TRANSIENT ISCHAEMIC ATTACK:

A PRIMARY CARE PERSPECTIVE OF

STROKE PREVENTION

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A thesis submitted in fulfillment of the requirements for the

degree of Doctor of Philosophy, July 2015.

Table of Contents

SECTION 4: MANAGEMENT PATHWAYS

SECTION 5: DISCUSSION

ABSTRACT

Transient Ischaemic Attack: a primary care perspective of stroke prevention

Transient ischaemic attacks (TIAs) are a warning sign for stroke. The early assessment and management of TIA can decrease the subsequent risk of stroke but the best model of care for TIA has not been established. General practitioners (GPs) in primary care have a significant role in secondary prevention for patients following a TIA and may also be the initial clinician assessing a patient with a suspected TIA. The clinical diagnosis of TIA can be challenging and there is limited literature describing how GPs assess and manage TIAs in practice. Diagnosis and assessment can be assisted by clinical scores and imaging, but these tools may not be accessible or have not been validated specifically in primary care. GPs with special interests (GPwSI) have been involved in providing expert care in areas where access to a specialist may be limited, and a GPwSI in stroke and TIA could be valuable in a TIA care pathway.

The aims of this research were to:

1. Determine GP knowledge on current stroke and TIA assessment and management.

2. Educate GPs on the assessment of acute neurological symptoms and the early management of TIA.

3. Examine if additional tools that assist in the assessment and diagnosis of TIA including plasma protein biomarkers can be used in primary care.

4. Determine if a collaborative strategy for TIA management, using GPwSI in a community-based rapid-access TIA clinic (COMBAT clinic) linked with a

specialist-based, hospital Rapid Access Clinic (RAC) is a feasible model of TIA care.

5. To assess the role of imaging in a community-based TIA clinic.

Methods and Findings

A cross-sectional study of GPs in Western Adelaide was conducted to determine the knowledge of TIA assessment and management, and identify perceived barriers. This self-administered questionnaire of 32 GPs found knowledge deficits in TIA care especially diagnosis and treatment. Participants also identified access to neurology specialists as a barrier and that specific education for GPs was needed. This research highlighted the need to improve TIA knowledge amongst GPs with education specifically designed for general practice and that improvement was needed in management pathways of TIA care locally, including access to specialist opinion.

A number of resources were thus developed to educate GPs and improve their knowledge and confidence around TIA care. A review of the literature was undertaken and published for GPs specifically. Given the difficulty in diagnosing TIAs and the numerous mimics that may present in primary care, an approach to a "funny turn" was developed and published in a "10-minute consultation" format. GPs respond to different modalities of education delivery and as such two further learning modules were developed. A self-directed learning module was developed for GP registrars and a case of a "funny turn" was written for the independent GP learning program "check". Time limitations in GP consultations can be a barrier to effective assessment and a comprehensive clinical neurological examination may be a challenge. A five-minute approach to a patient with a suspected TIA was

demonstrated in a video for GP registrars to access and improve their clinical skills for acute neurological cases.

Given the challenge of clinically diagnosing TIA, other tools including imaging can assist in the assessment. However access to magnetic resonance imaging (MRI) in Australia primary care is limited and blood biomarkers could potentially be more useful. A study to identify novel plasma biomarkers for diagnosing TIAs and distinguishing them from TIA mimics was conducted.

With limited evidence about the best model of TIA care and the suggestion that GPs perceived access to neurology specialists was a barrier, we tested a novel model of TIA care. A proof of concept study explored the potential of a community-based (COMBAT) and hospital-based rapid access clinic (RAC). Low risk patients were assessed at the community-based clinic by GPwSI whilst higher risk patients were assessed at the hospital RAC. The study was conducted over eight months with 33 patients seen at the COMBAT clinic, of which 15 were diagnosed with TIA, and 43 at the RAC, of which 15 were diagnosed with TIA and 12 with stroke. One patient assess at the RAC had a subsequent stroke within 90 days.

Imaging is a valuable to tool in assessing patients with a suspected TIA, but access to MRI can be limited. Computed Tomography (CT) and CT Angiography (CTA) were performed in 17 of the 33 patients seen in the COMBAT clinic and 7 had positive CTA findings. CTA was found to be valuable in assessing patients and affecting their course of management, and a response to a paper on CTA in TIA assessment was published confirming these findings.

The publications presented in this thesis contribute to the existing body of work around TIA with a primary care perspective, hitherto deficient in the published literature. The knowledge of GPs about TIA assessment and management could be improved, but the development of educational resources needs to be tailored to GPs specifically and consider the availability of local TIA services.

An accurate diagnosis of TIA and stratification of risk allows the appropriate triage of patients with suspected TIA. As presented in this thesis, the discovery of a potential blood biomarker associated with TIA would be a significant contribution to reaching an accurate and efficient evaluation of TIA in primary care.

A novel model of TIA care involving a COMBAT clinic and RAC clinic can be a feasible pathway. Triaging lower risk patients to a community pathway and the use of CTA allowed patients with suspected TIA to be assessed and managed rapidly. As a result the RAC with its limited capacity to see one patient a day, could concentrate on higher risk patients with only one subsequent stroke at 90-days in the groups combined. This pathway is an innovative collaboration between primary care and hospital services, with the potential to improve patient outcomes, decrease stroke risk and be cost effective.

The resources available in different areas will influence the best model of TIA care, but the role of primary care remains significant. In continuing to improve the assessment and management of TIA, engaging GPs in education and supporting the collaboration between specialist hospital services and GPs is achievable and critical to the improvement of health outcomes.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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ACKNOWLEDGEMENTS

Statement of Authorship

Title of paper	Transient Ischaemic Attacks: assessment and management
Publication status	Published
Publication details	**Leung ES**, Hamilton-Bruce MA, Koblar SA. Transient Ischaemic Attacks: assessment and management. Australian Family Physician. 2010; 39 (11): 820-4.

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Signature		Date	12/12/14

Statement of Authorship

Title of paper	TIAs Reply
Publication status	Published
Publication details	**Leung ES**, Hamilton-Bruce MA, Koblar SA. TIAs. Australian Family Physician. 2011; 40(1/2):9.

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Signature		Date	12/12/14

Statement of Authorship

Title of paper	Transient Ischaemic Attack (TIA) knowledge in general practice: a cross-sectional study of Western Adelaide general practitioners.
Publication status	Published
Publication details	Leung E, Hamilton-Bruce M, Price C, Koblar S. Transient Ischaemic Attack (TIA) knowledge in general practice: a cross-sectional study of Western Adelaide general practitioners. *BMC Research Notes.* 2012; 5(1): 278.

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Statement of Authorship

Title of paper	Funny turn. BMJ. 2011; 343.
Publication status	Published
Publication details	Leung ES, Hamilton-Bruce MA, Stocks N, Koblar SA. Funny turn. BMJ. 2011; 343.

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Signature	Date	12/12/14

Statement of Authorship

Title of paper	Letter to the Editor: Stroke.
Publication status	Published
Publication details	Leung E, Hamilton-Bruce M, Price C, Stocks N, Koblar S. Letter to the Editor: Stroke. Australian Family Physician. 2014; 43(11): 750-1.

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Signature		Date	12/12/14

Statement of Authorship

Title of paper	Identification of Novel Plasma Biomarkers for Diagnosing Transient Ischaemic Attack and Distinguishing from TIA-Mimic Conditions: A Human Proteomic Pilot Study
Publication status	Publication style
Publication details	Djukic M, Hamilton-Bruce MA, Jannes J, **Leung ES**, Nichols S, Chataway T, Lewis M, Koblar S. Identification of Novel Plasma Biomarkers for Diagnosing Transient Ischaemic Attack and Distinguishing from TIA-Mimic Conditions: A Human Proteomic Pilot Study

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Title of paper	COMBAT: COMmunity-Based rapid Access Transient ischaemic attack as a model of stroke prevention. A Proof of Concept Study.
Publication status	Submitted for Publication
Publication details	Leung ES, Hamilton-Bruce MA, Stocks N, Toner P, Jannes J, Koblar S. COMBAT: COMmunity-Based rapid Access Transient ischaemic attack as a model of stroke prevention. A Proof of Concept Study

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Statement of Authorship

Title of paper	Letter by Benedict et al regarding article, "What causes disability after transient ischaemic attack and minor stroke? Results from the CT and MRI in the triage of TIA and minor cerebrovascular events to identify high-risk patients (CATCH) study".
Publication status	Published
Publication details	Benedict A, Khoo EW, **Leung E,** Hamilton-Bruce A, Koblar S. (2013). Letter by Benedict et al regarding article, "What causes disability after transient ischaemic attack and minor stroke? Results from the CT and MRI in the triage of TIA and minor cerebrovascular events to identify high-risk patients (CATCH) study". *Stroke* 2013; 44(4):e32

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ABBREVIATIONS

ABCD2	Age, Blood pressure, Clinical features, Duration, Diabetes
AFP	Australian Family Physician
BEACH	Bettering the Evaluation and Care of Health
COMBAT	Community-based rapid access transient ischaemic attack
CPD	Continuing Professional Development
CT	Computed tomography
DWI	Diffusion weighted imaging
ECG	Electrocardiograph
ED	Emergency Department
EDS	Electronic Decision Support
GP	General practitioner
GPwSI	General practitioner with a special interest
MRI	Magnetic resonance imaging
NIHSS	National Institute of Health Stroke Scale
NHS	National Health Service
NSF	National Stroke Foundation
RAC	Rapid Access Clinic
RACGP	Royal Australian College of General Practitioners
SFGPET	Sturt Fleurieu General Practice Education and Trainings
TIA	Transient ischaemic attack

SECTION 1. INTRODUCTION

Stroke is a leading cause of disease in Australia, with approximately 50,000 strokes occurring per year(Australian Institute of Health and Welfare 2013; Senes 2006). The subsequent consequences can be devastating with 20% dying within a month of their first stroke(Thrift et al. 2000) and of the survivors, one third remain disabled(Hankey et al. 2002). The costs of stroke are also significant(Dewey et al. 2003; Gloede et al. 2014). Transient ischaemic attacks (TIAs) are a warning sign of stroke, with 20% of patients having a subsequent stroke within 90 days(Johnston, S. Claiborne et al. 2000). Herein lies an opportunity for stroke prevention, with evidence suggesting that urgent assessment and management of TIAs can reduce the risk of subsequent stroke and be cost-effective(Johnston, S. Claiborne et al. 2000; Lavallee et al. 2007; Luengo-Fernandez, Gray & Rothwell 2009; Rothwell et al. 2007).   With its associated morbidity and mortality, the prevention of stroke for our ageing population is a significant strategy to adopt and is recognised as a national health priority in Australia(National Health Priority Action Council (NHPAC) 2006a, 2006b).

Australian general practice involves the provision of primary whole-patient medical care to individuals, families and their communities. This includes being the first point of care for people seeking medical attention, and also the management of chronic disease(Royal Australian College of General Practitioners 2005). Whilst the majority of acute stroke management occurs in hospital, patients may present initially in primary care and the long-term management of stroke prevention is a key role for general practitioners. There are limited data on the assessment and management of TIA or stroke in primary care. The Bettering the Evaluation and Care of Health

1

(BEACH) program, a continuous cross-sectional survey of Australian GPs and patient encounters suggests that TIA management is low in general practice with two per hundred encounters(Charles, Pan & Miller 2010). With these numbers and the difficulty in identifying TIA cases in general practice and the community, researchers have tried to determine instead the knowledge of general practitioners in stroke care. Much of this work precedes evidence on the importance of early TIA assessment and management(Middleton et al. 2003; Tomaski et al. 2003).

The diagnosis of TIA can be difficult even amongst neurologists (Kraaijeveld et al. 1984) and previous studies of GP knowledge suggest the need for focused education in stroke and TIA(Middleton et al. 2003; Tomaski et al. 2003). With recent advances in imaging, especially magnetic resonance imaging (MRI), both the definition of TIA and the assessment of acute neurological symptoms has changed(Easton et al. 2009, Calvet, 2009 #99). Whilst the use of MRI can assist, issues of access and the cost of imaging contribute to the difficulty in diagnosis. The use of protein biomarkers could be a more accessible tool in diagnosing or stratifying TIAs, and as yet none has been found particularly useful(Cucchiara, BL, Messe, Sansing, MacKenzie, Taylor, Pacelli, Shah & Kasner 2009; Haapaniemi & Tatlisumak 2009; Nambi et al. 2009; Papas et al. 2008; Terruzzi et al. 2008; Whiteley, William, Tseng & Sandercock 2008). The findings from the previous studies provide evidence of a genetic risk for stroke, and genetic biomarkers may also contribute to stratifying risk and preventing stroke(Dichgans & Hegele 2009; Holliday et al. 2012; Jannes et al. 2004; Meschia 2004).

There is limited research on where best to manage TIA patients, in particular, the value of acute observation units (for example, acute stroke units). An audit of TIA services in Australia demonstrated the scarcity of TIA clinics and the deficiency of an effective rapid-access TIA clinic to meet Australian needs(Price et al. 2009). GPs with a special interest have been providing services in the United Kingdom to address the shortage of specialists, although there is no published literature describing the role GPwSI in TIA care(Nocon & Leese 2004).

The aims of this research were to:

1. Determine GP knowledge on current stroke and TIA assessment and management.

2. Educate GPs on the assessment of acute neurological symptoms and the early management of TIA.

3. Examine if additional tools that assist in the assessment and diagnosis of TIA including plasma protein biomarkers can be used in primary care.

4. Determine if a collaborative strategy for TIA management, using GPwSI in a community-based rapid-access TIA clinic (COMBAT clinic) linked with a specialist-based, hospital Rapid Access Clinic (RAC) is a feasible model of TIA care.

5. To assess the role of imaging in a community-based TIA clinic.

Findings and Implications

Determining the knowledge status of GPs in the assessment and management of TIA and stroke would allow the design of appropriate and focused education for GPs. With constantly emerging therapies and new guidelines, maintaining ongoing

education for GPs could be overwhelming. Given the significance of early intervention for TIA, education around acute neurological presentations could potentially improve patient risk stratification and subsequent outcomes.

The discovery of a plasma protein biomarker would have significant impact on the assessment of patients with suspected TIA. Access to specialists for assessment and MRI scans remains limited in Australia. A blood test could be particularly useful in rural and remote areas of Australia, providing an efficient and more accurate assessment. Thus it could potentially avoid unnecessary transport and referral to a specialist hospital service, with its associated high costs.

Similarly a community-based TIA clinic could allow rapid assessment of suspected TIA patients at low risk, and allow higher risk patients to be triaged to access limited hospital resources.

Together these interventions could contribute significantly to improving the assessment and management of TIA in Australia, whilst still allowing appropriate care of TIA mimics. With early appropriate management of higher risk TIAs in hospital-based units, the subsequent stroke risk could be decreased, and with better communication with primary care the longer term management of risk factors could be improved and therefore reduce the incidence of stroke. The impact on the cost of TIA and stroke care could also be significant.

Chapter 1: TIA Review of the Literature

<u>TIA Definition</u>

The World Health Organisation defined a TIA in 1978 as an episode of sudden focal neurological deficit lasting less than 24 hours and of vascular origin(Albers et al. 2002; Investigators 1988). This arbitrary time frame of 24 hours was determined at a time when there was limited imaging and treatment for stroke and TIA. The assumption was that that there was no permanent brain injury if symptoms resolved completely within 24 hours. The term reversible ischaemic neurological deficit (RIND) was applied to symptoms that lasted 24 hours to 7 days. But in a study of 1,343 patients with either TIA, RIND or stroke, Levy found that symptoms resolved within 30 minutes in 50% of patients and 60% had completely resolved within 60 minutes(Levy 1988). Albers et al thus proposed a new definition, being a brief episode of neurological dysfunction caused by focal brain or retinal ischaemia with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction(Albers et al. 2002).

However, with advances in medical imaging, especially magnetic resonance imaging (MRI), it became apparent that the 24-hour time frame was no longer useful and the assumption that resolution of symptoms meant no permanent ischaemic damage was incorrect. In particular diffusion weighted imaging (DWI) demonstrated that up to 48% of patients with TIA has evidence of ischaemia(Ay, H. et al. 2002; Calvet et al. 2009; Inatomi et al. 2004; Kidwell et al. 1999; Rovira et al. 2002). Other terms were proposed to account for these findings and classify TIA more accurately, including transient symptoms associated with infarction (TSI)(Ay, Hakan et al. 2005), stroke in

evolution, partial non-progressing stroke(Caplan 1983), transient neurological abnormality(Fred 2002) and acute cerebrovascular syndrome(Uchiyama 2014). In 2009 The American Stroke Association endorsed a new definition for TIA being "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction" and also recommend that all TIA patients undergo neuroimaging, preferably MRI scanning(Easton et al. 2009).

The current guidelines produced by the National Stroke Foundation in Australia(National Stroke Foundation 2010) makes reference to the tissue based definition proposed by Albers of an episode "lasting less than 1 hour and without evidence of infarction"(Albers et al. 2002) but also includes the original 24-hour definition.

Risk Stratification

A TIA can be a medical emergency with the risk of stroke varying between 10-20% in the following 90 days(Johnston, S. Claiborne et al. 2000). Half of these patients will have a stroke within the next 48 hours(Lovett et al. 2003). Risk stratification can assist clinicians in assessing this early risk of stroke. Johnston et al. devised an ABCD2 score to assist with predicting the risk of stroke in TIAs at 48 hours. The clinical score of **A**ge ≥ 60 years old (1 point), **B**lood pressure ≥ 140/90 (1 point), **C**linical features (unilateral weakness 2 points, or speech disturbance 1 point), **D**uration (10-59 minutes 1 point, >59 minutes 2 points) and **D**iabetes (1point) is allocated to a patient presenting with a TIA(Johnston, S. Claiborne et al. 2007). The National Stroke Foundation (NSF) has included this score in their guidelines and has categorised more than 4 points as being high risk(National Stroke Foundation 2010).

The initial assessment of a patient with a suspected TIA is likely to be by a non-stroke specialist, either a general practitioner or an emergency physician(Morgenstern et al. 2004). The ABCD2 score is a simple and efficient scoring system that can be performed in primary care without specific training. However, Bradley el al examined 101 referrals to a rapid access stroke prevention clinic and found only fair agreement between the referring physician and then stroke physician or resident(Bradley, D et al. 2013). They concluded that the ABCD2 score was frequently inaccurate by the referring physician and thus could not be relied on alone for risk stratification but that this could be potentially addressed with short-term training.

Other researchers have also outlined the limitations of the score and validation studies of the ABCD2 score have been primarily in hospital settings(Amarenco, P., Labreuche & Lavallee 2012; Amarenco, Pierre et al. 2009; Asimos et al. ; Bray, Coughlan & Bladin 2007; Cancelli et al. 2011; Carpenter et al. 2009; Chandratheva et al. 2010; Fothergill et al. 2009; Gulli & Markus 2011; Harrison et al. 2010; Josephson et al. 2008; Kinsella et al. 2011; Koton & Rothwell 2007; Perry et al. 2011; Purroy et al. 2009; Quinn et al. 2009; Ray, G et al. 2008; Ray, Gautamananda et al. 2009; Reeves et al. 2008; Sanders, Srikanth, Blacker, et al. 2012; Sanders et al. 2010; Sanders et al. 2011; Schrock, Victor & Losey 2009; Sheehan et al. 2010; Sheehan et al. 2009; Srikanth, Sanders & Phan 2010; Stead et al. 2011; Tsivgoulis & Heliopoulos 2010). Giles et al performed a systematic review of 20 validation studies and concluded that the ABCD2 score was clinically useful and studies with poor prediction results were from retrospective reviews of emergency department case

notes(Giles, Matthew F. & Rothwell 2010). The usefulness of the score in general practice remains to be determined.

To improve the accuracy of the score some researchers have suggested adding imaging findings to the score(Amarenco, Pierre et al. 2009; Ay, H. et al. 2009; Calvet et al. 2009; Cucchiara, BL, Messe, Sansing, MacKenzie, Taylor, Pacelli, Shah, Pollak, et al. 2009; Giles, M. F. et al. 2010; Kiyohara et al. 2014). These hospital-based studies rely on timely access to imaging services and the addition of an imaging score would not generally assist risk stratification in primary care given limited access to MRI services.

<u>Models of Care</u>

The assessment and management of TIAs can be difficult, particularly as the symptoms resolve quickly patients may be unaware of their importance and the urgency of early medical attention(Giles, Matthew F., Flossman & Rothwell 2006). The models of care are also variable, both nationally and internationally(Chan 2004; Donnan et al. 2006; Guarino et al. 2015; Johnston, S. Claiborne & Smith 1999). Kehdi et al. analysed a retrospective study of patients presenting to the emergency department in the South West Area Health Service in NSW with a TIA and found that patients who were discharged home had a higher rate of stroke or recurrent TIA compared to the admitted group in the first 28 days (5.3% versus 2.3%), concluding that the results were likely to reflect the more rapid and comprehensive investigation and management of the admitted patients(Kehdi et al. 2008). However, others have shown that an outpatient based TIA clinic can be an effective alternative(Fallon et al. 2006; Rothwell et al. 2007). A study of a 24-hour TIA clinic reported 74% of patients

were discharged home after prompt assessment and treatment, potentially lowering costs(Lavallee et al. 2007).

Sanders et al adopted a model of rapid management in an Australian emergency department followed by outpatient care and found a low (1.5%) 90-day stroke outcome(Sanders, Srikanth, Jolley, et al. 2012). They compared their model with a previous model of routine hospital admission and concluded that patients with TIA can be managed safely in an outpatient model with a specific protocol in place.

Australian Health Care System

With the increasing burden of chronic illness and the limitations of resources, the emergency departments (ED) of hospitals can be stretched whilst hospital bed capacity has decreased(Australian Medical Association 2008). Given the current Australian health care system, the delivery of early assessment and management may present a challenge, whilst the best model of care is yet to be established(Anderson 2008; Lindley 2006). A survey of Australian hospitals co-ordinated by the NSF confirmed the variable services for TIA assessment and management. The three models of TIA care reported being hospital admission, rapid access TIA clinics and primary care-centred models. With delays in both assessment and treatment, the study suggested there is a significant gap between the evidence and current practice, concluding that determining the best model of care requires urgent investigation(Price et al. 2009).

The health workforce is also a challenge for Australia and a number of solutions to address workforce shortages have been suggested, including task

substitution(Australian Government Productivity Commission 2005; Brooks,
Robinson & Ellis 2008; Ellis, Robinson & Brooks 2006; Gorman & Brooks 2009). In
the United Kingdom, the National Health Service (NHS) introduced GPwSI to
improve access to specialist clinics with long waiting lists. Whilst there is some data
on their clinical and cost-effectiveness, there is limited evidence in the literature of
GPwSI involved in TIA care(Boggis & Cornford 2007; Bradley, S & David
McKelvey 2005; Brennan & Spillane 2007; Cooper 2006; Crowley 2006; Franks
2004; Gerada, Wright & Keen 2002; Hayes 2006; Jones & Bartholomew 2002;
Moffat et al. 2006; Nocon & Leese 2004; Pinnock et al. 2005; Roland 2005; Rosen,
Stevens & Jones 2003; Salisbury et al. 2005).

Discharge to GPs

Patients admitted to hospital or seen in outpatient clinics are usually discharged to the
care of their GP, who provide ongoing long-term management, including the
prescription of new medications and monitoring the effects and side-effects of
treatment. The hospital discharge summary or outpatient letter is the primary method
for specialist hospital teams to communicate with the GP and plays an important role
in promoting continuity of care. However, deficits in communication can occur
which may adversely impact patient care, with one study demonstrating that GPs
received discharge summaries for only 27.1% of discharged patients with 36.4% of
the summaries audited containing errors including medication and allergy
errors(Wilson et al. 2001). Researchers in a recent audit found some improvements
with discharge summaries received for 92% of identified admissions but the
timeliness and quality was still poor(Belleli, Naccarella & Pirotta 2013). With a high
turnover of junior medical staff, who are usually responsible for discharge summaries,

the importance of this document with respect to its quality and timeliness may not be appreciated. A review of studies investigating discharge communication concluded that deficits in information transfer were common and could result in poorer quality of care, citing that one study found a greater risk of readmission among patients whose doctor had not received a discharge summary at the follow-up visit(Kripalani et al. 2007). The use of electronic discharge summaries may have improved communication, with a study in NSW surveying GPs showing that 93% agreed that an electronic discharge summary was an overall improvement, with the majority (83%) receiving them within 2 weeks(Alderton & Collen 2007). However, the transfer of these summaries is often done manually. For instance in South Australia, summaries are printed and either faxed or mailed to the GP or handed to the patient. Similarly hospital outpatient letters are often dictated and mailed to the GP. Importantly the involvement of a GP in specialist teams may improve the liaison between primary and specialist care, and in turn improve long term patient outcomes(Mitchell, Del Mar & Francis 2002).

Diagnosis of TIA

The clinical diagnosis of TIAs can be a challenge even for neurologists, with many other medical conditions posing as mimics(Ferro et al. 1996; Kraaijeveld et al. 1984, Castle, 2010 #421). One study reviewed 100 consecutive patients with transient neurological symptoms presenting to the emergency department and found only 40 were confirmed cases of TIA(Prabhakaran et al. 2008). TIA mimics in this study included toxic/metabolic causes, seizures (three from brain neoplasms), migraine, neuropathies, psychiatric conditions and seven were unclassifiable. In another study reviewing patients presenting to the ED with suspected stroke, a final diagnosis of

stroke was given in 68% of cases, with stroke mimics including neurological and non-neurological conditions(Hand et al. 2006).

Identifying accurately TIA mimics and 'chameleons' is important(Nadarajan et al. 2014). Dawson et al developed and validated a clinical scoring system to diagnose TIA(Dawson et al. 2009). However, researchers in another study found that the score is less accurate in primary care where it might have been most useful(Lasserson et al. 2015). Advances in imaging have improved diagnostic accuracy for TIA. The modality of choice would be MRI with DWI as a positive finding in TIA represents a higher risk of subsequent stroke(Souillard-Scemama et al. 2015).

Whilst the use of imaging can assist, particularly an MRI DWI scan, issues of access and the cost of imaging limit the ability of clinicians to use these aids. A systematic review suggested that MRI with DWI is not cost-effective and that the most cost-effective strategies for stroke prevention in TIA care are rapid specialist assessment and CT brain imaging(Wardlaw et al. 2014). The use of protein biomarkers found in blood could assist in diagnosis or the risk stratification of TIAs. Unfortunately none as yet have been found particularly useful(Cucchiara, BL, Messe, Sansing, MacKenzie, Taylor, Pacelli, Shah & Kasner 2009; Haapaniemi & Tatlisumak 2009; Nambi et al. 2009; Papas et al. 2008; Terruzzi et al. 2008; Whiteley, William, Tseng & Sandercock 2008; Whiteley, W. et al. 2012). In a large study of 1292 patients Segal et al examined 14 potential blood biomarkers and found limited predictive use(Segal et al. 2014).

Findings from previous studies have provided evidence of a genetic risk for stroke, and genetic biomarkers may also contribute to stratifying risk and preventing stroke(Dichgans & Hegele 2009; Holliday et al. 2012; Jannes et al. 2004; Meschia 2004).

Incidence of TIA

With non-specific symptoms, poor public knowledge, difficulty in diagnosis and the possibility of undiagnosed cases of TIA in the community, ascertaining numbers of TIA is challenging(Carroll et al. 2004; Centres for Disease Control and Prevention 2004; Greenlund et al. 2003; Johnston, S. C. et al. 2003; Kleindorfer, Dawn et al. 2009; Krishnamurthi et al. 2014; Lan Spark et al. 2011; Nicol & Thrift 2005; Wang et al. 2015). As such there are limited data on the incidence of TIAs both within Australia and internationally. Studies overseas have provided estimates of TIA incidence between 68 and 83 per 100,000 population, with the majority of cases occurring in the 75-84 year old age group(Brown et al. 1998; Kleindorfer, D. et al. 2005). Using a community-based registry, researchers in Italy found that between 2007 and 2009 the incidence rate of TIA to be 0.52 per 1000(Cancelli et al. 2011). In South Australia there are approximately 5,000 strokes per annum, with 1,000 anticipated to present first with a TIA(National Stroke Foundation 2007b).

The Australian Family Physician published around the theme of "Stroke" in 2007, and whilst there was reference to the importance of TIA as a warning of stroke, the publication did not include an updated review of the literature on TIA assessment and management for GPs(Dhamija & Donnan 2007; Leung, E. et al. 2008).

<u>GP Education</u>

Australian GP trainees are required to attend education meetings and complete programs as specified by regional general practice training providers. The Royal Australian College of General Practitioners supports Continuous Professional Development (CPD) and accredits education in order for GPs to meet the requirements for registration. CPD aims to assist GPs in maintaining and improving the quality of care provided to patients and improve health outcomes.

Results from previous research studies have demonstrated that mixed methods of education delivery and learning in smaller interactive groups may be most effective(Davis & Galbraith 2009; Mansouri & Lockyer 2007; Marinopoulos et al. 2007; Mazmanian, Davis & Galbraith 2009; Zaher & Ratnapalan 2012). In particular case discussions, role-play and practical sessions are more likely to affect changes in the performance of participants although the reliability and validity of tools to assess the effectiveness of CPD is limited(Dowling, Finnegan & Collins 2015).

Given the evidence around early assessment and management of TIA and in particular the addition of the ABCD2 score in the NSF Guidelines(National Stroke Foundation 2008), a review of the literature of TIA assessment and management for GPs was published in the issue of "Traps for the Unwary" of Australian Family Physician. Knowledge is a critical aspect for GPs to be able to provide current evidence-based care and written material in a GP journal is one method of disseminating such information.

This publication was also translated into Polish and published in *Lekarz Rodzinny (Family Doctor)*. 2011; ROK XVI, NR 3: 224-229.

Following the publication of "Transient ischaemic attacks: assessment and management" in *AFP* a Letter to the Editor by Golder(Golder 2011) was submitted suggesting that patent foramen ovale also needs to be considered in the assessment of TIA. The purpose of the original article was to provide a <u>succinct</u> summary of the assessment and management of TIA in general practice, and so the discussion of patent foramen ovale was not included. We provided a reply to the letter addressing this.

Leung ES, Hamilton-Bruce MA, Koblar SA. TIAs. Australian Family Physician. 2011; 40(1/2):9.

SECTION 3: Diagnosis of TIA

Chapter 1: TIA Knowledge

The diagnosis of TIA can be a challenge for GPs and researchers from previous studies have assessed the knowledge of GPs in stroke care(Middleton et al. 2003; Tomaski et al. 2003). These however preceded evidence demonstrating the need to provide urgent TIA assessment and management and the new TIA definition. Given knowledge is a crucial component of expertise(Davis & Galbraith 2009; Mazmanian, Davis & Galbraith 2009), we conducted a survey of GPs in Western Adelaide to determine their knowledge of TIA assessment and management. The involvement of GPs in establishing potential pathways of TIA care is important as GPs play a significant role both in initial assessment and subsequent long-term management. This survey also aimed to identify perceived barriers to TIA care in the Western Adelaide region.

Leung E, Hamilton-Bruce M, Price C, Koblar S. Transient Ischaemic Attack (TIA) knowledge in general practice: a cross-sectional study of Western Adelaide general practitioners. *BMC Research Notes.* 2012; 5(1): 278.

BMC
Research Notes

SHORT REPORT   **Open Access**

Transient Ischaemic Attack (TIA) Knowledge in General Practice: a cross-sectional study of Western Adelaide general practitioners

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Abstract

Background: With evidence to support early assessment and management of TIAs, the role of the general practitioner (GP) needs to be considered in developing a TIA service in Western Adelaide. We thus aimed to determine GP knowledge of TIA assessment and management and identify perceived barriers, in order to tailor subsequent GP education and engage primary care in the co-ordinated care of TIA patients.

Findings: A self-administered questionnaire was mailed to all GPs (n = 202) in the Adelaide Western General Practice Network. Response frequencies were calculated for all variables, and associations examined by univariate analysis.

32 GPs responded. All respondents correctly identified early risk of stroke following a TIA. Difficulty accessing neurological expertise was identified as a barrier (40.6 %), as was a lack of GP knowledge (18.8 %). Areas for improvement included access to neurologists (36.7 %), relevant guidelines and education (43.3 %).

Conclusions: Diagnosis of TIA is difficult and this study highlights the need for further education and practical guidelines for GPs. With this training, GPs could be better equipped to assess and manage TIAs effectively in the community in consultation with stroke physicians.

Keywords: Transient ischaemic attack, General practitioners, Clinical guidelines, Medical education

Findings

Background

The role of the general practitioner (GP) can be significant in the assessment and management of transient ischaemic attacks (TIAs). TIA patients may regard their symptoms with less urgency and present to primary care, and the diagnosis can be a difficult one. Increasing evidence supports early urgent assessment and management of TIAs to prevent subsequent stroke. An estimated 20 % of strokes are preceded by a TIA, with the risk of stroke following a TIA being between 10-20 % in the next 90 days [1], and half of these patients suffer a stroke within the first 48 hours [2]. A recent study of a 24-hour TIA clinic reported that 74 % of patients were discharged home after prompt assessment and treatment, potentially lowering costs [3]. Early assessment and initiation of treatment of TIAs has also been associated with an 80 % reduction of early subsequent stroke in another study by Rothwell et al [4]. However, the approach to care varies both nationally and internationally, with some advocating for admission and others suggesting ambulatory care.

There are currently no formal pathways for TIA care in Adelaide and it is unclear how GPs manage patients who present with suspected TIA in Australia. GPs in the Australian health system have a number of options including managing the patient themselves, referring onto an emergency department at either a public or private hospital, referring to a public neurology outpatient clinic with variable waiting times, referring to a private neurologist or to a TIA clinic is one exists in the region.

There have been some studies that have assessed the knowledge of GPs on stroke and TIA management. Middleton et al. assessed GPs' knowledge of TIA/stroke

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risk factors and stroke prevention and management in New South Wales in 2003 [5]. They concluded that GPs required more purposeful and effective education. Their study, however, concentrated mostly on stroke and risk factors, and preceded recent knowledge about early stroke risk and stratification of TIAs. Other studies overseas similarly preceded current knowledge of early treatment and focused on the GPs ability to diagnose TIA[6-8]. The diagnosis of TIA is difficult, even amongst neurologists [9,10] and this study instead aimed to determine the knowledge of TIA assessment and current management amongst GPs, given the release of the NSF guidelines highlighting the need for urgent care. We also sought to identify perceived barriers to the assessment and management of TIAs locally that may influence future planning of services.

Methods

Drawing on the postal questionnaire by Middleton et al, a questionnaire, comprising of 3 sections, was designed to evaluate the knowledge of GPs on the assessment and management of TIAs. Section one aimed to collect demographic data while the second section contained questions based on case scenarios. The case scenarios were written by the authors, two of whom are general practitioners and based on typical cases seen in general practice. The third section asked open questions enquiring about the perceived barriers to TIA assessment and current management in general practice. Participants were asked to comment on the barriers to assessment and management, and areas they considered required improvement.

All responses were read and general themes were extracted and coded into categories. With approval from the Royal Australian College of General Practitioners (RACGP) National Research and Evaluation Ethics Committee granted, the questionnaire was piloted on a group of 18 GP educators and supervisors to ensure that the questions were appropriate and would maximise response rates. Previous papers [11,12] have suggested methods to improve response rates, including a relevant topic, offering feedback, length of questionnaires, assurances of confidentiality, incentives, association with other stakeholders and personal contact. The pilot group addressed these and the initial questionnaire and cover letter were modified accordingly. Participants felt that a shorter questionnaire, 'less exam like', with assurances of feedback and confidentiality, paper based (rather than electronic) with a letter from the chief investigator (a GP registrar) rather than a well known academic would assist in encouraging GPs to participate.

With the assistance of the Adelaide Western General Practice Network (AWGPN), questionnaires were mailed to all 202 GPs on their database. The AWGPN covers an area of 205.4 square kilometres with the population of Western Adelaide reported as 212, 741 in 2006 [13,14]. The AWGPN funded the postage costs and stationery, and because of the *Privacy Act* 1988 were unable to disclose a list of GPs in the area. Subsequently the network's administrative staff performed the mail out to GPs in the area. The questionnaire was accompanied by a covering letter explaining the purpose of the study, that the study was supported of the AWGPN Chief Executive Officer, a participant information sheet and consent form. A self-addressed pre-paid envelope was provided for participants to return the completed form and questionnaire to the investigators. An advertisement was included in the AWGPN newsletter in the month that the questionnaires were posted, inviting GPs to participate.

A follow-up reminder facsimile was sent to all GPs by the AWGPN 3 weeks following the mail-out. A random selection of GP names was then generated using a random number generator, and the investigator visited practices to raise awareness about the questionnaire amongst practice administrative staff. Practice managers were asked to remind GPs of the study and further copies of the questionnaire were provided. No financial or other incentive was offered with any invitation to GPs to participate in this study.

Questionnaires returned were de-identified and responses entered into a database. All questionnaires were included in the study although some had missing responses. Responses to the case scenarios were coded in true, false, unsure or missing categories, as the scenarios were not designed to be purely correct or incorrect responses. The coding was determined before data was collected. Statistical analysis of the data was undertaken using SPSS version 15.0, with frequencies for questionnaire responses calculated for all variables.

Results

30 GPs responded to this questionnaire after the initial mailing and a further 2 responded after the follow up methods were employed. The response rate was 16 % from a total of 202 GPs invited to participate. A further two GPs returned questionnaires indicating they were not interested in participating (no reasons given) and three were addressed "return to sender".

The demographic data collected is shown in Table 1.

Most (n = 27) respondents have over 10 years of experience in general practice work, with 2 having had more than 41 years of experience. Most respondents (n = 18) were working more than 9 clinical sessions per week.

Diagnosis of TIA

The first case scenario asked questions about the diagnosis of TIA. The responses are presented in Table 2.

Table 1 Demographics of respondents

	Study data (%)	Australian data[15] (n = 22868)
Division of General Practice Worked	(n = 30)	N/A
Adelaide Western General Practice Network	28	
Adelaide North East Division of General Practice	1	
Other	1	
Member of the division	(n = 29)	N/A
Yes	28	
No	1	
Type of Practice	(n = 30)	37 %
Solo	9 (30.0)	
Partnership	5 (16.7)	
Group	15 (50.0)	
Other	1 (3.3)	
University	(n = 31)	Australian graduates 68.6 %
University of Adelaide	22 (71.0)	Overseas 31.4 %
Flinders University	7 (22.6)	
Interstate	2 (6.4)	
Overseas	0	
Year of graduation	(n = 31)	NA
1940–1960	2 (6.5)	
1961–1980	13 (41.9)	
1981–2000	12 (38.7)	
2000-	4 (12.9)	
Duration of GP experience (years)	(n = 31)	NA
0–10	4 (12.9)	
11–20	11 (35.5)	
21–30	10 (32.2)	
31–40	4 (12.9)	
>41	2 (6.5)	
Sessions worked per week	(n = 31)	NA
>10	5 (16.1)	
9–10	13 (41.9)	
7–8	8 (25.8)	
5–6	2 (6.5)	
3–4	1 (3.2)	
1–2	1 (3.2)	
0	1 (3.2)	
Worked in areas outside of general practice	(n = 29)	NA
Yes	8 (27.6)	
No	21 (72.4)	
Gender	(n = 31)	62.0 %
Male	15 (48.4)	38.0 %
Female	16 (51.6)	

Table 1 Demographics of respondents (Continued)

Age (years old)	(n = 31)	(<35) 9 %
20–30	2 (6.4)	(35–44) 25.1 %
31–40	2 (6.4)	(45–54) 32.4 %
41–50	10 (32.3)	(>54) 33.4 %
51–60	11 (35.5)	
61–70	4 (12.9)	
71+	2 (6.4)	
Fellow of	(n = 20)	NA
Royal Australian College of General Practitioners	16 (51.6)	
Australian College of Remote and Rural Medicine	1 (3.2)	
Other college	3 (10)	
Stroke interest	(n = 31)	NA
Yes	3 (9.7)	
No	28 (90.1)	
Recent stroke/TIA education	(n = 28)	NA
Yes	4 (14.3)	
No	24 (85.7)	

The responses consistent with the current evidence are highlighted in bold. The current evidence for our assessment is included in the column headed as 'Evidence'.

Stratification of TIA risk

The second part of the case evaluated knowledge about the risk of stroke following a TIA, wit h the results presented in Table 3.

TIA investigations

Another case scenario explored the possible investigations that could be arranged in primary care following a TIA. The results are presented in Table 4.

TIA management

The following case scenario explored the options of assessment and possible referral in a general practice setting. The results are presented in Table 5.

Table 2 Case scenario 1a

	True	False	Unsure	Evidence
	n	n	n	
1.She may have had a TIA	32	0	0	At the time of the study a TIA was defined as a sudden focal loss of neurologic function with complete recovery usually within 24 hours [16].The National Institutes of Health (NIH) committee on the Classification of Cerebrovascular Disease defined the time based definition of TIA. In 1965 the arbitrary 24-hour time limit definition was adopted, in a setting where there was limited imaging or treatments for stroke [17]. A tissue based definition has been adopted since, with TIA now being a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction [18].
2.She may have had a stroke	7	21	3	
3.A normal CT brain excludes a stroke	8	23	0	An early CT scan (within the first few hours) may be normal in ischaemic stroke. However, with experienced observers in up to 50 % of cases abnormalities can be seen on CT scan within 5 hours [19].
4.The differential diagnosis would include radiculopathy, cervical myelopathy or an intracranial pathology (e.g. tumour)	23	4	4	The diagnosis of TIA is clinical and can be challenging. The inter-observer diagnosis of TIAs even amongst neurologists has been reported to be poor [10]. The possible list of differential diagnoses can be extensive, ranging from significant neurological disorders to somatisation disorder.

Mrs JM, a 65 year old lady, presents with a history of tingling in her left arm and left leg whilst she was on holidays 2 weeks ago in Queensland. She smokes 8 cigarettes a day and is on Indapamide 2.5 mg daily for her hypertension. Her symptoms which lasted for about an hour resolved completely, and she thought that it was the hot weather that triggered it. Her BP today is 170/90. She is not a diabetic and her recent (total) cholesterol 7.9 mmol/L.

Table 3 Case scenario 1b

	True	False	Unsure	Evidence
	n	n	n	
1.She would have been considered at low risk of stroke within 48 hrs of symptom onset	0	32	0	The risk of stroke following a TIA is significant, with a recent meta analysis reporting a 9.9 % risk of stroke after 2 days. [20]
2.Duration of symptoms does not contribute to risk	10	21	1	Factors that influence the risk of stroke include age, blood pressure, specific clinical features, presence of diabetes, duration of symptoms, aetiology of index event (e.g. atrial fibrillation), frequency of TIA symptoms, history of previous TIAs and smoking.
3.Limb weakness increases stroke risk	24	3	5	
4.BP contributes to risk of stroke in next 48 hrs	26	2	4	Johnston et al devised and validated a unified ABCD2 score to predict the risk of stroke after TIA at 2 days [21].

On further questioning you discover that she had some associated weakness but no speech symptoms. She denies any dizziness or headache.

The final questions related to the instigation of treatment for the secondary prevention of stroke, with the results presented in Table 6.

Perceived barriers to assessment and management from a primary care perspective

Open questions then sought to explore the perceived barriers to the assessment and management of TIAs in general practice. Responses were analysed and themes extracted.

Difficulty in accessing neurological expertise or acute stroke units (ASU) was identified as a barrier by 13 respondents, whilst accessing investigations for the assessment of TIAs was considered a barrier by 7. The lack of knowledge both by GPs (n = 6) and the public (n = 7) was also identified as a barrier to TIA assessment and management. The lack of time in general practice consultations was identified by 5 of the 32 GPs in the survey as a barrier to effectively manage potential TIA cases.

In response to questioning about the areas for improvements, participants addressed the barriers identified earlier. Improved access to neurologists and/or ASUs (n = 11) and better access to investigations (n = 2)

were suggested. The establishment of relevant guidelines and specific education for GPs (n = 13) and public education (n = 6) were also considered as areas for improvement.

Participants were asked about their preferences for attending educational workshops. Participants indicated a conference venue as the most preferred venue (n = 22), followed by GP division offices (n = 17), own clinic (n = 6) and RACGP offices (n = 1) as the least preferred.

Discussions

The case scenarios suggested that respondents were less confident in selecting specific treatments in TIA, with 15/32 answering correctly about anti-hypertensive treatment and slightly more correct with respect to managing hyperlipidaemia (20/32). However all correctly identified the early risk of stroke following a TIA, and nearly all answered correctly on the appropriate blood tests to order in a TIA case. The diagnosis of TIA is recognised as difficult, and this study highlights that whilst knowledge on the assessment and risks of TIA is present, there is a need for further education and practical guidelines for GPs to improve knowledge with respect to specific management and pathways of care. The National

Table 4 Case scenario 3a

	True	False	Unsure	Evidence
	n	n	n	
1.A repeat CT scan in 7 days should be performed	6	11	15	Whilst diagnosis of a TIA is a clinical one, the use of imaging enables clinicians to confirm ischaemia, exclude haemorrhage or any other pathology mimicking a stroke. A CT scan after 8–10 days however, is less sensitive to haemorrhage and an MRI may be the more appropriate investigation [22].
2.Carotid duplex need not be done as symptoms were not in the carotid territory	5	25	2	As 'best clinical practice' the National Stroke Foundation [23] recommends that patients with carotid territory symptoms who would be candidates for surgery have a carotid duplex ultrasound. However, the reliability in determining the correct vascular territory clinically is only moderate in neurologists [24]. Bloods should be obtained routinely in all patients for a full blood picture, electrolytes, renal function, fasting lipids, erythrocyte sedimentation rate and/or C-reactive protein and glucose. An ECG should be performed in all patients, with attention to the presence of atrial fibrilliation (AF).
3.Bloods should be taken for FBE, ESR, BGL, lipids,UEC	31	1	0	
4.ECG not needed as PR is regular	2	28	2	

Mrs FH is a 58 year old lady who is discharged from the hospital Emergency Department yesterday following a TIA with symptoms of vertigo and ataxia, which have completely resolved. She presents to you for follow up having had a normal CT brain in the Emergency Department but no other investigations.

Table 5 Case scenario 2

	True	False	Unsure	Evidence
	n	n	n	
1.As symptoms have resolved there is no urgency in the assessment and management	2	30	0	Although the symptoms have resolved the risk of stroke remains significant. The $ABCD^2$ score for this patient is 7 and would place him at high risk of a subsequent stroke. A score of 6 or 7 was found to have an 8.1 % risk of subsequent stroke in the following 48 hours [21].
2.Management in GP setting with CT before starting aspirin	20	9	3	The patient's score is considered high risk, with the NSF recommending that a CT brain be performed within 24 hours [23].
				Whilst the use of aspirin after a CT is recommended, a study of 9000 patients randomised to aspirin without CT found no significant excess haemorrhages, even in those who had an initial haemorrhagic stroke [25]. However, in practice CT brain is performed prior to commencing aspirin.
3.Refer patient to neurology outpatients	7	20	4	Admission to an ASU would allow comprehensive monitoring and early access to treatment including thrombolysis if appropriate if this patient were to develop a subsequent stroke but the evidence remains unclear as to the best model of care.
4. Best practice would be to have him admitted to an Acute Stroke Unit (ASU).	16	7	9	

Mr DM is a 61 year old man who presents with a suspected TIA. His symptoms included weakness in his right arm yesterday, which resolved after 2 hours. He has a history of diabetes but has been managed on diet alone. He is an ex- smoker and his father had a stroke at 70 years. He has a history of hypertension for which he is on Perindopril 10 mg daily. His BP today is 150/68 and there are no significant neurological findings on examination.

Stroke Foundation Audit observed the decline in public hospital based TIA clinics in 2007 [33] and with the best model of TIA care yet to be established, the current system may be failing to address the needs of the community for efficient TIA assessment and management. Potentially low risk TIAs could be managed appropriately in general practice, and thus contribute to ease the burden on the public hospital system. With training, GPs could be better equipped to assess and manage low risk TIAs effectively in the community.

Table 6 Case scenario 3b

With regards to treatment the following statements are true or false.

	True	False	Unsure	Evidence
	n	n	n	
1.Aspirin or aspirin/dipyridamole should be started	29	1	1	Studies have demonstrated that antiplatelet treatment significantly reduces the risk of stroke [26], with the combination of aspirin and dipyridamole shown to be more effective than aspirin alone [27].
2.Clopidogrel is 1st line	5	22	4	Trials continue to assess the benefits of clopidogrel in stroke prevention with some studies suggesting that it is more effective than aspirin alone. However, the MATCH trial compared Clopidogrel and clopidogrel with aspirin and found no significant difference [28]. The NSF suggests that clopidogrel should be considered for those intolerant of aspirin or if aspirin is contraindicated [23].
3.Referral for carotid endarterectomy(CEA) if duplex reveal ipsilateral carotid stenosis of 70-99 %	22	2	7	Carotid endarterectomy has been found to reduce the risk of disabling stroke or death for patients with stenosis exceeding ECST-measured 70 % or NASCET-measured 50 %, in surgically-fit patients operated on by surgeons with low complication rates (less than 6 %) [29].
4.ECG reveals AF and warfarin should be started	31	0	1	A Cochrane review in 2004 concluded that anticoagulation can reduce the risk of stroke in patients with non- rheumatic atrial fibrillation (AF) [30]
5.A lipid lowering agent (statin) should be started only if her blood test reveal hypercholesterolaemia	9	20	3	Whilst earlier trials suggested increased rates of intracerebral haemorrhage and concerns were raised about liver toxicity, recent studies have demonstrated a modest decrease in stroke risk with statin therapy [31].
6.Anti-hypertensive should be commenced regardless of BP	15	12	5	Evidence suggests that patients should receive BP lowering treatment after a TIA unless contraindicated by symptomatic hypotension [32].

Given the current medical workforce climate, it was not surprising that difficulty in accessing neurological specialist opinion and hospital acute stroke units, in particular, were identified as a barrier. However, access to private radiological investigations, were not as notably identified. Miller et al report that GPs order a CT at a rate of 1 per 100 encounters and of these 2 % are for cerebral ischaemia [34]. The current Medical Benefits Scheme (MBS) does not allow GPs to request MRI scans.

Whilst respondents identified the lack of public knowledge about TIA symptoms, they were also aware of their own knowledge deficits. The National Stroke Foundation developed the *Clinical Guidelines for Acute Stroke Management* in 2007 in line with NHMRC standards, and included recommendations for TIA management. However, 6 respondents considered that there was a lack of knowledge and relevant guidelines to assist their practice. Similarly 7 respondents answered that there was a lack of knowledge amongst their patients with respect to the symptoms of TIA, thus resulting in late presentations for medical care. State-based Stroke Associations and the NSF provide information for consumers on stroke and TIA. However, there is limited evidence on the current public knowledge of stroke/TIA and the effects that an educational intervention will have. There is however some evidence that information and education for patients who have suffered a stroke will improve patient and carer knowledge of stroke, aspects of patient satisfaction, and reduce patient depression scores [35].

The long-term treatment goals of secondary prevention constitute the daily work of GPs. However, with continued workforce shortages in primary care, GPs face time pressures in providing comprehensive care to the community. Multidisciplinary care plans have been introduced by government initiatives and this may provide incentives to appropriate management of TIA [36]. Whilst the work of GPs routinely includes educating patients, with limited consultation time, education of the public needs to be addressed at a broader level. With regular liaison between community care and tertiary level hospitals, GPs can and should be able to recognise TIA early, as well as contribute to assessment and management.

Limitations
The response rate from the questionnaire limits this study, as the small sample of GPs may not be representative and open to bias. Previous studies have acknowledged the difficulty in engaging GPs to participate in postal surveys and have suggested a number of techniques [37]. The questionnaire and cover letter were piloted first and amendments made to optimise the response rate. This study was undertaken by a GP Academic Registrar and no financial or other incentive was

offered to invited participants which may have improved the response rate. The most common reason that medical practitioners decline involvement in surveys is time [38]. Methods to improve response rates to surveys have included an advance phone prompt from medical personnel or a small gift with the survey [39]. The Canadian National Physician Survey attempted to improve their response rates by implementing a number of strategies including a monetary incentive but were unsuccessful [40]. Others have suggested that there is no optimal response rate and whilst a high response rate is more likely to be representative of the sample, a low response rate may be valid if non-response effects are tested [41,42]. The follow-up methods employed in this study included a personal visit to random practices, as a 'personal' approach has been considered as important [43]. However, the contact details of invited GPs were not accessible to the investigators under the *Privacy Act* and the use of personally addressed letters and specific follow up of non-responders was not performed. The support of the Division was considered to be important, with previous studies reporting that appropriate stakeholders involvement would assist in improving response rates and thus use of a commercial list of GPs was not used [44].

GPs in the AWGPN constitute 12 % of the South Australian GP workforce. The AWGPN registers all GPs working in the area as members by default, but 4/32 participants replied that they did not consider themselves members of this division. Most respondents reported that they worked in group practices (n = 15) whilst 9 (30 %) respondents indicated that they were solo practitioners, compared to 37 % nationally [15]. 31.4 % of GPs nationally are overseas trained but none of the respondents in this study were trained overseas. The majority were female (n = 16) whilst nationally 62 % of GPs are male and most were over 41 years age, which is comparable to national data. Those invited to participate in the study were registered as GPs working within the area of AWGPN as supplied by their database, however, with the current workforce status there has been a fluctuation of GPs in and out of practices with 4/32 respondents indicating that they did not currently work in the AWGPN. The demographic details of the participants were mostly consistent with available Australian data, with the exception of location of training. Those who reported to be members of a division and/or fellows of a professional college were more likely to participate. Surprisingly, despite the limited time GPs give to participate in surveys, the majority of participants unexpectedly worked more than 8 sessions per week. The implementation of guidelines successfully depends in part on their applicability to a local region [45] and thus this study aimed to determine the knowledge in the Western

Division of General Practice in Adelaide. However, there is no data available on the characteristics of GPs in this area and comparison was thus limited to available Australian data.

The low response rate may suggest a disinterest in the topic, which is cause for concern as TIA assessment and management is in the domain of general practice and the risk of subsequent morbidity and mortality significant. Previous studies have shown that non-responders are more likely to be older, more experienced, solo practitioners, more stressed and less well qualified than responders[44] with the one of reasons for not participating other than time was that the topic was thought to not be relevant. If non-responders are less qualified, their knowledge in TIA assessment and management may also be less than that of the study participants.

Whilst there may have been value in having a control group to compare the results to, for example neurologists, we would expect different answers as the approach to an acute neurological episode in general practice has its own challenges and barriers, which is what the study aimed to evaluate.

The questionnaire itself has its limitations. Whilst the use of a pre- and post- test questionnaire may have provided additional information on the retention of knowledge, this questionnaire was not designed to necessarily contain "right" and "wrong answers". In order to maximise the response rate, and the authors wished to avoid an exam style approach to "testing" GPs. Similarly with a pre and post questionnaire GPs with good knowledge and interest may be more likely to participate and so presenting a biased sample. The authors consider instead that designing an educational intervention based on the questionnaire results, and then testing GPs after the education session may be more useful. Again though the questionnaire would have its limitations as it only suggests what GPs might do in an ideal clinical setting, which may be quite different to what occurs in real practice.

Since the study was conducted further research has been published on the assessment and management of TIA, which may have an impact on whether the responses are viewed as correct or incorrect. In particular the definition of TIA is now tissue based [18], and it may be worthwhile surveying GPs again to determine their awareness of this new definition and the subsequent changes to their clinical practice.

Within these limitations, this study nonetheless is suggestive of a need to improve knowledge amongst GPs, in particular the management pathways for TIA. A number of barriers to TIA care, including difficulties in accessing services, were also identified. Together with the low response rate, it seems that specific education to GPs to highlight the relevance and importance of this topic along with a review of the accessibility of services locally needs to be addressed so that we might in future contribute more effectively in caring for patients with TIAs in primary care.

Availability of supporting data
The data set supporting the results of this article are available in the Stroke Research Programme repository, http://www.adelaide.edu.au/srp/.

Ethical approval
The Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee granted approval for this study.

Abbreviations
TIA: transient ischaemic attack; GP: General practitioner; NSF: National Stroke Foundation; ASU: Acute Stroke Unit; RACGP: Royal Australian College of General Practitioners; AWGPN: Adelaide Western General Practice Network; MBS: Medicare Benefits Scheme; MRI: Magnetic Resonance Imaging; NHMRC: National Health and Medical Research Council.

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Authors' contributions
EL, AHB and SK contributed to the conception and design. EL carried out the collection and assembly of data, and the data analysis and interpretation. All authors contributed to manuscript writing and review, and approved the final manuscript.

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SECTION 3

Chapter 2: Education

Findings from the study of GP knowledge in the previous chapter suggested that GPs could benefit from further focused education on stroke and TIA management. The breadth of knowledge required by GPs and the ongoing need to continue updating this knowledge is significant. The presentation of acute neurological symptoms in a standard general practice consultation can be challenging and the potential differential diagnoses may require urgent treatment. Reflecting the reality of practice the following paper outlines an approach to a patient presenting with undifferentiated neurological symptoms, labeled a "funny turn". This paper was published in the "10-minute consultations" series of the BMJ, which aims to guide general practitioners in approaching a common clinical problem at the initial consultation, within a limited time-frame. Whilst the effectiveness of changing GP behaviour as a result of reading such a paper is not tested, the approach is directed at GPs and previous studies suggest a need for mixed methods of education deliver(Mansouri & Lockyer 2007).

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Leung ES, Hamilton-Bruce MA, Stocks N, Koblar SA. Funny turn. BMJ. 2011; 343.

PRACTICE

10-MINUTE CONSULTATION

Funny turn

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A 72 year old woman presents to your surgery complaining of "funny turns." She describes two episodes over the last week when she felt dizzy and had difficulty walking. She did not collapse but felt very unsteady and needed to lean against a wall. She has a history of hypertension for which she is taking irbesartan.

What you should cover

The phrase "funny turn" is commonly used to describe a set of symptoms that presents a diagnostic challenge to the general practitioner. The potential diagnoses vary widely, and include neurological, cardiovascular, metabolic, vestibular, and psychological conditions.

Patients may complain of dizziness, and the assessment of these often vague symptoms in a 10-minute consultation is a challenge, with some of the potential diagnoses being medical emergencies.

A careful history from the patient and any witnesses is essential, as the history alone may provide the diagnosis or at least guide to the appropriate test or specialist. However, a reliable history cannot always be obtained and this article focuses on an approach to determining the diagnosis of the funny turn in general.

Assessing symptoms

If the patient complains of dizziness, it is important to clarify this symptom:

- Vertigo: ask "Is the room spinning or are you spinning?"
- Lightheadedness: ask "Did you feel faint?"
- Disequilibrium: ask "Do you feel unsteady on your feet or off balance?"

Associated symptoms:

- Loss of consciousness? Or altered level of consciousness?
- Palpitations?
- Movements: limb jerking? tongue biting?
- Auras: strange taste, feeling odd, déjà vu?
- Automatisms: lip smacking, chewing?

Weakness or speech disturbance?

Mood disturbance or anxiety symptoms?

Specific attention should be given to the drug history including antihypertensives and any changes in dosing; and over the counter, complementary medicines (such as valerian).

Timing and onset

Did the symptoms occur suddenly or gradually?

- Sudden onset of symptoms more likely to be a stroke or transient ischaemic attack (TIA)

Were there any precipitating factors?

- Standing or exercise, suggesting postural hypotension
- Changing position in bed, suggesting benign paroxysmal postural vertigo

Episodic or constant?

Duration of the symptoms?

- >1 hour more likely to be TIA or minor stroke

Similar symptoms previously?

What you should do
Examination

- Pulse rate and rhythm, heart sounds: assess for cardiac causes
- Postural blood pressure: a drop in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg

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within 3 minutes of standing suggests orthostatic hypotension

- Neurological examination: assess for focal signs in particular to determine if a stroke is a potential diagnosis, including gait and eye movements

- Finger prick test for blood glucose concentration in diabetic patients on hypoglycaemic agents

ABCD^2 score

Patients with a suspected TIA should have an ABCD^2 score done to assist in stratifying the risk of subsequent stroke. ABCD^2 score: Age ≥60 years (1 point); blood pressure ≥140/90 mm Hg (1 point); clinical features: unilateral weakness (2 points), or speech disturbance (1 point); duration: ≥60 minutes (2 points), or 10 to 59 minutes (1 point); and diabetes mellitus (1 point). A score ≥4 indicates a high risk of stroke.

Investigations

- Blood tests, including full blood count, electrolytes and urea, fasting blood glucose, and cholesterol: especially for patients with suspected TIA or at risk of cardiovascular disease

- Electrocardiography: cardiac arrhythmias

Referral

A thorough history alone may provide the diagnosis in the first consultation. All patients with suspected TIA should be referred urgently for assessment and management. If available, a TIA clinic should assess patients at high risk urgently, whereas those at lower risk should be assessed within one week. Follow-up of patients is essential particularly if the diagnosis is uncertain. Ask patients and relatives who may be witnesses to record further episodes (either a written description or video).

Driving

Issues of driving and safety at work may need to be discussed until the diagnosis is confirmed.

Cite this as: *BMJ* 2011;343:d7465

Red flags for urgent referral

Transient ischaemic attack or minor stroke

- Focal neurological symptoms
- Negative symptoms, such as weakness instead of jerking movements, numbness instead of pins and needles
- Sudden onset of symptoms
- Symptoms maximal at onset
- Persisting symptoms or signs suggesting stroke
- ABCD^2 score ≥4

Cardiac

- Irregular heart rate
- Electrocardiogram abnormalities
- Associated chest pain or breathlessness

Useful reading

Barraclough K, Bronstein A. Vertigo. *BMJ* 2009;339:b3493

National Institute for Health and Clinical Excellence (NICE). Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) http://guidance.nice.org.uk/CG68; Management of transient loss of consciousness in adults and young people http://guidance.nice.org.uk/CG109

Department of Otolaryngology, University of Melbourne, patient information leaflet www.medoto.unimelb.edu.au/files/doto/DizzinessandBalanceDisorders.pdf

Vestibular Disorders Association www.vestibular.org

Meniere's Society (UK) www.menieres.org.uk

SECTION 3

Chapter 3: Educational module and video

The "10-minute consultation" paper in Chapter 2 provides GPs with an approach to a "funny turn". The history of any presentation is important to assessment but can be difficult to obtain, especially in an acute neurological episode that may also be an un-witnessed event. The clinical neurological examination can provide additional information in evaluation but conducting a comprehensive neurological examination in a standard general practice consultation may be difficult due to limited time and expertise of the GP.

We thus developed an approach to examination when assessing a patient with suspected TIA. This five-minute examination for stroke prevention is described in the following paper. In collaboration with Sturt Fleurieu General Practice Education and Training (SFGPET), a regional training provider of general practice education for registrars, we produced a video demonstrating the clinical examination and with a freely accessible link. The video thus utilises an alternative form of media to which certain participants may be more likely to access. Whilst the doctor performing the examination is a neurologist, the development of the approach was with two general practitioners. Two other neurologists interstate also reviewed the video and their comments and suggestions assisted in defining the items included in this approach. Whilst other neurological examination videos are readily available for clinicians to view including demonstrations of the National Institute of Health Stroke Scale (NIHSS), this approach aims to show GPs who may be unfamiliar with neurological examinations, how to conduct a brief examination predominantly in a chair.

Leung E, Hamilton-Bruce M, Price C, Stocks N, Koblar S. Letter to the Editor: Stroke. Australian Family Physician. 2014; 43(11): 750-1.

http://www.youtube.com/watch?v=BBJJ7-0XE6c

Consideration of the mode of delivery of education is also important in developing education programs as GPs respond to different learning styles(Fraser 2004). Further learning modules were thus developed with SFGPET and the Royal Australian College of General Practitioners (RACGP) and are included in the appendices. The candidate wrote the SFPGET program for registrars as an elective option with the content reviewed by a neurologist and two senior GP educators. The RACGP check case was written by the candidate and reviewed by the RACGP and National Stroke Foundation reviewers. These self-directed learning modules add to the resources now available to Australian GPs to improve their skills and knowledge about TIA care. These modules are based around case studies as researchers have demonstrated that interactive activities, including case discussions and reflecting on practice may be more effective(Davis & Galbraith 2009; Mazmanian, Davis & Galbraith 2009). A method for testing the effect of educational programs however is challenging. Given the difficulty in identifying TIAs in general practice, determining outcomes like a change in behaviour of a clinician before and after the educational intervention is not feasible. The most feasible method for determining the effectiveness of the education would be a pre- and post-questionnaire, similar to that presented in Section Three, Chapter One. There are limitations with this method particularly as results only suggest how GPs might behave in the ideal clinical setting.

Appendix 1: Sturt Fleurieu General Practice Education and Training. *GP-start: Funny Turns module 2011*

Appendix 2: Royal Australian College of General Practitioners. *Malcolm had a 'funny turn'. check 2010 January/February;454–455:3–6.*

SECTION 3

Chapter 4: **Biomarker Discovery**

Even with specialist education and training the clinical diagnosis of TIA can be difficult, with studies of stroke neurologists finding inter-observer agreement to be poor(Castle et al. 2010). Whilst MRI provides valuable information in the assessment of TIA, the availability of this resource remains limited in Australia(Australian Government The Department of Health 2014). Access to imaging is particularly limited in rural and remote Australia, and the possibility of a blood biomarker could potentially be a valuable tool in the assessment and stratification of TIA. Previous research on blood biomarkers have shown limited usefulness(Cucchiara, B & Nyquist 2011; Jensen et al. 2008; Segal et al. 2014; Whiteley, William, Tseng & Sandercock 2008; Whiteley, W. et al. 2012) but the discovery of one that could be utilized in 'point of care' testing would be a major clinical change in the diagnosis of TIA in primary care, especially in a remote or rural setting. This manuscript will be submitted to *Clinical Proteomics*.

Djukic M, Hamilton-Bruce MA, Jannes J, **Leung ES**, Nichols S, Chataway T, Lewis M, Koblar S. Identification of Novel Plasma Biomarkers for Diagnosing Transient Ischaemic Attack and Distinguishing from TIA-Mimic Conditions: A Human Proteomic Pilot Study. *Manuscript submitted*.

Identification of Novel Plasma Biomarkers for Diagnosing Transient Ischaemic Attack and Distinguishing from TIA-Mimic Conditions: A Human Proteomic Pilot Study

Michael Djukic, Monica Anne Hamilton-Bruce, Jim Jannes, **Elaine Leung**, Steve Nichols, Timothy Chataway, Martin Lewis, Simon Koblar.

Abstract

Introduction − Transient Ischaemic Attack (TIA) is a warning sign for an imminent ischaemic stroke. Correctly distinguishing TIA from mimic conditions such as atypical migraine or focal seizures is clinically problematic. This study explored the human plasma proteome for differentially expressed TIA-sensitive plasma proteins that could be potential diagnostic biomarkers.

Methods − We enrolled six well-defined TIA and six mimic patients from rapid-assessment TIA clinics. Blood plasma was sampled from each patient initially within 10-days of symptomatic ischaemia, and at 90-day follow-up. Healthy controls consisted of six volunteers who provided blood plasma initially and at 90-day follow-up. Paired plasma samples from each TIA patient, mimic patient, and healthy control volunteer were chromatographically depleted of abundant plasma proteins and analysed using Difference In-Gel Electrophoresis (DIGE) to determine differential protein expression. Principal component analysis was used to highlight appropriate protein expression patterns and group patients accordingly. One-way analysis of variance and paired t-test were used to classify these proteins of interest, which were identified by mass spectrometry and measured using targeted peptide quantification/multiple reaction monitoring (MRM).

Results – This is the first human plasma proteomics study using quantitative DIGE to profile TIA and mimic patients. Principal component analysis revealed that patients could be separated into three groups based on the expression profile of 10 differentially expressed proteins. We identified Apolipoprotein A-IV (APOA-IV) as exclusively elevated in TIA patient plasma, with Fibrinogen alpha-chain (FGA) and Complement C4-A (C4A) elevated in both TIA and mimic patients, while Apolipoprotein A-I (APOA-I), Gelsolin (GS), and Fibrinogen beta-chain (FGB) were significantly reduced in TIA patient plasma in comparison with mimic and/or healthy control cohorts. Multiple reaction monitoring independently quantified APOA-IV, APOA-I, GS, FGA, FGB and C4A as having significantly different expression levels between TIA and non-TIA cohorts.

Conclusion – This novel biomarker discovery method utilising DIGE and mass spectrometry based proteomic quantification has shown for the first time that several proteins are differentially expressed in human plasma of TIA patients when compared with patients presenting with mimic conditions and healthy control volunteers. These findings implicate markers of lipid transport and metabolism, inflammation, and coagulation to have the potential, either independently or in combination, as diagnostic and prognostic biomarkers, which warrants validation in larger cohorts.

Introduction

Between 15-26% of ischaemic strokes are preceded by a transient ischaemic attack[1],[2]. Evidence supports early assessment and management of TIAs, with a reported 80% risk reduction in subsequent stroke[3]. This is a significant reduction considering the risk of stroke is 10-20% in the 90-days post-TIA onset[4]. A true TIA diagnosis is accepted as a medical emergency, where up to 42% of ischaemic strokes that occur within 30 days post-TIA will occur within the first 24 hours[5], and up to 50% within the first 48 hours[6]. This provides a very limited time-frame to both diagnose TIA and prevent an iminent stroke. Accurate diagnosis and subsequent treatment of TIA is however made difficult by the presence of mimic presentations. Distinguishing TIA diagnosis from mimic conditions of a non-vascular aetiology would be greatly assisted by a biomarker panel comprising TIA-sensitive plasma proteins. Proteomic investigations of human body fluids identify plasma as the most easily accessable for clinical utility, containing the most abundant array of proteins with potential biomarkers for many conditions[5]. However, no studies that have examined the global proteome of TIA and mimic patient plasma. We investigated TIA-associated changes to the plasma proteome in direct comparison with mimic-associated and healthy control-associated proteome profiles to identify possible candidate biomarkers.

Methods

TIA Definition

Our study uses the revised TIA definition endorsed by the American Heart and Stroke Associations defining TIA as: "transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction"[2]. Patients

45

suspected of TIA were diagnosed by neurologists following clinical assessment, diffusion weighted magnetic resonance imaging (DWI-MRI) and/or computed tomography (CT) imaging to exclude the possibility of cerebral infarction and heamorrhage respectively.

Sample Size

This is the first discovery study of its kind to examine the human plasma proteome for differentially expressed plasma proteins that are associated with a TIA diagnosis. To determine the necessary sample size in our power calculation, two variables were considered; the random variation between other samples on different gels, and the extent of differential expression or fold-change[7]. The coefficients of variation and expected fold-changes have not been established and must therefore be based on previous human plasma two-dimensional gel electrophoresis studies. Assuming biological variation of 40% between patients, to detect a 50% or 1.5-fold change in protein abundance, 17 patients would be required to achieve a power of 80% at the alpha 0.05 level. We recruited 18 participants that each provided two biological replicates; initial and follow-up plasma samples. Using a DIGE method is superior to traditional case/control study designs in that biological variation is minimised by multiplexing samples from the same participant to highlight disease-specific changes, thus allowing a small sample size.

Study Design

To profile the plasma proteome of each participant, this study incorporates a paired-sample design where plasma was taken from six TIAs and six mimics that presented within 10-days of symptomatic-ischaemia onset and compared with a recovery sample

taken 90-days later. Six healthy controls were also recruited for proteomic comparison of plasma collected initially along with a 90-day follow-up sample. Clinical data including $ABCD^2$ stroke-risk stratification, lipid, and biochemical results were collected from all 18 participants, with MRI and CT scanning of the brain performed on TIA and mimic patients to confirm diagnosis. One TIA patient out of the six declined to undergo an MRI scan due to claustrophobia. Written informed consent was obtained from all participants and the The Queen Elizabeth Hospital Ethics Committee approved this study.

Patient recruitment and blood collection

Patients assessed at the community-based rapid access TIA (COMBAT) clinic and the Rapid Access Clinic (RAC) with suspected TIA were invited to paricipate in this study. Each consenting patient provided two blood samples; an initial sample within 10-days of symptomatic ischaemia onset, and a second sample within a 90-day follow-up period. Six individual patients from each of the two diagnosed groups (TIAs and mimics) were used in this analysis. Blood samples were further obtained from six healthy control volunteers recruited from the wider Adelaide Metropolitan Community.

Inclusion and Exclusion Criteria

Patients admitted to the acute stroke unit between February 2010 and January 2011 that had suffered either a TIA or TIA-minic condition were invited to participate in this study. Participating mimic patients were excluded of vascular aetiology by neurologists, and diagnosed as suffering either migraine, epileptic seizure, benign positional vertigo, vasovagal syncope or transient global amnesia. Selection of six

individual patients for each of the two diagnosed groups (TIAs and mimics) for proteomic analysis was based on diagnostic certainty as determined by a senior stroke physician and a neurologist. Control volunteers were deemed healthy by clinical assessment, which included blood pressure, blood glucose, lipid and biochemistry measurements (see Table 1C), and found to have no evidence and history of morbidities, cerebrovascular risk factors and were not taking any prescription medications. Blood samples found to be hemolytic were excluded from this proteomic investigation.

Sample Preparation

Peripheral blood samples (8.5 mL) were collected in sterile K_2EDTA BD vacutainers[®] containing 1.8mg EDTA per millimeter of blood (BD Scientific, Australia). Samples were centrifuged within 30 min of collection, and plasma was extracted and aliquoted into vials containing Halt[®]protease and phosphatase inhibitor cocktail (ThermoFisherScientific, Illinois, USA) and stored in liquid nitrogen at -195°C for later analysis.

Plasma was depleted of the top six most abundant proteins using a 4.6 x 100 mm multiple affinity removal liquid chromatography (MARS-LC) column (Agilent Technologies, Australia) connected to a fast pressure liquid chromatorgraphy (FPLC) system (AKTA, Amersham Biosiences). The MARS-LC column contains antibodies against albumin, transferrin, haptoglobin, IgG, IgA, and alpha-1 antitrypsin, depletes plasma, providing a flow-through fraction which is devoid of these six most abundant plasma proteins, enriching lower abundant proteins and subsequently enhancing the resolution of electrophoretic separation. Protein concentration of depleted plasma was

estimated in triplicate using an EZQ®protein quantification kit (Invitrogen, Oregon, USA) prior to Cydye fluorescent labelling.

Two-Dimensional DIGE Analysis and Statistics

Paired plasma samples depicting initial and follow-up plasma proteomes from each of the six TIA, mimic and healthy control participants were alternately labelled with either Cy3 or Cy5 dye DIGE Fluors (GE Healthcare, Rydalmere, Australia). A pool of equal volumes of plasma samples from all 18 participants were labelled with Cy2 dye and used as an internal standard to correct for potential loading or electrophoretic variation. The Cy2, Cy3 and Cy5 labelled samples (50ug of sample:200pmol of each Cydye) from the same participant were combined and loaded onto the first dimension immobilised pH gradient (pH 3-11 non-linear IPG Strip) with protein separation by isoelectric focusing using the IPGphor 3 isoelectric focusing system(GE Healthcare, Rydalmere, Australia). Second dimension electrophoretic separation was run using a 12.5% SDS-polyacrylamide gel, with protein separation by molecular weight. Gels were scanned using the Typhoon Trio variable mode imager (GE Healthcare, Rydalmere, Australia) with a resolution of 200μm, and PMT of 550V, 500V and 470V for Cy2, Cy3 and Cy5 labeled samples, respectively. Data was analysed using DeCyder Version 7.0 software (GE Healthcare, Rydalmere, Australia), with the Biological Variation Analysis (BVA) module used for intra-cohort comparison of intial vs. follow-up samples, as well as inter-cohort comparison based on diagnosis. Analyses were conducted blinded to patient characteristics. Prior to analysis, the protein set was filtered for the presence of the protein spot in at least 80% of the spot maps and for an ANOVA p-value ≤0.05. The filtering parameters were set to determine spot features that had a p-value ≤0.05 for the t-test, coupled with a one-way

analysis of variance (ANOVA) to measure the variation between the three groups and a >1.5 fold change in abundance between the groups. Principal component analysis was used to highlight protein patterns and group samples based on relevant biological patterns. Proteins of interests were visualised by EBT-silver staining, excised from 2D-gels, trypsin-digested into peptide fragments, and identified using a nanospray LTQ Orbitrap XL mass spectrometry system (Thermo Fisher Scientific, Illinois, USA).

Label-Free Validation Strategy

Multiple reaction monitoring (MRM) analysis is a label-free mass spectrometry-based method which utilises spectral counting and ion intensity-based quantification [21]. MRM assays were used to validate six candidate plasma proteins identified by 2D-DIGE and LC-MS/MS. Skyline 2.1 was used for method development, data analysis and interpretation of MRM results. Equal protein quantities of MARS-LC depleted plasma samples from acute and follow-up TIA, mimic and healthy control volunteers underwent trypsin digestion, with peptide enrichment and separation for MRM performed in duplicate on a TripleTOF[TM] 5600 system interfaced with nanoLC II (Thermo Scientific, Bremen, Germany) using MRMPilot[TM] software (AB SCIEX). Protein measurements from acute and follow-up categories within each diagnostic group were compared using a paired Student's t-test, with inter-group comparisons performed using an unpaired t-test and Mann-Whitney test using IBM SPSS Statistics (Version 20).

Results

Patient Characteristics

Study participant demographics are summarised in Table 1. Overall, TIA and mimic cohorts did not display any significant differences with regards to stroke risk stratification score, with all patients presenting with at least one conventional cardiovascular risk factor. High-sensitive C-reactive protein was significantly elevated in TIA patients compared with healthy controls, and marginally non-significant when compared with mimics (p=0.07). TIA and mimic patients similarly shared moderately elevated mean blood glucose levels (6.3mmol/L and 6.2 mmol/L respectively). TIA patients exclusively displayed a lower level of the protective high-density lipoprotein (1.15mmol/L, p<0.05) though within the clinically acceptable range of 1.0-5.5mmol/L. Patients presenting to either community-based or hospital based clinics with suspected TIA were prescribed but not limited to aspirin, statins, calcium channel blockers, nitrates, beta-1 blockers, and angiotensin converting enzyme inhibitors that were subject to dose adjustment between initial and follow-up phases of the study (see Table 1).

Proteomic Analysis

To minimise technical variation when comparing initial and follow-up plasma proteomes of individual patients, both samples were multiplexed and analysed on the same gel. A representative DIGE gel image (Figure 1) detected approximately 2200 gel spot features. Protein spots were matched across the 18 gels that represented the plasma proteome of the 18 patients and volunteers. Ten protein spots were found to be different in abundance when comparing between the three groups (i.e. inter-group comparisons of initial and follow-up samples from each group with 1-ANOVA

p<0.05) (see Table 2). Mass spectrometry successfully identified peptide sequences of 10 candidate protein spots, which corresponded with known proteins in the Universal Protein Resource (UniProt database). Proteins identified with ≥2 unique peptides were considered to have sufficient coverage of amino acid sequence to provide conclusive identification (Table 2). Apolipoprotein A-IV was found to be exclusively increased in TIA patients both at initial presentation and at three-month follow-up when compared with identically sampled mimic patients and healthy controls. Complement C4-A, Fibrinogen alpha-chain and beta-chain proteins were elevated in both TIA and mimic patients, while both Apolipoprotein A-I, Gelsolin and Fibrinogen beta-chain were significantly reduced in TIA patient plasma. No statistically significant difference was found in any of the six measured proteins when comparing their concentration between initial and follow-up samples from the same patient/volunteer.

Diagnosis Specific Analysis

To reduce the complexity of multidimensional data sets, and to clearly highlight trends within data, principal component analysis has been applied (Figure 2). The protein profiles of 10 candidate protein spots were matched on >80% of the spot maps, in which the first principal component (PC1) represented 45.2% of the total variance in the data set, while the second principal component (PC2) displayed an additional 21.6% of the variance (Figure 2). We observed a distinct clustering of spot maps into three main regions according to the three diagnostic groups. When examining initial and follow-up sample categories from each of the three experimental groups, a tighter scatter of the samples from TIA, mimic, and particularly healthy control volunteers (encircled in red, blue and green respectively) was observed (Figure 2). This indicates the small magnitude of experimental

52

variability when analysing biological replicates (initial vs. follow-up) of the same human sample from the particular diagnosed group. Briefly, mimics and healthy individuals were distributed in the right hand side of the plot, while TIA patients were located in the left area. The first principal component suggests that the diagnosis of TIAs, mimics, and health controls represents the largest form of variation in this study. This implies that the expression profile of ten differentially expressed proteins in this study might allow us to distinguish between TIA and non-TIA patients. Of the ten candidate protein spots, nine proteins were identified by mass spectrometry, with gelsolin appearing twice with an isoform. We have excluded human albumin, haemoglobin alpha subunit, and actin from further analysis based on their pre-analytical removal, over abundance, and wide dynamic concentration ranges limiting disease-specificity.

Validation by Multiple Reaction Monitoring (MRM)

Proteotypic peptides were selected from the discovery LC-MS/MS experiments and checked for homogeneity using protein BLAST search, with preference given to peptides containing a precursor charge of +2 and did not contain cysteine. The following proteotypic peptides were selected for MRM: ALVQQMEQLR ($z= +2$, $m/z= 608.3266$) for APOA-IV, DLATVYVDVLK ($z=+2$, $m/z= 618.3464$) for APOA-I, QFTSSTSYNR ($z=+2$, $m/z= 595.7749$) for fibrinogen α-chain, DNDGWLTSDPR ($z=+2$, $m/z= 638.2833$) for fibrinogen β-chain, GASQAGAPQGR ($z=+2$, $m/z= 500.2516$) for Gelsolin, and AEMADQAAAWLTR ($z=+2$, $m/z= 717.346$) for Complement C4-A (Figure 3). The MRM results from this validation experiment show that candidate proteins are both easily detected in depleted human

53

plasma from TIA, mimic and controls in agreement with LC-MS/MS identification, but also replicate the expression profile depicted in 2D-DIGE work.

Discussion

This is the first study of its kind to apply a discovery-based proteomic method that utilises 2D-DIGE, LC-MS/MS, and MRM quantification to profile the human plasma proteome, and six candidate biomarkers that can distinguish TIA from mimic and healthy control volunteers have been identified. This study demonstrates that lipid transport and metabolism markers (APOA-IV and APOA-I), extracellular actin scavenger protein (Gelsolin), coagulation proteins (Fibrinogen α- chain and β- chain), and the acute phase protein of the classical complement pathway (C4A) displayed a unique expression profile between the three diagnostic groups. A proposed role of these identified proteins in the acute presentation of a TIA is shown in Figure 4.

Apolipoprotein A-I is an anti-atherogenic marker that is predominantly found in HDL-cholesterol[8]. The protective effects of APOA-I against atherosclerosis, coronary heart disease and stroke have been well documented [8-10]. APOA-I has specifically been shown to predict ischaemic stroke in patients with previous TIA[11]. We have confirmed for the first time that reduced plasma APOA-I is associated with both acute and follow-up TIA patients, and can distinguish TIA from non-TIA diagnoses. APOA-I deficiency may also reflect the inherently high risk of stroke, which in this study is exclusively associated with TIA patients.

Apolipoprotein A-IV is predominantly synthesised in the small intestine where it is secreted into plasma to facilitate high-density lipoprotein transport and metabolism,

however a recent study has linked APOA-IV to satiety regulation and characterised protein distribution within the brain[12]. Specifically, APOA-IV detected in cerebral spinal fluid (CSF) was not derived from systemic circulation, as it was unable to cross the blood-brain-barrier, but rather produced within neuronal cells[12]. In a transient embolic or thrombotic cerebrovascular occlusion, a biochemical cascade of neurotoxicity is initiated, which compromises the structural integrity of the blood-brain-barrier by increasing permeability and in effect damaging neurons, glia and microvascular endothelium[13]. When considering the significant increase of APOA-IV in TIA compared with mimic patients, given that co-morbidities have been standardised between both groups (making diagnosis the major variable), brain-derived APOA-IV as an effect of TIA may be a source for this increased plasma concentration.

In a healthy human, plasma gelsolin functions as an actin scavenging protein that removes actin filaments shed from the cytoskeleton of damaged or dead cells into the systemic circulation. Circulating actin is directly toxic to endothelial cells[14], and is associated with secondary tissue injury[15]. Deficiency of plasma gelsolin compromises the sequestration of circulating actin as well as proinflammatory mediators, increasing the risk of further injury as seen in chronic inflammatory disorders such as rheumatoid arthritis[16]. Our study reports a significantly lower plasma gelsolin concentration in both TIA and mimic groups compared with healthy controls, signifying gelsolin's association as a biomarker of a healthy physiological state. This is the first study to report reduced plasma gelsolin concentration in TIA patients. However, given the lack of fluctuation of gelsolin abundance in each patient over a 3-month period, its deficiency may be a reflection of chronic systemic

morbidities rather than transient ischaemia. Nonetheless, Guoet. al. (2011) established that a reduced plasma gelsolin concentration less than 52ug/ml is an independent predictor for 1-year mortality after a first-ever ischemic stroke compared with healthy controls (73.0% sensitivity and 65.2% specificity)[17]. This finding warrants further validation studies to quantify plasma gelsolin in TIA patients and assess whether levels are comparable to ischaemic stroke patients, and if TIA and stroke patients share the same risk of mortality based on decreased plasma gelsolin.

Studies of human populations have shown Complement factor C4 (C4A) to be associated with increased levels of cardiovascular risk factors including diabetes, hypertension and obesity[21]. Although hepatic production is the main source of C4A, many studies suggest C-reactive protein (CRP) is a key activator of the classical complement pathway in response to atherosclerotic plaque[22-23]. A longitudinal study observed an increase incidence of CVD in patients with C4A in the top 10% of the sample distribution, demonstrating a potential link between elevated C4A and atherogenesis[24]. Activation of complement cascase has further been implicated in thrombosis and fibrin formation with direct inhibition of fibrinolysis[25]. Cardiovascular comorbidities were present in all our TIA and mimic patients, supporting the finding of increased plasma C4A when compared with healthy controls. The atherogenic biochemical pathway attributed to raising C4A plasma concentration is unlikely to make the protein a suitable candidate biomarker for distinguishing TIA from mimic condition, however, may be of clinical utility as a prognositic marker of cardiovascular disease and risk of atherothrombotic stroke.

This pilot study has identified differentially expressed proteins that can distinguish TIA from mimic and healthy control volunteers. Although the expression profile of the candidate biomarkers did not change significantly between initial and 3-month follow-up assessments in TIA and mimic patients, it remains to be determined whether the expression profile was the effect of the symptomatic-ischaemic attack or of a chronic condition stemming from underlying co-morbidities. Every effort was made to standardise TIA and mimic patients with regards to co-morbidities, however each of these proteins has been previously implicated in neurological[18], cardiovascular[19,20], infection[21], or inflammatory conditions[16,22], which should not be overlooked when considering their suitability in distinguishing TIA from non-TIA patients.

Our experimental method is one of many methods available to quantify the plasma proteome, however no method exists currently that can measure the entire plasma proteome. According to the Human Proteome Organisation - Human Plasma Proteomic Project (HUPO-HPPP), 15,519 non-redundant proteins have been identified[23]. Our electrophoresis-based study detected approximately 2,200 protein features in which 391 proteins were consistently detectable in all 18 patient/volunteer gels. Despite the use of immuno-depletion techniques to enrich low-abundant protein detection, we were only able to visualise 2.5% of total plasma proteins. Nevertheless, this 2D-DIGE technique detected moderate to high abundant plasma proteins (mg/mL to pg/mL) that are most clinically relevant with regards to quantification and use in a biochemistry test.

Conclusion

Our pilot study has identified six human plasma proteins that are differentially expressed between three clinically defined groups; TIA, mimic, and healthy controls. This is the first study to investigate the plasma proteome of well-characterised TIA patients. By identifying and measuring differentially expressed candidate proteins using proteomic profiling, future investigations can focus on validating in larger cohorts the suitability of a biomarker panel for diagnosing and distinguishing TIA from mimic conditions, as well as explore the prognostic implications of candidate biomarker profiles with regard to the development of ischemic stroke.

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Table 1. A. TIA patient characteristics and laboratory findings at acute presentation and at 3-month follow-up.
Cardiovascular Risk Factors denoted as: HTN = hypertension, IHD = Ischemic Heart Disease, HLD = Hyperlipidemia, T2DM = diabetes mellitus type 2. Clinics denoted as: COMBAT = community based rapid access TIA clinic, RAC = hospital based rapid assessment clinic. Medications are denoted as: ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, AP = antiplatelet therapy, BB = beta-1-receptor blocker, CCB = calcium channel blocker, DM = Diamicron, GTN = Glyceryl Trinitrate, IMDUR = Isosorbide Mononitrate, MF = Metformin, Stat = Statin. Blood biochemistry tests are denoted as: TC = total cholesterol, Trig = triglycerides, HDL-C = high density lipoprotein – cholesterol, LDL-C = low density lipoprotein – cholesterol, APOA-I = apolipoprotein A1, APOB = apolipoprotein B, hsCRP = high-sensitivity C-reactive protein.

	TIA 1	TIA 2	TIA 3	TIA 4	TIA 5	TIA 6
Age	77	86	82	80	84	55
Gender	F	M	M	F	F	F
Cardiovascular Risk Factors	HTN, IHD, HLD, T2DM	HTN	HTN	HTN, IHD, HLD	HTN	HTN, T2DM
Smoking	No	No	No	No	No	No
TIA Cause	Atrial Fibrilation	Left Internal Carotid Stenosis	Unknown	Unknown	Right Middle Cerebral Artery Stenosis	Patent Foramen Ovalae
Clinic Attended	COMBAT	RAC	COMBAT	RAC	COMBAT	RAC
Time from symptom onset to blood collection (days)	1	3	4	1	6	2

ACUTE PRESENTATION

	TIA 1	TIA 2	TIA 3	TIA 4	TIA 5	TIA 6
ABCD2 Score	6	3	4	3	4	6
Cardiovascular Meds	AP, Stat, IMDUR, ACE-I, CCB, MF, GTN	ACE-I	ARB	CCB, ARB, Stat, BB, GTN	Stat	ACE-I, MF, DM
TC (mmol/L)	3.10	5.00	3.90	4.40	4.30	4.1
Trig (mmol/L)	3.00	0.90	0.70	1.30	1.00	1.9
HDL-C (mmol/L)	1.20	1.1	0.90	1.30	1.20	0.9
LDL-C (mmol/L)	0.50	3.5	2.70	2.50	2.60	2.3
APOA-I (mmol/L)	1.48	1.13	1.01	1.25	1.26	1.10
APOB (mmol/L)	0.60	0.92	0.72	0.81	0.66	0.98
APOB:APOA-I	0.41	0.81	0.71	0.65	0.52	0.89
hsCRP (mg/L)	0.81	7.80	9.80	0.98	3.90	0.88
Glucose (mmol/L)	11.10	4.70	5.3	8.6	5.50	7.6

3 MONTH FOLLOW–UP

|	TIA 1	TIA 2	TIA 3	TIA 4	TIA 5	TIA 6
Cardiovascular Meds	AP, Stat, IMDUR, ACE-I, CCB, MF, GCTN	AP, Stat, ACE-I, CCB	AP, ARB	AP, ARB, Stat, BB, GCTN	AP, Stat, INHH	AP, Stat, MF, ACE-I, DM.
APOA-I (mmol/L)	1.45	1.07	1.09	1.21	1.33	1.12
APOB (mmol/L)	0.73	0.43	0.78	0.69	0.52	0.92
APOB:APOA-I	0.50	0.40	0.72	0.57	0.39	0.82
hsCRP (mg/L)	0.83	4.80	1.60	3.90	5.20	3.50

Table 1. B. Mimic patient characteristics and laboratory findings at acute presentation and at 3-month follow-up.
Risk Factors denoted as: HTN = hypertension, HLD = Hyperlipidemia, T2DM = diabetes mellitus type 2. Clinics denoted as: COMBAT = community based rapid access TIA clinic, RAC = hospital based rapid assessment clinic. ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, AP = antiplatelet therapy, BB = beta-1-receptor blocker, CCB = calcium channel blocker, GTN = Glyceryl Trinitrate, MF = Metformin, Stat = Statin. Blood biochemistry tests are denoted as: TC = total cholesterol, Trig = triglycerides, HDL-C = high density lipoprotein – cholesterol, LDL-C = low density lipoprotein – cholesterol, APOA-I = apolipoprotein A1, APOB = apolipoprotein B, hsCRP = high-sensitivity C-reactive protein, (*) = standard CRP assay.

	Mimic 1	Mimic 2	Mimic 3	Mimic 4	Mimic 5	Mimic 6
Age	52	68	83	82	55	70
Gender	F	M	F	F	F	F
Cardiovascular Risk Factors	HTN	HTN	HTN, HLD	HTN, HLD	HTN, HLD, T2DM	Nil
Smoking	No	No	No	No	No	No
Diagnosis (Mimic)	Migraine	Benign positional vertigo	Vasovagal Syncope	Epileptic Seizure	Migraine	Transient Global Amnesia
Clinic Attended	RAC	RAC	RAC	COMBAT	COMBAT	COMBAT
Time from symptom onset to blood collection (days)	1	1	10	2	5	7
A C U T E P R E S E N T A T I O N						
Cardiovascular Meds	ARB	AP, Stat, BB, ACE-I	AP, Stat, BB	AP, GTN, Stat, ARB	AP, MF, Stat, CCB, ARB	CCB
TC (mmol/L)	5.70	4.90	3.70	3.80	4.80	6.10
Trig (mmol/L)	1.80	2.0	0.80	1.40	0.60	1.00
HDL-C (mmol/L)	1.20	1.00	1.60	1.60	1.50	2.10
LDL-C (mmol/L)	3.70	3.60	1.70	1.60	3.00	3.50
APOA-I (mmol/L)	1.22	1.02	1.40	1.61	1.51	1.76
APOB (mmol/L)	1.12	0.84	0.58	0.54	0.86	0.85
APOB:APOA-I	0.92	0.82	0.41	0.34	0.57	0.48
hsCRP (mg/L)	4.80	1.00	0.22	3.90	1.40	15.0*
Glucose (mmol/L)	5.40	6.20	5.60	8.2	6.70	5.50
3 M O N T H F O L L O W – U P						
Cardiovascular Meds	ARB	AP, Stat, BB, ACE-I	AP, Stat, BB	AP, GTN, Stat, ARB	AP, MF, Stat, CCB, ARB	CCB
APOA-I (mmol/L)	1.26	1.16	1.32	1.54	1.44	1.62
APOB (mmol/L)	1.09	0.94	0.69	0.60	0.53	0.84
APOB:APOA-I	0.86	0.81	0.52	0.39	0.37	0.52
hsCRP (mg/L)	2.30	1.30	0.50	3.60	2.6	190*

Table 1. C. Healthy control volunteer characteristics and laboratory findings at initial presentation and at 3-month follow-up.
Blood biochemistry tests are denoted as: TC = total cholesterol, Trig = triglycerides, HDL-C = high density lipoprotein – cholesterol, LDL-C = low density lipoprotein – cholesterol, APOA-I = apolipoprotein A1, APOB = apolipoprotein B, hsCRP = high-sensitivity C-reactive protein.

	Healthy Control Volunteer 1	Healthy Control Volunteer 2	Healthy Control Volunteer 3	Healthy Control Volunteer 4	Healthy Control Volunteer 5	Healthy Control Volunteer 6
Age	61	50	69	43	53	54
Gender	M	F	M	F	F	F
Smoking	No	No	No	No	No	No
INITIAL PRESENTATION						
TC (mmol/L)	3.50	4.60	4.50	5.00	5.20	6.10
Trig (mmol/L)	0.90	1.10	0.60	0.60	0.60	0.60
HDL-C (mmol/L)	1.40	1.60	1.40	1.70	1.6	2.10
LDL-C (mmol/L)	1.70	2.50	2.80	3.00	3.3	3.70
APOA-I (mmol/L)	1.34	1.47	1.21	1.32	1.41	1.61
APOB (mmol/L)	0.52	0.74	0.74	0.73	0.80	0.84
APOB:APOA-I	0.39	0.50	0.61	0.55	0.57	0.52
hsCRP (mg/L)	3.10	0.91	1.90	0.45	1.60	1.10
Glucose (mmol/L)	4.80	4.60	4.80	4.20	5.6	4.8
3 MONTH FOLLOW–UP						
APOA-I (mmol/L)	1.25	1.58	1.09	1.51	1.42	1.73
APOB (mmol/L)	0.46	0.81	0.79	0.84	0.81	0.93
APOB:APOA-I	0.37	0.51	0.72	0.56	0.57	0.54
hsCRP (mg/L)	3.40	1.30	4.60	0.77	2.20	0.59
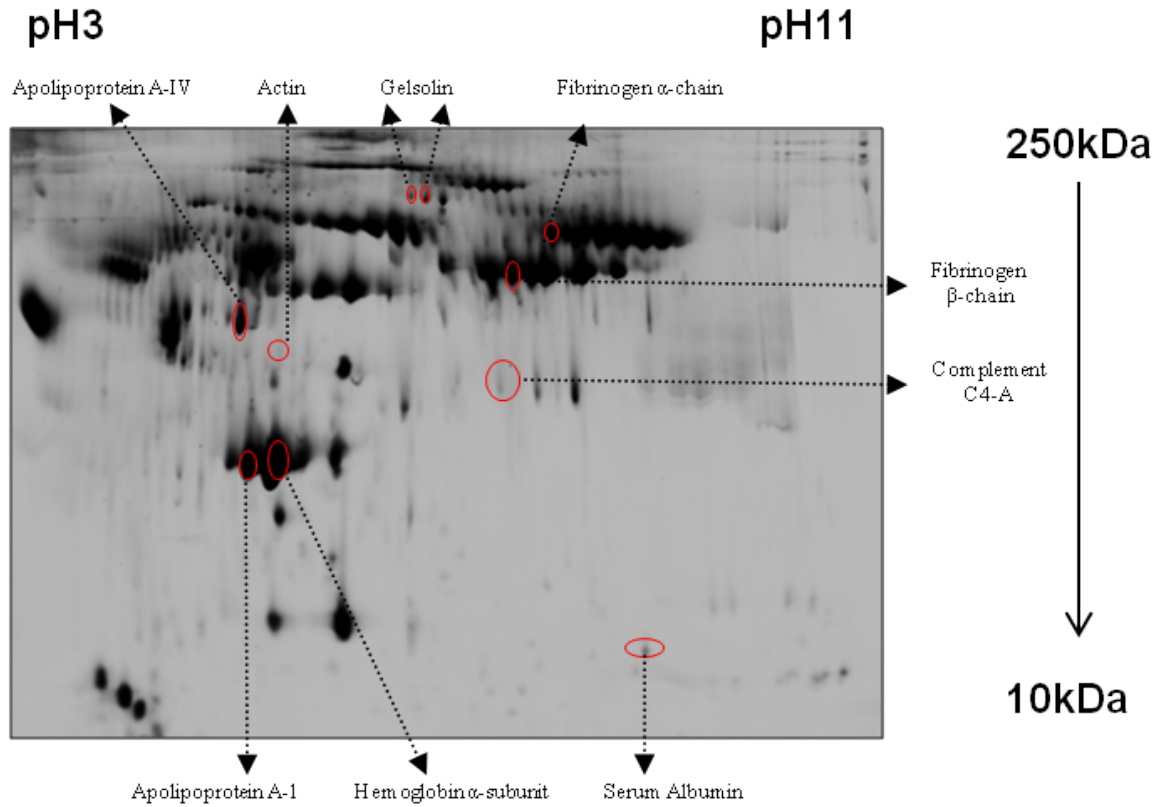
Figure 1: Analysis of plasma proteome by 2D-DIGE.

A representative 2D-DIGE image showing the plasma protein profile of a TIA patient. Ten differentially expressed protein spots were identified by DeCyder analysis and mass spectrometry. Initial and 3-month follow-up plasma samples were labelled with Cy3 and Cy5 respectively in this gel. Labelled plasma proteins are separated in the first dimension across a pH range of 3-11 (isoelectric focusing) and in the second dimension by molecular weight (from 250-10 kDa).

Table 2: Summary of differentially expressed plasma proteins in TIA, Mimic and Health Control Volunteer (HCV) cohorts identified by nanospray LTQ Orbitrap XL-MS/MS.
I.S. = pooled internal standard, MW= molecular weight, kDa= kilodaltons.

Protein	UniProt ID	Peptide matches	Fold change (p-value) [increased cohort vs. I.S.]	Increased cohort	% sequence coverage MS/MS	MW [kDa]
Apolipoprotein A-IV	P06727	22	1.61 (0.022)	TIA	60.86	45.4
Apolipoprotein A-I	P02647	7	1.35 (0.033)	HCV & M	29.59	30.8
Fibrinogen α- chain	P02671	8	1.22 (0.040)	TIA & M	16.86	94.9
Fibrinogen β- chain	P02675	16	1.17 (0.031)	M	53.97	55.9
Complement C4-A	P0C0L4	5	1.19 (0.036)	TIA & M	X	84.1
Gelsolin	P06396	10	1.14 (0.028)	HCV	22.89	85.6
Gelsolin	P06396	X	1.21 (x)	HCV	X	X
Hemoglobin alpha subunit	P69905	X	1.79 (x)	HCV	X	X
Actin, α-skeletal muscle	Q5T8M8	X	1.44 (x)	HCV	X	X
Serum Albumin	P02768	X	1.47 (x)	HCV	X	X

Figure 2: Principal Component Analysis of Significant TIA, Mimic and Healthy Control Plasma Proteins. Principal component analysis of 10 candidate proteins identified in 2D-DIGE that are separated according to the two largest sources of variance in the analysis (PC1 and PC2). (A) Represents the distribution of 36 individual spot maps. (B) Represents the distribution of each of the three groups. Ellipses surrounding related samples are displayed only to emphasise the group distribution in the plot.
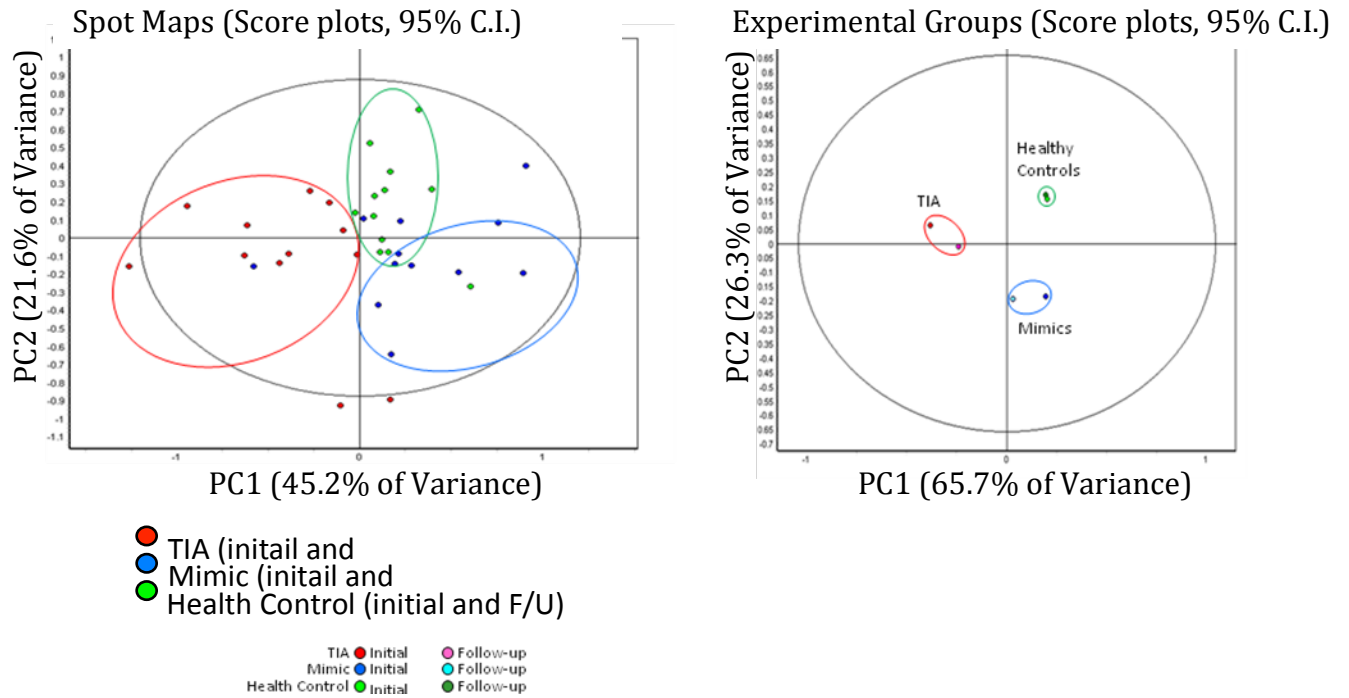
Figure 3: Representative MS/MS spectra of peptides from novel proteins identified from 2D-DIGE. (A) Apolipoprotein A-1, (B) Fibrinogen α-chain, (C) Gelsolin, (D) Apolipoprotein A-4, (E) Fibrinogen β-chain and (F) Complement C4-A.

A. Apolipoprotein A-1
DLATVYVDVLK

B. Fibrinogen α-chain
QFTSSTSYNR

C. Gelsolin
GASQAGAPQGR

D. Apolipoprotein A-4
ALVQQMEQLR

E. Fibrinogen β-chain
DNDGWLTSDPR

F. Complement C4-A
AEMADQAAAWLTR

68
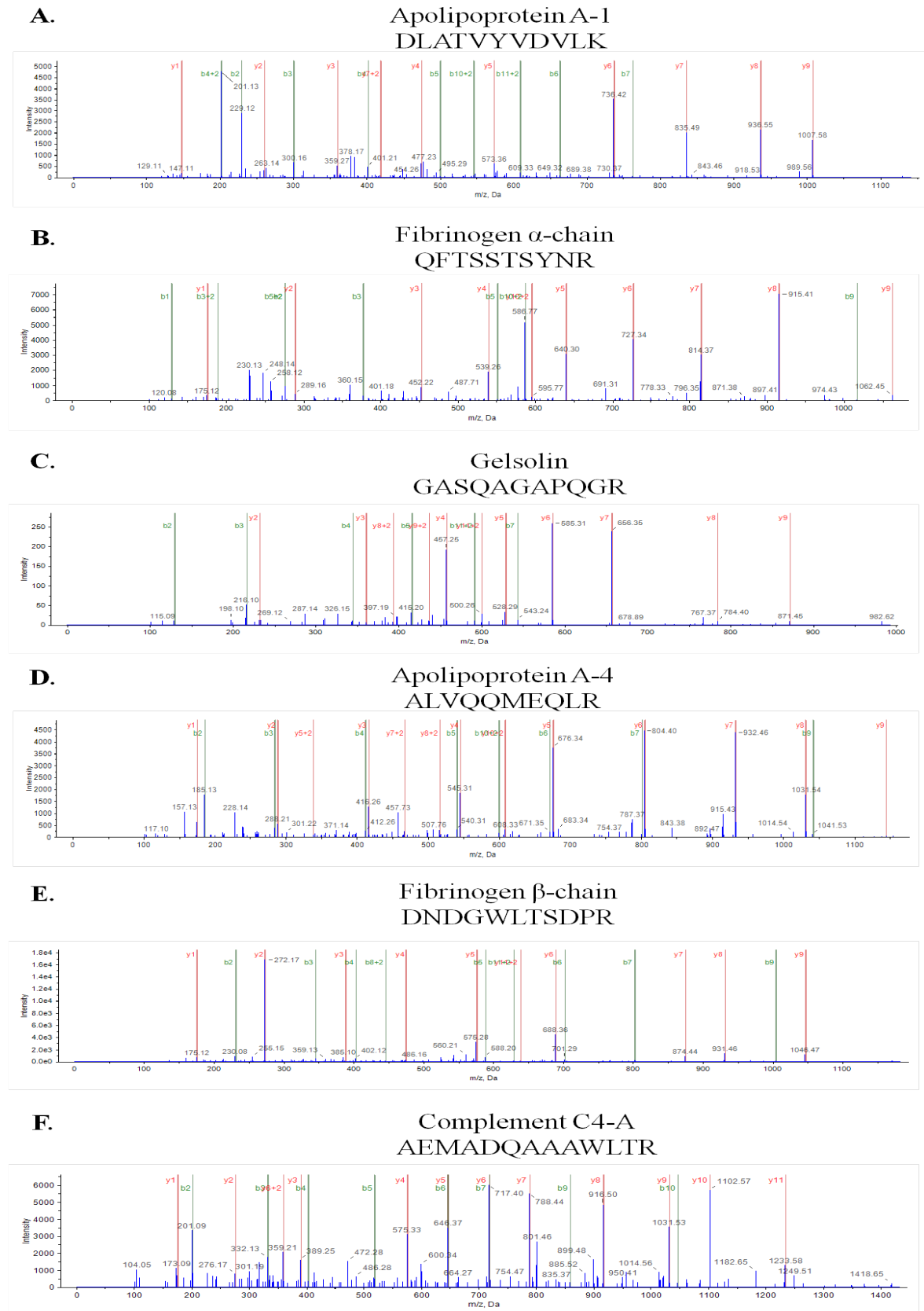
Figure 4: Proposed role of identified proteins in the acute presentation of a transient ischaemic attack.
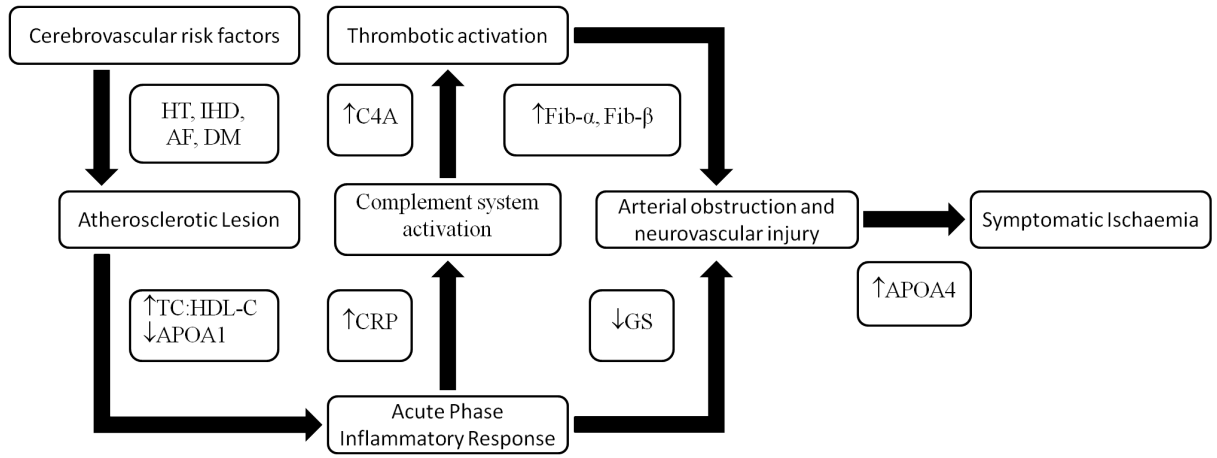
SECTION 4: Management Pathways

Chapter 1

Whilst further research is needed in identifying blood biomarkers for the diagnosis and stratification of TIA, the current model of care in Western Adelaide is referral to either the emergency department or a hospital-based TIA clinic if available. Given the limited availability of TIA clinics and overcrowding of hospital emergency departments, a novel model of care was proposed. GPs play a significant role in TIA care and a GP with a special interest in stroke and TIA could be trained to provide the initial assessment of TIA with the support of a hospital-based TIA clinic. A proof of concept study was conducted to test a novel model of TIA care involving a community-based and hospital-based TIA clinic. The manuscript has been submitted to the *International Journal of Stroke* .

Leung ES, Hamilton-Bruce MA, Stocks N, Toner P, Jannes J, Koblar SA. COMBAT: COMmunity-Based rapid Access Transient ischaemic attack as a model of stroke prevention. A Proof of Concept Study. Manuscript submitted.

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Abstract

COMBAT: COMmunity-Based rapid Access Transient ischaemic attack as a model of stroke prevention. A Proof of Concept Study.

Objectives – To determine if a collaborative strategy to TIA management, using general practitioners with a special interest (GPwSI) in a community-based rapid-access TIA clinic (COMBAT clinic) linked with a specialist-based, hospital Rapid Access Unit (RAC) is a feasible model of TIA care.

Design – Prospective proof of concept study

Setting – A community-based TIA clinic operated between September 2009 and April 2010 in an Australian metropolitan region, with links to a teaching hospital rapid access TIA clinic (RAC).

Participants – 33 participants from the COMBAT clinic and 43 from the RAC were assessed. All patients with suspected TIA referred to the clinics and who could provide informed consent were included in the study. Patients who were pregnant, terminally ill, experiencing dementia or other significant cognitive impairment or illiterate were excluded.

Main outcome measures - The primary outcome measure was subsequent stroke at 90 days.

 Results - Thirty-three patients were referred to the COMBAT clinic and 15 were diagnosed with TIA, 3 with stroke and the remaining 15 were mimics. Forty-two patients were assessed at the RAC and 15 were diagnosed with TIA, 12 with stroke and 16 were mimics. Of the 15 TIA patients seen at the COMBAT clinic, none presented with subsequent stroke at 90 days, and one patient seen at the RAC had a

subsequent stroke. Formal statistical analysis was not performed in this proof of concept study.

Conclusions - The concept of a community-based rapid access TIA clinic with GPwSIs is a feasible model of care in preventing stroke. Future research could incorporate an analysis of the cost-effectiveness of community and hospital-based TIA diagnosis and management.

Background

The risk of stroke following a transient ischaemic attack (TIA) is between 10-20% in the following 90 days[1] with half of these patients having a stroke within the next 48 hours[2]. Whilst there is evidence supporting early assessment and management of TIAs[3 4], there is limited research investigating the optimal model of care for TIA patients, in particular, the usefulness of acute observation units (including acute stroke units. Kehdi et al. found that patients who were discharged home had a higher rate of stroke or recurrent TIA compared to those admitted, most likely reflecting the more rapid and comprehensive investigation and management of admitted patients[5]. However, others have shown that an outpatient based TIA clinic can be an effective alternative[3 6], especially for lower risk patients[7].

A survey of hospitals confirmed that services for TIA assessment and management are variable in Australia. With delays in both assessment and treatment, the researchers from this study suggested that there is a significant gap between evidence and current practice, and that determining the best model of care requires urgent investigation[8].

Acute observation units require increased resources including personnel. The health workforce is a challenge in Australia and a number of solutions to address workforce shortages have been suggested, including task substitution[9-12]. In the United Kingdom, the National Health Service introduced general practitioners with a Special Interest (GPwSI) to improve access to specialist clinics with long waiting lists. With some limited data on their clinical and cost-effectiveness, there is no evidence in the literature of GPwSI involved in stroke or TIA care[13-27]. General practitioners play an

74

important role in the management of TIAs, although a clinical diagnosis can be challenging as it is just one of the many differentials in a patient presenting with transient neurological disturbance.[28] The involvement of a GP in a specialist team will allow for refinement of diagnostic acumen thus facilitating identification and referral of patients with highest risk of impending stroke. GPwSI may also greatly reduce the burden on specialist TIA services through independent management of low risk TIA patients and identification of patients with non-vascular causes thus avoiding inappropriate use of limited specialist resources[29].

We thus conducted a prospective observational study to test a proof of concept collaborative strategy for TIA management, namely using GpwSI in a community-based rapid-access TIA clinic (COMBAT clinic) linked with a specialist based, hospital Rapid Access Unit (RAC).

Hypothesis

A model of care involving collaboration between a specialist-based hospital RAC and a community-based GP TIA clinic is a feasible model to implement evidence-based assessment and management.

Aims

1. *To determine if a collaborative model of TIA care is feasible and allows implementation of TIA guidelines*

2. *To characterise the role of the GPswSI providing care in a community-based TIA clinic.*

Methods

A community–based TIA clinic operated from 30 September 2009 to 14 April 2010 within Western Adelaide, a region with a population of 212,741 and served by 202 GPs[30]. This region is also served by one tertiary referral teaching hospital and hosts a specialist run daily TIA RAC. Four GPwSIs, who received comprehensive training from stroke specialists at the local tertiary referral teaching hospital, staffed the COMBAT clinic. The GPwSI were familiar with the National Stroke Foundation guidelines and the local hospital TIA and stroke care pathways. The training included written educational modules, online-resources and face-to-face teaching within the hospital acute stroke unit.

GPs from the Adelaide Western General Practice Network (AWGPN) were invited to participate and refer any patient with a suspected TIA to the service through a telephone hotline (1300 COMBAT). The service was advertised at an educational meeting through the AWGPN and in monthly newsletters of the AWGPN and the Royal Australian College of General Practitioners (RACGP) South Australian Faculty.

Referring GPs who rang the hotline could discuss their case with either a stroke physician or a GPwSI, which allowed for stratification of stroke risk and subsequent triage to an appropriate clinic (Table 1). Patients deemed high risk were referred to the hospital- based RAC, whilst patients considered of low risk were offered an appointment at the COMBAT clinic within 48 hours. Low risk patients referred to the hospital-based TIA clinic (predominantly from the Emergency Department) were cross-referred to the COMBAT clinic. Assessment and management of patients was in

accordance with national guidelines[31]. All patients referred to the COMBAT clinic were offered an appointment.

Table 1: Risk stratification

Criteria	Low Risk	High Risk
ABCD2 Score	≤3	≥4
History of previous TIA in preceding week	No	Yes
Crescendo TIA (two or more TIAs within the last 7 days)	No	Yes
Known symptomatic carotid artery stenosis >50%	No	Yes
Atrial Fibrillation	No	Yes

A pathway of assessment is shown in (Figure 1).

COMBAT Assessment and management

The GPwSI assessed all patients in the COMBAT clinic initially and every case was discussed with a stroke physician. Those with an unclear diagnosis or mimic diagnoses for transient neurological symptoms were referred to a neurologist, with appointments available within 7 days for these patients.

Investigations including bloods, 12 lead electrocardiograph (ECG), CT brain, CT angiogram and/or carotid dopplers and echocardiogram if clinically indicated were arranged on the day of the appointment and management was instigated on evidence-based recommendations. Results were reviewed with the patient within 48 hours and patients were discharged with a detailed letter to their GP indicating diagnosis, treatment, prognosis and education. TIA was defined on a clinical basis.

Clinical data was recorded in general practice medical software ('Best Practice'). Data were then entered into a secure database.

RAC Assessment and management

The RAC had the capacity to assess one patient a day in a clinic located within the Stroke Unit. A TIA nurse performed the history and examination including NIHSS and ABCD2 score, and fasting bloods were taken. Patients were monitored whilst in the clinic with both telemetry and blood pressure. A 24-hour Holter monitor was arranged for the patient at discharge as required. All patients underwent the MRI/TIA protocol, a 45-minute MRI scan of head/neck and heart. Where MRI was contraindicated alternative imaging included CT brain, CT angiogram, carotid ultrasound and echocardiogram with or without a bubble study.

The stroke physician or fellow reviewed the patient to confirm the diagnosis and commenced appropriate secondary prevention therapy. A letter was faxed to the GP within 24 hours, and patients were discharged with a TIA information pack. Patients requiring hospital admission were admitted to the stroke unit.

Patients were either reviewed or contacted over the telephone for follow-up at 90 days. The hospital records were also accessed to determine stroke recurrence at 90 days.

The primary outcome was subsequent stroke at 90 days. Formal statistical analysis was not performed in this proof of concept study.

<u>Inclusion criteria</u>

All patients with suspected TIA referred to the clinics who were able to provide informed consent were included in the study.

<u>Exclusion criteria</u>

Patients who were pregnant, terminally ill, experiencing dementia and/or other significant cognitive impairment or illiterate were excluded.

Ethics approval was obtained from The Queen Elizabeth Hospital Human Ethics Committee, approval number 2009123. Participants gave written informed consent before taking part in the study.

Results

The RAC assessed 43 patients and the COMBAT clinic 33 patients between September 2009 and April 2010. All patients referred to the COMBAT clinic were given an appointment within 48 hours of the referral.

Table 2: Demographics

Baseline patient characteristics	RAC n=43	COMBAT n=33
Age (range)	Mean 60.5 (20-89)	72.3 (46-89)
Gender	Male 21 (48.8%) Female 22 (51.2%)	Male 13 (40.0%) Female 20 (60.0%)
Previous stroke Previous TIA	4 (9.3%) 6 (14.0%)	5 (15.2%) 4 (12.1%)
Hypertension	22 (51.2%)	26 (78.8%)
Hypercholesterolaemia	22 (51.2%)	22 (66.7%)
Diabetes mellitus	8 (18.6%)	10 (30.3%)
Ischaemic Heart Disease	6 (14.0%)	7 (21.2%)
Atrial Fibrillation	0 (0.0%)	2 (6.1%)
Peripheral vascular disease	3 (7.0%)	4 (12.1%)
Family history of stroke (1st degree relative)	8 (18.6%)	12 (36.4%)
Antiplatelet agent before event	17 (39.5%)	8 (24.2%)
Anticoagulant agent	0 (0%)	3 (9.1%)
Smoker Ex-smoker Never smoked	15 (34.5%) 9 (20.9%) 19 (44.2%)	3 (9.1%) 12 (36.4%) 17 (51.5%)
Heavy alcohol	3 (17%)	1 (3%)

The ABCD2 scores were repeated at the clinics (table 3).

Table 3

ABCD2 score	RAC n=43	COMBAT n= 33
1	0	3 (9.1%)
2	8 (8.6%)	10 (30.3%)
3	11(25.6%)	6 (18.2%)
4	14 (32.6%)	7 (21.2%)
5	4 (9.3%)	2 (6.1%)
6	5 (11.6%)	4 (12.1%)
7	1 (2.3%)	1 (3.0%)

Of the 33 patients seen in the COMBAT clinic, 15 were diagnosed with a TIA whilst

15 were diagnosed with mimics. In the RAC 12 patients were diagnosed with a stroke

(Table 5).

Table 5

Diagnosis	RAC n=43	COMBAT n=33
TIA	15 (34.9%)	15 (45.5%)
Stroke	12 (27.9%)	3 (9.0%)
Mimics	16 (37.2%)	15 (45.5%)

The two patients seen at the RAC with a final diagnosis of major stroke had ABCD2 scores of 4 and 5. Of the 10 patients with minor stroke, 2 had ABCD2 scores less than 4.

Table 6

Imaging	RAC (n= 43)	COMBAT (n=33)
MRI	40	6
CT Angiogram	4	15
Carotid Ultrasound	3	4

Of the 15 TIA patients seen at the COMBAT clinic, none presented with subsequent stroke at 90 days, and one patient seen at RAC had a subsequent stroke following an urgent carotid endarterectomy.

Discussion

With limited resources to assess all patients with suspected TIA in hospital and unclear evidence about the best model of care, we established a community-based clinic with specialised GPs to assess and manage patients determined to be at low risk. This prospective proof of concept study is a novel model of care for TIA, bringing together a hospital-based rapid assessment unit with a community-based clinic. Similar models of TIA care have not previously been described in the literature. The study ran for 10 months and demonstrated this to be a feasible model. The COMBAT clinic was well resourced, staffed by four GPwSI in association with a neurologist, with appropriately timed access to imaging and pathology services. This

allowed the RAC clinic, which had the capacity to admit only one patient a day, to see the higher risk patients. The 90-day outcomes of the COMBAT clinic were favourable, with no presentations of stroke. The GPwSI were able to implement TIA management and assess the mimics appropriately. The COMBAT clinic assessed 15 (45.5%) mimics compared to 16 (37.4%) in the RAC clinic, which is less than previously reported numbers of mimics seen in specialist TIA clinics[29]. Whilst some mimics may also require early intervention, the COMBAT clinic was able to provide that assessment and management and avoid inappropriate referral to the hospital TIA clinic. Given the primary outcome was subsequent stroke at 90 days and there was only one stroke (in the RAC group), no formal analysis of data was performed. A recent study in Australia suggested that the 90-day risk of stroke following a TIA has declined over the last ten years, with the overall risk being 3.1%[32]. Our model may be feasible although it would require an alternative outcome to analyse and assess the management arms.

The location of the COMBAT clinic being within a general practice allowed easier access for patients. The concept of a GPwSI in stroke was accepted by referring GPs, hospital staff and the patients themselves. The longer-term management of TIA and stroke prevention is the management of risk factors, of which GPs play a vital role. Including a GP perspective in the acute assessment and management of TIAs can also improve the transition to community care.

A GPwSI in stroke medicine having been trained in a local stroke unit can provide efficient and proficient care for patients with suspected stroke. It allowed the GPs to extend their role, involved them in acute medicine and research.

The ABCD2 score was utilized to assist with the triage of patients along with other clinical features. Differences in the initial ABCD2 score and the scores given at the clinics may account for some of the high scores seen in the COMBAT clinic. Previous studies have suggested that the ABCD2 score should be reserved for stroke specialists[33 34] and similarly Lasserson et al concluded that the Dawson TIA recognition tool was also less accurate in primary care[35]. The diagnosis of TIA in primary care can be a challenge with patients presenting late and with difficulty recalling symptom details. We engaged the local GP network and provided education around TIA and stroke care in an attempt to address this issue, and maintained use of the ABCD2 score given its apparent ease of use. Whilst not a validated approach, the stratification of patients by the GPwSI included other clinical variables and a discussion with a neurologist to overcome the potential shortcomings of the ABCD2 score alone.

Whilst MRI with DWI would be the imaging of choice and would have assisted in stratifying patients, the availability of such acutely remains limited[8 36]. The use of CT and CT angiogram allowed prompt imaging for the low risk COMBAT patients, with the findings providing valuable information assisting management[37].

The limitations of staffing the COMBAT clinic resulted in a clinic that was available three times a week (Mondays, Wednesday and Friday). Whilst this allowed most of the low risk patients to be seen within 48 hours, there was a risk that this was not adequate. Recruiting and training interested GPs, and retaining this workforce may also be a challenge in this model of care. The GPwSI were paid fee for service in this study, and funding for staff would need to be considered.

Whilst this model was able to operate in a metropolitan area, it would not be a feasible model of care in a rural centre. However, consideration of tele-health interventions integrated into this model could have potential value.

Future

The concept of a community-based rapid access TIA clinic is a feasible model of care in preventing stroke. With its associated morbidity and mortality, the prevention of stroke for our aging population is a significant strategy to adopt.

This study is valuable in estimating the service and the numbers needed for a future study. A future study would also incorporate an analysis with respect to the cost-effectiveness of community-based linked with hospital management.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have

an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Figure 1

Pathways of TIA Management: for a patient with suspected TIA

GP

Assessment including ABCD2 Score

Ring COMBAT Clinic Phone Line (1300 COMBAT)

ED

*High risk

Low risk

RAU TIA clinic

Patient given an appointment within 48 hrs

1. Assessment by TIA Nurse

2. Investigations- bloods, telemetry, MRI

3. Stroke Physician review

4. Management commenced

COMBAT Clinic: (GP-with special interest) Assessment Management

Difficult cases or uncertain diagnosis

Discharged back to GP care

Referral to: **Neurologist**

Admitted to stroke unit

High risk/stroke

*ABCD2≥4, atrial fibrillation, carotid territory symptoms or crescendo TIAs

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SECTION 4

Chapter 2

Patients with suspected TIA who were seen at the COMBAT clinic were assessed and managed in accordance with the NSF guidelines(National Stroke Foundation 2007a). Whilst MRI would be the preferred imaging modality, access is restricted and it may not be as cost-effective, particularly in this lower risk group(Wardlaw et al. 2014). With restricted access to MRI imaging, CT and CT-angiogram formed part of the assessment of these patients and are presented in the following publication.

As stipulated by the publisher, this is a non-final version of an article published in final form in *Stroke*.

Benedict A, Khoo EW, **Leung E**, Hamilton-Bruce A, Koblar S: Letter by Benedict et al Regarding Article, "What Causes Disability After Transient Ischemic Attack and Minor Stroke? Results From the CT and MRI in the Triage of TIA and Minor Cerebrovascular Events to Identify High-Risk Patients (CATCH) Study". *Stroke* 2013, 44(4):e32.

The final published form can be found at:

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CT Angiography in the Assessment of Transient Ischemic Attack (TIA)

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Coutts *et al* report the importance of CT brain/CT angiography (CTA) as valuable imaging techniques in the assessment of minor stroke and TIA [1]. They show that patients with abnormalities on the CT/CTA metric were at high risk for disability, even in the absence of a recurrent event. We wish to support this finding from data obtained from a community-based TIA clinic (COMBAT).

CTA offers a number of advantages: the possibility of morphological assessment of cerebral blood vessels, including site and length of occluded segments and assists selection of treatment for patients with TIA [2]. It can also be interpreted relatively rapidly by radiologists and is generally more available than Magnetic Resonance Imaging (MRI), which has limited availability outside specialist units [3,4]. MRI studies are more expensive than CTA, take longer to perform and can present logistical difficulties for monitoring and treatment of acutely ill patients inside the scanner [4]. Safety issues must be considered, such as the presence of metal clips, metal foreign bodies and pacemakers - all contra-indicative of MRI examination [4]. Drawbacks to CTA include radiation exposure, risk of allergic reaction to iodinated contrast agents and impairment of renal function (particularly in elderly and diabetic patients).

Due to limited evidence on the usefulness of CTA in assessing patients with TIA, we aimed to investigate whether CTA would provide clinically important information, which would alter the management of a significant proportion of patients with TIA. We conducted a study on a subset of the COMmunity-Based rapid Access TIA (COMBAT) study. COMBAT was a pilot clinic that recruited patients from September 2009 to April 2010, referred either by their General Practitioner (GP) or the Emergency Department of The Queen Elizabeth Hospital to the TIA Clinic for

assessment and management of their TIA. Based on their ABCD2 score they were

subsequently triaged to appropriate services. Patients scoring less than 4, the low-risk

limit [5], were given an appointment at the TIA clinic within 48 hours to see a GP

with a special interest in stroke. Local hospital ethics approval was obtained.

Seventeen of the 33 patients (52%) enrolled during the nine-month pilot underwent

CTA as part of their initial assessment (funding for MRI was unavailable under

Medicare). Patient management information and reports, including three-month

follow-up, were collected from hospital case notes, COMBAT clinic files and the

South Australian hospital database. Images from CTAs performed outside the public

health-care system were accessed via televiewer and reviewed by an independent

Neuroradiologist. Seven of these 17 patients (41%) had a positive finding on CTA

(defined by a consultant radiologist). Five patients with significant CTA findings

were considered for vascular intervention, two of whom had significant incidental

findings of aneurysm, contralateral ICA and cerebral artery stenosis. Given the high

risk for surgery, three of these patients were treated with maximal medical therapy

while the other two had significant ipsilateral internal carotid artery stenosis and

underwent vascular surgery.

The COMBAT clinic is a novel pathway for management of patients with TIA in the

community, an important area for study. Our findings require replication in a larger

community study, however we suggest that CTA can provide information, which may

significantly alter the management of patients with TIA, in agreement with the

findings of Coutts *et al* [1]. This recommendation is also worthwhile for regional

areas with limited imaging resources.

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SECTION 5: DISCUSSION

<u>Contribution and Impact</u>

The work presented in this thesis demonstrated that whilst gaps exist in TIA assessment and management from a primary care perspective, the appropriate development of resources and pathways could potentially overcome barriers to prevent stroke and improve health outcomes.

Section 3 of this thesis indicated that GP knowledge around TIA care could be improved and that resources can be developed in various modes to provide this targeted education.   The knowledge gap amongst GPs remains evident, with a recent study by Suzuki et al demonstrating that GPs lack confidence in the diagnosis of TIA, and that there is a need for education around the importance of urgent assessment and management(Suzuki et al. 2014).

Section 3, Chapter 3 described the development of education programs specifically designed for Australian GPs. These programs were developed in collaboration with the RACGP and SFGPET, organisations that are experienced in the delivery of clinical education and training in general practice. Along with case scenarios, active learning modules and a video demonstration, we also conducted face-to-face presentations for general practitioners in Adelaide(Leung, Elaine et al. 2009; Leung, Elaine & Koblar 2010).   These mixed methods of education delivery provided GPs in the region an opportunity to improve their knowledge and skills around TIA and stroke care at a time when new evidence was emerging about the importance of early assessment and treatment.

Advances in MRI scanning have contributed significantly to the diagnosis of TIA and the stratification of risk. Whilst the addition of MRI-DWI scanning can provide a more accurate assessment, access to this expensive resource remains limited. The discovery of a blood protein biomarker has the potential to be a more accessible and effective tool in providing clinicians, including those in rural and remote areas, a better assessment of TIA. Biomarkers have been used in assessing acute coronary symptoms since the 1950s(Aldous 2013). The current use of cardiac biomarker troponin, including point-of-care testing, along with electrocardiograph (ECG) evaluation has permitted an accessible and efficient means to assist in the diagnosis of acute myocardial infarction, especially in rural areas of South Australia(Aldous 2013; Tideman et al. 2014). For stroke and TIA, a more accurate assessment and better identification of mimics would allow patients at higher risk of TIA to be appropriately referred to an acute hospital setting for management. The work presented in Section 3, Chapter 4 of this thesis identified several biomarkers that may be associated with TIA. The impact of this clinically would significantly change the assessment of TIA and improve subsequent outcomes for patients presenting with an acute neurological event.

With evidence supporting early assessment and management of TIA, the practical implementation of the best pathway of care has yet to be established and validated in Australia. Blacker proposed that not all patients with suspected TIA need to be assessed in a stroke service and that a telephone call between the general practitioner and a stroke physician may suffice(D. J. Blacker 2009). With some of the initial assessment of TIA, and most of the longer-term prevention of stroke occurring in

primary care, it is fundamental to involve primary care in the development of models of care.

The collaboration of GPs in a community-based rapid access TIA clinic (COMBAT) linked with a specialist-based hospital Rapid Access Clinic (RAC) presented in Section 4 Chapter 1 is a novel and feasible model of TIA care. Suzuki et al also found that GPs lacked familiarity with respect to the referral criteria and knowledge regarding where to refer patients. They concluded that a close relationship between GPs and stroke specialists in hospitals needs to be established(Suzuki et al. 2014).

The COMBAT clinic was an acceptable pathway of care, and allowed higher risk patients to be seen at the RAC. The RAC had limited capacity for patient assessment with MR imaging capability to assess just one patient a day. All patients referred to the COMBAT clinic were given appointments within seven days of the referral, in accordance with the National Stroke Foundation Guidelines(National Stroke Foundation 2010), although not necessarily within seven days of the onset of symptoms. Magin et al found that 38.5% of low risk patients referred to a secondary referral TIA clinic were seen within seven days(Magin et al. 2013).

The referral process to the COMBAT and RAC clinics included the ABCD2 score in the triage of patients with suspected TIA, a recommendation by the NSF Guidelines(National Stroke Foundation 2010). The ABCD2 score has since been shown in some studies to be inaccurate and other scores have been proposed as being more useful(Cucchiara, BL et al. 2006; Fothergill et al. 2009; Giles, M & Rothwell 2008; Giles, Matthew F. & Rothwell 2010; Purroy et al. 2007). The score however, is

a simple tool that was used in conjunction with the clinical history and expertise of a stroke physician and our experience indicated utility without adverse events. Bradley et al found that the ABCD2 score was inaccurate when performed by non-stroke specialists but concluded that training could improve this performance(Bradley, D et al. 2013). The GPwSI had been given specific skills training with the RAC and stroke physicians in assessment and management of TIA, including use of the ABCD2 score. Ranta et al have since developed an Electronic Decision Support (EDS) tool to assist general practitioners in the assessment of TIA and found that it may be especially useful in areas where access to specialist services is limited(Ranta 2013; Ranta & Cariga 2013; Ranta et al. 2014). This tool may provide additional assistance in assessment and improve TIA management in primary care.

Section 4, Chapter 2 addresses the role of imaging in a community-based clinic. Medicare currently limits the use of MRI by general practitioners in Australia. As such the COMBAT clinic utilized CT/A in assessing patients with suspected TIA, a resource more readily available using a private radiological provider in conjunction with a public hospital. We found CTA was a useful alternative to MRI and contributed significantly to the management of patients.

Limitations

The survey of GP knowledge around TIA in Section 3, Chapter 1 sampled a small number of GPs in the Western Adelaide metropolitan area. A recent larger sample size study surveying 487 GPs confirmed our findings(Suzuki et al. 2014).

Educational resources for GPs were focused and readily available but need to translate into a change in clinical practice in order to be useful. The rate of GP encounters for TIA though is low with only 2 per 1,000 encounters(Charles, Pan & Miller 2010). The feasibility of a study to determine a change in practice following an educational intervention would thus be difficult. We therefore surveyed GPs and GP registrars following face-to-face presentations and use of the SFGPET GP-start Funny Turns module pre- and post-education. Participants were required to complete a pre-education questionnaire and subsequently a post-education questionnaire at 3 months to assess the usefulness of the education in improving knowledge in the assessment and management of TIAs (unpublished data). Assessment of knowledge and skills in an 'exam' style manner could help determine the effect of the education but are only a reflection of what might occur in real clinical practice.

The COMBAT and RAC study assessed 75 patients in the period from September 2009 to April 2010. Assuming that the prevalence of stroke is 15%, a sample of 251 patients would be required to assess a 30-80% risk reduction in stroke outcomes with 80% statistical power and an alpha level of 5%. With one stroke outcome only, statistical analysis of this proof of concept study was not performed. In order to demonstrate a significant outcome, alternative outcome measures need to be determined in a further study, as the incidence of stroke following TIA may be declining. Sundarajan et al found that rates of TIA are decreasing in Victoria and the risk of stroke at 90-days following a TIA is now 3.1% overall(Sundararajan et al. 2014). They concluded that improved primary and secondary prevention might be the reason for this trend. Similarly a study in Adelaide found that despite our ageing population the incidence of stroke has not increased(Leyden et al. 2013). The same

study also reported that 36% were cardioembolic strokes and that adequate anticoagulation may have prevented stroke in some cases, if appropriate and timely primary care management of atrial fibrillation had been instigated. A qualitative study of patient and carer experience and satisfaction would also be useful in assessing the role of the COMBAT clinic. GPs who referred patients to the COMBAT clinic were interviewed on the telephone and a study of their satisfaction in referring to a GPwSI would also be valuable. A recent study in Australia has demonstrated the increased use of preventative medications for stroke and TIA(Sluggett et al. 2014). This suggests the importance of the role of primary care in stroke prevention whereby the management of side effects, monitoring and compliance longer-term can be considered by a GP.

Future directions

An analysis of the usefulness of GP education around TIA assessment and management needs to be conducted. Designing an ideal study would be a challenge given the small numbers of TIA encounters seen in general practice, but would assist in the ongoing development of GP education programs.

The work presented in this thesis demonstrated that the involvement of GPs in a TIA clinic is feasible and may have potential benefits beyond providing rapid access to a clinician with a special interest and training. Further studies need to clarify the benefits in determining the acceptability, costs and longer-term benefits of collaborating with primary care. A large scale study of models of TIA care needs to be conducted in order to determine the best system for Australia. A prospective comparison of hospital-based and community-based care, in rural and urban settings

101

will allow health policy makers to provide and distribute appropriate health resources and funding to ensure the best TIA care. A randomized design would not be feasible but a comparison of models in different regions using a cluster design with cost-benefit analysis would be of great value.

As the work in this thesis highlights, the diagnosis of TIA is a challenge and GPs in particular find this difficult, as their exposure to cases can be minimal. The potential for additional tools to assist in the diagnosis of TIA would allow clinicians with less expertise, including those in rural settings to make more accurate assessments. The discovery of potential blood biomarkers is encouraging but larger studies are needed to validate them. Validating the ABCD2 score in primary care and testing an electronic decision support tool would similarly help GPs better evaluate patients with suspected TIA.

Conclusion

TIA is a precursor for stroke and the diagnosis challenging, although the incidence presenting in primary care may be small subsequent management remains with general practitioners. The role of GPs is thus significant, and as with all medical conditions, GPs must continue to update their knowledge and skills. The urgency of TIA assessment however, needs to be stressed to both clinicians and the public.

Researchers continue to determine other methods to assist in the clinical diagnosis and risk stratification of TIA. Given that GPs may have limited expertise in TIA assessment, these tools could contribute considerably to primary care and ideally should be tested and validated in primary care.

The benefit of early treatment of TIA is evident, with recent studies also suggesting that improved primary and secondary prevention has already made an impact(Sundararajan et al. 2014). The best model of care will vary depending on the location and resources available in different communities. We suggest in this thesis that all potential models need to consider the role of primary care and the involvement of skilled general practitioners to better prevent stroke after TIA presentations.

Appendix 1

Reproduced with permission from Sturt Fleurieu General Practice Education and Training.

GP-start Funny Turns module 2011

+ gp–start ™

Funny Turns
Clinical Skill Option 4

+ sturt fleurieu
educating doctors for a future in general practice

CLINICAL SKILL OPTION 4

Funny Turns

Learning Objectives

After completing this Clinical Skill Option, registrars will:

1. have a systematic approach to the assessment of patients presenting with transient neurological symptoms.

2. have a good knowledge of the features of transient ischaemic attacks (TIA) which distinguish it from other possible diagnoses.

3. be able to assess the severity and urgency of referral of transient neurological episodes and be aware of the available referral pathways in their local region.

4. be aware of the management of stroke/TIA in the outpatient and hospital settings.

5. have a knowledge of the long-term management of patients with TIA or stroke.

Introduction

Patients presenting with neurological symptoms are common in general practice. Whilst it is relatively straightforward when patients present with classical neurological syndromes, most present with non-specific or vague symptoms that are hard to classify. Because of this, it is important to have a systematic approach to patients with neurological symptoms so that problems of a serious nature which require urgent referrals are not missed.

The history

Like in all areas of medicine, the history forms the main component of the assessment process. History from a witness is invaluable. The onset and evolution of the episode give good clues to the likely cause of the symptoms.

Please refer to Reading 1 which reviews the diagnosis, assessment and management of transient ischaemic attacks (TIA). Table 1 of this reading summarises the TIA mimics.

CLINICAL CHECKPOINT 1
The History

Review a case you have seen of a patient with transient neurological symptoms. Compare your history with those suggested in Reading 1. How do you think you did? Develop a checklist of important questions to ask patients with transient neurological symptoms.

Focused Neurological Examination

Assessing a neurological episode within the timeframe of a standard general practice consultation is limiting. With much focus on the history taking, performing a full neurological examination +/- a cardiovascular examination depending on the case is not realistic. You may have already developed a focused neurological examination.

CLINICAL CHECKPOINT 2
The focused neurological examination

Consider what are the important aspects of the neurological examination of a patient presenting with an episode of neurological symptoms.

Do you have all the necessary equipment in your consulting room readily available?

Compare this to our video of a suggested approach which should take about 5 minutes. Will you change your practice and why?

The neurological examination video has been uploaded to you tube in a private section. Please click on the following link and use these login details to access the video.

Username: gpstartTIA
Password: sfgpet_12?

Video of neurological examination

Risk stratification and referral pathway

With limited resources, it is important to manage neurological symptoms according to its severity and its likelihood of progression, balanced with the resources and facilities available. For example, TIAs can be a medical emergency, with the risk of stroke between 10-30% in the following 90 days[1]. Half of these patients will have a stroke within 48 hours[2]. Therefore the ability to predict those patients who are more likely to develop a stroke in the short term is vital.

A number of tools have been developed to assist clinicians stratify the risk of subsequent stroke in patients with TIAs and in turn decide on the most appropriate avenue of further care. One of the most widely used tool to date is the ABCD2 tool. Reading 2 from the National Stroke Foundation discusses its use in clinical practice. Reading 1, Figure 1 outlines the TIA referral pathway.

CLINICAL CHECKPOINT 3
Risk stratification and referral pathway

Consider a patient you have seen with a suspected TIA. How did you assess and manage this patient?

In particular did you refer this patient and why/ why not? If so, where did you refer him/her?

Are you aware of your local Stroke Network?

How might your referral pattern change if you are working in a rural or remote area?

In South Australia, the South Australian Stroke Clinical network is developing a pathway for centralised TIA/stroke care (Reading 3).

Outpatient Stroke/TIA Management

Investigations

Whilst the history provides the main clues to diagnosis in transient neurological symptoms, the addition of appropriate investigations assist in determining the aetiology and the subsequently treatment. It is important to work out whether a stroke/TIA is cardioembolic or due to carotid artery stenosis, as this helps us determine further treatment and ways to prevent further cerebrovascular events.

Reading 2 suggests the routine investigations required for all patients with a suspected TIA.

CLINICAL CHECKPOINT 4
Investigations

What investigations would you routinely perform in a patient presenting with transient neurological symptoms?

Consider a case where you investigated a patient and whether the results assisted your diagnosis and management. Did you perform all the tests suggested in Reading 2?

Inpatient Acute Stroke/TIA Management

The treatment of acute stroke has changed significantly over the last 10 years. With the availability of thrombolytic therapy, early symptom recognition, tertiary hospital attendance and the management of patients in acute stroke units are vital in minimising morbidity and mortality from stroke. Evidence suggests that thrombolysis given up to 4.5 hours after the onset of stroke can be beneficial[3], but delays in presentation may limit its use. In Australia only 3% of patients with ischaemic stroke received thrombolysis treatment[4]. Issues of public knowledge of stroke symptoms and access to hospitals administering thrombolysis contribute to this delay.

Have you considered asking patients who are at risk of stroke what the symptoms of stroke are? Patients with hypertension, diabetes and hypercholesterolaemia may be aware of the symptoms of a 'heart attack' and would perhaps have no hesitation in calling an ambulance for chest pain but what would their response be to a 'brain attack'?

The National Stroke Foundation (Reading 4) has a number of patient education resources that you may add to your waiting room or consultation room so that patients will in future act FAST.

Reading 5 and Reading 6 discuss the acute treatment of stroke.

CLINICAL CHECKPOINT 6
Inpatient Acute Stroke/TIA Management

Review a patient you have seen who has had an acute stroke recently. What treatment did they receive in hospital?

Are you confident in explaining to a patient and/or their family members with a suspected acute stroke what kind of treatments they might expect when they are admitted at hospital?

Long-term Stroke/TIA management

Long-term stroke/ TIA management include maximising and improving function as well as preventing future stroke/ TIA and their complications. The role of a GP in stroke prevention is vital. Maintaining compliance with medications and reaching target treatment goals is required to prevent further strokes which may be more disabling or even fatal. The development of a Chronic Disease GP Management Care Plan (GPMP) and Team Care Arrangement (TCA) may assist you in providing the best co-ordinated care. Similarly a Home Medicines Review may be required to ensure medication adherence.

Do you have a template for a GPMP for a patient with cerebrovascular disease?

One of the common questions after an acute admission to hospital for the GP is regarding driving. Are you aware of the local guidelines for assessing fitness to drive after a stroke or TIA? Refer to the gp-start module 'Fitness To Drive' for further information.

There are a number of complications to consider after a patient has suffered a stroke. In particular disturbances in mood are under recognised. Reading 6 outlines in a table the common post stroke complications.

CLINICAL CHECKPOINT 7

Perform an audit of patients you have seen that have had a stroke and/or TIA.

Are your patients on the optimal treatment?

What medications should they be on?

Are there any medications that should be ceased?

Do they have a GP Management Plan in place?

What would your advice to these patients be about driving? Were they preventable?

Did any of them suffer complications of stroke? Were they preventable?

Readings

Required

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Clinical Review Questions

SBA

Case 1

A 68-year-old male presents with his wife stating he "lost 2 hours". His wife reports that he was suddenly confused and that he didn't know where he was or what he is was doing. He kept asking her the same questions especially where they were, even though they were at home. He knew his name and understood his wife but kept asking what he was doing there.

The episode lasted about 2.5 hours and has now completely resolved.

He has a history of mildly elevated cholesterol which you are managing with diet alone and is otherwise well. There is no family history of stroke.

He does not smoke and has no history of diabetes.

On examination he is oriented to time, place and person and has normal speech. He does not remember what happened but his recall now is normal. He scores 30/30 on the MMSE. His BP is 124/72 and his neurological examination is normal.

What is the most likely diagnosis?

A. Delirium
B. Transient ischaemic attack
C. Transient global amnesia
D. Stroke
E. Partial seizure

EM

Case 2

Theme- transient neurological symptom

A. Arrhythmia	K. Multiple sclerosis
B. Anxiety	L. Myasthenia gravis
C. Benign positional vertigo	M. Parkinson's disease
D. Dementia	N. Peripheral neuropathy
E. Hypoglycaemia	O. Postural hypotension
F. Seizure	P. Transient global amnesia
G. Stroke	Q. Transient ischaemic attack
H. Syncope	
I. Meniere's disease	R. Tumour
J. Migraine	S. Vestibular neuritis

What are the most likely diagnoses for the following presentations?

a) Ms LM is a 54-year-old lady who presents with an episode of tingling in her right arm and flashing lights. She denies any weakness and has no significant past medical history. She denies any headache but did feel nauseated. The symptoms came on gradually over a few minutes and lasted only 20 minutes.

b) Mr CW is a 68-year-old man who presents with "dizziness". He feels unsteady on his feet and has been generally feeling unwell for the last 4 days. He has a history of hypertension and hyperlipidaemia for which he is being treated. He is an anxious man and is particularly concerned his father had a stroke in his 70s. He has no weakness and no speech difficulty. On further questioning he has noticed recently that his hearing is worse but he thought that was part of aging. He has no numbness but he does feel his symptoms are worse with moving his head.

KFP

Case 3

A 78-year-old female presents with a 1.5hour history of speech disturbance. Her husband reports that she was talking "nonsense" this morning and that her right hand looked limp. They had been eating breakfast together and discussing their plans for the day when suddenly she dropped her cereal spoon. Her symptoms are now completely resolved.

She has a history of hypertension and hyperlipidaemia.

Her medications include atorvastatin 20mg daily, indapamide 2.5mg daily, caltrate/vitamin D and fish oil capsules.

On examination her blood pressure is 156/88 and her pulse rate was 72 and regular. She has no other significant findings on examination.

a) What is the most likely diagnosis and why?

b) What will be your next step of management?

Answers

Case 1

C. Transient global amnesia

Case 2

a) J. Migraine

b) S. Vestibular neuritis

Case 3

a) TIA

Sudden onset of focal neurological symptoms that have now completely resolved with a background history of cerebrovascular risk factors.

b) ABCD2 score is 6 placing her at high risk of a stroke.

She should be assessed and started on treatment immediately. Depending on the local facilities she should either be referred to the hospital ED or to be seen urgently in a TIA clinic.

She should have an urgent CT Brain, carotid duplex ultrasound and 12 lead ECG.

If her CT brain excludes a haemorrhage she should then be commenced on aspirin/dipyridamole. She is already on a statin and an antihypertensive agent and these should be continued or titrated if targets were not reached.

Appendix 2

Reproduced with permission from the Royal Australian College of General

Practitioners.

Malcolm had a 'funny turn'. check 2010 January/February;454–455:3–6.

The Royal Australian College of General Practitioners (2010). Case 1: Malcolm had a 'funny turn'.
Check (RACGP Independent Learning Program), Unit 454/455, pp. 3-6

Appendix 3

Conference Presentations

Stroke Society of Australasia Conference 2009, Cairns, Queensland. **Leung ES**,
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Stroke Society of Australasia Conference 2011, Adelaide, South Australia.

1. <u>**Leung ES**</u>, Hamilton-Bruce MA, Stocks N, Koblar SA. COMBAT stroke:
Community-based rapid access transient ischaemic attack. Oral platform.

2. Benedict A, <u>**Leung ES**</u>, Hamilton-Bruce MA, Khoo EW, Koblar SA. This study is
a subset of COMBAT stroke: community-based rapid access TIA. Oral platform.

Stroke Society of Australasia Conference 2014, Hamilton Island, Queensland. Djukic M, <u>Milton AG</u>, Hamilton-Bruce MA, Lewis MD, **Leung ES**, Jannes J, Chataway T, Koblar SA. Targeted peptide quantification of candidate plasma proteins to diagnose transient ischaemic attack (TIA).   Poster presentation.

Royal Australian College of General Practitioners Conference 2014, Adelaide, South Australia. **<u>Leung ES</u>**, Hamilton-Bruce MA, Price C, Stocks N, Koblar SA. A focussed neurological examination for stroke prevention. Poster presentation.

Awards

Australian Postgraduate Award

Royal Australian College of General Practitioners, Alan Chancellor Award 2011.

Best Poster Presentation (oral) Award, Stroke Society of Australasia Conference, Hamilton Island, Queensland, August 2014.

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