of patients with stroke found 3 randomised control trials (total of 340 patients) and 12 non-randomised studies (total of 4,081 patients) (Kwan and Sandercock 2005). This review showed evidence, mainly from the non-randomised studies, that patients with stroke managed with a clinical pathway were more likely to have a CT brain (OR 2.42, CI 1.12 – 5.25%), less likely to be re-admitted to hospital (OR 0.11, CI 0.03 – 0.39%) and less likely to suffer a urinary tract infection (OR 0.51, CI 0.34 – 0.79%). Six studies (2 randomised and 4 non-randomised) showed a non-significant trend towards a shorter mean length of stay (Kwan and Sandercock 2005). However, there was no evidence that a clinical pathway provided significant additional benefit over standard medical care in terms of death or discharge destination and evidence from the randomised trials
suggested lower patient satisfaction and quality of life in patients with stroke managed using a clinical pathway (Kwan and Sandercock 2005). The reason for this may be that the studies included in the aforementioned review largely looked at the effect of care pathways on stroke patients who were being managed in a stroke unit. Given that organised stroke unit care has been shown to improve outcome in patients recovering from an acute stroke (Stroke Unit Trialists' Collaboration 2007), a care pathway may not be as beneficial in this setting, adding little to improve the quality of care where the patient is already being cared for by skilled professionals who are experienced in the management of stroke patients.

Other hospital-based studies, which were published following the review by Kwan and Sandercock, have shown for patients with stroke and TIA who received inpatient management, the use of pre-printed order sheets, medication algorithms, distribution of evidence-based pocket cards outlining treatment goals and medication doses resulted in significant improvements in the discharge utilisation of lipid lowering agents and antihypertensives. Whilst the discharge utilisation of antiplatelet agents was much higher amongst patients who received inpatient management (93 – 95%), the studies detected an improvement in this as well (increased to 98%), which did not reach statistical significance (Ovbiagele, Saver et al. 2004; California Acute Stroke Pilot Registry (CASPR) Investigators 2005).

Two Australian studies, the first involving four regional hospitals, showed a beneficial effect following clinical pathway implementation in the acute management of patients with stroke, with statistically significant improvements in the rates of swallow assessments, allied health assessments, deep vein thrombosis prevention strategies, and blood glucose level estimation in the 45/120 (37%) of patients that were enrolled in the pathway (Read, Levy et al. 2006). The second study, also based in a regional hospital, showed significant improvements in swallow assessments within 24 hours of admission from 14/27 (51.8%) pre-clinical pathway implementation to 86/96 (92.5%) post-pathway implementation and rates of utilisation of antiplatelet agents in eligible patients within 24 hours following ischaemic stroke improved from 7/19 (36.8%) to 71/77 (92.2%) post-clinical pathway implementation (Wolff, Taylor et al. 2004).

The American Stroke Association (ASA) has also developed a “Get with the Guidelines - Stroke” module. Identical to the cardiac module, it is a hospital-based, quality
improvement program, aiming to increase the rate of in-hospital implementation of evidence-based guidelines for secondary prevention of TIA/stroke. It incorporates educational strategies and the web based Patient Management Tool, thus providing a clinical care pathway for patients with TIA/stroke. The program is available for implementation via the ASA website. This program has shown sustained and statistically significant improvements (p < 0.0001) in a wide variety of acute stroke care and secondary prevention measures as shown in data reviewed on 42,029 patients at 139 US hospitals over the first 2 years of implementation (Schwamm, La Bresh et al. 2006). This study showed increased administration of antithrombotics within 48 hours (89.2% to 95.4%), discharge utilisation of antithrombotics (93% to 97%), treatment of LDL cholesterol ≥ 2.6mmol/L (56.4% to 75.2%), counseling for smoking cessation (40.4% to 59.2%), and counseling for weight loss for those with a BMI > 25 (26.3% to 34.8%) at the end of this initial 2 year period. For the 2,479 patients in this cohort with atrial fibrillation the percentage of patients that were anticoagulated increased from 81% to 95.8% at the end of this initial 2 year period.

In a separate review of a cohort of 33,897 patients from 65 of the hospitals with 2 years of participation in the “Get With The Guidelines - Stroke” program, the percentage of patients with “Defect-Free” stroke care (ie they received all appropriate interventions for which they were eligible) showed a statistically significant improvement from 66.6% at baseline to 74.1% at the end of this initial 2 year period (p < 0.0001) (Schwamm, La Bresh et al. 2006). Following from these studies the four year Get with The Guidelines - Stroke data from 2003 – 2007 from the much larger cohort of 322,847 patients with ischaemic stroke or TIA from 790 volunteer hospitals across the US has been published (Schwamm, Fonarow et al. 2009). Over the 4 year study period there were continued, statistically significant improvements shown in the implementation of secondary preventive measures: increased administration of antithrombotics within 48 hours (91.46% to 97.00%), increased discharge utilisation of antithrombotics (95.68% to 98.88%), increased treatment of LDL cholesterol ≥ 2.6 mmol/L (73.63% to 88.29%), counseling or medication for smoking cessation (65.21% to 93.61%), and increased use of anticoagulation for atrial fibrillation from 95% to 98.4% (p value < 0.0001 for all comparisons).

These studies show the benefits of a clinical pathway in the management of patients with stroke. Given that TIA and stroke can be considered different ends of the spectrum
of the same disease process (cerebral ischaemia), both of which require the same investigation and management, a clinical pathway should also be able to be of benefit in the management of patients with TIA.

1.13 Conclusion

The perception of TIA has significantly changed over the past 20 years, with increasing evidence from imaging studies of an increased likelihood of infarction with increasing symptom duration. The 24 hour definition of a TIA was created at a time when there was no acute treatment for stroke and the need to distinguish between TIA and stroke was not a matter of urgency. However, with the advent of thrombolysis for the treatment of acute ischaemic stroke within 3 hours of symptom onset, the need to redefine the time frame for duration of a TIA has become a priority in order to prevent unnecessary delay in the treatment of acute stroke patients. Hence, the rationale behind the proposed new definition for TIA as a brief episode of neurological dysfunction caused by focal brain or retinal ischaemia, with clinical symptoms lasting typically less than one hour, and without evidence of acute infarction (Albers, Caplan et al. 2002).

Along with this change in TIA definition is the realisation that a TIA can no longer be deemed a benign entity with studies showing that the risk of stroke following TIA is much higher than previously anticipated, with 90 day stroke risk following TIA ranging from 6% to 15% (Whisnant, Matsumoto et al. 1973; Johnston, Gress et al. 2000; Coull, Lovett et al. 2004; Gladstone, Kapral et al. 2004; Hill, Yiannakoulias et al. 2004; Kleindorfer, Panagos et al. 2005; Bray, Coughlan et al. 2007). This risk is heavily time dependent, with up to 50% of subsequent strokes occurring within the first 48 hours post-TIA (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004; Sciolla and Melis 2008). Up to one quarter of completed stroke patients have a preceding TIA; of which, 43% occur in the preceding week, 17% occur on the same day , and 9% the day before stroke (Rothwell and Warlow 2005). Thus, time is of the essence in investigating and managing TIA patients so as to implement known, effective secondary preventive measures so as to reduce the risk of subsequent stroke, yet TIAs remain under-investigated and under-treated.
In an ideal healthcare system, with immediate access to all necessary investigations for patients with TIA, the question of inpatient versus outpatient management would be immaterial. Studies have shown that urgent outpatient management (same day or within 24 hours) is very effective at ensuring secondary preventive measures are implemented and at reducing the risk of subsequent stroke (Lavallée, Meseguer et al. 2007; Rothwell, Giles et al. 2007). The same speed of service delivery may not be achievable outside these study settings; thus, inpatient management of high-risk patients with TIA remains necessary to expedite their urgent investigation and management. Prognostic scoring systems, such as the ABCD² score (Johnston, Rothwell et al. 2007), are of great practical use for front line physicians to identify those at highest risk of subsequent stroke and might prove helpful in triaging patients where access to investigations and follow-up is limited. However, the ABCD² score requires further validation given the mixed results it has achieved to date in terms of predicting risk of subsequent stroke (Cucchiara, Messe et al. 2006; Tsivgoulis, Spengos et al. 2006; Bray, Coughlan et al. 2007; Purroy, Molina et al. 2007; Sylaja, Choi et al. 2007; Tsivgoulis, Vassilopoulou et al. 2007; Sciolla and Melis 2008; Selvarajah, Smith et al. 2008; Calvet, Touze et al. 2009).

The main issue for the management of patients with TIA is to ensure all appropriate, evidence-based treatment measures are implemented, and all necessary investigations are performed expeditiously so as to put an end to the under-treatment of patients with TIA seen in hospital- and community-based studies (Dennis, Bamford et al. 1990; Ricci, Celani et al. 1991; Goldstein, Bian et al. 2000; Chang, Holroyd et al. 2002; Douglas, Johnston et al. 2003; Gladstone, Kapral et al. 2004; Lisabeth, Ireland et al. 2004; Edlow, Kim et al. 2006; Selvarajah, Smith et al. 2008). A promising potential method to improve utilisation of guidelines in everyday practice is through translation of the guidelines into clinical pathways which are designed to assist clinical decision making regarding diagnosis, investigation, and acute treatment in a standardised, efficient manner, and are based on the best available research evidence and are consistent with established clinical guidelines in order to optimize and streamline patient care and improve outcomes (Baker, Miller et al. 1998; Lanska 1998). The use of a clinical pathway has not been studied in a cohort of patients with TIA and minor stroke, and this study aims to assess whether a clinical pathway, which incorporates the ABCD² prognostic scoring system and the recommendations of evidence-based guidelines for the management of patients with TIA, can improve patient outcome with
respect to appropriate medical management, investigation, and reduce the risk of future stroke.
Section II Methodology
2.1 Hypothesis

A structured clinical pathway of care, which incorporates the ABCD² prognostic scoring system and is consistent with the most recent evidence-based guidelines for TIA management, to guide the management of patients with TIA will improve patient outcome with respect to appropriate medical management, investigation, time to follow-up and reduce the risk of future stroke.

2.2 Objectives

The main objective of this study was to evaluate the impact of a TIA/stroke clinical pathway with respect to the implementation of evidence-based medical management for patients with TIA, ensuring all appropriate investigations are ordered, optimisation of the timeframe to obtain these investigations, decision making regarding inpatient versus outpatient management, timeframe to hospital clinic follow-up, and patient outcomes at 90 days. The sub-objectives of the study were to evaluate the validity of the ABCD² prognostic scoring system for an Australian cohort of patients and to evaluate the effect of dichotomizing the ABCD² prognostic scoring system to predict risk of subsequent stroke at 90 days.

2.3 Study Design

Hospital-based, retrospective, cohort study, comparing outcomes in cohorts of patients before and after implementation of a treatment pathway.

2.4 Study Setting

The Royal Brisbane & Women’s Hospital (RBWH), Brisbane, Queensland, Australia is a 986 bed tertiary referral teaching hospital, providing services to patients throughout the States of Queensland, Northern New South Wales, the Northern Territory, and from neighboring countries in the South-West Pacific. The majority of patients,
approximately 65%, are drawn from within fifteen kilometers of the hospital. The 1996 Census of Population and Housing indicated the population of the area served was 481,257. The estimated population of the area served to 2006 was 548,574.

2.5 Time Period of the Study

The study was divided into two phases:

1. In the first phase, data was collected retrospectively during a six month period from 1 July 2006 – 31 Dec 2006 prior to implementation of the TIA/Stroke clinical pathway, during which time there was no specific protocol within the ED for the treatment of patients with TIA or for whether they required inpatient versus outpatient management.

2. In the second phase, data was collected retrospectively during a six month period from 12 June 2007 – 12 Dec 2007 following implementation of a TIA/stroke clinical pathway.

2.6 TIA/Stroke Clinical Pathway Development

The development of the TIA/stroke clinical pathway was carried out over a 6 month period from 15 January 2007 – 01 June 2007. To assist with the development of the pathway two project officers, who were both registered nurses, were appointed by the Clinical Practice Improvement Centre (CPIC) at RBWH. A TIA/stroke clinical pathway working committee was formed which comprised a Consultant Neurologist, a General Physician, an Emergency Physician, Stroke Fellow (author), senior Neurology and ED nurses, and the two project officers from CPIC.

The most recent guidelines for the management of TIA and stroke were reviewed from the American Stroke Association (Sacco, Adams et al. 2006; Adams, del Zoppo et al. 2007), National Stroke Association (Johnston, Nguyen-Huynh et al. 2006), the Royal College of Physicians (Intercollegiate stroke working party 2004; National Pre-hospital Guidelines Group 2006) and the Australian National Stroke Foundation (National Stroke Foundation 2003). Subsequent to the initial development of the TIA/stroke clinical pathway the Australian National Stroke Foundation released a new set of
guidelines for the management of TIA and stroke (National Stroke Foundation 2007), which were reviewed and no change to the content of the pathway was required. Significant studies of the management of TIA patients were reviewed, in particular the SPARCL study (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) (Amarenco, Bogousslavsky et al. 2006) which was published after the American Stroke Association, National Stroke Association and Royal College of Physicians most recent set of guidelines for the management of TIA. This evidence was incorporated into the management advice outlined in the TIA/stroke pathway.

Expert opinion was sought from all members of the working committee to ascertain where problems were felt to occur in the management of patients with TIA within the hospital and, in particular, what problems they encountered within their own departments.

The main problems highlighted by the TIA/stroke working group were;

1. Choice of antiplatelet agent

The question of which antiplatelet therapy of aspirin, combination aspirin and modified release dipyridamole, or clopidogrel should be recommended as first line was answered by reviewing the most recent stroke and TIA guidelines and the clinical trial evidence supporting these recommendations.

Following review of the relevant studies (Algra and van Gijn 1996; CAPRIE steering committee 1996; The ESPS-2 Group 1997; Algra and Van Gijn 1999; Diener, Bogousslavsky et al. 2004; The ESPRIT study group 2006) and the recent Australian and international guidelines for the management of stroke and TIA, it was decided to incorporate advice with regard to antiplatelet choice as outlined in Table 2.1, with aspirin plus modified release dipyridamole being advised as the long term agent of choice, (The ESPRIT study group 2006) with clopidogrel preferred if there was any contra-indication to Aspirin.

A titrated introduction of dipyridamole was incorporated into the clinical pathway given the problems seen both in the ESPRIT study and the second European Stroke Prevention Study (Diener, Cunha et al. 1996) where headache was the primary reason
for premature cessation of the study medication in the dipyridamole containing groups in approximately one quarter of patients.

**Table 2.1 Clinical Pathway Recommendations for Choice of Antiplatelet Agent**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>300mg</td>
<td>Oral</td>
<td>STAT</td>
<td><strong>ALL PATIENTS</strong> in whom haemorrhage has been excluded on CT Brain (unless contraindicated or the patient is receiving thrombolysis)</td>
</tr>
<tr>
<td>Asasentin SR (Aspirin/Dipyridamole)</td>
<td>25/200mg</td>
<td>Oral</td>
<td>BD</td>
<td>Headaches can be a side effect of taking Asasentin. To reduce the risk of the patient developing headaches, consider: Week 1: Asasentin SR 25/200mg once daily and Aspirin 100-150mg once daily Week 2: Increase to Asasentin SR 25/200mg bd and CEASE Aspirin.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75mg</td>
<td>Oral</td>
<td>Once Daily</td>
<td><strong>ONLY if Aspirin is contraindicated or patient is intolerant of Aspirin</strong></td>
</tr>
</tbody>
</table>

- For patients intolerant of Dipyridamole SR: Aspirin or Clopidogre is recommended.
- If the patient is currently taking Aspirin / Dipyridamole SR 25/200mg or Clopidogre: it is recommended that this be continued.
- If the patient is in Atrial Fibrillation, it is recommended they be admitted for Warfarinisation.

Evidence from 2 studies has shown that a titrating dose of modified release dipyridamole from 200mg per day to 400mg per day over a period of 5 days in 1 pilot study (n = 57) (Lindgren, Husted et al. 2004) and over 10 days in the second study (n = 146) (Chang, Ryu et al. 2006) causes fewer headaches, thereby increasing compliance.

2. **The use of a lipid lowering agent**

The second issue highlighted by the working group was which patients required treatment with a lipid lowering agent. The SPARCL study (Amarenco, Bogousslavsky et al. 2006) was published after the most recent set of guidelines from the American Stroke Association (Sacco, Adams et al. 2006), National Stroke Association (Johnston, Nguyen-Huynh et al. 2006; Johnston, Nguyen-Huynh et al. 2006), and the Royal College of Physicians (Intercollegiate Stroke Working Party 2004). Consequently, they do not automatically advise a lipid lowering agent for all patients (Table 1.14). The Australian NSF clinical guidelines for acute stroke management released in 2007 (National Stroke Foundation 2007) were published following the results of the SPARCL study and do recommend therapy with a statin for all patients with ischaemic stroke or TIA. They also recommend that patients with high cholesterol levels should
also receive dietary review and counseling with a specialist. This advice was incorporated into the TIA/stroke clinical pathway which advises that all patients with ischaemic stroke or TIA be treated with a lipid lowering agent.

3. Delays in acquiring outpatient investigations
The third issue highlighted by the working group was the delay in acquiring an outpatient carotid duplex and echocardiogram. This reflected a local problem within RBWH with regard to availability of these services, which may well be shared by many other centres both nationally and world wide. Discussions with representatives from both the departments of cardiology and vascular surgery were held and it was agreed that on the request-forms for these tests it would be documented whether or not the patient was deemed to be a high- or low-risk TIA patient (as per their ABCD² score) so as to assist each of these departments in their triage process. The time frame to investigation proposed was 2 days for those patients deemed to be high-risk (ABCD² score ≥ 4) and within 10 days for those deemed to be low-risk (ABCD² score < 4).

4. Availability of rapid access clinic review for patients discharged home
The fourth issue highlighted by the working group was the lack of availability of early clinic review for those patients discharged home after ED presentation. A weekly rapid access TIA clinic was established for the post-pathway phase (phase 2) of the study which was run by the stroke fellow (author) and stroke consultant. A medical “hot clinic” process was already in place prior to clinical pathway implementation within the hospital. This provided at least 2 clinic vacancies each day for patients discharged from the ED who required urgent review (within 1 week) post-discharge. The ED staff could book patients with TIA who were discharged from ED into a medical “hot clinic” during both phases of the study and had the option of utilizing the rapid access TIA clinic in phase 2 of the study.

5. Deciding which patients require inpatient versus outpatient management
The final issue highlighted by the working group was the uncertainty regarding which TIA patients required admission and who could be safely discharged for outpatient investigation. It was decided to utilize the ABCD² prognostic scoring system (Johnston, Rothwell et al. 2007) to address the question of which patients required admission for observation and rapid investigation versus those who could be safely discharged home. The ABCD² prognostic score has a maximum score of 7 and categorises patients into
high-risk (6 – 7 points), moderate-risk (4 – 5 points) and low-risk (0 – 3 points), Table 2.2. Those at moderate-risk have a risk of subsequent stroke of 4.1% at 2 days, 5.9% at 7 days, and 9.8% at 90 days (Johnston, Rothwell et al. 2007). The members of the TIA/stroke pathway working committee felt that this level of risk of subsequent stroke amongst those at moderate-risk warranted urgent management and investigation. Thus it was decided for the purpose of the TIA/stroke clinical pathway to dichotomise the ABCD² score into high-risk (≥ 4 points) and low-risk (0 – 3 points). Bray et al (2007) had already shown that the earlier ABCD score could be safely dichotomised into high and low-risk categories. Given that they deemed high-risk to be ≥ 5 points and low-risk ≤ 4 points, it was felt that the dichotimisation we had chosen was safe. The Australian National Stroke Foundation guidelines for the management of TIA and Stroke (National Stroke Foundation 2007), released following the development of the TIA/stroke clinical pathway, also based their management guidelines on a similar dichotimisation of the ABCD² score (high-risk ≥ 4 points, low-risk < 4 points).

There are a number of high-risk features for subsequent stroke not taken into account by the ABCD² score, where hospital admission may be warranted for urgent investigation and management irrespective of the patient’s ABCD² score. Examples included: atrial fibrillation or other cardio-embolic source of TIA, especially if requiring initiation of anticoagulation; poorly controlled hypertension; poorly controlled or newly diagnosed diabetes; recurrent or crescendo TIs; and internal carotid artery stenosis, especially if symptomatic and potentially requiring urgent revascularisation. The TIA/stroke working committee felt that it was prudent to incorporate these high-risk features into the management advice offered by the TIA/stroke pathway and recommend that in all of these instances the patient should be considered high-risk and admitted irrespective of their ABCD² score.

Patients with concurrent non-stroke comorbid problems were also eligible for admission if these problems were thought to require inpatient management.

The ED at the RBWH was accustomed to the utilisation of clinical pathways for many different conditions and the design of the TIA/stroke clinical pathway was modeled on the format already in use within the department (figure 2.1).
Table 2.2 ABCD² Prognostic Score (Johnston, Rothwell et al. 2007)

<table>
<thead>
<tr>
<th>Components of ABCD² Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60</td>
<td>1 point</td>
</tr>
<tr>
<td>Blood Pressure:</td>
<td></td>
</tr>
<tr>
<td>Systolic ≥ 140mmHg</td>
<td>1 point</td>
</tr>
<tr>
<td>Or</td>
<td></td>
</tr>
<tr>
<td>Diastolic ≥ 90mm Hg</td>
<td></td>
</tr>
<tr>
<td>Clinical Signs:</td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2 points</td>
</tr>
<tr>
<td>Speech Disturbance without weakness</td>
<td>1 point</td>
</tr>
<tr>
<td>Other</td>
<td>0 points</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 minutes</td>
<td>0 points</td>
</tr>
<tr>
<td>10-59 minutes</td>
<td>1 point</td>
</tr>
<tr>
<td>≥ 60 minutes</td>
<td>2 points</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 point</td>
</tr>
</tbody>
</table>

Ethical approval was granted for the study by The Royal Brisbane and Women’s Health Service District Human Research Ethics Committee and The Griffith University Human Research and Ethics Committee. The TIA/stroke clinical pathway was approved by both the RBWH Drug Committee and Forms Committee.

2.7 Pathway Implementation

An introductory educational period regarding the utilisation of the TIA/stroke pathway was performed in a tutorial format for ED, Internal Medicine, and Neurology staff. Separate tutorials were carried out with the ED nursing staff as their role was pivotal in initiating the pathway, triaging patients appropriately and, if necessary, contacting the
stroke team directly to review a potential thrombolysis patient. The tutorials continued throughout the second phase of the study, so as to educate any new staff members, and this also served as a forum to address any issues that arose during the study. An electronic version of the TIA/stroke clinical pathway was circulated to all ED and Internal Medicine doctors and ED nursing staff, so as to ensure that all involved staff members could familiarise themselves with the clinical pathway.

2.10 Subject Selection

A computerized system was in use within the ED (Emergency Department Information System (EDIS version 9, iSOFT, Australia, 2006), to record patient details, presenting symptoms, departure status, departure destination, and diagnosis as per the International Classification of Diseases code (ICD-10 code). Patients were identified by searching EDIS for the appearance of any of the following search terms in the presenting complaint: sensory loss of face, arm or leg; weakness of face, arm, or leg; speech disturbance (expressive dysphasia, receptive dysphasia, dysarthria, slurred speech); visual disturbance (hemianopia, amaurosis fugax, diplopia); ataxic gait/gait disturbance/unsteady gait; reduced co-ordination/ataxia; and dysphagia. In order to ensure complete acquisition of all TIA and mild stroke patients presenting to the ED who may have been missed by using the above search terms a search was also carried out of the ICD-10 code diagnosis entered in EDIS so as to include all patients with a discharge diagnosis of TIA (ICD code G45.9), stroke (ICD code I64) and cerebrovascular disease (ICD code I67.9) regardless of their presenting complaint.

2.11 Definition of Key Terms

For the purposes of this study the following definitions for key terms were adopted:

A transient ischemic attack (TIA) was defined as “rapidly developed clinical signs of focal or global disturbance of cerebral function lasting fewer than twenty-four hours, with no apparent non-vascular cause,” (Johnston, Nguyen-Huynh et al. 2006).
Figure 2.1 TIA/Stroke Clinical Pathway

This form should only be used for patients that have acute onset of one or more of the following:

- Weakness:
  - Face
  - Arm
  - Leg

- Sensory loss:
  - Face
  - Arm
  - Leg

(Tick as appropriate)

Assessment

- Primary and Secondary survey
- Symptoms < 6 hours of duration AND persistent neurological deficits
  - consider TRIAGE CATEGORY 2
  - contact STROKE TEAM
- Perform BSL on arrival (notify MO and treat if BSL < 3.5 or >10mmol/L, then reassess symptoms)
- Perform recommended blood tests and investigations
  - FBC, EILFT, Coags, ESR
  - Chest X-Ray
  - ECG
  - Non-contrast CT Brain

RMO to follow TIA flowchart overlay, and use as a guide to make clinical decisions based upon the recommendations

Recommendations for Anti-platelet therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>300mg</td>
<td>Oral</td>
<td>STAT</td>
<td>ALL PATIENTS in whom haemorrhage has been excluded on CT Brain (unless contraindicated or the patient is receiving thrombolysis)</td>
</tr>
<tr>
<td>Asasantin SR (Aspirin/Dipyridamole)</td>
<td>25/200mg</td>
<td>Oral</td>
<td>BD</td>
<td>Headaches can be a side effect of taking Asasantin. To reduce the risk of the patient developing headaches, consider: Week 1: Asasantin SR 25/200mg once daily and Aspirin 100-150mg once daily Week 2: Increase to Asasantin SR 25/200mg bd and CEASE Aspirin</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75mg</td>
<td>Oral</td>
<td>Once Daily</td>
<td>ONLY if Aspirin is contraindicated or patient is intolerant of Aspirin</td>
</tr>
</tbody>
</table>

- For patients intolerant of Dipyridamole SR: Aspirin or Clopidogrel is recommended.
- If the patient is currently taking Aspirin / Dipyridamole SR 25/200mg or Clopidogrel: it is recommended that this be continued.
- If the patient is in Atrial Fibrillation, it is recommended they be admitted for Warfarinisation

Signature Log

To be completed by all staff who initial this pathway

<table>
<thead>
<tr>
<th>DATE</th>
<th>NAME (print)</th>
<th>SIGNATURE</th>
<th>DESIGNATION</th>
</tr>
</thead>
</table>

76
A *stroke* was defined as “rapidly developing clinical symptoms and signs of focal, and at times global, disturbance of cerebral function, lasting more than twenty-four hours or leading to death, with no apparent cause other than that of vascular origin (Hatano 1976).

The modified Rankin Scale (van Swieten, Koudstaal et al. 1988) was used to distinguish between mild stroke and moderate-severe strokes (Table 2.3). If the stroke resulted in the patient having a modified Rankin Scale of < 3 it was deemed to be a *mild stroke*. If the stroke resulted in a modified Rankin Scale ≥ 3 it was deemed to be a *moderate–severe stroke*.

**Table 2.3 The Modified Rankin Scale (van Swieten, Koudstaal et al. 1988)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all.</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms: able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability: requiring some help, but able to walk without assistance.</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.</td>
</tr>
</tbody>
</table>

Patients were deemed to have a past history of *hypertension* if they had been prescribed an antihypertensive agent prior to the time of their presentation, whether or not they were adherent/compliant with therapy.
Patients were deemed to have a past history of dyslipidaemia if they had been prescribed a lipid lowering agent prior to the time of their presentation, whether or not they were adherent/compliant with therapy.

Patients were deemed to have atrial fibrillation if there was evidence of this on their admission electrocardiograph (ECG) or had a known history of paroxysmal atrial fibrillation in the past. Telemetry was not routinely available for those patients admitted to hospital.

2.12 Inclusion Criteria

1. All patients with one or more of the following symptoms lasting less than 24 hours in duration were included in the study:
   - Weakness of limbs+/- face
   - Sensory loss of limbs +/- face
   - Speech disturbance
     - Expressive dysphasia
     - Receptive dysphasia
     - Dysarthria
   - Visual disturbance
     - Hemianopia
     - Amarasis fugax.
     - Diplopia
   - Gait ataxia/Gait disturbance
   - Limb ataxia/Reduced co-ordination
   - Dysphagia

   All patients for whom an alternate diagnosis, other than TIA or stroke, for the above symptoms was not evident prior to their discharge from the ED were included.

2. All patients with an ED diagnosis of TIA, regardless of their presenting complaint, were eligible for inclusion.
3. Chart review was performed for all patients with an ED diagnosis of ischaemic stroke. If it was deemed to be a mild ischaemic stroke (modified Rankin Scale < 3) the patient was eligible for inclusion.

It was decided to include patients with mild ischaemic stroke for a number of reasons. The first being evidence from studies which have shown a wide variation in the diagnostic accuracy of TIA cases by Emergency Physicians ranging from 4/31 cases (13%) in a Portuguese study (Ferro, Falcao et al. 1996), to 1,604 /1,707 cases (94%) in a multi-centre study in California (Johnston, Gress et al. 2000). The second reason being the definition used for a mild stroke in this study was a stroke which resulted in a modified Rankin Scale of < 3, meaning the patient may have slight or no disability due to their symptoms. Ideally these patients should be admitted to hospital to expedite their investigation and medical management, however, in practical terms, such a patient may potentially be misdiagnosed as a TIA and discharged from ED. Supporting this is evidence from the larger of the 2 main study cohorts from which the ABCD² score was derived which included a percentage of patients with stroke despite only including those patients with an ED diagnosis of TIA: in the multi-centre study in California there were 182/1707 patients (10.6%) in whom their neurologic symptoms improved, but did not completely resolve, within 24 hours (Johnston, Gress et al. 2000) and 19/182 of these patients (10.4%) suffered a further stroke during the 90 day follow up. The third reason being evidence from neuroimaging studies of patients with TIA which have shown evidence of infarction in 8 – 30% in CT based studies (Ladurner, Sager et al. 1979; Calandre, Gomara et al. 1984; Bogousslavsky and Regli 1985; Bogousslavsky, Hachinski et al. 1986; Dennis, Bamford et al. 1990; Koudstaal, van Gijn et al. 1992; Sempere, Duarte et al. 1996; Kimura, Minematsu et al. 1999) and in 21 – 67% in MRI based studies (Kidwell, Alger et al. 1999; Rovira, Rovira-Gols et al. 2002; Crisostomo, Garcia et al. 2003; Inatomi, Kimura et al. 2004; Ay, Koroshetz et al. 2005; Coutts, Simon et al. 2005; Lamy, Oppenheim et al. 2006), suggesting that a proportion of the patients who meet the 24 hour time-frame definition for TIA used in this study may have suffered a mild ischaemic stroke.
2.13 Exclusion Criteria

Given that the only distinguishing factor between a stroke and a TIA is the duration of symptoms, the search terms used to identify potential study candidates identified both patients with TIA and patients with stroke. Upon review of the chart the patient was excluded if any of the following were found:

1. Moderate-severe ischaemic stroke (Modified Rankin Scale ≥ 3)
2. Haemorrhagic stroke
3. Other aetiology evident to the nursing staff at the time of triage that would explain any of the above presentations (for example known history of intra-cerebral space occupying lesion, multiple sclerosis causing focal neurological symptoms, complicated/hemiplegic migraine, abscess, spinal cord or disc disease, resolution of neurological symptoms with correction of hypoglycaemia, vestibular disorders, and local eye trauma).

2.14 Data Collection and Analysis

A retrospective chart review was performed by the author, using a standardized electronic form. The following details were recorded for each patient:

- Hospital identification number
- Age
- Gender
- Date of presentation to the ED
- Time of triage at the ED
- Presenting complaint and duration of symptoms
- Blood pressure and heart rate
- Whether an ECG was performed
- Blood sugar level
- Prior history of diabetes
- Whether a CT brain scan or MRI brain scan was performed, and the time from triage to first brain scan (CT or MRI)
• Whether the patient was previously treated with an antithrombotic agent, antihypertensive agent or statin, and if the dose of any of these medications was adjusted or a new agent commenced
• If and when a carotid duplex, echocardiogram, fasting lipids and glucose were performed
• Other stroke risk factors: personal or family history of ischaemic heart disease, family history of cerebrovascular disease, and smoking history
These data were utilised to calculate an ABCD² prognostic score for each patient so as to risk stratify patients into high-risk (4 – 7 points) or low-risk (0 – 3 points), and this was performed blinded as to the 90 day follow-up.

2.15 Patient Follow-up

Patients were followed up until they had a primary or secondary outcome event or reached 90 days from the index TIA or minor stroke; unless an alternate diagnosis had been reached for their index presentation during this period. This was performed by chart review of patient records of subsequent clinic reviews, presentations with recurrent TIA, subsequent stroke, vascular event, or for any other cause. For those patients with no record of follow-up in their hospital record at or after 90 days, phone call follow-up was performed.

In the second phase of the study the TIA/stroke clinical pathway recommended that all patients categorized as high-risk were to be admitted to hospital for a period of up to forty-eight hours so as to enable regular neurological observations to monitor for the occurrence of a subsequent stroke and allow all necessary investigations to be performed expediently. The TIA/stroke clinical pathway advised that patients categorized as low-risk could be discharged home with recommendations regarding appropriate medical management, outpatient investigation within 10 days and follow-up in clinic within 14 days of their initial presentation.
2.16 Definition of Outcome Events

The primary outcome was stroke occurring within 90 days of first presentation. The combined secondary outcome comprised first presentation with any of the following: stroke; recurrent TIA; other vascular event (angina, myocardial infarction, congestive cardiac failure, limb ischaemia, admission for other cardiac cause); or death due to any cause within 90 days of first presentation. If a patient presented with an outcome event on more than one occasion during the 90 day follow-up period only the first presentation was included for analysis.

2.17 Statistical Analysis

Data was initially entered into a Microsoft Office Excel 2003 (version 11, Microsoft) spreadsheet and then transferred to SPSS Statistics (version 17.0, SPSS Corporation) for analysis. An intention-to-treat approach was used in the post-pathway phase to analyse the data. In phase 2 of the study all eligible patients were included whether or not the TIA/stroke clinical pathway was actually used in their case.

A graphical method of exploratory data analysis using normal probability plots was performed on each quantitative variable to determine data distribution. A non-normal distribution was found in all cases and non-parametric tests were used for all calculations performed on quantitative data.

Baseline characteristics between the pre-pathway cohort, post-pathway cohort, and pathway-enrolled subgroup were analyzed to determine if there was a statistically significant relationship between the groups using cross-tabulation and a p value calculated using chi-square testing. If the sample size was too small to allow chi-square testing (any cell with an expected count of less than 5) Fisher’s exact test was applied to calculate a p value. Median age was compared between the 2 groups and a p value calculated using the Mann-Whitney U test.
The post-pathway cohort and the pathway-enrolled subgroup were assessed for any significant difference between these groups with respect to ED diagnosis and final diagnosis following investigation and review. A p value was calculated using chi-square testing.

To assess if there was a significant improvement in the medical management and performance of investigations for patients with TIA following implementation of the TIA/stroke clinical pathway for both the overall post-pathway cohort and for the subgroup of pathway-enrolled patients (unless any cell had an expected count of less than 5, in which case Fisher’s exact test was applied to calculate the p value). The same analysis was also performed comparing subgroups based on risk stratification, admission status and for the TIA subgroup (which excluded all patients who suffered a stroke).

To assess if there was any significant improvement in the timeframe for performing investigations and specialist follow-up following implementation of the TIA/stroke clinical pathway for both the overall post-pathway cohort and the subgroup of pathway-enrolled patients a p value was calculated using the Mann-Whitney U test.

To assess if there was any significant change in the rates of admission following implementation of the TIA/stroke clinical pathway a p value was calculated using chi-square testing, as the data collected was nominal data. The same analysis was also performed comparing subgroups based on risk stratification, and the TIA and stroke subgroups.

Fischer’s exact test was used to assess whether there was any significant difference in the primary outcome event of subsequent stroke between the pre- and post-pathway cohorts. This analysis was also performed comparing the subgroup of patients admitted versus those discharged from ED, and the TIA subgroup (which excluded all patients who suffered a stroke) versus the stroke subgroup.

To assess if there was any significant reduction in the number of secondary outcome events following implementation of the TIA/stroke clinical pathway a p value was calculated
using chi-square testing as the data collected was categorical data. This analysis was also performed comparing the subgroup of patients admitted versus discharged from ED. Fischer’s exact test was used to calculate a p value to assess if there was any significant difference in the number of secondary outcome events in the TIA subgroup (which excluded all patients who suffered a stroke) versus the stroke subgroup.

To assess if there was any significant difference between the ABCD² score for TIA or mild stroke versus a TIA mimic the median ABCD² score was calculated for both groups and a p value calculated using the Mann-Whitney U test. This was repeated comparing the median ABCD² score for the TIA subgroup (which excluded all patients who suffered a stroke) to that of the stroke subgroup.

A p value was calculated using cross tabulation and chi-square testing to assess if there was a significant relationship between the ABCD² score in the high-risk group of patients compared to the low-risk group of patients with respect to outcome events.

Data was entered to VassarStats: Website for Statistical Computation (Richard Lowry, 2001 – 2010) to calculate the sensitivity, specificity, positive predictive value and negative predictive value of the dichotomized version of the ABCD² score for primary and secondary outcome events. This calculation tool also calculated a 95% confidence interval for each result.
Section III: Results
3.1 Baseline Characteristics

In total, 921 patients were retrospectively identified as potential candidates for inclusion: 479 in the pre-pathway phase and 442 in the post-pathway phase. Of these patients, 11 were excluded as their case notes were missing (4 in the pre-pathway phase and 7 in the post-pathway phase). Following retrospective review of the case notes the total number eligible for inclusion was 238 patients (104 in the pre-pathway cohort and 134 in the post-pathway cohort) as shown in figure 3.1. Using presenting symptoms to identify patients for inclusion, in addition to ED diagnosis, allowed the identification of 24/238 (10%) patients; 10 in the pre-pathway phase and 14 in the post-pathway phase.

Figure 3.1 Cases Eligible for Inclusion
Of the 24 patients identified on the basis of their presenting symptoms, no diagnosis was reached in ED in 15 (62.5%) cases; 6 in the pre-pathway phase and 9 in the post-pathway phase. An alternate diagnosis was reached in the remaining 9 (37.5%) cases; 4 in the pre-pathway phase and 5 in the post-pathway phase. The final diagnosis in 23/24 (95.8%) cases following investigation and review was TIA.

Of the 134 patients in the post-pathway cohort the pathway was used in only 60 patients (44.8%), as evidenced by the pathway document being filed in the medical record. This subgroup was labelled pathway-enrolled, and some of the analysis was conducted on this subgroup. There were a higher proportion of patients with an ED diagnosis of TIA/stroke in the subgroup of pathway-enrolled patients compared to the subgroup who were not enrolled on the pathway, which just reached statistical significance. However, there was no significant difference in the final diagnosis following investigation and review as outlined in Table 3.1.

Table 3.1 Comparison of Diagnoses in the Pathway-Enrolled Subgroup Compared to those Not Enrolled on the Pathway

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pathway-enrolled (n = 60)</th>
<th>Non-pathway-enrolled (n = 74)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ED diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TIA/minor ischaemic stroke</td>
<td>58 (96.6%)</td>
<td>62 (83.8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>• Alternate diagnosis</td>
<td>1 (1.7%)</td>
<td>4 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>• No diagnosis</td>
<td>1 (1.7%)</td>
<td>8 (10.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Final diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TIA/minor ischaemic stroke</td>
<td>42 (70.0%)</td>
<td>49 (66.2%)</td>
<td>0.64</td>
</tr>
<tr>
<td>• Mimic</td>
<td>18 (30.0%)</td>
<td>25 (33.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Overall, there were no significant differences in the baseline characteristics between each cohort as outlined in Table 3.2.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre–Pathway (n = 104)</th>
<th>Post–Pathway (n = 134)</th>
<th>p value</th>
<th>Pathway enrolled (n = 60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (Interquartile range)</td>
<td>65 (29) years</td>
<td>67 (30) years</td>
<td>0.58</td>
<td>66 (35-92) years</td>
<td>0.98</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.96</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Male</td>
<td>50 (48.1%)</td>
<td>64 (47.8%)</td>
<td></td>
<td>29 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54 (51.9%)</td>
<td>70 (52.2%)</td>
<td></td>
<td>31 (51.7%)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>31 (29.8%)</td>
<td>49 (36.6%)</td>
<td>0.27</td>
<td>21 (35%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (48.1%)</td>
<td>64 (47.8%)</td>
<td>0.96</td>
<td>29 (48.3%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>34 (32.7%)</td>
<td>55 (41%)</td>
<td>0.19</td>
<td>26 (43.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (16.3%)</td>
<td>23 (17.2%)</td>
<td>0.87</td>
<td>9 (15%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>25 (24%)</td>
<td>27 (20.1%)</td>
<td>0.47</td>
<td>15 (25%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7 (6.7%)</td>
<td>15 (11.2%)</td>
<td>0.24</td>
<td>6/(10%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Warfarinised</td>
<td>3/7 (43%)</td>
<td>6/15 (40%)</td>
<td>0.63</td>
<td>3/6 (50%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Antithrombotic agent at presentation</td>
<td>43 (41.3%)</td>
<td>67 (50%)</td>
<td>0.18</td>
<td>31 (51.7%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Current smoker</td>
<td>29 (27.8%)</td>
<td>29 (21.6%)</td>
<td>0.14</td>
<td>16/ (26.7%)</td>
<td>0.63</td>
</tr>
</tbody>
</table>
3.2 Impact of TIA/Stroke Clinical Pathway on the Implementation of Evidence-based Medical Management of TIA Patients

There was a significant increase in the proportion of patients taking antithrombotic agents and statins at discharge following pathway implementation, although no significant change was seen in the use of warfarin in patients with AF or in the proportion of patients taking an antihypertensive agent at the time of discharge. This data is summarised in Table 3.3.

Table 3.3 Medical Management Pre- and Post-TIA/Stroke Pathway Implementation

<table>
<thead>
<tr>
<th>Treatment on discharge</th>
<th>Pre-Pathway n = 104</th>
<th>Post-Pathway n = 134</th>
<th>p value</th>
<th>Pathway-enrolled n = 60</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic agent</td>
<td>73 (70.2%)</td>
<td>120 (89.6%)</td>
<td>&lt;0.001</td>
<td>56 (93.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>40 (38.5%)</td>
<td>80 (59.7%)</td>
<td>0.001</td>
<td>42 (70.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive agent</td>
<td>52 (50%)</td>
<td>76 (56.7%)</td>
<td>0.30</td>
<td>35 (58.3%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Warfarinised for AF</td>
<td>3/7 (43.0%)</td>
<td>6/15 (40.0%)</td>
<td>0.63</td>
<td>3/6 (50.0%)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

The significant increase in the proportion of patients prescribed an antithrombotic agent and a statin at their time of discharge was restricted to those patients who were discharged from ED (Table 3.4).
Table 3.4 Medical Management for those Admitted versus Discharged from ED

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-Pathway n = 104 n (%)</th>
<th>Post-Pathway n = 134 n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti thrombotic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Admitted</td>
<td>37/46 (80.4%)</td>
<td>66/74 (89.2%)</td>
<td>0.18</td>
</tr>
<tr>
<td>- Discharged</td>
<td>36/58 (62.1%)</td>
<td>54/60 (90.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Admitted</td>
<td>25/46 (54.3%)</td>
<td>49/74 (66.2%)</td>
<td>0.19</td>
</tr>
<tr>
<td>- Discharged</td>
<td>15/58 (25.9%)</td>
<td>31/60 (51.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Antihypertensive agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Admitted</td>
<td>28/46 (60.9%)</td>
<td>47/74 (63.5%)</td>
<td>0.77</td>
</tr>
<tr>
<td>- Discharged</td>
<td>24/58 (41.1%)</td>
<td>29/60 (48.3%)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Of the 58/134 (43.3%) patients in the post-pathway cohort of this study who were not commenced on an antihypertensive agent the reason for this is outlined in Table 3.5.

Table 3.5 Reasons why Patients were not commenced on an Antihypertensive Agent in the Post-Pathway Cohort

<table>
<thead>
<tr>
<th>Reason for not commencing an antihypertensive agent</th>
<th>Post-pathway cohort n = 58 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension (Systolic BP &lt; 100mmHg)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Normotensive (BP &lt; 140/90mmHg)</td>
<td>35 (60.3%)</td>
</tr>
<tr>
<td>Normotensive on follow-up (BP &lt; 140/90mmHg)</td>
<td>6/(10.3%)</td>
</tr>
<tr>
<td>Advised to follow-up with GP for repeat BP testing</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>No documented reason and BP ≥ 140/90mmHg</td>
<td>11 (19%)</td>
</tr>
</tbody>
</table>
In total there were 22 patients with atrial fibrillation in this study (7 pre-pathway, 15 post-pathway cohort), of whom 12/22 (54.5%) were not warfarinised. For 5/12 (41.7%) patients the reason for not commencing warfarin was due to their high risk of haemorrhage (1 of these 5 patients represented 3 days later with a recurrent TIA and was subsequently warfarinised). In 2/12 (16.7%) cases the patient’s care was changed to palliative during their hospital admission (1 patient suffered a subsequent stroke on day 1 following the index TIA, the other was initially diagnosed as a TIA in the ED, but their final diagnosis was a total anterior circulation stroke). In 3/12 (25%) cases the patient’s advanced age was the reason quoted for not commencing warfarin; 2 of these patients were aged over 90, the third was aged 84 and had a history of mild dementia. The latter 84 year old patient was discharged home on Asasantin SR, but subsequently changed to warfarin 4 days later in clinic following discussion with both the patient and her daughter. In 1/12 (8.3%) cases that were not warfarinised no reason was documented for this decision. Full details of these patients are outlined in Table 3.6.

Of the 22 patients in atrial fibrillation, 4 (18.2%) were deemed to be low-risk, as per their ABCD² score, and there were no outcome events within this group. Of the 18 (81.8%) patients deemed to be high-risk, as per their ABCD² score (≥ 4 points); 90 day follow was available for 17 patients. Of these high-risk patients 8/17 (47%) had an outcome event within the 90 day follow-up; 1 primary outcome event at day 1 and 8 secondary outcome events. In 5 of these 8 cases (62.5%) the patient had not been warfarinised.

### 3.3 Impact of TIA/Stroke Clinical Pathway on the Performance and Timeliness of Investigations

No significant change was seen in the rate of neuroimaging within 24 hours of ED presentation. An increase in the performance of MRI brain scanning post-clinical pathway implementation just reached significance (p = 0.05); however, MRI was only used in a minority of cases (Table 3.7).
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Age</th>
<th>Reason why unsuitable for warfarin</th>
<th>ABCD² Score</th>
<th>Antithrombotic used</th>
<th>Recurrent event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>84</td>
<td>Advanced age &amp; history of dementia</td>
<td>6</td>
<td>Asasantin SR</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>Advanced Age</td>
<td>5</td>
<td>Nil (GP later commenced aspirin)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>Prior subdural haematoma while on warfarin.</td>
<td>5</td>
<td>Aspirin</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>Not documented.</td>
<td>4</td>
<td>Aspirin</td>
<td>Unable to follow-up</td>
</tr>
<tr>
<td>Post-pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>78</td>
<td>History of ethanol misuse and prior melaena.</td>
<td>5</td>
<td>Asasantin SR</td>
<td>Death (Cardiac arrest 9 days later)</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>Diagnosed with breast cancer during admission requiring surgery.</td>
<td>5</td>
<td>Asasantin SR</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>Prior subdural haematoma while on warfarin.</td>
<td>5</td>
<td>Aspirin</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>Prior GI bleed. History of bowel cancer</td>
<td>4</td>
<td>Asasantin SR</td>
<td>TIA (3 days later).</td>
</tr>
<tr>
<td>5</td>
<td>93</td>
<td>Advanced age</td>
<td>5</td>
<td>Clopidogrel</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>History of Parkinsons disease and dementia; family declined warfarinisation</td>
<td>4</td>
<td>Aspirin</td>
<td>CCF (37 days later)</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>Care changed to palliative during admission.</td>
<td>6</td>
<td>Asasantin SR</td>
<td>Death (19 days later)</td>
</tr>
<tr>
<td>8</td>
<td>87</td>
<td>History of dementia, non compliant with warfarin for 4/52.</td>
<td>4</td>
<td>Nil</td>
<td>Stroke (Day 1). Care changed to palliative.</td>
</tr>
</tbody>
</table>
Table 3.7 Investigations Performed Pre and Post TIA/Stroke Pathway Implementation

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Pre-Pathway n = 104</th>
<th>Post-Pathway All patients n = 134</th>
<th>p value</th>
<th>Post-pathway Pathway-enrolled n = 60</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Neuro-imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Total</td>
<td>92 (88.5%)</td>
<td>112 (83.6%)</td>
<td>0.29</td>
<td>56 (93.3%)</td>
<td>0.31</td>
</tr>
<tr>
<td>• Within 3 hours</td>
<td>42 (40.4%)</td>
<td>45 (33.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Within 24 hours</td>
<td>91 (87.5%)</td>
<td>110 (82.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Within 30 days</td>
<td>92 (88.5%)</td>
<td>112 (83.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Total</td>
<td>14 (13.5%)</td>
<td>32 (24%)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• within 24 hours</td>
<td>3 (2.8%)</td>
<td>5 (3.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• within 30 days</td>
<td>10 (9.6%)</td>
<td>23 (17.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipids</td>
<td>41 (39.4%)</td>
<td>88 (65.7%)</td>
<td>&lt;0.001</td>
<td>51 (85%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>33 (31.7%)</td>
<td>64 (47.8%)</td>
<td>0.01</td>
<td>38 (63.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid Duplex</td>
<td>60 (57.7%)</td>
<td>82 (61.2%)</td>
<td>0.55</td>
<td>46 (76.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>41 (39.4%)</td>
<td>62 (46.3%)</td>
<td>0.49</td>
<td>37 (61.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>ECG</td>
<td>90 (86.5%)</td>
<td>115 (85.8%)</td>
<td>0.87</td>
<td>56 (93.3%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>
There were 34 patients who did not undergo neuroimaging within 30 days; 12/104 (11.5%) pre-pathway and 22/134 (16.4%) post-pathway. In 3/34 (8.8%) the patient refused to have neuroimaging, in the remaining 31 (91.2%) neuroimaging was not ordered by the attending doctor. In 1/34 (3%) case, from the post-pathway cohort, the patient underwent an MRI brain scan at day 30 following the index TIA when she re-presented with a recurrent TIA.

There was no change in the percentage of patients who underwent ECG. There was a statistically significant increase in the percentage of patients who had fasting lipids and fasting glucose testing performed (Table 3.7). The improvement in fasting lipid testing was seen regardless of whether or not the patient was admitted or discharged from ED, however, the significant improvement seen in fasting glucose testing was restricted to the subgroup of patients who were admitted to hospital (Table 3.8).

For the overall post-pathway cohort there was no significant increase in the percentage of patients who underwent carotid duplex or echocardiogram, regardless of admission status (Tables 3.7 and 3.8). However, in the subgroup of pathway-enrolled patients there was a significant increase in the rate of utilisation of both these tests (Table 3.7).
For those patients who did not undergo a carotid duplex; 44/104 (42.3%) pre-pathway and 52/134 (38.8%) post-pathway; the reasons for this are outlined in Table 3.9.
Table 3.9 Patients who did not have a Carotid Duplex

<table>
<thead>
<tr>
<th>Reason</th>
<th>Pre-Pathway n = 44</th>
<th>Post-Pathway n = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Not ordered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Total</td>
<td>21 (47.7%)</td>
<td>18 (34.6%)</td>
</tr>
<tr>
<td>• Arterial territory causing symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anterior circulation</td>
<td>15 (34.1%)</td>
<td>13 (25.0%)</td>
</tr>
<tr>
<td>• Posterior circulation</td>
<td>6 (13.6%)</td>
<td>5 (9.6%)</td>
</tr>
<tr>
<td>Not an operative candidate</td>
<td>1 (2.3%)</td>
<td>13 (25.0%)</td>
</tr>
<tr>
<td>Patient declined investigation</td>
<td>1 (2.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Ordered, but not performed</td>
<td>3 (6.8%)</td>
<td>0</td>
</tr>
<tr>
<td>TIA mimic</td>
<td>18 (40.9%)</td>
<td>21 (40.4%)</td>
</tr>
</tbody>
</table>

A significant improvement in the timeliness of carotid duplex was seen, but not for echocardiography (Table 3.10). However, data was incomplete as some of these outpatient investigations were performed at private institutions. If the patient was unable to recall the date of the investigation it was not included for analysis.

Table 3.10 Timeframe to Investigations Pre- and Post-TIA/Stroke Pathway Implementation

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Pre-Pathway n Median number of days (Interquartile range)</th>
<th>Post-Pathway n Median number of days (Interquartile range)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid duplex</td>
<td>50 (11 (29))</td>
<td>73 (6 (11))</td>
<td>0.001</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>34 (8 (86))</td>
<td>50 (7 (45))</td>
<td>0.89</td>
</tr>
</tbody>
</table>
3.4 Impact of TIA/Stroke Clinical Pathway on Decision Making Regarding Inpatient versus Outpatient Management

Dichotomising the ABCD² score categorised a similar percentage of patients as high-risk of subsequent stroke in both cohorts (Table 3.11). Whilst there was a non-significant, approximately 9%, increase in the total proportion of patients admitted following clinical pathway implementation, there was a significant increase in the proportion of high-risk patients admitted for urgent investigation and observation (Table 3.11).

On review of the 18 low-risk patients in the post-pathway cohort who were admitted to hospital for urgent investigation and management, only 2 were due to reasons specified by the pathway as “complicating factors requiring admission.” In both cases the reason for admission was recurrent TIA. Only 1/18 (5.6%) patient in this subgroup had a history of atrial fibrillation and was already on treatment with warfarin prior to admission.

### Table 3.11 Risk Stratification of Patients

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>Pre-Pathway</th>
<th>Post-Pathway</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of patients</strong></td>
<td>104 (100%)</td>
<td>134 (100%)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Total admitted</strong></td>
<td>46/104 (44.2%)</td>
<td>74/134 (55.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>High-risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number (%)</td>
<td>65/104 (62.5%)</td>
<td>86/134 (64.2%)</td>
<td></td>
</tr>
<tr>
<td>Admitted (% of total high risk)</td>
<td>31/65 (47.7%)</td>
<td>56/86 (65.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Low-risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (% of cohort)</td>
<td>39/104 (37.5%)</td>
<td>48/134 (35.8%)</td>
<td></td>
</tr>
<tr>
<td>Admitted (% of total low-risk)</td>
<td>15/39 (38.5%)</td>
<td>18/48 (37.5%)</td>
<td>0.93</td>
</tr>
</tbody>
</table>
3.5 Impact of TIA/Stroke Clinical Pathway on Timeframe to Specialist Follow-up

For patients discharged from the ED, 58/104 (55.8%) of the pre-pathway cohort and 60/134 (44.8%) of the post-pathway cohort, there was no significant increase in the percentage of patients who received hospital clinic follow-up: 30/58 (52%) pre-pathway and 35/60 (58.3%) post-pathway (p = 0.47). However, there was a significant reduction in the median number of days to hospital clinic follow-up, from 13.5 days pre-pathway (interquartile range 24) to 8 days post-pathway (interquartile range 10) (p = 0.02).

3.6 Patient Outcomes at 90 Days

Follow-up for outcome events at 90 days was available for 95/104 (91.3%) patients in the pre-pathway cohort and for 123/134 (91.8%) patients in the post-pathway cohort. The patients lost to follow-up were those who did not have a record of being reviewed at, or after, 90 days in their hospital medical record and were unable to have phone-call follow-up, either due to a change in contact details (pre-pathway n = 2, post-pathway n = 1) or failure to return the consent form to give consent for phone-call follow-up (pre-pathway n = 7, post-pathway n = 10). In the pre-pathway cohort follow-up was obtained by review of medical records in 73 (70.2%) cases and by telephone enquiry in 22 (21.1%) cases. In the post-pathway cohort follow-up was obtained by review of medical records in 102 (76.1%) cases and by telephone enquiry in 21 (15.7%) of cases.

3.6.1 Primary Outcome Events

The primary endpoint of stroke occurred in 3/95 (3.2%) patients in the pre-pathway cohort and in 1/123 (0.8%) patients in the post-pathway cohort (p = 0.22). In 2/4 (50%) patients the stroke occurred within the first 48 hours. All 4 of these patients were deemed to be high-risk as per their ABCD² score. The single stroke in the post-pathway cohort occurred on day 1 post TIA in an 87 year old lady with atrial fibrillation who had been non-
compliant with her warfarin for 1 month prior to presentation. Details regarding each patient with a primary outcome event are outlined in Table 3.12.

### 3.6.2 Secondary Outcome Events

Whilst there was an increase in the percentage of patients with the combined secondary endpoint of first presentation with any of the following: stroke, recurrent TIA, other vascular event (angina, myocardial infarction, congestive cardiac failure, limb ischaemia or admission for other cardiac cause), or death due to any cause within 90 days of first presentation, this did not reach statistical significance: 10/95 (10.5%) patients in the pre-pathway cohort and 17/123 (13.8%) patients in the post-pathway cohort (p = 0.46). Patient details are outlined in Tables 3.13 and 3.14.
### Table 3.12 Details of Patients with a Primary Outcome Event (Subsequent Stroke) within 90 Days

<table>
<thead>
<tr>
<th>Pre-Pathway</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms of initial TIA</th>
<th>ABCD² score</th>
<th>Admitted</th>
<th>ECG</th>
<th>Carotid duplex</th>
<th>Echo</th>
<th>Fasting lipids &amp; glucose</th>
<th>Days to stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>F</td>
<td>Left arm &amp; leg weakness.</td>
<td>5</td>
<td>No</td>
<td>SR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>Ataxia, diplopia &amp; dizziness.</td>
<td>5</td>
<td>Yes</td>
<td>SR</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>F</td>
<td>Left arm &amp; leg weakness &amp; numbness.</td>
<td>4</td>
<td>No</td>
<td>SR</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-Pathway</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms of initial TIA</th>
<th>ABCD² score</th>
<th>Admitted</th>
<th>ECG</th>
<th>Carotid duplex</th>
<th>Echo</th>
<th>Fasting lipids &amp; glucose</th>
<th>Days to stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>F</td>
<td>Right arm weakness &amp; expressive dysphasia.</td>
<td>4</td>
<td>Yes</td>
<td>AF</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Sinus Rhythm (SR). Atrial Fibrillation (AF)
Table 3.13 Details of Pre-Pathway Patients with Secondary Outcome Event within 90 Days

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Age</th>
<th>Sex</th>
<th>Initial TIA Symptoms</th>
<th>ABCD² score</th>
<th>Admitted</th>
<th>ECG</th>
<th>Recurrent event</th>
<th>Days to event</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA 1</td>
<td>90</td>
<td>F</td>
<td>Vertigo &amp; nausea</td>
<td>2</td>
<td>Yes</td>
<td>SR</td>
<td>Left face &amp; arm weakness</td>
<td>10</td>
</tr>
<tr>
<td>TIA 2</td>
<td>77</td>
<td>M</td>
<td>Left sided weakness</td>
<td>5</td>
<td>Yes</td>
<td>SR</td>
<td>Left arm &amp; leg weakness</td>
<td>57</td>
</tr>
<tr>
<td>TIA 3</td>
<td>82</td>
<td>F</td>
<td>Right arm weakness &amp; expressive dysphasia</td>
<td>5</td>
<td>Yes</td>
<td>AF</td>
<td>Right arm weakness &amp; expressive dysphasia</td>
<td>78</td>
</tr>
<tr>
<td>Vascular Event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Event 1</td>
<td>83</td>
<td>F</td>
<td>Expressive dysphasia</td>
<td>5</td>
<td>Yes</td>
<td>SR</td>
<td>CCF</td>
<td>77</td>
</tr>
<tr>
<td>Vascular Event 2</td>
<td>92</td>
<td>F</td>
<td>Left facial numbness &amp; weakness</td>
<td>4</td>
<td>No</td>
<td>SR</td>
<td>Angina</td>
<td>84</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death 1</td>
<td>66</td>
<td>F</td>
<td>Left sided weakness &amp; dysarthria.</td>
<td>4</td>
<td>No</td>
<td>SR</td>
<td>Lung Ca</td>
<td>15</td>
</tr>
<tr>
<td>Death 2</td>
<td>87</td>
<td>F</td>
<td>Left sided weakness</td>
<td>5</td>
<td>No</td>
<td>SR</td>
<td>Aspiration pneumonia</td>
<td>46</td>
</tr>
</tbody>
</table>

Congestive cardiac failure (CCF), Sinus Rhythm (SR). Atrial Fibrillation (AF).
Table 3.14 Details of Post-Pathway Patients with a Secondary Outcome Event within 90 Days

<table>
<thead>
<tr>
<th>Outcome event</th>
<th>Age</th>
<th>Sex</th>
<th>Initial TIA symptoms</th>
<th>ABCD² score</th>
<th>Admitted</th>
<th>ECG</th>
<th>Recurrent event</th>
<th>Days to event</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>Ataxia &amp; visual disturbance</td>
<td>4</td>
<td>Yes</td>
<td>AF</td>
<td>Homonymous hemianopia</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>M</td>
<td>Amarosis Fugax</td>
<td>0</td>
<td>PD</td>
<td>SR</td>
<td>Left arm weakness</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>F</td>
<td>Left sided numbness</td>
<td>4</td>
<td>Yes</td>
<td>AF</td>
<td>Left sided weakness &amp; numbness</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>M</td>
<td>Right arm &amp; leg numbness*</td>
<td>4</td>
<td>Yes</td>
<td>SR</td>
<td>Right hemi-sensory loss</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>M</td>
<td>Right sided weakness &amp; numbness</td>
<td>3</td>
<td>Yes</td>
<td>SR</td>
<td>Bilateral loss of vision &amp; vertigo</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>81</td>
<td>M</td>
<td>Right sided weakness &amp; numbness x 3 episodes</td>
<td>5</td>
<td>Yes</td>
<td>SR</td>
<td>2 episodes of right sided weakness &amp; numbness</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>F</td>
<td>Left face &amp; arm numbness &amp; dysarthria</td>
<td>4</td>
<td>No</td>
<td>SR</td>
<td>Left face &amp; arm numbness</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>F</td>
<td>Expressive &amp; receptive dysphasia*</td>
<td>5</td>
<td>Yes</td>
<td>SR</td>
<td>Expressive Dysphasia</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>F</td>
<td>Confusion</td>
<td>2</td>
<td>Yes</td>
<td>SR</td>
<td>Confusion</td>
<td>89</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>57</td>
<td>M</td>
<td>Right facial weakness &amp; numbness</td>
<td>4</td>
<td>PD</td>
<td>SR</td>
<td>Angina requiring stent insertion</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>M</td>
<td>Left sided weakness &amp; expressive dysphasia</td>
<td>6</td>
<td>Yes</td>
<td>AF</td>
<td>Ischaemic left foot</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>M</td>
<td>Right sided weakness</td>
<td>4</td>
<td>No</td>
<td>AF</td>
<td>CCF</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>F</td>
<td>Facial numbness</td>
<td>3</td>
<td>No</td>
<td>SR</td>
<td>Admission with rapid AF</td>
<td>62</td>
</tr>
</tbody>
</table>
Table 3.14 continued. Details of Post-Pathway Patients with a Secondary Outcome Event within 90 Days

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Age</th>
<th>Sex</th>
<th>Initial TIA symptoms</th>
<th>ABCD² score</th>
<th>Admitted</th>
<th>ECG</th>
<th>Recurrent event</th>
<th>Days to event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>Left face &amp; arm weakness</td>
<td>5</td>
<td>Yes</td>
<td>AF</td>
<td>Cardiac arrest</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>F</td>
<td>Right sided weakness &amp; expressive dysphasia†</td>
<td>6</td>
<td>Yes</td>
<td>AF</td>
<td>Due to initial event</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>F</td>
<td>Right sided weakness</td>
<td>4</td>
<td>No</td>
<td>SR</td>
<td>Myocardial infarction</td>
<td>80</td>
</tr>
</tbody>
</table>

*Minor ischaemic stroke.

Sinus Rhythm (SR). Atrial fibrillation (AF)

Patient declined (PD)

Congestive cardiac failure (CCF)

† Included as the ED diagnosis was TIA, however it was a major ischaemic stroke (modified rankin scale = 6)
There was no significant difference between the numbers of outcome events in those admitted versus those discharged from ED following pathway implementation (Table 3.15).

Table 3.15 Outcome events for those Admitted versus Discharged from ED

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Pathway n = 95 n (%)</th>
<th>Post-Pathway n = 123 n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Admitted</td>
<td>1/45 (2.2%)</td>
<td>1/70 (1.4%)</td>
<td>0.75</td>
</tr>
<tr>
<td>• Discharged</td>
<td>2/50 (4.0%)</td>
<td>0/53 (0.0%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Secondary outcome event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Admitted</td>
<td>5/45 (11.1%)</td>
<td>11/70 (15.7%)</td>
<td>0.49</td>
</tr>
<tr>
<td>• Discharged</td>
<td>5/50 (10.0%)</td>
<td>6/53 (11.3%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

3.7 Evaluation of the Validity of the ABCD² Prognostic Scoring System

In this study approximately one third of patients were ultimately deemed to be a TIA mimic (77/238, 33%). The most frequently encountered causes of a TIA mimic in this study are outlined in Table 3.16.

The median ABCD² score was 4 (interquartile range 2) for those with a TIA or stroke and 3 (interquartile range 2) for those found to be a TIA mimic, a difference which was statistically significant (p < 0.001) (Figure 3.2).
Table 3.16 Most Common Diagnoses among TIA Mimics in this Study

<table>
<thead>
<tr>
<th>TIA Mimic Diagnosis</th>
<th>Frequency of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>19 (24.6%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>7 (9.1%)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>5 (6.5%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4 (5.2%)</td>
</tr>
<tr>
<td>Demyelination</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Cardiac arrythmia</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Peripheral nerve palsy</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Total number of TIA mimics</td>
<td>77 (100%)</td>
</tr>
</tbody>
</table>

Figure 3.2 Median ABCD² score and Interquartile Range for TIA/Minor Stroke and TIA Mimics
There were 151 high-risk patients in this study, of which 116 (76.8%) were deemed to be a TIA or stroke. There were 87 low-risk patients in this study, of which 45 (51.7%) were deemed to be a TIA or stroke (see Table 3.17).

**Table 3.17 Percentage of Patients with TIA/Stroke versus TIA Mimic in each Risk Category**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>TIA/stroke</th>
<th>TIA mimic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk (ABCD² score ≥ 4)</td>
<td>116 (76.8%)</td>
<td>35 (23.2%)</td>
<td>151 (100%)</td>
</tr>
<tr>
<td>Low-risk (ABCD² score &lt; 4)</td>
<td>45 (51.7%)</td>
<td>42 (48.3%)</td>
<td>87 (100%)</td>
</tr>
<tr>
<td>Totals</td>
<td>161</td>
<td>77</td>
<td>238</td>
</tr>
</tbody>
</table>

The frequency of each ABCD² score for both the TIA/stroke and TIA mimic cohorts is shown in Table 3.18.
Table 3.18 Frequency of each ABCD² Score in TIA/Stroke Group compared to TIA Mimic Group

<table>
<thead>
<tr>
<th>ABCD² score</th>
<th>TIA/stroke n (%)</th>
<th>TIA mimic n (%)</th>
<th>Totals n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (66.7%)</td>
<td>1 (33.3%)</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>10 (76.9%)</td>
<td>3 (23.1%)</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>13 (39.4%)</td>
<td>20 (60.6%)</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>20 (52.6%)</td>
<td>18 (47.4%)</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>54 (69.2%)</td>
<td>24 (30.8%)</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>43 (81.1%)</td>
<td>10 (18.9%)</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>17 (94.4%)</td>
<td>1 (5.6%)</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>2 (100.0%)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>161 (67.6%)</td>
<td>77 (32.4%)</td>
<td>238 (100%)</td>
</tr>
</tbody>
</table>

In this study a low-risk ABCD² score (< 4) could not be used to distinguish a TIA from a TIA mimic. However, there was a statistically significant association between a high-risk ABCD² score (≥ 4) and 90 day risk of an outcome event (p = 0.05). The frequency of each ABCD² score in the overall patient cohort and for those who had an outcome event is shown in Table 3.19.
Table 3.19 Frequency of ABCD² Scores and Outcome Events

<table>
<thead>
<tr>
<th>ABCD² scores</th>
<th>Patients n (% of total cohort)</th>
<th>Primary outcome event (Stroke) n (%)</th>
<th>Secondary outcome event within 90 days (excluding stroke) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3 (1.3%)</td>
<td>0 0</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>1</td>
<td>13 (5.4%)</td>
<td>0 0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>33 (13.8%)</td>
<td>0 0</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>3</td>
<td>38 (16.0%)</td>
<td>0 0</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>4</td>
<td>78 (32.8%)</td>
<td>1 (50%) 2 (50%)</td>
<td>9 (39.1%)</td>
</tr>
<tr>
<td>5</td>
<td>53 (22.3%)</td>
<td>1 (50%) 2 (50%)</td>
<td>7 (30.5%)</td>
</tr>
<tr>
<td>6</td>
<td>18 (7.6%)</td>
<td>0 0</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>7</td>
<td>2 (0.8%)</td>
<td>0 0</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>238 (100%)</td>
<td>2 (100%) 4 (100%)</td>
<td>23 (100%)</td>
</tr>
</tbody>
</table>

3.8 Effect of Dichotomizing the ABCD² Score

To determine whether high-risk patients benefitted more than low-risk patients from pathway care, each cohort was dichotomized into high- and low-risk groups, according to their ABCD² score, and analysed to assess the impact of the pathway on various processes of care in these groups.

In both high- and low-risk groups a significant improvement was seen in the utilisation of antithrombotic agents. Statin utilisation significantly improved amongst the high-risk patients, with a clinically important, but non-significant, improvement in low-risk patients. No significant differences were seen with respect to antihypertensive therapy (Table 3.20).
Table 3.20 Medical Management Pre-and Post-TIA/Stroke Pathway Implementation According to Patient Risk Stratification

<table>
<thead>
<tr>
<th>Treatment on discharge</th>
<th>Pre-pathway</th>
<th>Post-pathway</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>50/65 (76.9%)</td>
<td>80/86 (93%)</td>
<td>0.005</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>23/39 (59%)</td>
<td>40/48 (83.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>32/65 (49.2%)</td>
<td>61/86 (70.9%)</td>
<td>0.007</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>8/39 (20.5%)</td>
<td>19/48 (39.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Antihypertensive agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>38/65 (58.5%)</td>
<td>59/86 (68.6%)</td>
<td>0.20</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>14/39 (35.9%)</td>
<td>17/48 (35.4%)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

No significant changes in the performance of neuroimaging, carotid duplex, echo, or ECG were seen between high- and low-risk patients. Improvement was seen in assessment of fasting lipid profiles in both high- and low-risk groups, but improvement in fasting glucose testing was restricted to high-risk patients only (Table 3.21).

Whilst there were a very small number of primary outcome events (stroke at 90 days) in the overall cohort, all 4 cases were deemed to be high-risk as per the dichotomized version of the ABCD² score. Dichotomizing the ABCD² score into high-risk (≥ 4 points) and low-risk (< 4 points) had 100% (95% CI 40 – 100%) sensitivity for risk of subsequent stroke, but only 36% (95% CI 30 – 43%) specificity. This gives a negative predictive value of 100% (95% CI 94 – 100%) and a positive predictive value of only 2.8% (95% CI 1 – 8%).

There were a greater number of the combined secondary outcomes in the overall cohort, 27/218 (12.4%). Of these 22/27 (81.5%) were deemed to be high-risk as per the dichotomized version of the score. Dichotomizing the ABCD² score into high- and low-risk had a sensitivity of 81% (95% CI 61 – 92%), specificity of 38% (95% CI 31 – 45%), negative predictive value of 93.5% (95% CI 85 – 97%), and positive predictive value of 15.6% (95% CI 10 – 22%) for risk of secondary outcome event within 90 days.
Table 3.21 Investigations Performed Pre and Post-TIA/Stroke Pathway Implementation According to Patient Risk Stratification

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Pre-pathway n = 104</th>
<th>Post-pathway n = 134</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>58/65 (89.2%)</td>
<td>76/86 (88.4%)</td>
<td>0.87</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>34/39 (87.2%)</td>
<td>36/48 (75%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fasting lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>29/65 (44.6%)</td>
<td>61/86 (70.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>12/39 (30.8%)</td>
<td>27/48 (56.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>23/65 (35.4%)</td>
<td>44/86 (51.2%)</td>
<td>0.05</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>10/39 (25.6%)</td>
<td>20/48 (41.7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Carotid duplex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>41/65 (63.1%)</td>
<td>58/86 (67.4%)</td>
<td>0.74</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>19/39 (48.7%)</td>
<td>24/48 (50%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Echo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>30/65 (46.2%)</td>
<td>46/86 (53.5%)</td>
<td>0.65</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>11/39 (28.2%)</td>
<td>16/48 (33.3%)</td>
<td>0.40</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk</td>
<td>59/65 (90.8%)</td>
<td>76/86 (88.4%)</td>
<td>0.64</td>
</tr>
<tr>
<td>• Low-risk</td>
<td>31/39 (79.5%)</td>
<td>39/48 (81.3%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

3.9 Impact of Including Patients with Mild Ischaemic Stroke

There were 4 patients in the pre-pathway cohort with mild ischaemic stroke and 15 in the post-pathway cohort; of which one suffered a major ischaemic stroke (modified rankin scale = 6) which was included as the ED diagnosis was TIA (Table 3.22). This subgroup was labeled the stroke subgroup. The remaining 219 patients, which excluded all patients with stroke, was labelled the TIA subgroup.
Table 3.22 Number of patients in the Overall Cohort and the TIA Subgroup

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pre-pathway</th>
<th>Post-pathway</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort (n=238)</td>
<td>104</td>
<td>134</td>
<td>0.67</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>100</td>
<td>119</td>
<td></td>
</tr>
</tbody>
</table>

In both the overall cohort and TIA subgroup a significant improvement was seen in the utilisation of antithrombotic agents and statins. No significant improvement was seen with respect to utilisation of antihypertensive therapy (Table 3.23).

Table 3.23 Medical Management Pre-and Post-TIA/Stroke Pathway Implementation in the Overall Cohort versus the TIA Subgroup

<table>
<thead>
<tr>
<th>Treatment on discharge</th>
<th>Pre-pathway</th>
<th>Post-pathway</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overall cohort (n=238)</td>
<td>73/104 (70.2%)</td>
<td>120/134 (89.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• TIA subgroup (n=219)</td>
<td>69/100 (69%)</td>
<td>107/119 (90.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overall cohort (n=238)</td>
<td>40/104 (38.5%)</td>
<td>80/134 (59.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>• TIA subgroup (n=219)</td>
<td>38/100 (38%)</td>
<td>69/119 (58%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Antihypertensive agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overall cohort (n=238)</td>
<td>52/104 (50%)</td>
<td>76/134 (56.7%)</td>
<td>0.30</td>
</tr>
<tr>
<td>• TIA subgroup (n=219)</td>
<td>50/100 (50%)</td>
<td>66/119 (55.5%)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

No significant changes in the performance of neuroimaging, carotid duplex, fasting lipids and glucose, echo, or ECG were seen between these groups (Table 3.24).
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Pre-pathway</th>
<th>Post-pathway</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuro-imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort (n=238)</td>
<td>92/104 (88.5%)</td>
<td>112/134 (83.6%)</td>
<td>0.29</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>88/100 (88.0%)</td>
<td>98/119 (82.4%)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Fasting lipids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort (n=238)</td>
<td>41/104 (39.4%)</td>
<td>88/134 (65.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>37/100 (37%)</td>
<td>74/119 (62.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Fasting glucose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort (n=238)</td>
<td>33/104 (31.7%)</td>
<td>64/134 (47.8%)</td>
<td>0.01</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>31/100 (31.0%)</td>
<td>53/119 (44.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Carotid duplex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort (n=238)</td>
<td>60/104 (57.7%)</td>
<td>82/134 (61.2%)</td>
<td>0.55</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>57/100 (57.0%)</td>
<td>70/119 (58.8%)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Echo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort (n=238)</td>
<td>41/104 (39.4%)</td>
<td>62/134 (46.3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>38/100 (38.0%)</td>
<td>51/119 (42.9%)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort (n=238)</td>
<td>90/104 (86.5%)</td>
<td>115/134 (85.8%)</td>
<td>0.87</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>86/100 (86.0%)</td>
<td>102/119 (85.7%)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Follow up data was available for 200/219 (91.3%) of the TIA subgroup and 18/19 (94.7%) of the stroke subgroup. There were no significant differences in primary or secondary outcome events between the 2 subgroups (Table 3.25).
Table 3.25 Outcome Events in the TIA Subgroup versus Stroke Subgroup

<table>
<thead>
<tr>
<th>Outcome event</th>
<th>TIA subgroup (n=200)</th>
<th>Stroke subgroup (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome event</td>
<td>3 (1.5%)</td>
<td>1 (5.6%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Secondary outcome event</td>
<td>19 (9.5%)</td>
<td>4 (22.2%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

There was no significant difference in the proportion of patients admitted to hospital (Table 3.26).

Table 3.26 Comparisons of Admission Rates Pre- and Post-TIA/Stroke Pathway Implementation in the Overall Cohort, TIA Subgroup and Stroke Subgroup

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pre-pathway</th>
<th>Post-pathway</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort (n=238)</td>
<td>46/104 (44.2%)</td>
<td>74/134 (55.2%)</td>
<td>0.32</td>
</tr>
<tr>
<td>TIA subgroup (n=219)</td>
<td>44/100 (44.0%)</td>
<td>62/119 (52.1%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Stroke subgroup (n=19)</td>
<td>2/4 (50.0%)</td>
<td>12/15 (80.0%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The rate of clinical pathway utilisation was similar in all 3 groups (Table 3.27).
Table 3.27 Comparison of Utilisation of the TIA/Stroke Pathway in the Overall Cohort, TIA Subgroup and Stroke Subgroup

<table>
<thead>
<tr>
<th>Post-Pathway Cohort</th>
<th>Enrolment on Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort (n=134)</td>
<td>60 (45.5%)</td>
</tr>
<tr>
<td>TIA cohort (n=119)</td>
<td>53 (44.5%)</td>
</tr>
<tr>
<td>Stroke cohort (n=15)</td>
<td>7 (46.7%)</td>
</tr>
</tbody>
</table>

The median ABCD² score was 4 (interquartile range 2) for the TIA subgroup and 5 (interquartile range 1) for the stroke subgroup, a difference which was statistically significant (p < 0.001) (Figure 3.3).

Figure 3.3 Median ABCD² Score and Interquartile Range for TIA Subgroup and Stroke Subgroup
Section IV: Discussion and Conclusion
4.1 Summary of Results.

The aim of this study was to show that a structured clinical pathway of care to guide the management of patients with TIA would improve patient outcome with respect to appropriate medical management, investigation, time to follow-up and reduce the risk of future stroke. The clinical pathway developed incorporated the ABCD² prognostic scoring system and was consistent with the most recent evidence-based guidelines for TIA management.

The study did not show an improvement in the primary outcome event of stroke at 90 days or the combined secondary outcome event of stroke, recurrent TIA, other vascular event (angina, myocardial infarction, congestive cardiac failure, limb ischaemia or admission for other cardiac cause), or death due to any cause at 90 days. There was a significant association between a higher ABCD² score and 90 day risk of an outcome event.

Following implementation of the TIA/stroke clinical pathway there was no significant increase in the total number of patients admitted to hospital; however, there was a significant increase in the percentage of high-risk patients admitted for urgent investigation and observation, showing a positive change in terms of the appropriate use of hospital admission.

After pathway implementation there were also significant improvements in the prescription of antiplatelet agents and statins, testing for fasting lipids and glucose, and the timeliness of carotid duplex and specialist follow-up. There were no significant improvements in the other care processes looked at in this study.

These results show positive changes in some of the processes of care studied and I will discuss them in more detail in the following sections.
4.2 Outcome Event Findings

4.2.1 Primary Outcome Events

There was no significant improvement seen in the primary outcome of stroke within 90 days of the index TIA following implementation of the TIA/stroke clinical pathway. However, the number of primary outcome events was too small to allow a statistically meaningful analysis. The overall risk of subsequent stroke in this cohort was 2/218 (0.9%) at 7 days and 4/218 (1.8%) at 90 days, which is markedly lower than the 10 – 15% 90 day risk of stroke following a TIA found in other studies (Whisnant, Matsumoto et al. 1973; Johnston, Gress et al. 2000; Coull, Lovett et al. 2004; Hill, Yiannakoulis et al. 2004; Kleindorfer, Panagos et al. 2005). As has been shown in previous hospital-based cohorts (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004), we also found that the risk of subsequent stroke is heavily time dependent, with 50% of subsequent strokes in this study occurring within the first 48 hours following TIA or minor stroke.

Potential explanations for this lower than anticipated 90 day risk of subsequent stroke includes:

1. *The identification of patients based on their presenting symptoms rather than only including those with a discharge diagnosis of TIA*
   This resulted in a larger cohort of patients (n = 238) than would have otherwise been obtained (n = 214).

2. *Increased percentage of patients already receiving treatment with secondary preventive measures prior to study enrolment*
   The increasing awareness of the importance of primary and secondary prevention of vascular disease and its risk factors was evidenced in this study by the percentage of patients already receiving secondary preventive medical management prior to presentation; 43/104 (41.3%) of the pre-pathway and 67/134 (50%) of the post-pathway cohorts were receiving an antiplatelet agent prior to presentation,
similarly 34/104 (33%) of the pre-pathway and 55/134 (41%) of the post-pathway cohorts were receiving a lipid lowering agent prior to presentation. Other recent studies of patients with TIA have also shown lower 90 day risk of subsequent stroke following the index TIA (Lavallée, Meseguer et al. 2007; Rothwell, Giles et al. 2007). As seen in the present study, these studies have also shown an increased proportion of patients already being treated with secondary preventive measures on enrolment, with 24 – 45% of patients receiving antithrombotic medications and 20 – 32% receiving a statin at the time of study enrolment. This much lower rate of subsequent stroke within 90 days has been shown in two recent specialist stroke service-based studies in Paris. The first, the SOS-TIA study, was a hospital clinic-based study carried out between 2003 – 2005 (Lavallee, Meseguer et al. 2007) which showed a 0.2% risk of subsequent stroke at 7 days and 1.53% risk at 90 days amongst the 845 patients that were deemed to be a true or possible TIA or mild ischaemic stroke. A hospital-based stroke unit study carried out between 2003 – 2007 showed a 1.5% risk of subsequent stroke at 7 days and 2.9% risk at 90 days (Calvet, Touze et al. 2009). Similarly, in an Australian retrospective cohort study of 481 patients presenting to hospital with a suspected TIA the risk of subsequent stroke at 90 days was 1.66% (95% CI 0.7 – 3.3%) (Sanders, Srikanth et al. 2010), but no detail was provided by the authors with regard to proportion of patients already receiving secondary preventive measures in this study.

3. **Incomplete follow-up**

Follow-up was available for 95/104 (91.3%) patients in the pre-pathway cohort and for 123/134 (91.8%). Given that there are 4 other public hospitals and 5 private hospitals with an ED within Brisbane city, the potential exists that patients lost to follow-up may have presented to any of these alternate hospitals with a subsequent stroke or other secondary outcome event.

4. **Excluded patients**

There were 11 patients excluded as their case notes were missing (4 in the pre-pathway phase and 7 in the post-pathway phase). This could have been due to active ongoing management in another hospital department (for example, specialist
4.2.2 Secondary Outcome Events

There was an increase in the percentage of secondary outcome events in the post-pathway cohort which did not reach statistical significance. Combining both cohorts gave a 90 day risk of a secondary outcome event of 27/218 (12.4%) for this study, which is lower than 25.1% 90 day risk of an adverse event (including stroke, cardiovascular hospitalisation, death, or recurrent TIA) found by Johnston et al (2000) in their hospital-based retrospective study of the management of 1,707 patients with TIA presenting to an ED. This shows that patients with TIA are at significant risk of other vascular events in addition to their risk of subsequent stroke and the importance of ongoing vigilance in modifying the shared vascular risk factors common to all these conditions.

4.3 Impact of Pathway on Processes of Care

4.3.1 Utilisation of Investigations

Neuroimaging and ECG were performed in more than 80% of both cohorts. There was an upward trend in the utilisation of all other investigations following the implementation of the TIA/stroke clinical pathway, none of which reached statistical significance. Compared to other TIA management studies the rate of utilisation of investigations in this study was favourable following pathway implementation (see figure 4.1).

4.3.2 Neuroimaging

It was encouraging to find that more than 80% in both cohorts had neuroimaging performed within 24 hours of presentation. This is markedly higher than the rate of 59% seen in the UK National Sentinel Stroke Audit in 2008 (Royal College of Physicians Clinical
Effectiveness and Evaluation Unit and Intercollegiate Stroke Working Party 2009), but less than that seen in the most recent National Stroke Foundation (NSF) acute services audit where 91% underwent CT brain within 24 hours (National Stroke Foundation 2007).

Of the patients from both cohorts who did not have neuroimaging within 30 days (n = 34) approximately half had symptoms other than weakness or speech disturbance. In 1/238 (0.4%) case the patient presented on day 30 with a recurrent TIA and underwent an MRI brain scan at the time of their re-presentation. A further 3/238 (1.3%) declined neuroimaging. The remaining 30/238 (12.6%) did not undergo neuroimaging at any stage.

**Figure 4.1 Comparison of Rates of Utilisation of Investigations in Retrospective Hospital-Based Studies of patients with TIA**
In this study less than 4% in both cohorts underwent acute MRI imaging (within 24 hours), which is similar to the rate of less than 5% seen by Edlow et al in their 10 year study from 1992 – 2001 of ED management of TIA in various regions across the US (Edlow, Kim et al. 2006). When both cohorts in this study were combined the rate of utilisation of MRI brain imaging within 30 days of the index TIA was 33/238 (13.9%), which is higher than the rate of 3% (n = 364 patients with TIA) seen in the study based in 4 emergency departments in Ontario, Canada in 2000 when they analysed the subgroup of patients with TIA (Gladstone, Kapral et al. 2004). However, the most recent American Heart Association (AHA)/American Stroke Association (ASA) scientific statement on the definition and evaluation of TIA recommends MRI, including DWI, as the preferred brain diagnostic imaging modality, and only if MRI is not available a CT brain should be performed (Easton, Saver et al. 2009). This recommendation is based on evidence from MRI studies which have shown evidence of infarction on DWI in 21 – 67% of patients with TIA as defined by the 24 hour time criterion (Kidwell, Alger et al. 1999; Rovira, Rovira-Gols et al. 2002; Crisostomo, Garcia et al. 2003; Inatomi, Kimura et al. 2004; Ay, Koroshetz et al. 2005; Coutts, Simon et al. 2005; Lamy, Oppenheim et al. 2006; Prabhakaran, Chong et al. 2007). The proposed new definition of TIA in the AHA/ASA scientific statement (Easton, Saver et al. 2009) as a brief episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia without acute infarction moves away entirely from the time criterion and makes the diagnosis of TIA dependent upon MRI so as to exclude any area of acute infarction.

In practical terms, MRI remains a resource of limited availability (as seen in this study) within many hospitals in Australia. Approximately 58% of hospitals reported having access to MRI when surveyed by the National Stroke Foundation in 2009. This percentage was higher in urban compared to rural hospitals and in hospitals who had a stroke unit compared to those hospitals with no stroke unit as shown in figure 4.2 (National Stroke Foundation 2009). However, it is not clear whether it is practically possible at the centres reporting access to MRI for MR imaging to be conducted in a timely fashion in what might be considered an urgent or emergency situation. In addition, MRI may be contraindicated or unable to be obtained in certain groups of patients; for example, patients with a pacemaker, certain metal prostheses, and patients with claustrophobia. Consequently,
whether a patient with transient focal neurology is assessed with an MRI versus CT brain scan in the acute instance will depend upon each hospital’s local environment and resources and will likely be assessed on a case-by-case basis.

Figure 4.2 Availability of MRI in Australia by State, Stroke Unit Status, and Rurality (National Stroke Foundation 2009)

4.3.3 Carotid Duplex

The rate of utilisation of carotid duplex did not significantly increase post-pathway implementation; 60/104 (57.7%) pre-pathway to 82/134 (61.2%) post-pathway (p = 0.55). However, a carotid duplex may not be warranted in all cases. For example, the treating physician may decide not to pursue carotid duplex in cases where the TIA/minor stroke is due to a posterior circulation event or where the patient is not a suitable operative candidate for a carotid endarterectomy or carotid stenting even if a significant carotid artery stenosis was detected. In the post-pathway cohort 13/134 (9.7%) did not have a carotid duplex
performed as they were deemed not to be a suitable operative candidate. Of the remaining patients in the post-pathway cohort who did not have a carotid duplex only 13/134 (9.7%) were due to an anterior circulation event which warranted further investigation with a carotid duplex (Table 3.9). Thus, in the post-pathway cohort a carotid duplex was performed in 82/95 (86.3%) cases in which it was warranted.

There was a statistically significant reduction in the median number of days to carotid duplex; 11 days pre-pathway (interquartile range 29 days) to 6 days (interquartile range 11 days) post-pathway (p = 0.001). The range in the number of days to carotid duplex reflects problems with local access to carotid duplex within the hospital. Issues with access to carotid duplex have been shown in surveys conducted by the National Stroke Foundation (2009) with carotid duplex being available in 82% of Australian hospitals. Close to 100% of all hospitals with a stroke unit have access to carotid duplex compared to approximately 76% of hospitals without a stroke unit (see figure 4.3). The RBWH is one of the largest stroke units in Queensland, yet there was a median 6 days delay to carotid duplex following implementation of the pathway. The likelihood is that the wait is even longer in a rural setting without a stroke unit. This is an issue which needs to be addressed so as to ensure rapid identification of those patients with significant ipsilateral internal carotid artery stenosis so as to enable carotid endarterectomy as expeditiously as possible given that the greatest benefit from carotid endarterectomy is for surgery performed within 2 weeks from the index event, where the number needed to treat has been shown to be 5, compared with 125 at 12 weeks (Rothwell, Eliasziw et al. 2004). Data was not collected in this study on the results of each carotid duplex to determine how many patients had significant carotid stenosis which warranted surgical intervention.

4.3.4 Cardiac Investigations

There was no significant improvement in the rate of utilization and timeliness of echocardiography. However, whether or not all patients with TIA require an echocardiogram remains an unanswered question. In one study of 250 patients with an anterior circulation TIA and no history of a prior stroke, 23% were found to have a
potential cardiac source of embolus, usually in the context of symptomatic heart disease (Bogousslavsky, Hachinski et al. 1986). Of the 205 patients in this study who underwent both cerebral angiography and cardiac investigations, only 6% were found to have an isolated potential cardiac source of emboli. The authors concluded that whilst the search for a potential cardiac source is strongly indicated for patients with an anterior circulation territory TIA and a known history of heart disease, that the yield is low for those patients with no cardiac history (Bogousslavsky, Hachinski et al. 1986).

A study of 200 patients with stroke or TIA who underwent outpatient investigation found that a transthoracic echocardiogram was performed in 142/200 (71%) cases (Douen, Pageau et al. 2007). Pertinent cardiac findings were uncovered in only 6 (4%) of patients. The results of transthoracic echocardiography did not alter antithrombotic treatment in any of the 142 patients studied.
The yield from echocardiography appears to be higher in those patients where all other potential sources of emboli have been excluded, in particular if they undergo trans-oesophageal echocardiography as shown in one study of 237 patients with cryptogenic stroke or TIA, where a potentially treatable cardio-embolic source was found in 146/237 (61%) of this cohort of patients (Yahia, Shaukat et al. 2004). Consequently, the most recent AHA and ASA supported scientific statement on the evaluation of patients with TIA recommend that echocardiography is reasonable, especially in patients in whom no cause has been found in other elements of the workup (Easton, Saver et al. 2009).

There was no significant improvement in the performance of ECG which was performed in more than 85% of both cohorts. Whilst this is less than the rate of 93% seen in the NSF acute services audit (National Stroke Foundation 2007), given that 32.3% of the overall cohort were ultimately deemed to be a TIA mimic, it likely under-estimates the percentage of patients with a true TIA who underwent ECG.

It was encouraging to see that whilst echocardiography was performed in less than half of each cohort, ECG was performed in a much higher proportion of patients. Whilst echocardiography may be a low-yield investigation in terms of it leading to a change in medical management based on the findings of the study in an unselected group of patients with TIA or stroke (Douen, Pageau et al. 2007), the finding of paroxysmal atrial fibrillation often does lead to an alteration in management as there is evidence that anticoagulation is more effective than antiplatelet therapy for long-term secondary prevention of stroke and TIA (Koudstaal 2004). In this study patients were deemed to have atrial fibrillation if there was evidence of this on their admission ECG or if they had a known history of paroxysmal atrial fibrillation in the past. Neither telemtry nor holter monitoring were routinely available for those patients admitted to hospital. No comment regarding the superiority of continuous cardiac monitoring over ECG for the detection of atrial fibrillation can be made on the basis of this study as data was not collected on the percentage of patients who underwent cardiac monitoring. However, one outpatient study of 149 patients with stroke or TIA found 24-hour Holter monitoring was no better than a 12 lead ECG for detection of AF (Douen, Pageau et al. 2007). The authors found only 3 (2%) new cases of AF with Holter
monitoring; all 3 cases were detected on ECG as well. There is evidence to suggest that prolonged (7 days) Holter monitoring is of benefit in detecting paroxysmal AF, with one study of 224 patients with stroke or TIA and no prior history of AF showing an overall detection rate of 12.5% for 7 days, which was significantly higher than the rate of 4.8% for any 24 hour period (p = 0.015) (Stahrenberg, Weber – Kruger et al. 2010). In this study the Holter recordings were started at a median of 5.5 hours (IQR 3.5 – 8.4 hours) after admission and 9.5 hours (IQR 6.0 – 16.3) after symptoms onset. There was no evidence of a higher detection rate on day 1, nor was there a recognizable pattern of detection rate favouring any given time point during the 7 day period. This evidence suggests that a 7 day holter monitor may be of benefit, in particular for those patients where an alternate cause for their TIA has not been identified during their investigations or where the stroke pattern is strongly indicative of a cardioembolic aetiology.

4.3.5 Antithrombotic Agents

There was a significant improvement in the utilisation of antithrombotic medication following implementation of the pathway; 73/104 (70.2%) pre-pathway to 120/134 (89.6%) post-pathway (p < 0.001). This is lower than the rate of 1,591/1,747 (91%) seen in the Australian National Stroke Foundation clinical audit (2007) and 96% seen in the UK national sentinel stroke audit in 2008 (Royal College of Physicians Clinical Effectiveness and Evaluation Unit and Intercollegiate Stroke Working Party 2009). However, in both of these audits the patient had suffered a definite stroke, whereas in this study approximately one third of patients were ultimately deemed to be a TIA mimic (Table 3.16) which would not require treatment with an antithrombotic agent. Thus, the percentage of 89.6% of all patients in the post-pathway cohort receiving treatment with an antithrombotic medication at their time of discharge under-estimates the treatment rate for those who had a definite ischaemic event and is a very good result. It is also a substantial improvement compared to most other hospital-based retrospective studies of the ED management of TIA patients, with only one large retrospective study (Johnston, Gress et al. 2000) showing a higher rate of utilisation of antithrombotic agents (figure 4.4).
Whilst the number of patients with atrial fibrillation in this study was small (7/104 (6.7%) pre-pathway and 15/134 (11.2%) post-pathway), the percentage of patients with AF who were discharged on an anticoagulant was approximately 40% in each cohort which is greater than the previously found rate of 23% in an Australian multi-centre, retrospective audit (Duffy, Phillips et al. 2003) and 24% in the UK national sentinel stroke audit in 2008 (Royal College of Physicians Clinical Effectiveness and Evaluation Unit and Intercollegiate Stroke Working Party 2009), but less than that found by the international, observational REACH registry where 60% of those in atrial fibrillation were anticoagulated (Hill, Roether et al. 2007). These previous studies did not look at why the patient was not anticoagulated. In this study, of the 22 patients with atrial fibrillation 12 (54.5%) were not warfarinised. Of these 12 patients, there was a reason documented in the notes as to why they were not warfarinised in 11 (92%) cases as outlined in Table 3.6.

**Figure 4.4 Comparisons of Rates of Utilisation of Antithrombotic Agents at Time of Discharge from ED in Retrospective Hospital-Based Studies of Patients with TIA**
4.3.6 Antihypertensive agents

There was no significant increase in the rate of utilisation of antihypertensive agents; 52/104 (50%) pre-pathway, 76/134 (56.7%) post-pathway (p = 0.30). This is much lower than the rate of 74% in the most recent Australian NSF clinical audit (National Stroke Foundation 2007) and 76% seen in an Australian multi-centre, retrospective audit (Duffy, Phillips et al. 2003). Disappointingly, of the 58 (43.3%) patients in the post-pathway cohort of this study who were not commenced on an antihypertensive agent, 11 (19%) had a blood pressure \( \geq 140/90 \text{mmHg} \) on presentation to ED. No reason was documented in the chart as to why they were not commenced on an antihypertensive agent. This is greater than the rate of 14% of patients in the UK national sentinel stroke audit in 2008 (Royal College of Physicians Clinical Effectiveness and Evaluation Unit and Intercollegiate Stroke Working Party 2009) who were hypertensive on admission, but not commenced on treatment at discharge.

Potential contributors to this less than ideal rate of utilisation of antihypertensive agents include:

1. **Concern regarding the use of an antihypertensive agent in the acute setting**

The concern with regard to blood pressure lowering in the acute period after stroke and TIA arises due to evidence from trials where the vast majority of the cohort are stroke patients, which show that early and late mortality in relation to admission blood pressure follows a U shaped curve, with both hypertension and hypotension causing increased rates of mortality (Leonardi-Bee, Bath et al. 2002; Vemmos, Tsivgoulis et al. 2004). In a retrospective analysis of the 17,398 patients enrolled in the International Stroke Trial within 48 hours of onset of their ischaemic stroke there was a 17.9% increased risk of early death (death within 14 days) for every 10mmHg fall in blood pressure below 150mmHg (\( p < 0.0001 \)) and a 3.8% increased risk of early death for every 10mmHg rise in blood pressure above 150mmHg (\( p = 0.016 \)) (Leonardi-Bee, Bath et al. 2002). In a prospective trial of 1,121 patients with their first presentation with stroke who were hospitalised within 24 hours of symptom onset, for every 10mmHg decrease in systolic blood pressure below 130mmHg
the relative risk of death at 1 month and 1 year rose by 28.2% (95% CI 2.2 – 12.3%) and 17.5% (95% CI 3.1 – 34%) respectively (Vemmos, Tsivgoulis et al. 2004). The risk of death at 1 month and 1 year increased to a lesser extent for every 10mmHg increase in systolic blood pressure above 130mmHg; 10.2% (95% CI 4.2 – 16.6%) at 1 month and 7.2% (95% CI 2.2 – 12.3%) at 1 year. The authors found the optimal blood pressure to minimize mortality being 121–140 mmHg systolic blood pressure and 81–90 mmHg for diastolic blood pressure (Vemmos, Tsivgoulis et al. 2004).

In the long-term a reduced blood pressure is desirable for secondary prevention against future stroke, however, in the acute setting low blood pressure may increase the ischaemic brain injury. Following an acute ischaemic stroke cerebral auto-regulation is impaired (Eames, Blake et al. 2002) and cerebral blood flow becomes passively dependent on the mean arterial pressure. A pilot study of 15 stroke patients with a large diffusion-perfusion mismatch on their MRI brain scan showed that the 9 patients randomised to induced hypertension showed significant improvement from day 1 to day 3 in their National Institute of Health Stroke Scale (NIHSS) score, cognitive score, and volume of hypoperfused tissue (Hillis, Ulatowski et al. 2003). Animal studies have also shown that induced hypertension can reduce focal cerebral injury by improving perfusion to the area of focal ischaemia (Drummond, Oh et al. 1989). However, these studies have all been carried out in patients with acute stroke, not patients with TIA.

Given the new definition of a Transient Ischaemic Attack as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without infarction (Easton, Saver et al. 2009), TIA patients should not have an ischaemic penumbra that requires an increased cerebral blood flow to salvage, nor should there be any loss of cerebral auto-regulation. Accordingly, there is no need to delay the commencement of an antihypertensive agent in patients with TIA.

Data on the safety of commencing an antihypertensive agent in patients with TIA or minor stroke at the time of initial presentation is harder to find. Phase 2 of the EXPRESS study and the SOS-TIA study incorporated antihypertensive prescription on initial patient assessment as part of their protocol, but only if the patient’s systolic blood pressure was ≥
130mmHg in EXPRESS and > 140/90mmHg for non-diabetics and > 130/85mmHg in diabetics in SOS-TIA (Lavallée, Meseguer et al. 2007; Rothwell, Giles et al. 2007). In phase 2 of the EXPRESS study (n = 281), where median delay to assessment in the study clinic was less than 1 day (range 0 – 3), all patients with TIA and minor stroke with a systolic BP ≥ 130mmHg were commenced on an antihypertensive agent on the day of assessment (Rothwell, Giles et al. 2007). At 1 month, 231 (82%) patients were being treated with 1 or more antihypertensive agents. Overall the study showed a significant reduction in the 90 day risk of subsequent stroke from 10.3% (32/310 patients) in phase 1 to 2.1% (6/281 patients) in phase 2 (p = 0.0001). In the SOS-TIA study (n = 1,085), 574 (53%) patients were seen within 24 hours of symptom onset, 665 (61%) within 48 hours and 810 (75%) within 7 days (Lavallée, Meseguer et al. 2007). Of the 701 patients with definite TIA or minor stroke, an antihypertensive agent was either commenced or modified in 199 (28%) patients, in addition to an appropriate antithrombotic agent. Advice was given to GPs for the remaining patients in this group regarding target blood pressure. A lipid lowering agent was also commenced or modified in 315 (45%) patients. There were 13 subsequent strokes at 90 days amongst the 1,052 (97%) patients that were available for follow-up. This resulted in a 90 day stroke risk of 1.24% (95% CI 0.72 – 2.12%), which was much lower than the expected 90 day stroke risk for this group based on their ABCD² score of 5.96%.

Whilst in both of the above studies the relative benefit of early initiation of an antihypertensive agent alone cannot be determined as the patients were commenced on a combination of secondary preventive agents, there did not appear to be any adverse effects from this approach. This data supports early combination therapy with an antithrombotic agent, antihypertensive agent and a statin to reduce the risk of stroke at 90 days following TIA or minor stroke.

2. **ABCD² score for hypertension at the time of presentation**

Greater than half of the patients in the post-pathway cohort that were not commenced on an antihypertensive agent did not receive a point for elevated blood pressure on the ABCD² score, potentially rendering them normotensive in the mind of the attending doctor. This is despite the most recent recommendations from both the Australian National Stroke
Foundation and American Stroke Association which recommend that all TIA patients, whether normotensive or hypertensive, should receive an antihypertensive unless contraindicated by symptomatic hypotension (Sacco, Adams et al. 2006; National Stroke Foundation 2007). The results of this study show that despite implementation of the TIA/stroke clinical pathway, which incorporates a reminder regarding the commencement of an antihypertensive agent, this recommendation has yet to traverse the evidence-to-practice gap.

3. Guideline variation in definition of hypertension

Reluctance on the part of the attending doctor to commence an antihypertensive agent may stem from the variation in definition of hypertension in each of the published guidelines as shown in Table 4.2 (Intercollegiate stroke working party 2004; Johnston, Nguyen-Huynh et al. 2006; Sacco, Adams et al. 2006; National Stroke Foundation 2007). Adding to this confusion is the fact that neither the Australian guidelines nor the American guidelines give advice with respect to when is the optimal time to commence an antihypertensive agent following a TIA. The National Stroke Association guidelines recommend that an antihypertensive agent be commenced at 7 – 14 days following a TIA (Johnston, Nguyen-Huynh et al. 2006), and the United Kingdom Guidelines recommend commencing at 2 weeks following TIA, if the patient remains hypertensive as per their definition of hypertension (see Table 4.1) (Intercollegiate stroke working party 2004).

4.3.7 Lipid Lowering Agents

There was a statistically significant increase in the rate of utilisation of lipid lowering agents from 40/104 (38.5%) to 80/134 (59.7%) post-pathway implementation (p = 0.001), which is lower than the rate of 82% seen in the UK national sentinel stroke audit in 2008 (Royal College of Physicians Clinical Effectiveness and Evaluation Unit and Intercollegiate Stroke Working Party 2009), but similar to the rate of 62% seen in the Australian NSF clinical audit (National Stroke Foundation 2007). One reason for this may be a reluctance to commence a patient on a lipid lowering agent prior to reviewing the results of the
patient’s fasting lipid profile (as would be the case for most patients being discharged from the ED).

**Table 4.1 Definition of Normal Blood Pressure as Defined by the Stroke and TIA Guidelines**

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<td>No diabetes; • &lt; 140/90mmHg Diabetes; • 130/85mmHg</td>
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The SPARCL study (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) (Amarenco, Bogousslavsky et al. 2006) showed an absolute difference in Kaplan Meier rates of subsequent stroke at five years of 2.2% in favour of those treated with atorvastatin compared to placebo. Yet, the FASTER study (Fast assessment of stroke and transient ischaemic attack to prevent early recurrence) (Kennedy, Hill et al. 2007), which looked at the use of a statin in the acute period (within 24 hours of symptom onset) following a TIA or minor stroke, showed a non-significant increase in the 90 day risk of stroke from 21/199 (10.6%) in the group taking simvastatin 40mg daily compared to 14/193 (7.3%) in the group taking placebo. This gives an absolute risk increase of 3.3% (95% CI -2.3 – 8.9%), p = 0.25. However, the FASTER study had a significantly smaller cohort (199 patients in the statin treatment arm, 193 patients in the placebo arm) compared to the SPARCL study which had follow-up data available for 2,272 patients in the statin treatment arm and 2,253 in the placebo arm. The 95% CI of -2.3 – 8.9% for the absolute risk increase found in the FASTER study is quite wide and does not exclude a modest benefit. In addition, the study had to stop early due to failure to recruit patients at the pre-
specified minimum enrolment rate, the main reason for this was that it became increasingly difficult over the course of the study to find eligible patients that were not previously on a statin. Whilst this was problematic for the authors of the FASTER study, it is encouraging to see this increased awareness of primary prevention of vascular disease.

The FASTER authors felt the increased absolute risk was probably an effect of the small number of strokes at 90 days seen in their study. Yet, the 90 day risk of stroke in the overall statin versus placebo cohort was 35/392 (8.9%) which is similar to the 90 day stroke risk of 32/310 (10.3%) seen in phase 1 of the EXPRESS study (Rothwell, Giles et al. 2007), but much higher than the 90 day stroke risk of 6/281 (2.1%) seen in phase 2 of EXPRESS (Rothwell, Giles et al. 2007) and 13/845 (1.53%) seen in the SOS-TIA study (Lavallée, Meseguer et al. 2007). This may have been a reflection of the fact that the FASTER study was from a hospital-based cohort, whereas the EXPRESS and SOS-TIA studies were largely community-based studies. Ultimately, the TIA/stroke clinical pathway adopted the evidence provided by the SPARCL study (Amarenco, Bogousslavsky et al. 2006) and advised a lipid lowering agent for all patients with TIA.

This study tried on behalf of the attending doctor to alleviate the reluctance to initiate a lipid lowering agent by incorporating this recommendation into the clinical pathway for all patients with TIA. As only 80/134 (59.7%) of the post-pathway cohort were discharged on a lipid lowering agent, this indicates a clear evidence-to-practice gap. The highest rate of use of a lipid lowering agent at the time of discharge was seen in the pathway-enrolled cohort, 42/60 (70%), showing that a systematic prompt to remind the attending doctor to initiate this medication is of benefit.

4.4 Utilisation and Effect of the TIA/Stroke Clinical Pathway

The pathway was utilised in only 60/134 (44.8%) patients in the post-pathway cohort. This may have been an underestimation as the pathway was deemed to have been used only if it was filed in the medical record. Thus, there may have been cases where it was not
appropriately filed or instances where the treating doctor may have followed the pathway without filling it in.

Other studies implementing a clinical pathway for patients with TIA or stroke have shown varying success of pathway utilisation from 37% to 85% (Kwan, Hand et al. 2004; Read, Levy et al. 2006; Brown, Reeves et al. 2007). The most successful rate of utilisation was a computerised management pathway in a prospective, ED-based pilot study (Brown, Reeves et al. 2007). However, the authors did report that the adherence of 85% may have been falsely high as the research staff in the study were instructed to ask physicians whether or not they utilised the pathway, which may have resulted in a bias towards a “yes” answer.

There were a number of potential obstacles to pathway implementation and patient enrolment on the pathway, including:

1. Problems with the dissemination process of the clinical pathway

Given the shift-work nature of the ED, and rotation of new junior medical officers to the ED on a 3 monthly basis, it is possible that new staff members were simply not aware of the management pathway despite the introductory educational period regarding the utilisation of the TIA/stroke clinical pathway, which continued throughout the post-pathway implementation phase of the study, and circulation of an electronic version of the TIA/stroke clinical pathway to all current and new staff at the beginning of each staff rotation.

2. Problems with the adoption process of the clinical pathway

Whilst we aimed to keep the pathway as user-friendly as possible, such that it consisted mainly of tick boxes, it was an additional piece of paperwork to be filled in by the nursing and medical staff and there may have been reluctance to complete this additional piece of paperwork. There were no issues raised by the ED staff at any of the regular educational sessions, and they seemed quite pleased with the pathway. The department was already very familiar with the utilisation of clinical pathways prior to the implementation of the TIA/stroke clinical pathway; ten clinical pathways were already in use for other conditions that commonly present to the ED.
Some significant improvements in the process of care, if not in the primary and secondary clinical outcomes, were demonstrated following implementation of the TIA/stroke clinical pathway. This was despite the pathway being utilised in slightly less than half of the post-pathway cohort and may be a reflection that both the TIA/stroke clinical pathway and the teaching sessions with regard to recognising and managing patients with TIA all played a role in the improvements seen in this study. When data was analysed to look at the pathway-enrolled subgroup (n = 60), in addition to the improvements seen in the overall post-pathway cohort there was also a significant improvement in the utilisation of carotid duplex (p = 0.03) and echocardiography (p = 0.02). This shows that the clinical pathway was of benefit when it was used. The clinical pathway appears to serve as a reminder in a busy ED to order these important investigations and help bridge the evidence-to-practice gap.

Interestingly, the significant increase in the proportion of patients prescribed an antithrombotic agent and a statin at their time of discharge was restricted to those patients who were discharged from ED (Table 3.4), suggesting that it is expected by ED staff that appropriate medical management will be implemented in those patients who are admitted to hospital by the treating medical team, whereas the TIA/stroke clinical pathway has an important role to play to ensure those patients who are discharged from ED receive appropriate medical management. Admission status made no difference to the rate of utilisation of antihypertensive agents or performance of investigations, other than fasting glucose testing where the significant increase in the rate of performance of this investigation was restricted to those patients who were admitted to hospital as shown in Table 3.8.

4.5 Validity of the ABCD² Score and Efficacy of Dichotomising the ABCD² Score

A dichotomised version of the ABCD score has previously been studied in an Australian cohort and found to be over-inclusive, but highly predictive in identifying patients with
TIA at high-risk of subsequent stroke (Bray, Coughlan et al. 2007). This is the first study to apply a dichotomised version of the ABCD² score to a cohort of patients with probable or definite TIA or minor ischaemic stroke presenting to an ED. This study had similar findings to that of Bray et al (2007) with the ABCD² score having 100% sensitivity (95% CI 40 – 100%) for prediction of those at highest risk of subsequent stroke but was also over-inclusive, with a specificity of only 36% (95% CI 30 – 43%) and positive predictive value of 2.8% (95% CI 1 – 8%) for risk of subsequent stroke at 90 days. This study showed that the dichotomised version of the ABCD² score was less sensitive for secondary outcome events (sensitivity 81%, 95% CI 61 – 92%) with a similar specificity of 38%, (95% CI 31 – 69%) and a positive predictive value of 15.6%. The low positive predictive value of the ABCD² score for both primary and secondary outcome events may be falsely low due to the aggressive modern management approach, regardless of whether or not a clinical pathway is used. We do not know the natural history of what would happen if these measures were not implemented.

It has been questioned as to whether or not the prognostic capability of the ABCD² score is simply that it identifies those patients who have suffered a TIA rather than a TIA mimic, and is more a diagnostic rather than prognostic tool. In this study approximately one third of patients were ultimately deemed to be a TIA mimic. There was a statistically significant difference in the median ABCD² score of 4 for those with a TIA or stroke compared to 3 for those deemed to be a TIA mimic (p < 0.001). When this analysis was repeated to compare the median ABCD² score of the TIA subgroup (which included all TIA mimics) compared to the stroke subgroup, the median scores were 4 and 5 respectively (p < 0.001). Of all high-risk patients (n = 151) in this study 35 (23.2%) were deemed to be a TIA mimic. Of all the low-risk patients (n = 87) in this study 45 (51.7%) were deemed to be a true TIA (see Table 3.17). Thus, in this study the ABCD² score could not be used as a diagnostic tool, as a lower ABCD² score could not reliably be used to distinguish a TIA from a TIA mimic. However, there was a higher rate of TIA mimics in the low-risk group (42/87, 48.3%) compared to the high-risk group (35/151, 23.2%). Whilst the ABCD² score may be over-inclusive, given it has 100% sensitivity for the primary outcome event of subsequent stroke and 81% sensitivity for a secondary outcome event, it makes the score a useful screening tool for TIA and stroke.
All 27 outcome events occurred in patients deemed to be a true TIA or minor ischaemic stroke. Whilst 5 (18.5%) of those with an outcome event were low-risk according to their ABCD² score, there was still a significant association between a high-risk ABCD² score (≥ 4) and 90 day risk of an outcome event (p = 0.05).

This same question of whether the ABCD² score is a diagnostic rather than prognostic tool for TIA has been looked at in a review of the ED based study of 1,707 patients which identified the 5 risk factors associated with 90 day stroke risk and formed the basis of the ABCD² score (Josephson, Sidney et al. 2008). On review of these cases by a medical record analyst, 713 patients (42%) were deemed to have a questionable TIA. These cases were then reviewed by an expert neurologist and 90% of the 713 cases were deemed to be a true TIA. They found that the 90 day stroke risk was significantly higher in the group deemed to have a true TIA (24%) compared to the group deemed unlikely to be TIA (1.4%) (p < 0.0001). Overall the ABCD² scores were higher in the group deemed to be a true TIA, and within this group the 90 day stroke risk increased as the ABCD² score increased, whereas this was not the case amongst the group deemed unlikely to be a TIA. The authors concluded that the predictive capability of the ABCD² score was partially attributable to the identification of those patients with true TIA, which is an important aspect of the score when being used by non-neurologists. For those deemed to be a true TIA by a neurologist a higher ABCD² score remained predictive of an increased 90 day stroke risk.

A retrospective study carried out in a hospital-based TIA clinic in Glasgow also looked at this question to determine whether a low ABCD² score (which was defined as 0 – 2 points) simply distinguished true TIAs from non-cerebrovascular events (Quinn, Cameron et al. 2009). They retrospectively calculated an ABCD² score for all patients assessed in the clinic over a 12.5 year period from 1992 – 2005. There were 3,646 patients in their cohort, of whom 1,769 (48.5%) were deemed to have had a non-cerebrovascular event. They demonstrated a positive association between low ABCD² score and a non-cerebrovascular diagnosis with reasonable sensitivity (52.6%), but poor specificity (82.8%). They also showed a positive association between increasing ABCD² score and a true cerebrovascular diagnosis. Overall they concluded that whilst patients with a low ABCD² score are more
likely to have a non-cerebrovascular event, there were still enough true TIA cases within this group such that a low ABCD² score could not be considered “benign” and that all low-risk patients still require prompt assessment and management, which is similar to the findings in the present study.

One prospective study of 75 consecutive referrals to a hospital-based TIA clinic found 43 (57.3%) were a true TIA or stroke and the median ABCD² score for this group was 4 (which is the same score found in the present study) compared to a median ABCD² score of 2 in the 32 (42.7%) referrals found to be due to a non-cerebrovascular event (Ray, Wright et al. 2009). However, they did note that 20% of their patients with a low (0 – 2) ABCD² score were found to be a true TIA and one third of the patients with an ABCD² score > 2 were found to be due to a non-cerebrovascular event.

Whilst the above studies and the present study provide evidence that a lower ABCD² score is often associated with non-vascular mimics of a TIA, the score alone is insufficient to distinguish between TIA and TIA mimic. Consequently, these patients still require prompt investigation and management, unless an alternate diagnosis becomes evident in the interim.

Realising that there are high-risk factors not taken into account by the ABCD² score, the TIA/stroke clinical pathway addressed this by incorporating some additional high-risk features including: new or poorly diagnosed diabetes, poorly controlled hypertension, new or untreated AF, internal carotid artery stenosis, and recurrent TIAs. The idea being that if a patient was classed as low-risk, based on their ABCD² score, any of these high-risk features would prompt admission. This resulted in only 2 additional admissions, both of which presented with recurrent TIAs. This would suggest that consideration of these complicating factors may not be absolutely necessary to include on a TIA/stroke clinical pathway. The other alternative being that the score is still able to identify those patients at highest risk of subsequent stroke within these high-risk groups, which it appears to be able to do in patients with AF, as seen in this study and the Oxford Vascular Study cohort (Koton and Rothwell 2007). Data was collected regarding the cohort of patients with AF, but not
regarding diabetic control, blood pressure control, or the results of the carotid duplex to allow further analysis of these other high-risk groups.

In this study there were 22 patients with atrial fibrillation; 4 (18.2%) were deemed to be low-risk by their ABCD² score and there were no outcome events within this group. Of the 18 (81.8%) patients deemed to be high-risk, 90 day follow was available for 17 patients. Of these 17 high-risk patients 8 (47%) had an outcome event within the 90 day follow-up period; one primary outcome event at day 1 and 7 secondary outcome events within 90 days. In 5 of these 8 cases (62.5%) the patient had not been warfarinised. This shows that whilst the ABCD² score does not include AF, the score adequately identifies patients with AF at high risk. This is similar to the results of Rothwell and colleagues when they reviewed their data from the Oxford Vascular Study cohort. They found that, whilst there was no clear relationship between either the ABCD or ABCD² scores and the prevalence of Atrial Fibrillation or ≥ 50% carotid artery stenosis, both scores appear to identify patients with these risk factors at high-risk of stroke (Koton and Rothwell 2007). In our study the high rate of combined primary and secondary outcome events amongst the group with AF highlights the importance of implementing anticoagulant therapy in this group.

4.6 Decision Making Regarding Inpatient versus Outpatient Management

The TIA/stroke clinical pathway recommended that all high-risk patients or patients with complicating factors be admitted for urgent investigation and observation. This raised concerns prior to pathway implementation that there would be a significant increase in the number of patients requiring admission in a hospital system where there is always a shortage of beds. However, there was no significant increase in the total proportion of patients admitted following clinical pathway implementation, but there was a significant increase in the percentage of appropriate high-risk patients admitted for urgent investigation and observation compared to low-risk patients. The admission rate of 55.2% seen in the post-pathway cohort in this study is lower than that seen in a retrospective review of ED presentations of patients with TIA which was carried out in 6 hospitals in metropolitan and rural Sydney between 2001 – 2005 where 71.6% were admitted to
hospital (Kehdi, Cordato et al. 2008). The admission rate varied amongst the 6 hospitals involved in the study from 66% to 78%.

Whilst studies have shown that an outpatient model of care for TIA patients is effective (Lavallée, Meseguer et al. 2007; Rothwell, Giles et al. 2007) the problem in Australia is the limited availability of such clinics. In the UK 78% of hospitals had a neurovascular clinic for the rapid assessment of TIA and mild stroke patients when surveyed in 2006 (Royal College of Physicians of London Clinical effectiveness and Evaluation Unit and Intercollegiate stroke working party 2007) which increased to 98% when assessed in 2008 (Royal College of Physicians London Intercollegiate Stroke Working Party 2008). In comparison, only 5% of Australian hospitals had a neurovascular clinic when surveyed in 2007 (National Stroke Foundation 2007), which increased to 20% in the 2009 Australian NSF audit of acute services (National Stroke Foundation 2009). As a result in many centres urgent assessment and treatment of patients with TIA may only be possible if the patient is hospitalised.

An Australian survey of 74 hospital-based TIA services (64% of which had a stroke unit) showed that for those patients with TIA discharged home from the ED more than 60% of hospitals reported a wait of greater than 1 week for follow-up, and in 30% of hospitals the wait was greater than one month (Price, Blacker et al. 2009). This is much longer than the 7 – 10 days recommended by the NSF guidelines (National Stroke Foundation 2007). The actual delay to follow-up may even be longer than this, as the survey only had a 55% response rate and thus the results may be biased towards sites with an active interest in stroke management rather than a true reflection of TIA services in Australia. Whilst this shortage of rapid access TIA clinics persists in Australia and prevents rapid outpatient assessment and investigation, tools such as our TIA/stroke clinical pathway may be useful in a busy ED to identify those patients who warrant admission for urgent investigation and observation because they are at the highest risk of a subsequent event within 90 days.

Our study did not show a significant difference between the numbers of outcome events in those admitted versus discharged from ED following pathway implementation (Table 3.15). This may be due to the small size of the present cohort. A larger, Australian, hospital-based, observational, retrospective review of the management of 2,535 patients with TIA
presenting to the ED of 6 hospitals in metropolitan Sydney and adjacent rural districts showed that there were significant early benefits of hospital admission (Kehdi, Cordato et al. 2008). In this study 1,816 (71.6%) patients were admitted to hospital and 719 (28.4%) patients were discharged from ED. The 28 day risk of subsequent stroke and recurrent TIA was lower in those patients who were admitted to hospital compared to those who were discharged home (2.3% versus 5.3%, p < 0.001) (Kehdi, Cordato et al. 2008). In the subgroup of 485 patients with TIA where the ABCD² score was calculated, this early benefit of hospital admission was independent of risk status as there were equal proportions of low, medium, and high-risk patients in both the admitted and discharged cohorts of this subgroup. The benefit of hospital admission was restricted to the early risk of subsequent stroke, as there was no significant difference in rate of subsequent stroke or TIA during the 29 – 365 day follow-up period (see Table 4.2) or the cumulative 1 year event rate; 133/1,816 (7.33%) for the admitted group and 68/719 (9.46%) for the discharged group (OR 1.3, 95% CI 0.98 – 1.7, p = 0.10). Amongst those who were discharged home, the median time to representation was 2 days, which means that even if there was widespread availability of rapid access TIA clinics in Australia, the current National Stroke Foundation recommendation of specialist TIA clinic review within 7 – 10 days (National Stroke Foundation 2007) would be too late. The authors attributed this early benefit of hospital admission to the fact that hospitalised patients are more likely to receive early comprehensive investigation and initiation of evidence-based secondary preventive measures and education regarding lifestyle modification. The authors suggested potential reasons why this early benefit was not sustained in the 29 – 365 day period may include insufficient numbers to detect a difference, sub-optimal management in some of the admitted group, failure to maintain secondary preventive measures after 1 month in the admitted group, a catch-up in care of the discharged group, a higher proportion of TIA mimics among the discharged group, or that the risk of a subsequent cerebrovascular event is highest in the acute period, as has been shown in other studies (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004; Sciolla and Melis 2008).
4.7 Impact of Including Stroke Patients in the Analysis

In total there were 19/238 patients (8%) with stroke included in this study. This is less than the rate of 10.6% seen in the multi-centre study in California (Johnston, Gress et al. 2000) which was 1 of the 2 main study cohorts from which the ABCD² score was derived. Follow-up was available for 18/19 patients (94.7%) in the stroke subgroup. The risk of subsequent stroke within 90 days was 1/18 (5.6%), which is less than the rate of 10.4% seen amongst the subgroup of stroke patients enrolled in the California study (Johnston, Gress et al. 2000).

Table 4.2 Effect of Admission versus Discharge on the Rate of Subsequent Stroke or Recurrent TIA (Kehdi, Cordato et al. 2008)

<table>
<thead>
<tr>
<th>Outcome Events</th>
<th>Admitted n = 1,816</th>
<th>Discharged n = 719</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 28 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>41/1,816 (2.3%)</td>
<td>38/719 (5.3%)</td>
<td>2.54 (1.60-4.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>12/1,816 (0.7%)</td>
<td>15/719 (2.1%)</td>
<td>3.46 (1.59-7.51)</td>
<td>0.002</td>
</tr>
<tr>
<td>Recurrent TIA</td>
<td>29/1,816 (1.6%)</td>
<td>23/719 (3.2%)</td>
<td>2.16 (1.23-3.81)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Day 29-365</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>92/1,816 (5.1%)</td>
<td>30/719 (4.2%)</td>
<td>0.84 (0.55-1.29)</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke</td>
<td>45/1,816 (2.5%)</td>
<td>9/719 (1.3%)</td>
<td>0.52 (0.25-1.07)</td>
<td>0.06</td>
</tr>
<tr>
<td>Recurrent TIA</td>
<td>47/1,816 (2.6%)</td>
<td>21/719 (2.9%)</td>
<td>1.16 (0.69-1.96)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Median time to presentation</strong></td>
<td>9 days</td>
<td>2 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was no significant difference in the rate of secondary outcome events between the TIA or stroke subgroups. Whilst the number of primary outcome events in this study was too small to allow a statistically meaningful analysis, the lack of a significant difference in the risk of subsequent stroke or of a secondary outcome event
between the TIA and stroke subgroups suggests that a TIA may carry the same risk as a mild stroke. Alternatively, it could be a reflection of the increasing body of evidence from MRI studies which show an increased likelihood of evidence of infarction on DWI with increasing symptom duration (Crisostomo, Garcia et al. 2003; Lamy, Oppenheim et al. 2006; Prabhakaran, Chong et al. 2007; Calvet, Touze et al. 2009), showing that whilst patients may meet the 24 hour time-frame definition for TIA the correct diagnosis may be mild ischaemic stroke.

There was no significant difference to the medical management and performance of investigations following exclusion of all patients with stroke. Interestingly, not all patients with mild ischaemic stroke were admitted to hospital. Whilst there was a percentage increase in the proportion of stroke patients admitted post-pathway implementation it did not reach significance.

The rate of pathway utilisation was similar in the overall cohort, compared to the TIA and stroke subgroups (44.5-46.7%). The fact that pathway enrolment was uniformly poor in all 3 of these groups supports the earlier reasoning that this was likely due to problems with both the dissemination and adoption processes of the clinical pathway rather than staff only enrolling those patients when confident of the diagnosis.

4.8 Strengths and Weaknesses of this Study

Previous studies of TIA patients have included only patients with a diagnosis of TIA made by either a general practitioner or ED doctor (Whisnant, Matsumoto et al. 1973; Dennis, Bamford et al. 1990; Johnston, Gress et al. 2000; Coull, Lovett et al. 2004; Hill, Yiannakoulas et al. 2004; Kleindorfer, Panagos et al. 2005). Given that the diagnosis of a TIA is purely a clinical diagnosis based upon patient history, for which there is no objective confirmatory test; the diagnostic accuracy is dependent on the clinical skill and expertise of the attending doctor. Diagnostic accuracy can vary from 19 – 78% amongst general practitioners (Dennis, Bamford et al. 1989; Quik-van Milligen, Kuyvenhoven et al. 1992; Ferro, Falcao et al. 1996; Tomasik, Windak et al. 2003; Whitehead, Mc Manus et al. 2005) and from 13 – 94% amongst emergency physicians (Kothari, Brott et al. 1995; Ferro,
Falcao et al. 1996; Johnston, Gress et al. 2000; Morgenstern, Lisabeth et al. 2004). This is the first study of patients with TIA to identify patients for inclusion on the basis of presenting symptoms rather than only including those with a discharge diagnosis of TIA or minor ischaemic stroke. This was done with the aim of overcoming any potential diagnostic inaccuracies that may have arisen in order to capture a more accurate picture of patients with TIA presenting to an ED. This method of patient identification resulted in an additional 24 (10% of the cohort) patients being identified, of which only 1 (4.2%) was ultimately deemed to be a TIA mimic. Interestingly, no diagnosis had been reached in ED in 14/24 (58.3%) of these patients.

The study took into consideration the effect of the TIA/stroke clinical pathway on the outcome measures of medical management and performance of investigations in the following important subgroups: admitted versus discharged, high- versus low-risk, and the pathway-enrolled subgroup. Primary and secondary outcome events were assessed both for the overall pre- and post-pathway cohorts and the subgroup of admitted versus discharged patients where no significant difference was found.

The study reviewed why the patients with TIA and a history of atrial fibrillation were not warfarinised. Previous studies have documented low utilisation rates of warfarin for patients in atrial fibrillation (Duffy, Phillips et al. 2003; Hill, Roether et al. 2007). This allows the assumption that this is due to failure on the part of the treating doctor, which may not be the case as not all patients are suitable for warfarin (usually cases where the patient has a known risk of haemorrhage or a history of previous unheralded haemorrhage). In other instances the patient may decline treatment with warfarin due to their concern with regard to bleeding risk or due to the inconvenience of the regular blood tests required to ensure the warfarin dosage maintains their international normalised ratio (INR) within the therapeutic range. In this study 12 of the 22 patients (54.5%) with atrial fibrillation were not warfarinised and there was a reason documented in the notes as to why they were not warfarinised in 11 (92%) of these 12 cases, thus showing that treatment with warfarin was considered in 21 (95.5%) of these cases with atrial fibrillation.
Similarly, a carotid duplex may not be warranted in all cases. This study looked at the cohort of patients who did not have a carotid duplex and found, following exclusion of those patients who would not be a suitable operative candidate for carotid artery surgery and those patients with a posterior circulation stroke, only 13/134 (9.7%) of the post-pathway cohort were due to an anterior circulation event which warranted further investigation with a carotid duplex (Table 3.9). Thus, of the 95 cases which warranted a carotid duplex in the post-pathway cohort it was performed in 82 (86.3%) cases.

Limitations of this study include the retrospective nature of the study which allowed potential for recall bias in particular where follow-up was performed by phone for outcome events and may have resulted in some secondary outcome events being missed or possibly prompted.

There was potential for recall bias for time-frame to investigations performed privately which resulted in exclusion of those cases for analysis where the patient was unable to recall the date of the investigation. This resulted in 50/60 (83.3%) of those patients who underwent carotid duplex in the pre-pathway cohort and 73/80 (91.3%) of the post-pathway cohort being included for analysis of the timeframe to carotid duplex. Similarly, only 34/41 (83%) of the pre-pathway cohort who underwent echocardiography and 50/62 (80.6%) of the post-pathway patients were included for analysis for timeframe to echocardiography. Given that these investigations were performed at private institutions it is likely that they may have been performed more expediently than in the public hospital system and potentially the results obtained in this study may be an over-estimation of the timeframe to these investigations.

There was incomplete follow-up in both cohorts at 90 days, 95/104 (91.3%) patients in the pre-pathway cohort and 123/134 (91.8%) patients in the post-pathway cohort, which may have resulted in some outcome events being missed.

This study was carried out by chart review, if the pathway was not filed in the chart it was deemed not to have been used, which may have underestimated the percentage of cases in
which it was used as it may have been followed, but not filled in, or simply not filed in the chart.

A 6 month study period was chosen pre- and post-implementation of the TIA/stroke clinical pathway to enable uniformity of data collection by one person (author). However, given the small number of primary outcome events a longer study time period may have been of benefit to better assess the effect of the clinical pathway on this outcome.

The small number of primary outcome events prevented a meaningful analysis for the effect of the pathway on this outcome, yet given the main aim of TIA management is the prevention of subsequent stroke it is encouraging to see such a small number.

4.9 Conclusions and Future Directions

This study has provided a number of important lessons regarding the emergency management of TIA and minor stroke presenting to hospital emergency departments, and how clinical pathways might improve the processes of care and, potentially, improve outcomes.

Whilst there were improvements in some processes of care, for example the use of antithrombotic agents and statins, other areas require further improvement. Some of these areas may require specific strategies, such as educational programs to ensure adequate treatment of hypertension, which remained an area which our results suggest can be improved upon.

The clinical pathway, which aimed to ensure that all appropriate investigations were performed, highlighted access issues within the study hospital to certain investigations, especially echocardiography and carotid duplex testing, which prevented these tests being performed within the desired time-frame. Ideally additional equipment and skilled personnel could help rectify this situation.

There were only a small number of MRI scans performed, both acutely (within 24 hours) and within 30 days, in this study. Given the AHA/ASA scientific statement on TIA
recommends MRI, including DWI, as the preferred brain diagnostic imaging for patients with TIA (Easton, Saver et al. 2009) it will be interesting over the coming years to see if there is a dramatic increase in the utilisation of MRI, rather than CT, as the first line investigation for patients with TIA.

In an effort to reduce the waiting time for specialist review a weekly TIA clinic was established as part of this study which allowed urgent review with a neurologist within one week, but this did not guarantee that the carotid duplex and echocardiogram would be performed prior to the clinic review. An ideal model to aim for in the future might be a daily “one-stop” TIA clinic with the ability to access same day neuroimaging, carotid duplex testing, ECG and echocardiography (if deemed necessary), such as has been studied in the French SOS-TIA and UK EXPRESS cohorts.

Until “one-stop” TIA clinics are a more widespread phenomenon, the ABCD² score appears to be a viable method of triaging patients in a primary care setting and ED setting so as to ensure those at highest risk are assessed and managed more urgently. This study adds support to previous studies which have independently assessed the ABCD² score and found it to be of benefit in identifying those at high-risk of a subsequent stroke (Tsivgoulis, Vassilopoulou et al. 2007; Selvarajah, Smith et al. 2008). The small number of primary outcome events in this study prevented any statistically meaningful analysis to be performed, but all 4 subsequent strokes within 90 days of the index TIA in this study had an ABCD² score ≥ 4. When primary and secondary outcome events were combined there was a statistically significant association between a high-risk ABCD² score (≥ 4) and 90 day risk of an outcome event (p = 0.05). A larger study is required to further assess this.

The question still remains as to whether patients with TIA require hospital admission or not. This study found risk stratification of patients based on a dichotomised version of the ABCD² score was beneficial in assisting the decision regarding which patients required hospital admission for urgent assessment and management. However, another larger Australian study found hospital admission beneficial for patients with TIA regardless of their ABCD² score (Kehdi, Cordato et al. 2008). The low number of primary outcome events in this study suggests that the number of patients was too small to answer this...
question and a randomised, controlled trial with a larger cohort of patients with TIA would be required to adequately address this question. Given the high early risk of subsequent stroke (Johnston, Gress et al. 2000; Gladstone, Kapral et al. 2004) potentially all TIA patients should be admitted for investigation and initiation of appropriate medical management until same day rapid access TIA clinics are available.

Overall, this study shows that a clinical pathway can be used successfully in an effort to bridge the evidence to practice gap that exists in the management of patients with TIA. The TIA/stroke clinical pathway has been well received at meetings of the Queensland Stroke Network and Queensland Clinical Neuroscience meetings. Consequently, since the conclusion of this study the clinical pathway we developed has been made available for use in all public hospitals in Queensland.
Section V: Bibliography


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161


