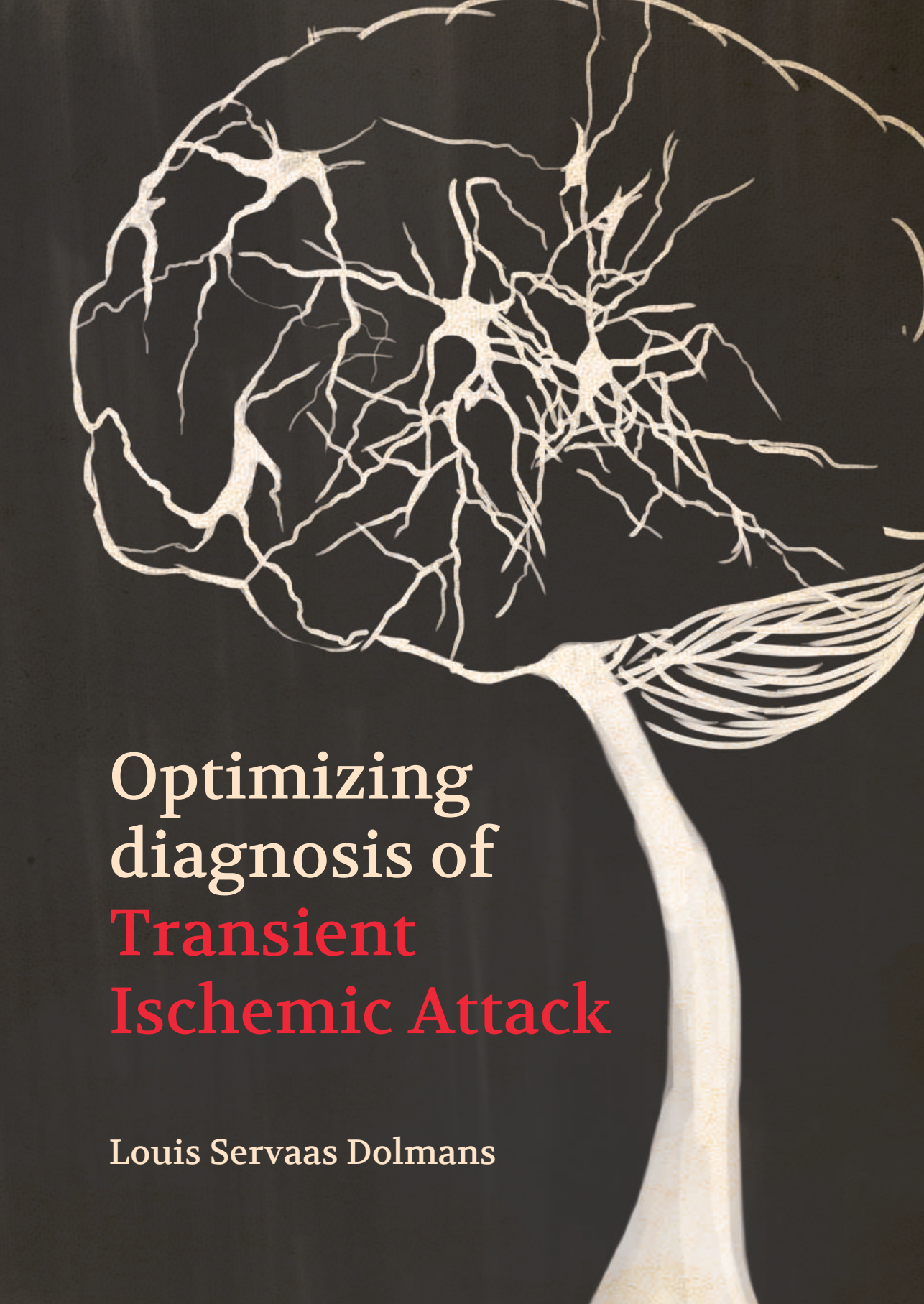

# Optimizing diagnosis of Transient Ischemic Attack

Louis Servaas Dolmans

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Louis Servaas Dolmans

**Optimizing diagnosis of TIA**

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, the Netherlands.
PhD thesis, with a summary in Dutch.

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|---|---|
| Author: | L.S. (Faas) Dolmans |
| ISBN: | 978-94-028-1651-8 |
| Lay-out and design: | Elisa Calamita, persoonlijkproefschrift.nl |
| Printed by: | Ipskamp Printing, proefschriften.net. |

# Optimizing diagnosis of Transient Ischemic Attack

**Het optimaliseren van de diagnostiek van Transient Ischemic Attack (met een samenvatting in het Nederlands)**

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 3 oktober 2019 des ochtends te 10.30 uur

door

Louis Servaas Dolmans

geboren op 21 september 1985
te Zoetermeer

## PROMOTOREN

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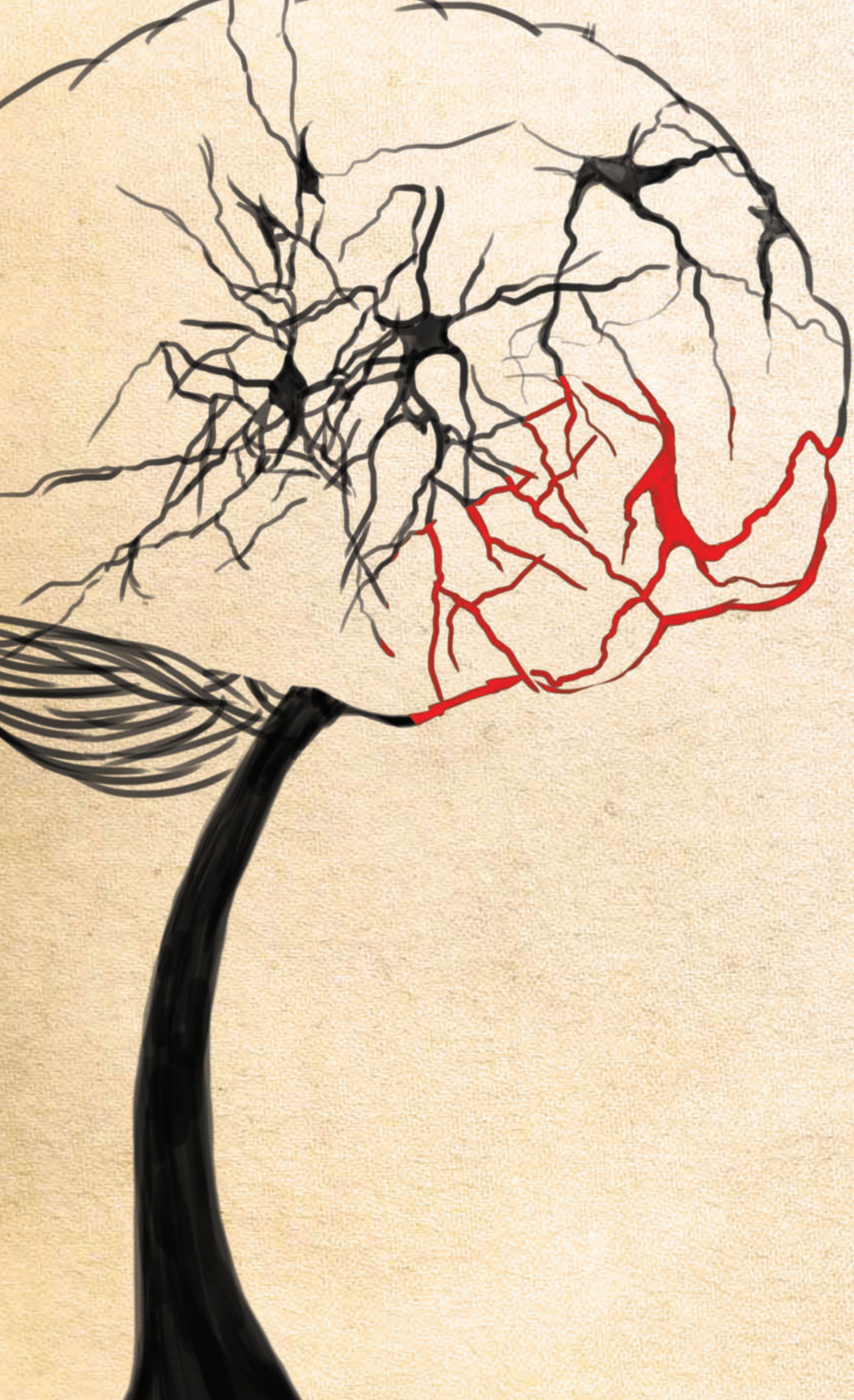
Dr. M.E.L. Bartelink

‘Stichting Beroepsopleiding Huisartsen (SBOH)’, employer of GP trainees in the Netherlands, financially supported the printing of this thesis.
Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

## CONTENTS



# Chapter 1

## General introduction

***Case***

*A 63-year-old woman consults her general practitioner (GP) because yesterday evening she suddenly experienced an unpleasant sensation of dizziness while sitting on her couch. She felt as if she was drunk. When she stood up and made her way to the kitchen she had the feeling to be pulled to the right. She did not experience other symptoms, e.g. headache, diplopia, or signs of limb weakness/impaired sensibility. She went to bed 1,5 hour later, and this morning all symptoms were gone, although her head was feeling a bit heavy.*

*She has a history of migraine, with attacks approximately once a month. Just a week ago, she had a branch retinal vein occlusion. She is a current smoker (30 pack years now), and her brother had his first myocardial infarction at age 59.*

*Neurological examination by the GP showed no abnormalities. Her pulse was 72 beats/minute and her office blood pressure 135/70 mmHg.*

*The GP thinks a peripheral vestibular syndrome is the most likely diagnosis, but he also considers a Transient Ischemic Attack (TIA) of the vertebrobasilar system. Finally, also a migraine attack is in his differential diagnosis. Based on potential medical consequences he decides to refer her to a TIA service for the next day, and prescribes aspirin 80 mg (two tablets today and one tomorrow morning).*

*The next morning, duplex ultrasonography of the carotid artery showed some plaque formation, but no relevant stenosis. MRI of the brain showed multiple periventricular white matter lesions, probably of vascular origin, but no signs of an ischemic event. The neurologist is not sure whether she experienced a TIA. What to decide? Should she receive life-long medication for stroke prevention?*

## TIA and minor stroke: the matter of terminology

A Transient Ischemic Attack (TIA) is a short episode of neurological deficits due to acute brain ischemia, that resolves without any remaining symptoms. Towards patients it is often referred to as a mini-stroke. TIA, minor and major ischemic stroke together form the spectrum of acute brain ischemia. A TIA was originally defined based on duration of symptoms less than 24 hours, now called the 'time-based' definition. Around 2009 a new definition was proposed, after high-resolution CT and especially diffusion-weighted MRI studies had demonstrated that in many patients with ischemic episodes with symptoms lasting less than 24 hours small areas of new brain infarction could be shown on imaging.[1] In addition, those patients with such ischemic lesions proved to have a much higher risk of a subsequent ischemic stroke than those without. The new 'tissue-based' definition classifies TIA as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction on brain imaging. However, to date both definitions are still used in everyday clinical practice, but also in research. In many occasions and settings neuroimaging, notably diffusion weighted MRI (DW-MRI), is not readily available. From a clinical point of view, the key characteristic of a TIA remains that symptoms occur at once and quickly resolve without any remaining symptoms.

The term minor stoke fills up the grey area between TIA and major ischemic stroke. For the differentiation between minor and major stroke at least six different classifications exist, based on the degree of remaining symptoms after 24 hours.[2] The common factor of these classifications is that the remaining symptoms in case of minor stroke should be mild and non-disabling.

## Incidence and prevalence of TIA and stroke

Despite improvements in primary prevention and acute treatment over the last decades, stroke is still a devastating disease. In 2013, stroke was the second most common cause of deaths worldwide after ischemic heart disease (11.8% and 14.8% of all deaths, respectively), and the third most common cause of disability.[3] In Europe, the age-standardized incidence of stroke is estimated to range from 9.5 to 29/10,000 per year, meaning that around 1.1 million people suffer a stroke each year, with ischemic stroke accounting for approximately 80% of these cases.[4] There are large inequalities in the rate of strokes and mortality due to stroke across Europe, with higher rates and poorer outcomes being consistently found in Eastern European compared to Western European countries.[3]

Prevalence studies are relatively rare compared to incidence studies. In the Netherlands, based on GP registries, the one-year prevalence of stroke (a

combination of known cases and incident cases during that year) was estimated to be 20.9 per 1000 men and 18.7 per 1000 women in 2016.[5]

Overall, the incidence rates of stroke in Western societies are declining. However, studies from France and Sweden have demonstrated a rising trend of (absolute) stroke rates in young adults (age < 65 years). Moreover, because of the growing and ageing population, the total number of strokes is thought to dramatically increase in the coming years. It is expected that by 2025, 1.5 million European people will suffer a stroke each year.[4]

Data on the incidence and prevalence of TIA are limited, due to methodological difficulties. Probably, incidence rates are underestimated because signs and symptoms of a TIA may not be recognized by physicians, or even not reported by patients.[3]

In the Netherlands, based on GP registries, in 2016 the overall incidence of TIA was estimated to be 3.2 per 1000 per year in men and 3.5 per 1000 per year in women. For the age group 65-74 years, the incidence was 8.7 per 1000 men and 8.5 per 1000 women. Among people aged 85 years and over, the incidence is around 24.8 per 1000 men and 28.0 per 1000 women. Although the age-specific incidence is higher in men than women for all age categories except 85 years and over, the overall incidence is higher in women, due to the higher life expectancy of women.[5,6]

## Importance and barriers of a timely diagnosis

A TIA is a warning signal that a patient is at risk of a full stroke in the near future. Importantly, this risk of a subsequent ischemic stroke is highest in the first days after a TIA, and gradually declining in the following weeks. In a meta-analysis published in 2007 it was estimated that 10% of TIA patients will have a stroke within three months, with almost half of these strokes occurring within the first 48 hours.[7]

Both the EXPRESS study (2007) and SOS-TIA study (2007) showed, in an observational design comparing two time periods, that a strategy of urgent diagnostic assessment at a TIA service followed by a timely start of stroke preventive treatment in TIA/minor stroke patients drastically reduced the risk of an early stroke.[8,9] In the EXPRESS study median delay to first prescription of treatment was shortened from 20 (IQR 8–53) days in the period 2002-2004 to 1 (IQR 0-3) day in 2004-2007, resulting in an 80% reduction of recurrent stroke within three months.[8] A recent study by Rothwell et al. (2016), by pooling the individual patient data from randomized trials of aspirin versus control after a TIA or stroke, confirmed that the early start of antiplatelet therapy is the key intervention; aspirin

reduced the six-week risk of recurrent ischemic stroke by about 60%.[10] Hence, timely diagnosis of a TIA is crucial.

The diagnosis of TIA can be difficult for both non-specialists and neurologists because it can only be based on history taking. About one third of patients referred to a TIA clinic ultimately receives an alternative diagnosis. Symptoms of a TIA are typically short-lasting, can be mild or vague, and hard to reproduce for patients and bystanders. Moreover, the differential diagnosis is broad, with notorious TIA mimicking diseases like migraine with aura or seizures. In the majority of patients suspected of TIA, brain imaging will show no ischemic lesions, and availability of the most sensitive modality, DW-MRI, is limited. As a consequence both establishing and excluding the diagnosis can be troublesome. Also a definite diagnosis by the neurologist after additional investigations holds a degree of uncertainty.



An additional issue hampering a timely diagnosis is patients' delay in reporting their symptoms to a medical service. Symptoms of a TIA can be easily misinterpreted or trivialized by patients and bystanders. Studies from the UK indicated that in the period 2002 till 2007 around 30-40% of TIA or minor stroke patients delay their first contact with a medical service for more than 24 hours.[8,11,12] Data from countries other than the UK are limited, and little is known about the determinants of patient delay.

### Are blood biomarkers the key?

A possible solution for the diagnostic difficulties of TIA might be a blood biomarker. The past two decades a growing range of potential blood biomarkers of brain ischemia has been evaluated, mainly in the domain of (suspected) stroke. Not only the diagnostic value of such markers were evaluated, but also their etiological and prognostic value. Previous studies showed that some markers have potential for evaluation in the domain of suspected TIA because biomarker levels were increased from the first hour after an ischemic event until days or even a week thereafter. However, most often these studies compared biomarker levels of patients with an established TIA or stroke with 'healthy' persons, instead of an evaluation in a the clinically relevant population of suspected TIA or stroke patients. Moreover, most studies applied test research without considering clinical parameters and the added value of biomarkers beyond clinical items, including symptoms and patient characteristics.[13]

A biomarker that can rapidly and reliably detect brain ischemia in the clinical domain of suspected TIA would be extremely valuable, notably for general practitioners who can only rely on the clinical evaluation, and especially if point-

of-care options would become available. It would help improve early diagnosis and subsequent targeted treatment as well as safe exclusion of TIA.

## Objectives and outline of this thesis

This thesis focuses on (i) the value of tests or tools to support the clinical diagnosis of TIA, in particular blood biomarkers and clinical prediction models, and on (ii) time delay to diagnosis and treatment of TIA, notably patient delay and its determinants.

**Chapter 2** is a systematic literature review on patient delay in patients suspected of a TIA. In **chapter 3** we describe the results of our survey on time delay among 93 patients suspected of a TIA recruited from two TIA services in Utrecht. With standardized interviews before the diagnosis was established, we determined different components of delay (including both patient and physician delay) until the assessment at a TIA service and the start of antithrombotic treatment. In **chapter 4** we assessed among participants of the 'Markers in the Diagnosis of TIA (MIND-TIA) study' which clinical determinants had an independent relation with patient delay.

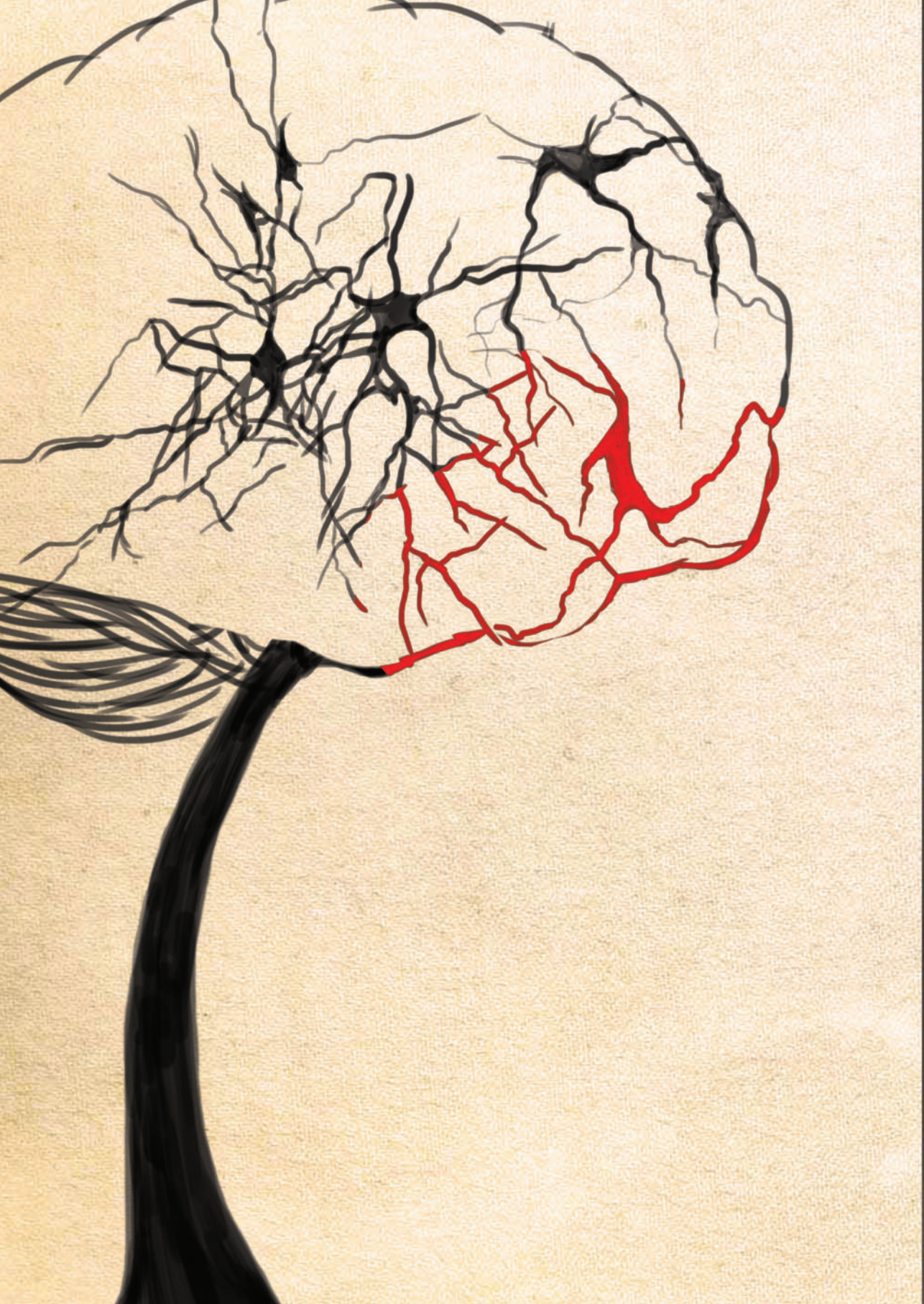
**Chapter 5** describes the protocol of our cross-sectional diagnostic study MIND-TIA, aimed at determining the (added) diagnostic value of serum biomarkers in patients suspected of a TIA. The rationale, design and methods are outlined. **Chapter 6** presents a systematic review on the value of available biomarkers for diagnosing TIA. In **chapter 7** we present the main findings of the MIND-TIA study. In total seven biomarkers were evaluated among 206 participants suspected of a TIA by their GP. We determined the (added) value of these markers beyond signs and symptoms using logistic regression analyses resulting in a final concise multivariable diagnostic model.

In **chapter 8** a recently proposed set of criteria for the diagnosis of TIA, the so-called 'explicit diagnostic criteria for TIA (EDCT)', is validated in our MIND-TIA cohort.

Finally, in **chapter 9** the main findings and conclusions of this thesis are discussed. In addition, translational aspects are discussed and recommendations likely to facilitate a more timely and accurate diagnosis of TIA are provided.

## REFERENCES


1. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-93.
2. Fischer U, Baumgartner A, Arnold M, Nedeltchev K, Gralla J, De Marchis GM, et al. What is a minor stroke? Stroke. 2010;41(4):661-6.
3. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. Circ Res. 2017;120(3):439-48.
4. Bejot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Med. 2016;45(12 Pt 2):e391-e8.
5. Buddeke J VDI, Visseren FLJ, Vaartjes I, Bots ML. Hart- en vaatziekten in Nederland 2017, cijfers over leefstijl, risicofactoren, ziekte en sterfte. Den Haag: Hartstichting, 2017.
6. Verburg AF, Tjon ATMR, Verstappen WH, Beusmans GH, Wiersma T, Burgers JS. [Summary of the 'Stroke' guideline of the Dutch College of General Practitioners' (NHG)]. Ned Tijdschr Geneeskd. 2014;158(1):A7022.
7. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med. 2007;167(22):2417-22.
8. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-42.
9. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6(11):953-60.
10. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016;388(10042):365-75.
11. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behavior immediately after transient ischemic attack and minor stroke in 1000 consecutive patients: lessons for public education. Stroke. 2010;41(6):1108-14.
12. Wilson AD, Coleby D, Taub NA, Weston C, Robinson TG. Delay between symptom onset and clinic attendance following TIA and minor stroke: the BEATS study. Age Ageing. 2014;43(2):253-6.
13. Moons KG, de Groot JA, Linnet K, Reitsma JB, Bossuyt PM. Quantifying the added value of a diagnostic test or marker. Clin Chem. 2012;58(10):1408-17.



# Chapter 2

# Patient delay in TIA: a systematic review

L Servaas Dolmans, Arno W Hoes, Marie-Louise EL Bartelink,
Niels CT Koenen, L Jaap Kappelle, Frans H Rutten

*Journal of Neurology 2018; 266 (5): 1051-1058.*

## ABSTRACT

### Background

Patients who suffer a transient ischemic attack (TIA) have a high short-term risk of developing ischemic stroke, notably within the first 48 h. Timely diagnosis and urgent preventive treatment substantially reduce this risk. We conducted a systemic review to quantify patient delay in patients with (suspected) TIA, and assess determinants related to such delay.

### Methods

A systematic review using MEDLINE and EMBASE databases up to March 2017 to identify studies reporting the time from onset of TIA symptoms to seeking medical help.

### Results

We identified nine studies providing data on patient delay, published between 2006 and 2016, with 7/9 studies originating from the United Kingdom (UK). In total 1103 time-defined TIA patients (no remaining symptoms > 24 h), and 896 patients with a minor stroke (i.e., mild remaining symptoms > 24 h) were included (49.1% men, mean age 72.2 years). Patient's delay of more than 24 h was reported in 33.1–44.4% of TIA patients, with comparable proportions for minor stroke patients. Delays were on average shorter in patients interviewed at the emergency department than among patients seen at TIA outpatient clinics. Univariably associated with a shorter delay were (1) a longer duration of symptoms, (2) motor symptoms, (3) a higher ABCD2 score, and (4) correct patient's recognition as possible ischemic cerebrovascular event.

### Conclusions

More than a third of patients experiencing a TIA delays medical attention for more than a day, thus critically extending the initiation of stroke preventive treatment. There still seems to be insufficient awareness among lay people that symptoms suggestive of TIA should be considered as an emergency. Additional data and multivariable analyses are needed to define main determinants of patient delay.

## INTRODUCTION

Symptoms of a transient ischemic attack (TIA) are typically short-lasting, often not very specific and can easily be misinterpreted or trivialized by both patients and physicians. Early recognition of TIA, however, is essential to enable a rapid start of stroke prevention, as the risk of a subsequent ischemic stroke is highest in the first days after the TIA.[1,2]

The EXPRESS study evaluated the effect of introducing a rapid access assessment by physicians of suspected TIA, and showed a reduction of median delay to first prescription of treatment from 20 days to 1 day, which led to an impressive decrease of 90-day recurrent stroke rate from 10.3 to 2.1%.[3] Similar low recurrence risks were reported in the SOS-TIA study evaluating the impact of a round-the-clock access clinic.[4] The introduction of rapid access TIA outpatient clinics since the beginning of this century has improved timely diagnostic assessment by neurologists, but also created a more common awareness among general practitioners that patients with symptoms suspected of TIA should be assessed and when diagnosed be treated immediately. Thus, the physician's delay was reduced dramatically in the last decade. An important remaining challenge is the reduction of the patient's delay.

In 2008, a systematic review was published on determinants of patient delay in seeking medical attention after TIA. However, just one study included only patients with TIA; the other eight studies included both patients with stroke and (a minority of) TIA patients.[5] Most (7/9) studies were performed in the emergency department (ED) among patients suspected of stroke (still symptomatic) within the scope of thrombolysis, and provided 'prehospital delay' without subdivision in patient's delay, general practitioner's delay, and transportation time. Thus, conclusions on patient delay in (suspected cases of) TIA could not be drawn from this review.

Patients suspected of TIA are distinct from patients suspected of stroke in that the duration of symptoms is shorter, symptoms are often milder, and by definition transient. This has a large impact on the interpretation of symptoms by patients, possible bystanders, but also physicians. Better knowledge of patient delay and its determinants within the specific domain of TIA could help improving public education to increase lay awareness.

We aimed to quantify patient delay and assess its determinants in patients (suspected of) TIA and performed a systematic review.

## METHODS

We conducted a literature search following PRISMA guidelines, and using MEDLINE and EMBASE databases from 1966 to March 1, 2017.[6] The key terms presented in Box 1 were used to identify papers evaluating patient delay in TIA patients. Alternative terms for 'delay' had no added value in the search strategy.

**Box 1. Search terms used**
**PubMed search terms**
(TIA [tiab] OR transient isch* [tiab]) AND (delay* [tiab])
**Embase search terms**
tia:ab,ti OR (transient NEXT/1 isch*):ab,ti AND delay*:ab,ti

All abstracts were screened for relevance. We included primary studies assessing the time from onset of TIA symptoms to medical help-seeking. Since the domain of suspected TIA in daily practice also includes patients that are subsequently labeled with a diagnosis of minor stroke (i.e., mild remaining symptoms lasting longer than 24 h), studies reporting on both TIA and minor stroke were included in the review. If populations consisted of both major ischemic stroke and TIA patients, we only considered studies that provided separate data for TIA patients. We excluded articles in other languages than English or Dutch and conference abstracts. Full text versions of the potentially eligible studies were reviewed by two reviewers, and reference lists of all relevant articles were cross-checked for other relevant papers. Any disagreement was resolved by discussion.

Data were extracted using a standardized data extraction form, including an assessment of risk of bias (related to patient selection and the assessment of time delay and other variables) and applicability to our research objective. Next to data on delay to the first medical contact, we collected the results from analyses of possible determinants of such delay.

We considered studies that either used the 'time-based' or the 'tissue-based' definition of TIA. In both definitions the transiency of symptoms is the key characteristic distinguishing TIA from (minor) stroke. The time-based definition is based on a maximum duration of symptoms of 24 h, and the tissue-based definition on the absence of acute infarction with brain imaging.[7] We assessed the definitions distinguishing minor from major stroke handled in the original studies, since a uniform definition is lacking. Main differences concern the chosen value of the National Institutes of Health Stroke Score

(NIHSS, a score ranging from 0 to 42 points that quantifies the severity of a stroke on different domains) to define minor stroke, usually ranging from ≤3 to ≤9.

Because of the heterogeneity of the data we did not aim to pool the data.

## RESULTS

Our search yielded a total of 1284 studies. Figure 1 shows the flowchart of the review process. Eighteen studies could be selected for full text screening, and nine studies met our eligibility criteria. Table 1 gives an overview of the included studies, originating from the UK (n=7), Spain (n=1) and Norway (n=1), and published between 2006 and 2016. Overall, taking into account overlap in study populations, these studies included 2657 participants with a cerebrovascular event. Delay data of 1103 (41.5%) TIA patients and 896 (33.7%) minor stroke patients were included in the analysis (49.1% men, mean age 72.2 years).



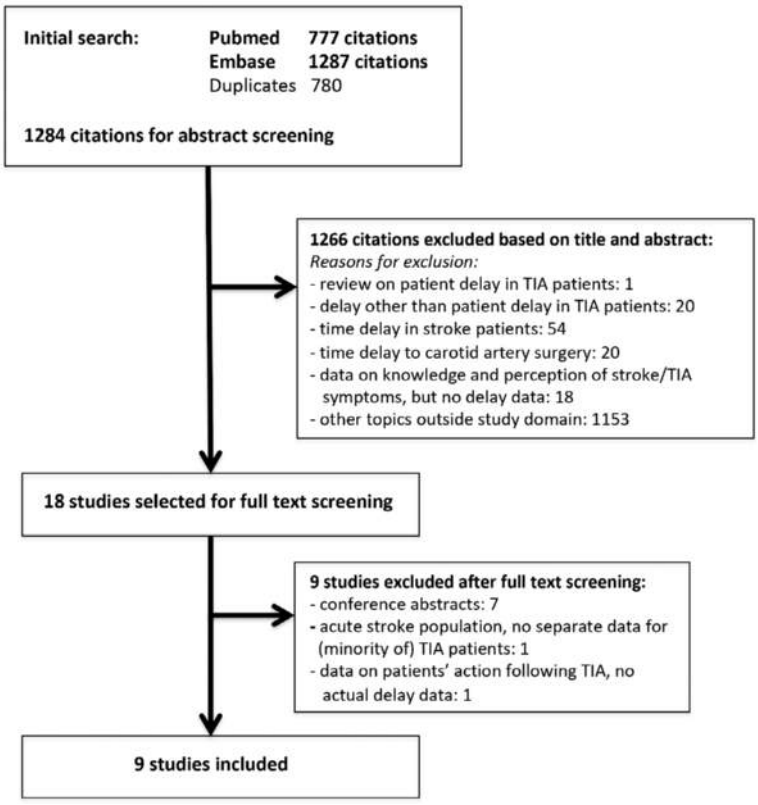



**Figure 1.** Flowchart of the literature review process

**Table 1.** Studies that assessed TIA patient's delay.

| First author, Year of publication | N (TIA/total) | Type of patients* | Setting | Delay TIA patients | Factors assessed |
|---|---|---|---|---|---|
| **Studies using a quantitative approach for analysis of patient interviews** | | | | | |
| Giles, 2006 | 241/241 | TIA | Population-wide (OXVASC) and TIA clinics, UK | 44.4% > 24h | Clinical characteristics, patient's perception, stroke risk |
| Rothwell, 2007 | 485/1278 | TIA, MS | Population-wide (OXVASC), UK | 41.8% > 24h (TIA/MS) | - |
| Lasserson, 2008 | 359/793 | TIA, MS | Population-wide (OXVASC), UK | Median time to contact GP: surgery hours 4.0 h, out of office hours 24.8 h (TIA/MS) | Time of onset of symptoms |
| Chandratheva, 2010 | 459/1000 | TIA, MS | Population-wide (OXVASC), UK | TIA: 47.2% < 3h, 33.1% > 24h; MS: 46.4% < 3h, 26.1% > 24h. | Clinical characteristics, patient's perception, stroke risk |
| Geffner, 2012 | 70/388 | TIA, MS, IS, ICH | Single ED, Spain | Median 0.5 h (IQR 0.25–1.50) (TIA only) | - |
| Faiz, 2013 | 100/440 | TIA, MS, IS, ICH | Single ED/stroke unit, Norway | Median 2.0 h (IQR 0.5-12.8) (TIA only) | - |
| Wilson, 2014 | 222/278 | TIA, MS | Single TIA clinic, UK | TIA: Median 3.5 h (IQR 0.5-41.5); MS: Median 6.0 h (IQR 0.5-25.8). | Clinical characteristics, patient's perception, time of onset of symptoms |
| Hurst, 2016 | 103/150 | TIA, MS | Single TIA clinic, UK | 38.7% > 1h 27.3% > 24h (TIA/MS) | - |
| **Study using a qualitative approach for analysis of patient interviews** | | | | | |
| McSharry, 2014 | 20/20 | TIA | 3 TIA clinics, UK | 60% <1h 20% >24h | Patient's perception, Role family/friends |

TIA, Transient Ischemic Attack; OXVASC, the Oxford Vascular Study; UK, United Kingdom; ED, emergency department; MS, minor stroke; IS, (major) ischemic stroke; ICH, intracerebral hemorrhage; IQR, interquartile range.

*TIA was defined by the time-based definition in all studies.

All included studies applied the time-based definition of TIA. Two studies restricted their study population to TIA patients only.[8,9] Five studies also included minor stroke patients with an NIHSS ranging from less than 6 to less than 8.[3,10-13] Two studies included patients with (major) stroke, and only a small number of TIA patients. Both studies were executed in the ED setting.[14,15] The other seven studies recruited patients from TIA outpatient clinics (n = 551) or were population-based (n = 1278). All studies included only cases that were confirmed to have TIA or minor stroke instead of suspected cases, and assessed the delay time after the diagnostic confirmation.

Four publications were generated by one single research group, including different (and overlapping) numbers of patients recruited over consecutive time periods and together constituting a cohort named the 'Oxford Vascular study (OXVASC)'. This is a population-based collection of data of prospectively occurring acute vascular events in 91,000 adults registered at nine large group practices of general practitioners in Oxfordshire, UK.

The timing of the interview to assess patient's delay was reported in four studies,[8,10,13,14] and ranged from up to 72 h after the onset of symptoms in the ED studies to a median of 22 days in the primary care OXVASC population.

## Delay

A summary of included studies with the data provided on delay is presented in Table 1. There is a large heterogeneity in the reporting of delays. Three studies provided data on TIA patients only, and recruited from TIA outpatient clinics or the population at large. Giles et al. (2006) and Chandratheva et al. (2010), both studies from the OXVASC group, showed that of the TIA patients (n = 241 and n = 459, respectively, with an overlap of 138 patients), 44.4 and 33.1% had a delay of more than 24 h.[8,10] Wilson et al. (2014) reported a median delay of 3.5 (IQR 0.5–41.5) h in 222 TIA patients from a single British TIA outpatient clinic.[11] Chandratheva et al. only presented median delays for males and females separately: 4.0 (IQR 0.5–45.5) for men and 4.9 (IQR 0.8–48.9) h for women.

Three studies presented delays for TIA and minor stroke patients combined. Rothwell et al. (2007) provided delay data of all OXVASC patients referred to the EXPRESS clinic; 41.8% (247/591) had a delay of more than 24 h.[3] Lasserson et al. (2008) performed a subgroup analysis within largely the same (OXVASC) study population showing that the median time to calling a general practitioner (GP) during out of office hours is much longer than during working hours [24.8 (IQR 9.0–54.5) versus 4.0 (IQR 1.0–45.5) h].[12] Hurst et al. (2016) evaluated delays of TIA and minor stroke patients (n = 150) in a single TIA outpatient clinic in Oxford (UK), and found that 38.7% (58/150) reacted by immediately seeking medical attention, while 27.3% (41/150) had a delay of more than 24 h.[13]

The delays of TIA patients reported by Geffner et al. (2012) and Faiz et al. (2013) originate from a Spanish and Norwegian ED population, respectively. In the Spanish cohort, 70 TIA patients had a median delay of 0.5 (IQR 0.3–1.5) h, versus 1.0 (IQR 0.3–7.0) h in 318 stroke patients (of which 281 minor and major ischemic stroke and 37 intracerebral hemorrhage). The 100 TIA patients in the Norwegian cohort had a median delay of 2.0 (IQR 0.5–12.8) h, versus 1.9 (0.5–5.9) h in 290 minor and major ischemic stroke patients, and 0.5 (0.2–2.0) h in 50 intracerebral hemorrhage patients.[14,15]

### Determinants of patient delay

Three studies assessed potential determinants of delay using a quantitative approach (Table 2). Three different statistical methods were used, namely Chi square for comparing proportions, (presumably) Wilcoxon–Mann–Whitney for comparing delay times, and univariate Cox proportional hazards analysis. The largest study by Chandratheva et al. identified seven variables that were univariably associated with shorter delay: (1) the patient realizes the symptoms could be caused by a TIA, (2) presence of motor symptoms, (3) long persistence of symptoms, (4) a high ABCD2 score (a score for stroke risk prediction, including age, blood pressure, clinical features, duration and diabetes), (5) presence of speech symptoms, (6) a history of previous stroke and (7) a lower Mini Mental State Examination (MMSE) score.[10] The first four of these variables were also found to be associated with shorter delay in one of the other two studies.[8,11] None of the studies performed multivariable analyses.

McSharry et al. (2014) explored possible determinants of patient delay in a qualitative manner using a semi-structured interview in 20 TIA patients from three British TIA clinics.[9] Concerning recognition of symptoms they concluded that awareness of typical stroke symptoms could lead to urgent action when symptoms were more severe. On the other hand, if symptoms were not severe or vague, delay was longer. Seven of the 20 patients realized that a TIA could be the cause of their symptoms. Nevertheless, four of them decided to wait and see, because they considered the symptoms as not being serious or requiring immediate action. Importantly, often friends and family were involved in the decision making, and if this was the case, delays were often shorter. In 5/20 cases the decision to seek medical help was fully taken by a witness of the symptoms of the patient (four times family/friends, once a nurse), and medical services were contacted by them within 1 h. In 8/20 cases the decision to seek health care advice was made by the patient and their relatives together. In the remaining 7/20 cases the patient sought medical care on his own, and in these cases the longest delays were seen.[9]

**Table 2.** Overview of determinants of patient's delay in three studies that performed univariable analysis.

| Study | N | Statistical method | Variables that were evaluated |
|---|---|---|---|
| Giles et al, 2006 | 241 (TIA) | *Not reported in Methods* Chi² for trend in proportions (for immediate, same day, next day and ≥2 days action) | Positive association<br>With shorter delay:<br>**Motor symptoms** p trend 0.011<br>**Duration of symptoms ≥ 60 min** p trend 0.004<br>**Higher ABCD2 score** p trend 0.001<br>No association with<br>Age, sex, correct recognition as TIA, (brain) territory, blood pressure at clinic, a history of hypertension/ diabetes/TIA/stroke/acute coronary syndrome/atrial fibrillation, smoking |
| Chandratheva et al, 2010 | 459 (TIA) | *Not reported in Methods* Compared stratified medians, presumably using Wilcoxon-Mann-Whitney | Positive association with<br>**Correct recognition as TIA**<br>- Yes: median 2.3 h (IQR 0.5 – 24.3)<br>- No: median 7.3 h (IQR 1.0 – 50.2) p 0.005<br>**Motor symptoms**<br>- Yes: median 1.6 h (IQR 0.3 – 20.1)<br>- No: median 16.0 h (IQR 1.4 – 66.5) p <0.001<br>**Speech symptoms**<br>- Yes: median 2.2 h (IQR 0.5 – 22.5)<br>- No: median 11.5 h (IQR 1.0 – 59.5) p <0.001<br>**Duration of symptoms**<br>- <10 min: median 25.0 h (IQR 5.1 – 111.9)<br>- 10-59 min: median 4.1 h (IQR 0.7 – 48.0)<br>- ≥60 min: median 2.0 h (IQR 0.5 – 24.8) p <0.001<br>**ABCD2 ≥ 5**<br>- Yes: median 1.8 h (IQR 0.5 – 18.0)<br>- No: median 15.3 h (IQR 1.0 – 63.1) p <0.001<br>**Previous stroke**<br>- Yes: median 1.0 h (IQR 0.5 – 13.7)<br>- No: median 5.2 h (IQR 0.8 – 48.5) p 0.006<br>**Mini Mental State Examination**<br>- ≤24: median 2.0 h (IQR 0.3 – 25.1)<br>- >24: median 4.4 h (IQR 0.8 – 48.7) p 0.006<br>No association with<br>Age, sex, blood pressure at clinic, a history of hypertension/ diabetes/TIA/myocardial infarction/ atrial fibrillation, educational level, social class |
| Wilson et al, 2014 | 278 (TIA/ MS) | Univariate Cox proportional hazards analysis | Positive association with<br>**Correct recognition as possible TIA/stroke**<br>- Yes: median 2.0 h (IQR 0.5 – 48.0)<br>- No: median 6.5 h (IQR 0.3 – 22.2) p 0.009<br>No association with<br>Age, sex, FAST, type of symptoms, duration, previous TIA/stroke, weekend presentation, before/during/after FAST campaign, lay input |

TIA, Transient Ischemic Attack; ABCD2, prognostic score for early stroke risk prediction, including the items Age, Blood pressure, Clinical symptoms, Duration and Diabetes; FAST, Face Arm Speech Time, tool for the early recognition of stroke symptoms; IQR, interquartile range; MS, minor stroke.

## DISCUSSION

Our systematic review of nine studies shows that around 40% of TIA patients delays seeking medical attention for more than 24 h, and this was similar for patients that eventually showed to have a minor stroke. Three studies provided data on determinants of patient's delay, and fast disappearance of symptoms, symptoms not being recognized as possible TIA, absence of motor symptoms and a lower ABCD2 score were associated with a longer delay.

We could only identify studies among patients with established TIA (or minor stroke). To the best of our knowledge, there are no studies that evaluated patients *suspected* of TIA, that is, the domain of the actual diagnostic dilemma. In view of the uncertainty around the diagnosis of TIA for both patient and clinician, also evidence on the delay of all suspected cases is important. In a substantial portion of patients with suspected symptoms, a clear and definite diagnosis can not be made by the neurologist even after multiple additional investigations. Including only those with established TIA may create a selection of the more typical cases, which is likely to bias (and most probably will underestimate) delay times and the determinants related to delay. Moreover, interviewing patients *after* they underwent additional investigations and were informed about their final diagnosis induces the risk of 'recall bias' and is likely to identify those symptoms typically known to be associated with established TIA.

Another important concern about the included studies is that those from the UK (notably Oxfordshire) were over-represented with also some patients reported in more than one manuscript. Therefore, some caution is warranted generalizing the results of this review, more because the organization and accessibility of care that can differ per region and country has an impact on patient delay.

Delays were on average much shorter in patients interviewed at the ED than those seen at TIA outpatient clinics, underlining the impact of the study setting on delay. The ED population must be regarded as a selection of patients that act rapidly to receive medical help, and very likely experience more 'severe' or typical symptoms. Surveys at TIA outpatient clinics provide a better reflection of patient delay in the complete spectrum of TIA patients presenting via different health care routes.

Bruins Slot et al. investigated the prehospital delay of patients with symptoms suspected of acute coronary syndrome (ACS) in the Dutch primary care setting, excluding patients who required instant hospital referral. The median patient delay was just 2.2 h, much shorter than the delays of the TIA patients in our review.[16] This is in line with the general opinion that symptoms such as chest pain and acute

dyspnoea create much more sense of urgency in patients (but also in bystanders and relatives) than symptoms suggestive of neurological dysfunction. A general lack of knowledge about the need for urgency in the case of a TIA may account at least partly for this immense difference in delay between patients with suspected ACS symptoms and TIA symptoms.

The three studies that aimed to find determinants of patient delay quantitatively showed some similar results but also reported discrepancies. These studies used different questionnaires and applied different statistical methods, and per study relatively small numbers of participants (ranging from 241 to 459) were evaluated. None of the studies applied multivariable analyses, and it is therefore impossible to draw conclusions about which variables independently predict delay. Most likely, event characteristics like the type of symptoms do influence delay, but relations are more complex and interactions exist with other factors such as severity of symptoms. This may partly explain why some items are not identified in all studies.



The importance of recognition of symptoms remains heavily debated. The qualitative study by McSharry et al. may provide an explanation for the conflicting data on the role of recognition, stating that awareness of typical stroke symptoms may lead to action in case of more severe symptoms but may cause delay when symptoms are mild or vague.[9] Furthermore, recognizing TIA symptoms is one thing, but many lay people are still unaware of the need for urgency, and, importantly, the fact that urgency remains even if symptoms disappear rapidly.

The most important limitation of this review is the heterogeneity between studies. The differences in study population and setting complicate the interpretation of the data. In addition, selective reporting in the original papers made it impossible to present delay times in a uniform way. Therefore, we reported what was available, e.g., either a median delay or delays categorized by a cut-off point, and we were not able to pool the findings.

Our review demonstrates that delay by patients frequently hampers a rapid start of treatment to prevent a subsequent stroke. As much as this poses a clinical problem, this also offers ample opportunity to implement measures to reduce delay time. Campaigns like Face Arm Speech Time (FAST) that educate on recognizing stroke symptoms are important examples of initiatives to gain time. The few data on the impact of the FAST campaign suggest a positive effect on awareness of stroke symptoms. However, the effect on patient's response is limited, and thus it is emphasized that future campaigns should strengthen the response to stroke symptoms; the need to immediately respond and contact a health care professional.[17,18] Lay people need to be better informed about the early risk of stroke and the need for an urgent call after a TIA, also when symptoms are short-lasting.

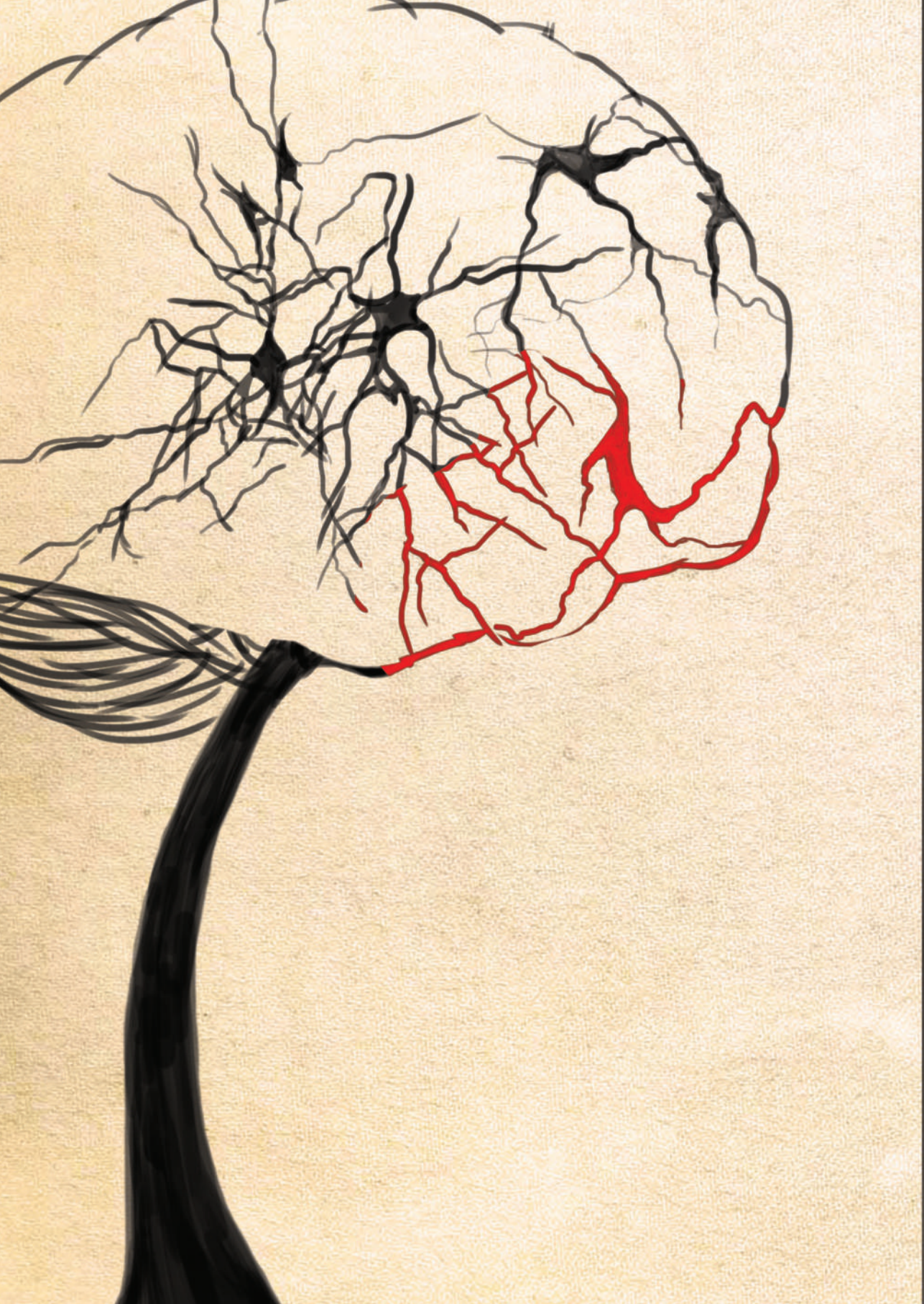
Additional data on patient's perception and determinants of delay are needed. Given aforementioned considerations, we would like to recommend that future studies consider (1) including patients suspected of TIA, (2) conducting interviews before the eventual diagnosis is set by a neurologist, and (3) performing multivariable analyses to adequately weigh determinants of delay.

We conclude that too many patients with TIA delay seeking medical attention for a substantial time period, and thus risk a delay in receiving treatment to prevent subsequent stroke. More public education and attention for the symptoms of TIA are needed, stressing the importance of immediate action to prevent the occurrence of a stroke.

## REFERENCES


1. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007;6(12):1063-72.
2. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med. 2007;167(22):2417-22.
3. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-42.
4. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6(11):953-60.
5. Sprigg N, Machili C, Otter ME, Wilson A, Robinson TG. A systematic review of delays in seeking medical attention after transient ischaemic attack. J Neurol Neurosurg Psychiatry. 2009;80(8):871-5.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med. 2009;6(7):e1000100.
7. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-93.
8. Giles MF, Flossman E, Rothwell PM. Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. Stroke. 2006;37(5):1254-60.
9 Mc Sharry J, Baxter A, Wallace LM, Kenton A, Turner A, French DP. Delay in seeking medical help following Transient Ischemic Attack (TIA) or “mini-stroke”: a qualitative study. PLoS One. 2014;9(8):e104434.
10. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behavior immediately after transient ischemic attack and minor stroke in 1000 consecutive patients: lessons for public education. Stroke. 2010;41(6):1108-14.
11. Wilson AD, Coleby D, Taub NA, Weston C, Robinson TG. Delay between symptom onset and clinic attendance following TIA and minor stroke: the BEATS study. Age Ageing. 2014;43(2):253-6.
12. Lasserson DS, Chandratheva A, Giles MF, Mant D, Rothwell PM. Influence of general practice opening hours on delay in seeking medical attention after transient ischaemic attack (TIA) and minor stroke: prospective population based study. BMJ. 2008;337:a1569.
13. Hurst K, Lee R, Sideso E, Giles M, Handa A. Delays in the presentation to stroke services of patients with transient ischaemic attack and minor stroke. Br J Surg . 2016;103(11):1462-614.

14. Geffner D, Soriano C, Perez T, Vilar C, Rodriguez D. Delay in seeking treatment by patients with stroke: who decides, where they go, and how long it takes. Clin Neurol Neurosurg. 2012;114(1):21-5.
15. Faiz KW, Sundseth A, Thommessen B, Ronning OM. Prehospital delay in acute stroke and TIA. Emerg Med J. 2013;30(8):669-74.
16. Bruins Slot MH, Rutten FH, van der Heijden GJ, Doevendans PA, Mast EG, Bredero AC, et al. Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care. Fam Pract. 2012;29(3):332-7.
17. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PLoS One. 2014;9(8):e104289.
18. Dombrowski SU, Mackintosh JE, Sniehotta FF, Araujo-Soares V, Rodgers H, Thomson RG, et al. The impact of the UK 'Act FAST' stroke awareness campaign: content analysis of patients, witness and primary care clinicians' perceptions. BMC Public Health. 2013;13:915.



# Chapter 3

# Delay in patients suspected of transient ischaemic attack: a cross-sectional study

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*BMJ Open 2019; 9 (2): e027161.*

## ABSTRACT

**Objectives**

Suspected transient ischaemic attack (TIA) necessitates an urgent neurological consultation and a rapid start of antiplatelet therapy to reduce the risk of early ischaemic stroke following a TIA. Guidelines for general practitioners (GPs) emphasise the urgency to install preventive treatment as soon as possible. We aimed to give a contemporary overview of both patient and physician delay.

**Methods**

A survey at two rapid-access TIA outpatient clinics in Utrecht, the Netherlands. All patients suspected of TIA were interviewed to assess time delay to diagnosis and treatment, including the time from symptom onset to (1) the first contact with a medical service (patient delay), (2) consultation of the GP and (3) assessment at the TIA outpatient clinic. We used the diagnosis of the consulting neurologist as reference.

**Results**

Of 93 included patients, 43 (46.2%) received a definite, 13 (14.0%) a probable, 11 (11.8%) a possible and 26 (28.0%) no diagnosis of TIA. The median time from symptom onset to the visit to the TIA service was 114.5 (IQR 44.0–316.6) hours. Median patient delay was 17.5 (IQR 0.8–66.4) hours, with a delay of more than 24 hours in 36 (38.7%) patients. The GP was first contacted in 76 (81.7%) patients, and median time from first contact with the GP practice to the actual GP consultation was 2.8 (0.5–18.5) hours. Median time from GP consultation to TIA service visit was 40.8 (IQR 23.1–140.7) hours. Of the 62 patients naïve to antithrombotic medication who consulted their GP, 27 (43.5%) received antiplatelet therapy.

**Conclusions**

There is substantial patient and physician delay in the process of getting a confirmed TIA diagnosis, resulting in suboptimal prevention of an early ischaemic stroke.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- We interviewed patients suspected of transient ischaemic attack (TIA) before the definite diagnosis was established, thus without bias caused by knowledge of the final diagnosis.
- We were able to provide precise estimates of the different components of the total pre-hospital delay time.
- We also assessed whether antiplatelet therapy was initiated prior to the neurologist's assessment.
- In 11 of 93 cases, we used an expert panel to determine the diagnosis of TIA, in absence of a conclusion of the consulting neurologist.
- Our cohort is relatively small, but large enough to provide these estimates of current time delay in patients suspected of TIA.



## INTRODUCTION

A transient ischaemic attack (TIA) is a medical emergency, as the risk of a subsequent ischaemic stroke following a TIA is highest in the early stage. Urgent neurological consultation followed by proper stroke preventive treatment reduces this risk substantially, with the rapid start of an antiplatelet agent as key intervention.[1,2]

Previous studies indicated that around 30%–40% of patients with TIA delay contacting a medical service for more than 24 hours.[1,3-5] Over the past decade, patient awareness campaigns like 'Act FAST' aimed for better recognition of and a quick response to symptoms suspected of stroke to enable thrombolysis or invasive treatment within the first hours.[6] Although TIA is part of the acute ischaemic brain spectrum, it is uncertain whether campaigns like this also positively affect acting on symptoms that are transient, typically short-lasting and often less distinct. A before and after evaluation of the 'Act FAST' showed an improvement of patient delay in stroke patients, but in patients with a TIA or minor stroke there was no improvement in use of emergency medical services or time to first seeking medical attention within 24 hours.[7]

The EXPRESS study (2007) laid the foundation for a drastic decrease of physician delay to diagnosis and treatment of TIA, (1) by the development of rapid-access TIA servicesand (2) guidelines for general practitioners (GPs).[1,8] The Dutch GP guidelines recommend GPs to refer all patients suspected of TIA to a TIA service within 24 hours, and to immediately initiate a platelet aggregation inhibitor, unless it is certain that the patient will be examined by a neurologist on the same day.[9] The UK GP guidelines emphasise an immediate start of medication by the GP in any

suspected TIA patient, and have recommended the use of the prognostic ABCD2 score (age, blood pressure, clinical features, duration, diabetes) to define high-risk patients that have to be examined by the neurologist within 24 hours.[10] However in the latest update of the UK national clinical guideline for stroke in 2016, the use of the ABCD2 score was abandoned, since new studies showed that the ABCD2 is an inaccurate predictor of early stroke.[11-13] This guideline now also recommends to refer all suspected TIA patients to a TIA service within 24 hours.

We aimed to assess current patient and physician delay from onset of suspected TIA symptoms to specialist consultation.

## METHODS

We conducted a survey among patients suspected of TIA who were referred to one of two participating rapid-access TIA services in the city of Utrecht, the Netherlands. Availability of TIA services in the Netherlands is restricted to weekdays. During 6 months in the period 2013–2014, consecutive patients were asked to participate when arriving at the TIA service. Patients were excluded in the case of: (1) ongoing symptoms; (2) onset of symptoms in-hospital or outside the Netherlands; (3) severe cognitive impairment and (4) inability to clarify the time of onset of symptoms.

Participants suspected of TIA were interviewed at the start of their day at the TIA service before knowing their final diagnosis. We collected information about the following items in a standardised questionnaire (included as an online supplementary file): (1) the interval from onset of symptoms to the patient's first contact with a medical service (patient delay), the interval to the GP visit and the interval to the TIA service visit; (2) the initiation of an antiplatelet agent; (3) the type and duration of symptoms; (4) the initial reaction of the patient (what did the patient do?); (5) the initial perception (what did the patient think?) and (6) general knowledge of TIA. Responses were written down by the interviewer. In case a patient had experienced multiple recent (suspected) TIAs, we evaluated the last event.

We considered the consulting neurologist's diagnosis of TIA as reference. Diagnoses were categorised as definite TIA or minor stroke, probable TIA, possible TIA or no TIA. In 11 cases (11.8%), the neurologist's conclusion was unclear or absent, and three clinicians (LSD, LJK and FHR) decided in a consensus meeting on the diagnosis.

In this observational study, with estimations of delay, a method for sample size calculation is lacking. We therefore included a convenient number of participants.

Delay is presented as median with 25%–75% IQR. We used Mann-Whitney U tests for comparing delay across subgroups. In an overview of results per interview

item, we additionally compared results between those with a definite or probable TIA (or minor stroke), and those with no or a possible TIA, applying $\chi^2$ tests.

### Patient and public involvement

There were no patients or public involved in the design or conduct of this study.

## RESULTS

A total of 103 patients consented to participate. Ten patients were excluded because of: (1) ongoing symptoms (n=3), (2) onset of symptoms in-hospital or abroad (n=2), (3) an unclear onset of symptoms (n=3) and (4) severe cognitive impairment (n=2). Table 1 shows characteristics of the 93 participants. Mean (SD) age was 65.2 (13.4) years and 55 (59.1%) were male. The median time from symptom onset to our interview at the TIA service was 4.8 (IQR 1.8–13.2) days. Table 2 shows an overview of the different parts of time delay to the assessment at the TIA service.



**Table 1.** Patient characteristics of 93 patients suspected of TIA

| Characteristics | Total (N = 93) |
|---|---|
| Mean age in years (SD) | 65.2 (13.4) |
| Male, n (%) | 55 (59.1) |
| Prior TIA/ischaemic stroke, n (%) | 23 (24.7) |
| Living situation, n (%) | |
| Alone | 25 (26.9) |
| With a partner | 66 (71.0) |
| In a nursing home | 2 (2.1) |
| Weekend onset of symptoms, n (%) | 31 (33.3) |
| Symptoms, n (%) * | |
| Motor | 32 (34.4) |
| Sensory | 21 (22.6) |
| Visual | 27 (29.0) |
| Speech | 30 (32.3) |
| Median duration of neurological deficits in hours (25-75% IQR) | 0.5 (0.1 – 2.4) |
| Diagnosis, n (%) ** | |
| TIA or minor stroke | 43 (46.2) |
| Probably TIA | 13 (14.0) |
| Possibly TIA | 11 (11.8) |
| No TIA (TIA mimic) | 26 (28.0) |

* Patients may have experienced more than one symptom

** In 11 patients the definite diagnosis was made by a panel consisting of three of the authors.

TIA, transient ischaemic attack; IQR, interquartile range.

**Table 2.** Delay for the 93 patients suspected of a TIA.

| Type of delay time | Median time (IQR), hours | |
|---|---|---|
| **Patient delay** | | |
| Time from symptom onset to first contact with medical service | 17.5 (IQR 0.8-66.4) | |
| Onset during weekdays (N=31) | 8.8 (IQR 0.5-103.5) | |
| Onset during weekend (N=62) | 21.0 (IQR 13.0-65.3) | p=0.29 |
| Prior TIA or stroke | 3.0 (IQR 0.8-40.5) | |
| No prior TIA or stroke | 19.0 (IQR 1.0-67.5) | p=0.29 |
| **GP delay** | | |
| Time from contact with GP to actual GP consultation (N=76) | 2.8 (0.5-18.5) | |
| GP during office hours (N=69) | 3.0 (0.5-9.5) | |
| GP out of hours service (N=7) | 1.4 (0.4-7.8) | p=0.34 |
| **Referral delay** | | |
| Time from GP consultation to assessment at TIA service (N=76) | 40.8 (IQR 23.1-140.7) | |
| GP during office hours (N=69) | 30.5 (IQR 23.2-141.3) | |
| GP out of hours service (N=7) | 58.4 (IQR 13.7-96.4) | p=0.62 |
| History of TIA/ stroke | 105.0 (IQR 27.3-228.8) | |
| No history of TIA/stroke | 30.0 (IQR 22.5-98.5) | p=0.09 |
| **Total delay** | | |
| Time from symptom onset to assessment at TIA service | 114.5 (IQR 44.0-316.6) | |

IQR, interquartile range; TIA, transient ischaemic attack; GP, general practitioner.

## Patient delay

The median delay from symptoms to the first contact with a medical service was 17.5 (IQR 0.8–66.4) hours and did not differ significantly between patients with definite or probable TIA/minor stroke (19.0 [IQR 0.9–63.2] hours) and those with possible or no TIA (16.6 [IQR 0.7–92.4] hours). Thirty-six (38.7%) patients delayed seeking medical help for more than 24 hours. In 76 (81.7%) patients, the GP was the first contacted healthcare provider; in 7/76 (9.2%) during out of office hours. The emergency department or ambulance service was contacted directly by seven patients (7.5%) and ten patients (10.8%) first reported their symptoms to a medical specialist (other than a neurologist) via an outpatient clinic. In total, four (4.3%)

patients had experienced similar symptoms in the previous three months, however, without contacting a healthcare provider.

In the 31 (33.3%) patients with symptom initiation during the weekend patient delay was 21.0 (IQR 13.0–65.3) hours, and 8.8 (IQR 0.5–103.5) hours in those with symptoms during weekdays (p=0.29). Patients who had a prior TIA or stroke (n=23, 24.7%) contacted the GP in 78.3% of cases (during office hours, n=17; GP out of hours service, n=1), and the median delay to first contact was 3.0 (IQR 0.8–40.5) hours, which was lower than in those without prior TIA/stroke; 19.0 (IQR 1.0–67.5) hours, p=0.29.

### Delays until consultation at the TIA service



Among the 76 patients who contacted the GP, the median time from onset of symptoms to the actual GP consultation was 25.5 (IQR 4.0–128.0) hours. The (median) GP delay, i.e. the time from the first contact by the patient with the GP practice to the actual GP consultation, was 2.8 (0.5–18.5) hours. The subsequent median time from GP consultation to the consultation at the TIA service (referral delay) was 40.8 (IQR 23.1–140.7) hours.

In the patients who consulted their own GP during office hours (n=69), referral delay was 30.5 (IQR 23.2–141.3); in the patients who (first) consulted a GP out of hours service (n=7) this was 58.4 (IQR 13.7–96.4) hours (p=0.62). The referral delay was 105.0 (IQR 27.3–228.8) hours in the 23 (24.7%) patients who had a prior TIA or stroke, and 30.0 (IQR 22.5–98.5) in those without prior TIA/stroke (p=0.09).

For the complete cohort, the median time from onset of symptoms to the visit to the TIA service was 114.5 (IQR 44.0–316.6) hours. Figure 1 shows the proportions of patients that contacted a medical service, visited the GP, and visited the TIA service, at subsequent points in time from symptom onset.

Of the 62 patients who were naïve to antithrombotic medication, 27 (43.5%) received a platelet aggregation inhibitor from the GP prior to the TIA service visit. Comparing these 27 patients with the 35 patients that did not receive a platelet inhibitor, both the delay from GP to the neurologist's assessment (32.7 [22.1–94.6] vs 30.0 [22.3–141.0] hours) and the distribution of definite diagnoses (8/27 [29.6%] vs 10/35 [28.6%] diagnosed as no TIA) were similar.

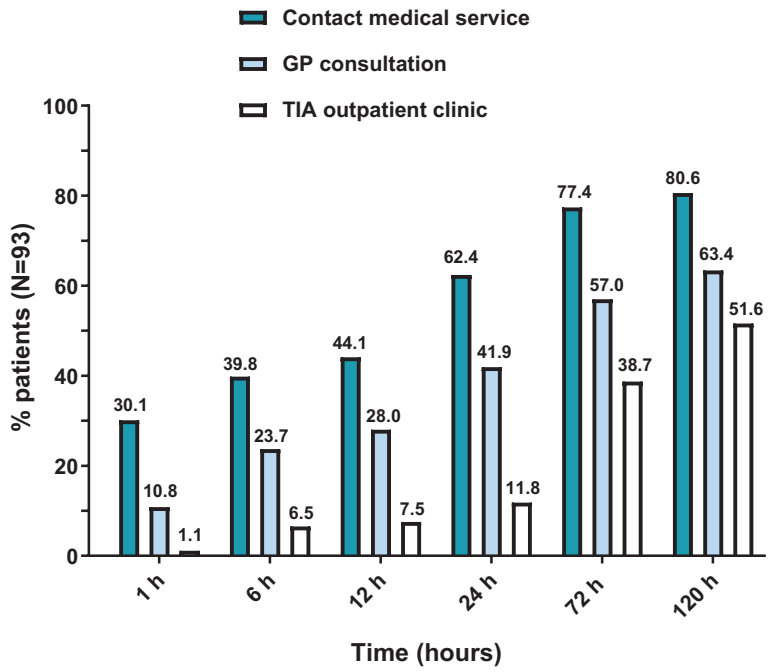



**Figure 1.** Proportions of patients that contacted a medical service, visited the GP, and the TIA outpatient clinic, at subsequent points in time from symptom onset.
Legend: GP, general practitioner; TIA, transient ischaemic attack.

## Initial patient's response and perception of symptoms

Data on the initial response, perception of symptoms and the (general) knowledge of TIA are summarised in table 3. Fifty-four (58.1%) patients initially decided to 'wait and see'. Sixty-five patients (69.9%) did not call for medical help within the first hour after symptom onset. The main reasons for not calling were disappearance of symptoms (27/65, 42.4%), and not considering the symptoms to be threatening (15/65, 23.4%).

Thirty (32.3%) patients interpreted their symptoms as a medical emergency. Asking about initial thoughts on the possible cause of their symptoms, 65 (60.2%) did not consider a TIA. Most patients were familiar with the medical term TIA (76/93, 87.1%), but 40 (43.0%) patients had no or an incorrect idea about the symptoms related to TIA.

**Table 3.** Initial response, perception of symptoms, and general knowledge of TIA, in 93 patients suspected of TIA, divided in those with a certain or probably TIA/minor stroke, and in those with no or possibly TIA according to the neurologist*.

| Interview item | Total (N = 93) | Certain or probably TIA/minor stroke (N = 48) | No or possibly TIA/ minor stroke (N = 34) |
|---|---|---|---|
| | n (%) | n (%)** | n (%)** |
| **Initial response to symptoms** | | | |
| *Initial response* | | | |
| Wait and see | 54 (58.1) | 27 (56.3) | 20 (58.8) |
| Direct call to health care provider | 18 (19.4) | 8 (16.7) | 6 (17.7) |
| Asking a relative for advice | 17 (18.3) | 10 (20.8) | 7 (20.6) |
| Other | 4 (4.4) | 3 (6.2) | 1 (2.9) |
| *Reasons for not seeking medical attention within 1 hour (N=65)* | | | |
| Symptoms had disappeared | 27 (41.5) | 15 (45.5) | 10 (41.7) |
| Symptoms not considered as threatening | 15 (23.1) | 8 (24.2) | 6 (25.0) |
| Convinced that symptoms would resolve spontaneously | 9 (13.8) | 4 (12.1) | 3 (12.5) |
| Because it occurred during out of office hours | 4 (6.2) | 2 (6.1) | 1 (4.2) |
| Other | 10 (15.4) | 4 (12.1) | 4 (16.6) |
| **Perception of symptoms** | | | |
| Interpreted as an emergency | 30 (32.3) | 17 (35.4) | 8 (23.5) |
| Considered a TIA as possible cause | 37 (39.8) | 16 (33.3) | 14 (41.2) |
| Experienced severity of symptoms on a scale from 0 to 10 (N=90) | | | |
| 1 to 4 | 32 (35.6) | 15 (32.6) | 16 (48.5) |
| 5 to 7 | 35 (38.9) | 20 (43.5) | 9 (27.3) |
| 8 to 10 | 23 (25.5) | 11 (23.9) | 8 (24.2) |

**Table 3.** Continued.

| Interview item | Total (N = 93) | Certain or probably TIA/minor stroke (N = 48) | No or possibly TIA/ minor stroke (N = 34) |
|---|---|---|---|
| | n (%) | n (%)** | n (%)** |
| **Knowledge of TIA** | | | |
| Ever heard of a TIA | 76 (87.1) | 35 (72.9) | 30 (88.2) |
| Correctly knowing key TIA symptoms | 63 (57.0) | 24 (50.0) | 20 (58.8) |
| Considers rapid treatment (within 24 hrs) necessary | 54 (58.1) | 25 (52.1) | 22 (64.7) |
| Knows that TIA may be a precursor of stroke | 44 (47.3) | 22 (45.8) | 17 (50.0) |

* In 11 patients a definite neurologist's diagnosis could not be retrieved from the medical files.

**No significant differences between the 'certain or probable TIA/minor stroke' patients and 'no or possible TIA' patients were found, applying Chi square tests.

TIA, transient ischaemic attack.

## DISCUSSION

The majority of patients with symptoms suspected of a TIA in this outpatient population delayed seeking medical help, resulting in a delay of more than 24 hours in 38.7% of patients (median 17.5 [IQR 0.8–66.4]). Although the actual GP consultation took place after a median of only 2.8 (0.5–18.5) hours from the first contact with the GP practice (GP delay), it took another 40.8 (IQR 23.1–140.7) hours before the patient was seen at the TIA clinic (referral delay). Only a minority (43.5%) of patients naïve to antithrombotic medication received an antiplatelet agent from the GP prior to the assessment by the neurologist.

The extent of patient delay in our study corresponds with the delay reported in previous studies from the UK, published between 2006 and 2016.[1,3-5,14,15] Both the Dutch and British healthcare systems have a strong primary care system and rapid-access TIA services. In the Netherlands, there have been campaigns promoting recognition of stroke symptoms similar to the UK 'Act FAST' campaign. Our results indicate that during the last decade no clear reduction in patient delay was achieved, despite these campaigns explaining the most important stroke symptoms and stressing its urgency. As in the UK studies, we found that a majority of patients or their relatives do not respond (directly) to transient symptoms that could be caused by brain ischaemia. The disappearance of symptoms was the main reason for delay, followed by considering the symptoms as not threatening. Even though most participants were familiar with the medical term TIA, a minority actually considered the diagnosis.

Given the time from symptom onset to the visit of the rapid-access TIA service, it can be concluded that there is room for improvement of the current Dutch system of TIA management. In everyday practice, the guidelines' recommendation of an assessment by the neurologist at a rapid-access TIA service the same or next day is not met. The strong gatekeeper's function of the GPs in the Dutch healthcare system has beneficial effects on selection of referral and health budgets, however, it may also cause undesirable delays in those who actually had a TIA.

Beyond limiting the delay to a complete diagnostic assessment to identify aetiological factors like atrial fibrillation or significant carotid stenosis, probably the most crucial step forward is initiating secondary prevention with antiplatelets in the pre-hospital setting. Recent guidelines clearly recommended immediate initiation of antiplatelets in patients suspected of TIA, but our study shows there is still insufficient awareness among GPs of this requirement: only in 44% of patients with a suspected TIA antiplatelets were initiated. Unlike the UK guidelines that recommend GPs to start such treatment in any suspected TIA patient, the Dutch guidelines

recommend GPs to start only if assessment by the neurologist is not feasible the same day. We consider a clear-cut recommendation to start an antiplatelet in any suspected TIA patient (naïve to antithrombotics) as the best option.

If all GPs would follow the recommendation on antiplatelet therapy, the delay time to treatment would only be 2.8 (0.5–18.5) hours. We therefore consider enforcing this recommendation more important than the recommendation on assessment by the neurologist within 24 hours. Our results help to convince GPs that more timely action is needed in patients suspected of TIA.

An alternative care system would be the 'French' model with (1) a 24/7 TIA rapid-access service and (2) public campaigns raising awareness among lay people that every acute neurological deficit should be considered a medical emergency similarly to acute chest pain, also requiring ambulance transportation, certainly if symptoms persist (possibly stroke). However, this would mean a large shift in the organisation of healthcare in the Netherlands, a large increase in healthcare costs.

One of the strengths of our study is that we were able to provide precise estimates of the different components of pre-hospital delay. Moreover, we interviewed not only those with definite TIA, but the larger domain of suspected TIA cases, importantly, before the definite diagnosis was established and without bias caused by this knowledge. Recall errors still need to be considered. A limitation was that in 11.8% of cases presence or absence of TIA was determined in consensus by a panel based only on history taking, that is without the conclusion of the consulting neurologist.

Our study indicates that there is still a need for both patient and physician education regarding the required urgency in case of a suspected TIA. Lay people need to be better informed that also mild stroke-like symptoms that quickly disappear have to be reported to a physician as soon as possible. GPs should be better educated about the rationale for an early start of antiplatelet therapy and that they can safely instal this medication. Furthermore, neurologists should advocate the early start of treatment during their contacts with GPs. Further research is needed to explore the main determinants of patient delay and the main reasons for the lack of prescribing antiplatelet therapy by GPs.

## CONCLUSION

Current patient and physician delay in suspected TIA is considerable. Our results emphasise the need for both patient and physician education, aimed at quick consultation at a TIA outpatient clinic and an early start of secondary prevention by GPs in any case of a suspected TIA.

## REFERENCES


1. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-42.
2. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016;388(10042):365-75.
3. Sprigg N, Machili C, Otter ME, Wilson A, Robinson TG. A systematic review of delays in seeking medical attention after transient ischaemic attack. J Neurol Neurosurg Psychiatry. 2009;80(8):871-5.
4. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behavior immediately after transient ischemic attack and minor stroke in 1000 consecutive patients: lessons for public education. Stroke. 2010;41(6):1108-14.
5. Wilson AD, Coleby D, Taub NA, Weston C, Robinson TG. Delay between symptom onset and clinic attendance following TIA and minor stroke: the BEATS study. Age Ageing. 2014;43(2):253-6.
6. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PLoS One. 2014;9(8):e104289.
7. Wolters FJ, Li L, Gutnikov SA, Mehta Z, Rothwell PM. Medical attention seeking after transient ischemic attack and minor stroke before and after the UK Face, Arm, Speech, Time (FAST) public education campaign: Results from the Oxford Vascular Study. JAMA Neurol. 2018;75(10):1225-1233.
8. Kamal N, Hill MD, Blacquiere DP, Boulanger JM, Boyle K, Buck B, et al. Rapid assessment and treatment of transient ischemic attacks and minor stroke in Canadian emergency departments: time for a paradigm shift. Stroke. 2015;46(10):2987-90.
9. Verburg AF, Tjon ATMR, Verstappen WH, Beusmans GH, Wiersma T, Burgers JS. [Summary of the 'Stroke' guideline of the Dutch College of General Practitioners' (NHG)]. Ned Tijdschr Geneeskd. 2014;158(1):A7022.
10. National Collaborating Centre for Chronic Conditions. Stroke: national clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). London: Royal College of Physicians, 2008.
11. Rudd AG, Bowen A, Young GR, James MA. The latest national clinical guideline for stroke. Clin Med (Lond). 2017;17(2):154-155.
12. Hill MD, Weir NU. Is the ABCD score truly useful? Stroke. 2006;37(7):1636.
13. Perry JJ, Sharma M, Sivilotti ML, Sutherland J, Symington J, Worster A, et al. Prospective validation of the ABCD2 score for patients in the emergency department with transient ischemic attack. CMAJ. 2011;183(10):1137-1145.
14. Giles MF, Flossman E, Rothwell PM. Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. Stroke. 2006;37(5):1254-60.
15. Hurst K, Lee R, Sideso E, Giles M, Handa A. Delays in the presentation to stroke services of patients with transient ischaemic attack and minor stroke. Br J Surg. 2016;103(11):1462-614.

## SUPPLEMENTARY FILE

### Questionnaire – Delay in patients suspected of TIA

*-Translated from Dutch-*

### Time points for determining delay

| | |
|---|---|
| 1 | When did the symptoms start?<br><br>Date __-__-__ time __.__ h |
| 2 | Who did you tell first about the symptoms?<br>a. Relative or friend<br>b. Relative or friend with medical knowledge<br>c. Medical institution<br>i. General practice<br>ii. GP out of hours service<br>iii. Emergency department<br>iv. Ambulance service<br>v. Other<br><br>This was at: date __-__-__ time __.__ h |
| 3 | If question 2 was answered with a or b:<br>Your first contact with a medical service was with?<br>a. General practice<br>b. GP out of hours service<br>c. Emergency department<br>d. Ambulance service<br>e. Other<br><br>This was at: date __-__-__ time __.__ h |
| 4 | The moment you made an appointment with the GP was at?<br><br>Date __-__-__ time __.__ h |
| 5 | The GP consultation was at?<br><br>Date __-__-__ time __.__ h |
| 6 | The TIA outpatient clinic visit was at?<br><br>Date __-__-__ time __.__ h |

## Clinical characteristics, knowledge, interpretation and response to symptoms

1 *Patient characteristics*
- a. Age: ___ years
- b. Sex: male / female
- c. History of TIA or stroke?
  - i. Yes
  - ii. No
- d. Living situation
  - i. Alone
  - ii. With a partner or relatives
  - iii. Nursing or care home
- e. Highest level of education? *(the original version includes Dutch levels of education)*
  - i. Primary education
  - ii. Lower secondary education
  - iii. Upper secondary education
  - iv. Post-secondary non-tertiary education
  - v. Tertiary education
  - vi. Other, namely: _____

2 *Knowledge of TIA before the event*

Were you familiar with TIA before this episode?
- a. No
- b. Yes
  - i. What are signs or symptoms of a TIA?
    1. No idea
    2. The following:

       _____
       _____
       _____
  - ii. A TIA can be a precursor of a certain disease. What disease?
    1. No idea
    2. Precursor of: _____

Did you think a TIA requires urgent medical assessment?
- a. Yes
- b. No
- c. Does not know

3 *Symptoms experienced*
- a. Type of symptoms?

  Was/where there:
  - i. Paresis, weakness of:
    1. Face
    2. Arm/hand
    3. Leg/foot

    Left/right

3 *Symptoms experienced*

ii. Numbness/paresthesia of:
1. Face
2. Arm/hand
3. Leg/foot

Left/right

iii. Visual impairment/symptoms:
1. Diplopia
2. Blurry vision (both eyes)
3. Blindness/loss of vision in a part of visual field (both eyes)
4. Blindness/loss of vision in one eye

iv. Communication problem:
1. Impairment of speech or comprehension of language (dyphasia)
2. Slurred speech, problems with articulation/pronunciation (dysarthria)

v. Loss of consciousness

Duration of symptoms? ___ hours and ___ min

Can you fully remember what happened?
i. Yes
ii. No

b. Did you consider these symptoms to be an emergency?
vi. Yes
vii. No

c. How severe did you consider these symptoms were?
i. 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

d. What was your first response to symptoms?
i. Nothing specific because symptoms quickly resolved
ii. Wait and see
iii. I asked a relative or friend for advice

Advice: _____

iv. Self-treatment
v. Seeking medical attention
vi. Other: _____

e. Did you have an idea what caused the symptoms?
i. No
ii. Yes, namely: _____

f. What was the situation at that time?
i. Alone
ii. In company of: _____

Did your bystanders considered the event an emergency?
1. Yes
2. No

3 *Symptoms experienced*

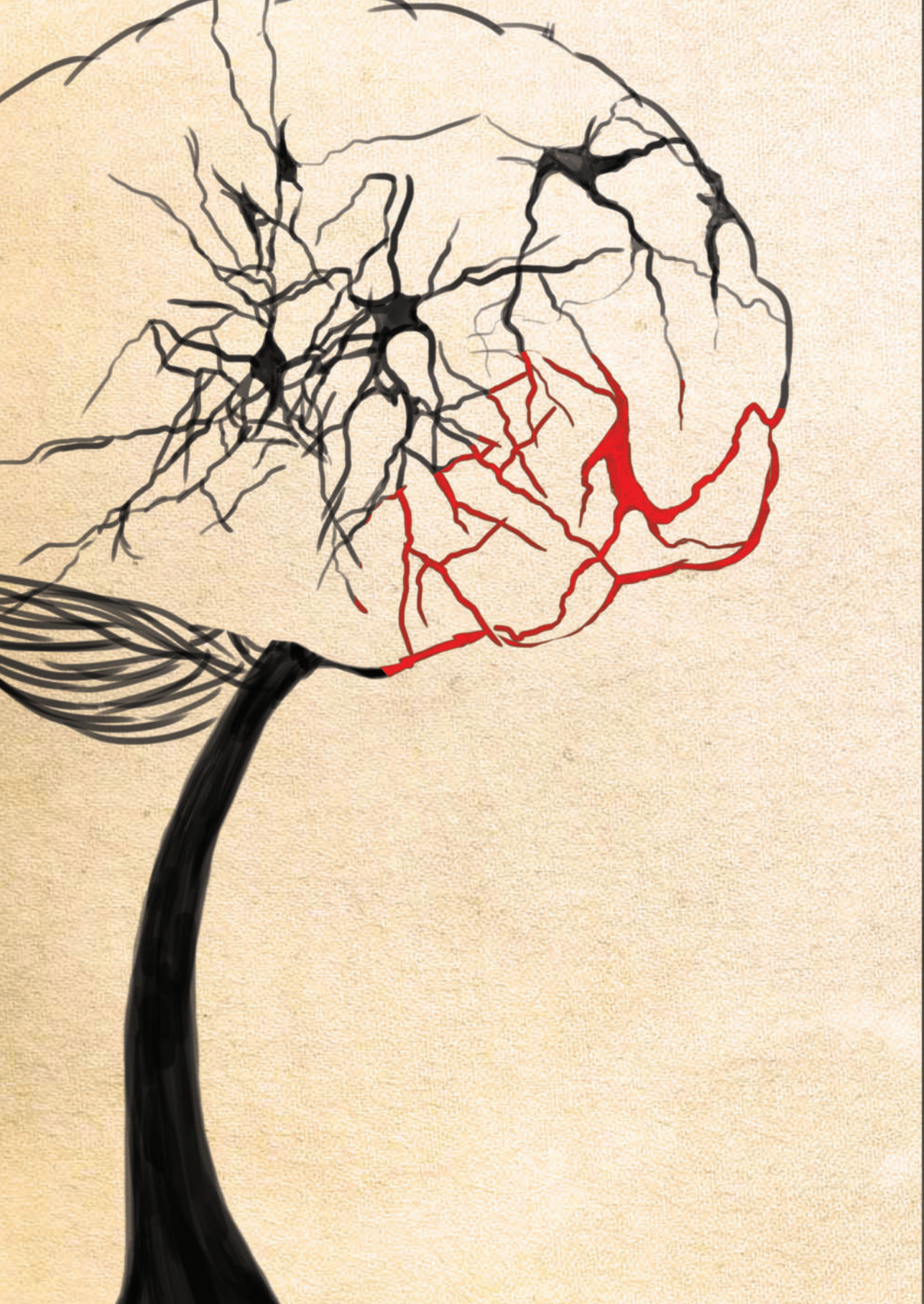
g. Did you contact a medical service within one hour?
  i. Yes
  ii. No, because:
    1. Symptoms resolved
    2. Thought that the symptoms would resolve
    3. Did not consider it severe enough
    4. Others said it could wait
    5. Unable because of the symptoms
    6. Transportation issues
    7. It happened during outside office hours
    8. Other, namely: _____

4 *Treatment by the GP, if applicable*

a. Did the GP start any medication?
  iii. No
  iv. Yes, namely:
    9. Aspirin
    10. Dipyridamole
    11. Anticoagulant
    12. Statin
    13. Antihypertensives
    14. Other, namely: _____

b. If not, did you already use antithrombotic, or cardiovascular medication?
  i. No
  ii. Yes, namely:
    1. Aspirin
    2 Dipyridamole
    3. Anticoagulant
    4. Statin
    5. Antihypertensives
    6. Other, namely: _____
    7. Does not know

GP, general practitioner.



# Chapter 4

# Determinants of patient delay in TIA

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*European Neurology 2019*

## ABSTRACT

### Background

Early diagnosis and stroke preventive treatment in patients with transient ischemic attack (TIA) are crucial, but hampered by delayed reporting of symptoms. Previous studies on causes of patient delay provided inconsistent results. We aimed to assess determinants of patient delay among patients with symptoms suggestive of TIA.

### Methods

We interviewed participants referred by their general practitioner to an outpatient TIA clinic within 72 hours from symptom onset. We determined (i) the exact time from symptom onset to the first contact with a medical service (patient delay); (ii) demographic and clinical characteristics; (iii) patient's initial perception, and reaction to symptoms; and (iv) patient's knowledge about TIA. We used multivariable linear regression to identify determinants of patient delay.

### Results

We interviewed 202 suspected TIA patients (mean age 67.7 (SD 13.7) years, 111 (55.0%) male), of whom 123 (60.9%) received a definite diagnosis of TIA or minor stroke. Median patient delay was 1.5 (IQR 0.4-14.6) hours. Of all patients, 119 (58.9%) considered a TIA (or stroke) as the cause of their symptoms. Among them, 30 (25.2%) thought it was a medical emergency, while of the 83 not considering TIA as the cause of symptoms 38 (45.8%) thought of a medical emergency. Independently related to increased delay were (i) symptom onset out of hours, (ii) absence of dysarthria, (iii) being unaware that TIA requires urgent treatment, (iv) not considering the event an emergency, and (v) knowledge of TIA symptoms. Results for patients with a definite diagnosis of TIA/minor stroke were similar to those with alternative diagnoses.

### Conclusions

Patients still tend to wait till office hours to report TIA symptoms. Speech difficulties, and specifically dysarthria, are related to shorter delay. To reduce patient delay, awareness of TIA symptoms should increase and more importantly lay people should be educated to consider a TIA an emergency.

## INTRODUCTION

A transient ischemic attack (TIA) is characterized by short-lasting and often mild signs and symptoms, which easily results in trivialization or misinterpretation. Moreover, the clinical manifestations of TIA vary strongly, and can resemble many other conditions. Patients should, however, report symptoms suggestive of a (TIA) as soon as possible. A rapid diagnostic assessment followed by an early start of stroke preventive treatment in those with a confirmed diagnosis is crucial to keep the risk of a subsequent ischemic stroke as low as possible.[1-3] However, previous studies showed that there is substantial patient delay; 30 to 40% of patients delay contacting a medical service for more than 24 hours.[4]

Little is known about the determinants of this patient delay. In a study from the UK, delay among TIA or minor stroke patients before contacting a general practitioner (GP) was much longer during out of office hours than during office hours (24.8 vs. 4.0 hours).[5] Three quantitative studies that aimed to assess potential determinants of patient delay among patients with a neurologist's diagnosis of TIA or minor stroke showed conflicting results; for example recognition of symptoms was inconsistently associated with delay.[6-8] These studies had two important limitations. First, these studies only applied univariable analyses and the independent contribution of individual determinants to delay was not assessed. Second, the studies only included those with established TIA or minor stroke. Multivariable analyses are needed to better quantify different determinants of patient delay, preferably in the domain of diagnostic interest and from the perspective of the patient, that is, patients *suspected* of TIA.

A qualitative interview study among 20 TIA patients from the UK reported that patients' recognition of typical stroke symptoms could result in urgent action by patients if symptoms are more severe, but on the other hand could result in delay if symptoms are non-severe or vague.[9]

We aimed to assess determinants of patient delay with a multivariable quantitative approach among patients who were referred to an outpatient TIA clinic with symptoms suggestive of TIA.

## MATERIALS AND METHODS

This study was part of the MIND-TIA (Markers in the Diagnosis of TIA) study, designed to determine the (added) value of serum biomarkers in the diagnosis of TIA.[10] In total, 206 patients suspected of a TIA by their GP were recruited from

October 2013 to October 2016. A research nurse visited participants within 72 hours from the onset of symptoms and standardized history was taken using a pre-specified questionnaire that also included questions on patient delay.

Exclusion criteria were (i) the presence of ongoing symptoms during GP consultation, i.e. suspicion of an ongoing stroke, (ii) severe cognitive impairment or insufficient knowledge of the Dutch language, and (iii) a life expectancy of less than 6 months. Additionally, we excluded patients if they had already sought medical help in response to symptoms that preceded the episode that was assessed, and we were thus unable to determine patient delay.

The standardized questionnaire (added as online supplementary file, see www.karger.com/doi/10.1159/000501077) included the following items: (1) the exact time from onset of symptoms to the first contact with a medical service (patient delay); (2) demographic characteristics; (3) the onset, type and duration of signs and symptoms; (4) the initial patient's response to signs and symptoms (what did the patient do?); (5) the initial patient's perception (what did the patient think about the cause of their symptoms and its severity? Was it considered to be an emergency?); (6) the general knowledge about the disease TIA (does the patient know (i) which symptoms and signs may be provoked by a TIA, and (ii) that TIA is a precursor of stroke?).

A panel of three neurologists made a definite diagnosis, differentiating TIA or minor stroke from alternative diagnoses based on all available diagnostic information, including brain imaging and 6 months of follow-up. The follow-up period, providing information on possible additional cerebrovascular events or new symptoms that put the initial event in a different perspective, was used to assist the panel in deciding whether at the time of presentation a TIA was present.[11] The panel applied the time-based diagnosis of TIA to discriminate TIA from minor stroke.

Delay is presented as median with 25-75% interquartile range (IQR). We used linear regression analyses to investigate the relation between patient delay and potential determinants. Delay was logarithmically transformed because of its skewed distribution. We defined 'correct knowledge of TIA' as being aware of (i) key symptoms and signs provoked by a TIA, and (ii) TIA being a precursor of stroke. Multivariable analyses applying stepwise backward selection (using a cut-off of $p<0.05$) were performed (i) for the total study population of patients suspected of TIA, and (ii) separately for those patients with a definite diagnosis of TIA or minor stroke according to the panel.

## RESULTS

We included 202 of in total 206 participants; two patients did not complete the survey on delay, and two patients were excluded because the GP was consulted because of symptoms that preceded the suspected TIA that was assessed. Table 1 shows the characteristics of the 202 participants. Mean age was 67.7 (SD 13.7) years, 111 (55.0%) were male, and the expert panel classified 60.9% of cases as TIA (N=102) or minor stroke (N=21). On average, the interview by the research nurse took place 48.0 (IQR 28.1-58.0) hours after symptom onset.

**Table 1.** Patient characteristics of 202 patients suspected of TIA by their GP and referred to the TIA outpatient clinic.

| **Characteristics** | **Total (N = 202)** |
|---|---|
| **Mean age in years (SD)** | 67.7 (13.7) |
| **Male, n (%)** | 111 (55.0) |
| **History of TIA or ischemic stroke, n (%)** | 45 (22.3) |
| **Living situation, n (%)** | |
| Alone | 52 (25.7) |
| With a partner | 145 (71.8) |
| In a nursing home | 5 (2.5) |
| **Onset of symptoms out of hours, n (%)** | 102 (50.5) |
| Weekend days | 47 (23.3) |
| Weekdays out of hours | 55 (27.2) |
| **Median duration of symptoms in hours (IQR)** | 0.4 (0.2-1.5) |
| **Symptoms, n (%) *** | |
| Motor | 83 (41.1) |
| Sensory | 85 (42.1) |
| Visual | 63 (31.2) |
| Blurred vision | 23 (11.4) |
| Diplopia | 16 (7.9) |
| Hemianopsia | 14 (6.9) |
| Monocular loss of vision | 10 (5.0) |
| Communication | 97 (48.0) |
| Dysarthria | 38 (18.8) |
| Dysphasia | 59 (29.2) |
| **Diagnosis according to expert panel, n (%)** | |
| TIA or minor stroke | 123 (60.9) |
| Alternative diagnoses | 79 (39.1) |

* Patients may experience multiple symptoms
TIA, Transient Ischemic Attack; IQR, interquartile range**.**

The median patient delay of all 202 patients was 1.5 (IQR 0.4-14.6) hours. In the 123 patients with a definite diagnosis of TIA or minor stroke this was similar; 1.5 (IQR 0.3-14.5) hours. In 102 (50.5%) patients symptoms occurred during out of office hours, and the median patient delay in this subgroup was 9.0 (IQR 0.73-17.6) hours, compared to 0.8 (IQR 0.3-2.3) hours in the 100 patients with symptoms occurring during office hours.

In 80.7% the first contacted healthcare provider was the GP during office hours, in 16.8% it was the GP out-of-hours service, and 2.5% of patients directly contacted the ambulance service or directly visited the hospital emergency department.

Sixty-eight (33.7%) patients interpreted their symptoms as a medical emergency, 58.9% considered the possibility of a TIA/stroke as the underlying cause of their symptoms, 47% had correct general knowledge about TIA, and 82.7% considered it important that a TIA is treated urgently.

Table 2 provides the results of the univariable linear regression analyses, for both the total study population and selectively for the 123 patients with a definite diagnosis of TIA/minor stroke. Age and sex were not related to delay. The results for the larger population show eight variables with a beta coefficient with a p-value <0.10. Related to increased delay were (i) a negative family history of cardiovascular disease <65 years, (ii) general knowledge of TIA, (iii) not being aware that TIA requires urgent treatment, (iv) symptom onset during the weekend and (v) out of hours in general, (vi) communication problems, and specifically (vii) dysarthria, and (viii) not considering the event to be an emergency. Overall, the results for the subgroup of TIA/minor stroke patients (N=123) were very similar. Particularly the aforementioned variables showed comparable beta coefficients.

**Table 2.** Univariable analyses of determinants of patient delay in the total study population, and in the subgroup of 123 patients with a definite diagnosis of TIA/minor stroke.

| Variable | Total study population N=202 | | Patients with definite TIA/MS N=123 | |
|---|---|---|---|---|
| | ***B (95% CI)*** | ***P-value*** | ***B (95% CI)*** | ***P-value*** |
| **Patient characteristics** | | | | |
| Age per year | 1.00 (0.98-1.02) | 0.78 | 1.00 (0.97-1.03) | 0.94 |
| Male | 1.09 (0.63-1.88) | 0.76 | 0.91 (0.44-1.87) | 0.80 |
| Higher level of education[1] | 1.24 (0.71-2.17) | 0.44 | 1.43 (0.70-2.92) | 0.33 |
| Living alone | 1.41 (0.76-2.62) | 0.28 | 1.69 (0.27-1.29) | 0.18 |
| History of TIA or ischemic stroke | 0.81 (0.42-1.56) | 0.52 | 1.11 (0.40-2.05) | 0.89 |
| Positive family history of CVD <65 years | 0.60 (0.34-1.05) | 0.08 | 0.77 (0.36-1.65) | 0.45 |
| General knowledge about TIA[2] | 1.71 (1.00-2.74) | 0.05 | 1.36 (0.66-2.78) | 0.40 |
| Aware that TIA requires urgent treatment | 0.37 (0.18-0.75) | <0.001 | 0.37 (0.15-0.94) | 0.04 |
| **Event characteristics** | | | | |
| Duration of symptoms[3] | 1.49 (0.90-1.20) | 0.59 | 1.08 (0.89-1.32) | 0.44 |
| Sudden onset of symptoms | 0.69 (0.26-1.83) | 0.45 | 0.40 (0.09-1.85) | 0.24 |
| Weekend onset | 4.01 (2.17-7.43) | <0.001 | 5.26 (2.44-12.50) | <0.001 |
| Onset out of hours (incl weekend) | 4.05 (2.43-6.73) | <0.001 | 3.85 (1.92-7.69) | <0.001 |
| Motor symptoms | 0.86 (0.49-1.49) | 0.59 | 1.01 (0.49-2.02) | 0.98 |
| Sensory symptoms | 0.66 (0.38-1.14) | 0.14 | 0.73 (0.36-1.49) | 0.39 |
| Communication problem | 0.61 (0.35-0.96) | 0.07 | 0.56 (0.27-1.12) | 0.10 |
| Dysarthria | 0.38 (0.19-0.75) | 0.01 | 0.42 (0.18-0.99) | 0.05 |
| Dysphasia | 1.12 (0.62-2.05) | 0.70 | 1.00 (0.46-2.19) | 0.99 |
| Visual symptoms | 1.03 (0.57-1.85) | 0.93 | 0.90 (0.40-2.04) | 0.80 |
| Blurred vision | 0.61 (0.26-1.44) | 0.26 | 0.59 (0.14-2.50) | 0.47 |
| Diplopia | 1.24 (0.45-3.41) | 0.67 | 0.68 (0.15-3.17) | 0.62 |
| Hemianopsia | 1.37 (0.47-4.01) | 0.56 | 1.33 (0.31-5.64) | 0.70 |
| Monocular sight loss | 1.49 (0.42-5.23) | 0.53 | 1.24 (0.32-4.88) | 0.75 |
| Presyncope | 1.94 (0.83-4.55) | 0.13 | 3.29 (0.91-12.5) | 0.07 |
| Vertigo | 1.06 (0.54-2.08) | 0.87 | 0.89 (0.36-2.22) | 0.81 |
| ABCD2 score | 1.03 (0.85-1.24) | 0.75 | 1.07 (0.84-1.37) | 0.59 |
| Being alone at the time of event | 0.93 (0.53-1.60) | 0.78 | 1.08 (0.52-2.22) | 0.84 |
| Final diagnosis TIA/minor stroke | 0.93 (0.53-1.62) | 0.79 | - | - |
| **Perception/reaction to event** | | | | |
| First contacted a relative or friend | 1.29 (0.63-2.62) | 0.48 | 0.83 (0.31-2.23) | 0.71 |
| Experienced severity (scored on VAS) | 0.65 (0.37-1.13) | 0.13 | 0.54 (0.26-1.11) | 0.09 |
| Event considered an emergency | 0.20 (0.12-0.35) | <0.001 | 0.14 (0.07-0.27) | <0.001 |
| Did consider a TIA | 1.04 (0.60-1.80) | 0.90 | 0.96 (0.46-2.00) | 0.91 |

The outcome patient delay (a continuous variable in minutes) was naturally log-transformed.
TIA, Transient Ischemic Attack; MS, minor stroke; B, unstandardized beta coefficient; CI, confidence interval; CVD, cardiovascular disease; ABCD2, prognostic score for early stroke risk prediction, including the items Age, Blood pressure, Clinical symptoms, Duration and Diabetes; VAS, visual analogue scale.
[1] Post-secondary education; [2] Knowing symptoms of TIA and aware that TIA is a precursor of stroke; [3] naturally log-transformed.

The final concise multivariable model for the total study population is shown in Table 3. In the final model five variables remained independently related to patient delay: (i) absence of dysarthria, (ii) onset of symptoms out of hours, (iii) the patient being unaware that a TIA requires urgent treatment, (iv) not considering the event to be an emergency, and (v) general knowledge of TIA symptoms. The final multivariable model for only TIA and minor stroke patients (also in Table 3) consists of three of these five variables (with consistent beta coefficients): (i) dysarthria, (ii) onset out of hours and (iii) considering the event an emergency.

**Table 3.** Final multivariable linear regression model of determinants of patient delay, in the 202 patients suspected of TIA, and in the subgroup of 123 patients with a definite diagnosis of TIA/minor stroke.

| Variable | B (95%CI) | *P-value* |
|---|---|---|
| ***Total study population (N=202)*** | | |
| Dysarthria | 0.53 (0.29-0.96) | 0.04 |
| Onset of symptoms out of hours | 3.01 (1.87-4.83) | <0.001 |
| Event considered an emergency | 0.25 (0.15-0.42) | <0.001 |
| General knowledge about TIA | 1.64 (1.02-2.66) | 0.04 |
| Aware that TIA requires urgent treatment | 0.53 (0.28-0.99) | 0.05 |
| ***Patients with definite TIA/minor stroke (N=123)*** | | |
| Dysarthria | 0.49 (0.24-1.01) | 0.05 |
| Onset of symptoms out of hours | 2.97 (1.63-5.39) | <0.001 |
| Event considered an emergency | 0.25 (0.15-0.42) | <0.001 |

The outcome patient delay (a continuous variable in minutes), was naturally log-transformed because of a skewed distribution.
Backward selection of variables was applied, using a cut-off of p <0.05.
B, unstandardized beta coefficient; CI, confidence interval.

Additional analyses showed no association between considering the event a medical emergency and general knowledge about TIA. There was a relation between considering a TIA as the cause of symptoms and the sense of experiencing a medical emergency, however, this was a negative association. Among the patients who thought they could actually have had a TIA, 30 of 119 (25.2%) considered it a medical emergency, versus 38 of 83 (45.8%) patients who did not consider a TIA (RR 0.55 [0.37-0.81]). Among the 123 patients who showed to have a TIA/minor stroke this was similar: 27.3% versus 43.5%, respectively (RR 0.63 [0.38-1.03]). The only other variable associated (positively) to the sense of experiencing a medical emergency was being aware that a TIA requires urgent treatment.

## DISCUSSION

Our study provides relevant new insights in the potential reasons for patient delay in suspected TIA. Of the typical TIA symptoms, speech difficulties, and more specifically dysarthria, were independently related to a shorter patient delay. In previous studies there were conflicting results about the role of patient's recognition of symptoms. We could show that patient's recognition of symptoms, or general knowledge about TIA symptoms, do not necessarily lead to an urgent call for medical advice. A more important determining factor seems to be the patient's knowledge that a TIA warrants urgent treatment. Furthermore, we showed that delays are much longer during out of office hours, even in a healthcare system with 24 hours availability of GP care.

In contrast with previous studies, we analyzed a larger population of patients with symptoms suggestive of a TIA, and performed a separate analysis among patients with a confirmed TIA or minor stroke. The larger population represents the clinical domain in which a quick response to symptoms is required. Moreover, as in around a quarter of referred suspected TIA cases the consulting neurologist is uncertain about the final diagnosis, delay studies including only confirmed TIA patients are hampered by selection of more typical TIA cases. Interestingly, our results from both suspected TIA patients as confirmed TIA patients point out the same determinants of patient delay, with consistent beta coefficients from univariable as well as multivariable analyses.

Motor symptoms and speech difficulties have been inconsistently associated with shorter delays by TIA patients.[6-8] Unlike previous studies we distinguished dysarthria from dysphasia, and in multivariate analyses specifically dysarthria was an independent predictor of delay. Either this specific neurological deficit triggers patients or their relatives to seek for medical help rapidly, or dysarthria is part of a combination of symptoms that creates more urgency. We found no evidence for a relation between motor symptoms and delay. A possible explanation is that milder and short-lasting motor deficits can be easily misinterpreted or trivialized.

Earlier studies did not provide a conclusive answer regarding the role of patient's recognition of symptoms suggestive of TIA.[6-9] Our study showed that recognition of symptoms alone is not a key trigger to respond to symptoms rapidly. The participants that did consider a TIA even showed less sense of urgency than those who did not. Moreover, general knowledge of TIA (symptoms) was associated with longer instead of shorter delays. Possibly, this can be explained taking into account the comforting effect of symptoms that resolve rather quickly. In the acute stage this effect might be even stronger in patients that recognize a TIA, than in

patients who have no clear idea what they experienced. It appears logical that knowledge about the required urgency in suspected TIA was associated with both shorter delays and the sense of urgency. However, taken all together these data suggest a general lack of sense of urgency in lay people in case of suspected TIA.

Out of hours symptom onset shows to be a strong determinant of patient delay. Patients tend to wait until office hours to report their symptoms. This is in line with the findings by Lasserson et al in 2008, who attributed the effect of time of symptom onset largely to the lack of accessible GP care out of hours.[5] A relevant difference with this study, however, is that the Dutch health care system nowadays includes an easily accessible round the clock GP out-of-hours service, which is commonly used by patients. Moreover, in the past decade campaigns comparable to the UK 'Act FAST' campaign have encouraged people to respond to stroke-like symptoms immediately.[12] Nevertheless, still 80% of patients reported their symptoms during routine office hours.

Compared to other studies assessing patient delay we interviewed patients early after symptom onset, in this way limiting recall bias. Still some degree of recall bias must be considered, especially concerning our questions about knowledge of TIA. In our standardized questionnaire we specifically asked for the knowledge prior to the suspected event, however answers could be influenced by their search for medical advice and GP consultation. Furthermore, it is important to realize that patients with symptom onset more than 72 hours before contacting the GP were not included in the study.

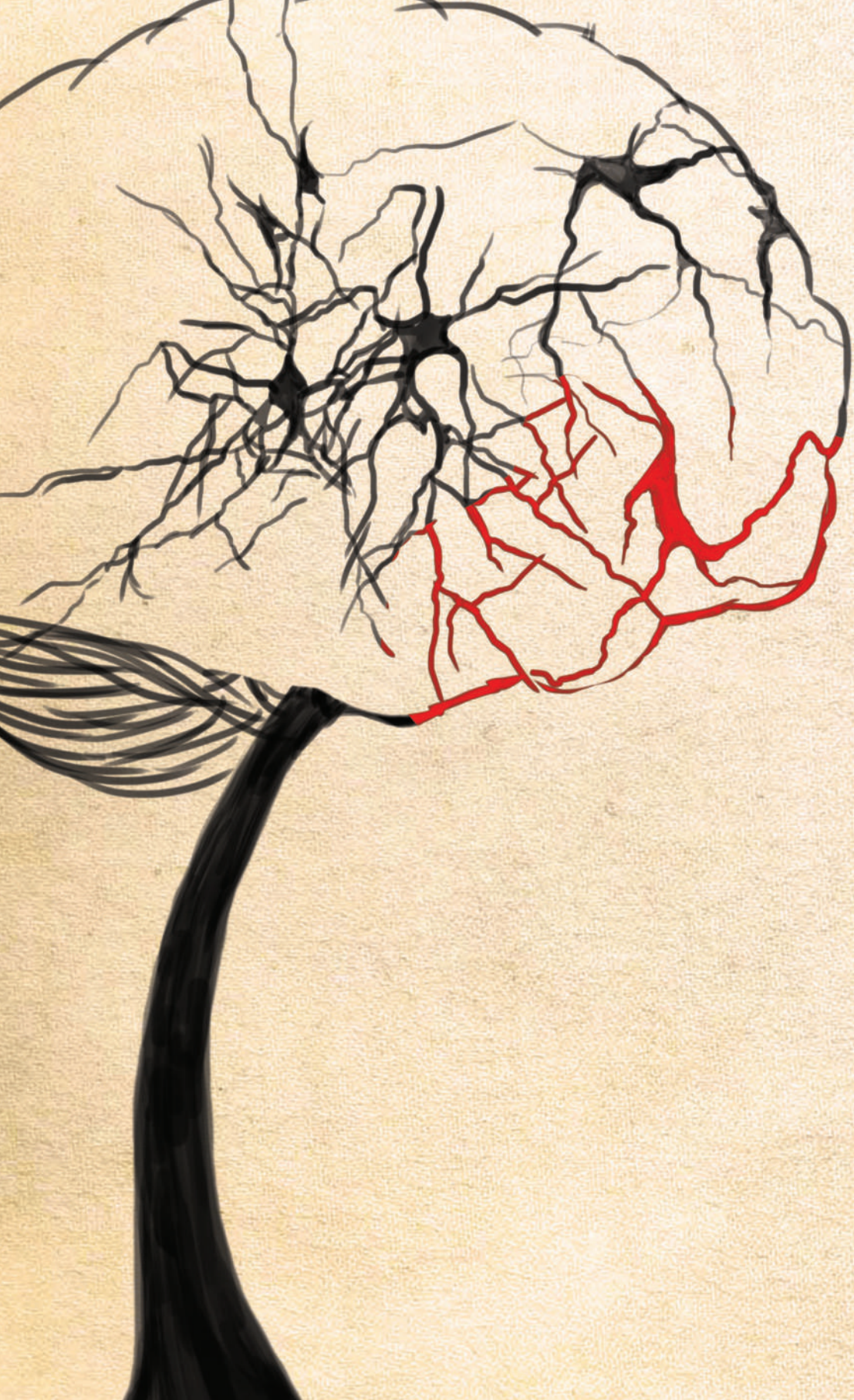
Translating our results to clinical practice, this study highlights that beyond knowing and recognizing stroke-like symptoms, lay people still need to learn to act in case of symptoms suggestive of a TIA, explicitly also if symptoms are mild and/or short-lasting.

## CONCLUSION

Patients still tend to delay till office hours to report TIA symptoms. Speech difficulties, and specifically dysarthria, are related to shorter patient delay. To reduce patient delay, awareness of TIA symptoms should increase and more importantly lay people should be educated to consider a TIA as an emergency.

## REFERENCES


1. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-42.
2. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016;388(10042):365-75.
3. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6(11):953-60.
4. Dolmans LS, Hoes AW, Bartelink MEL, Koenen NCT, Kappelle LJ, Rutten FH. Patient delay in TIA: a systematic review. J Neurol. 2018.
5. Lasserson DS, Chandratheva A, Giles MF, Mant D, Rothwell PM. Influence of general practice opening hours on delay in seeking medical attention after transient ischaemic attack (TIA) and minor stroke: prospective population based study. BMJ. 2008;337:a1569.
6. Giles MF, Flossman E, Rothwell PM. Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. Stroke. 2006;37(5):1254-60.
7. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behavior immediately after transient ischemic attack and minor stroke in 1000 consecutive patients: lessons for public education. Stroke. 2010;41(6):1108-14.
8. Wilson AD, Coleby D, Taub NA, Weston C, Robinson TG. Delay between symptom onset and clinic attendance following TIA and minor stroke: the BEATS study. Age Ageing. 2014;43(2):253-6.
9. Mc Sharry J, Baxter A, Wallace LM, Kenton A, Turner A, French DP. Delay in seeking medical help following Transient Ischemic Attack (TIA) or “mini-stroke”: a qualitative study. PloS One. 2014;9(8):e104434.
10. Dolmans LS, Rutten FH, El Bartelink ML, Seppenwoolde G, van Delft S, Kappelle LJ, et al. Serum biomarkers for the early diagnosis of TIA: The MIND-TIA study protocol. BMC Neurol. 2015;15:119.
11. Bertens LC, Broekhuizen BD, Naaktgeboren CA, Rutten FH, Hoes AW, van Mourik Y, et al. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. PLoS Med. 2013;10(10):e1001531.
12. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PloS One. 2014;9(8):e104289.



# Chapter 5

# Serum biomarkers for the early diagnosis of TIA: the MIND-TIA study protocol

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*BMC Neurology 2015; 15: 119.*

## ABSTRACT

### Background

A Transient Ischaemic Attack (TIA) bears a high risk of a subsequent ischaemic stroke. Adequate diagnosis of a TIA should be followed immediately by the start of appropriate preventive therapy, including antiplatelets. The diagnosis of a TIA based on symptoms and signs only is notoriously difficult and biomarkers of brain ischaemia might improve the recognition, and target management and prognosis of TIA patients. Our aim is to quantify the added diagnostic value of serum biomarkers of brain ischaemia in patients suspected of TIA.

### Methods/design

Study design: a cross-sectional diagnostic accuracy study with an additional six month follow-up period.

Study population: 350 patients suspected of TIA in the primary care setting.

Patients suspected of a TIA will be recruited by at least 200 general practitioners (GPs) in the catchment area of seven TIA outpatient clinics willing to participate in the study. In all patients a blood sample will be drawn as soon as possible after the patient has contacted the GP, but at least within 72 h after onset of symptoms. Participants will be referred by the GP to the regional TIA outpatient clinic for additional investigations, including brain imaging. The 'definite' diagnosis (reference standard) will be made by a panel consisting of three experienced neurologists who will use all available diagnostic information and the clinical information obtained during the outpatient clinic assessment, and a six month follow-up period. The diagnostic accuracy, and value in addition to signs and symptoms of candidate serum biomarkers will be assessed in terms of discrimination with C statistics, and calibration with plots.

We aim to include 350 suspected cases, with 250 patients with indeed definite TIA (or minor stroke) according to the panel.

### Discussion

We hope to find novel biomarkers that will enable a rapid and accurate diagnosis of TIA. This would largely improve the management and prognosis of such patients.

## BACKGROUND

Cerebrovascular disease is the second leading cause of death in Europe and a leading cause of long- term disability.[1] A Transient Ischaemic Attack (TIA) by definition does not result in permanent damage of brain tissue,[2] but the risk of a subsequent ischaemic stroke is substantial, especially within the first 2 weeks. Moreover, high-resolution MRI of the brain showed that many TIAs should be regarded as a minor stroke by revealing small ischaemic lesions. About 5 % of TIA patients will have a major stroke within 48 h, and another 5 % within 3 months.[3,4] Urgent treatment of TIA patients with preventive treatment reduced the risk of stroke within 3 months by up to 80 % in a non-experimental study. An absolute reduction in stroke incidence from 10.3 % to 2.1 % was observed with implementing urgent diagnostic assessment followed immediately by adequate treatment including antiplatelets, when compared to a historical cohort in the same hospital in the UK.[5] Therefore, early recognition of TIA is of great importance. Recent studies underline the fact that TIA is a medical emergency[6] and adequate antithrombotic treatment reduces disability and health care related costs.[7] However, a rapid start of treatment may be hampered by patient and physician delay, waiting time involved in referral to the TIA outpatient clinic, and difficulties in establishing the correct diagnosis.



Diagnosing TIA is notoriously difficult for physicians. It is primarily based on history taking, since symptoms and signs often have resolved by the time the patient consults a physician, typically a general practitioner (GP). Symptoms may be inadequately observed by the patient or eyewitnesses, and the history can be distorted by difficulties in recalling the event. It is often difficult for lay persons to narrate the experienced symptoms. Moreover, TIAs can have a non-specific presentation and the differential diagnosis is broad. Particularly TIAs that originate from the vertebrobasilar artery system are difficult to recognise and hard to distinguish from other more benign causes of symptoms like dizziness. Neuroimaging techniques such as CT and MRI scanning of the brain are not performed to confirm the diagnosis of TIA, but to rule out other cerebral diagnoses, including cerebral haemorrhage.[8] In patients referred to a TIA service by the GP in Western Europe, the diagnosis TIA is confirmed by the neurologist in about 70 % of cases.[9-11] Even among experienced neurologists, however, there is substantial interobserver disagreement in TIA diagnosis, with Cohen's kappa statistics varying from 0.65 to 0.78.[11]

A possible solution to the diagnostic difficulties in TIA would be a serum biomarker that can reliably detect (transient) brain ischaemia in an early phase after symptom onset. This would enable a more accurate diagnosis within a shorter time frame. Especially in the primary care setting, but also in the emergency

department, such a test would be very useful when available, preferably as a point of care (POC) test.

Biomarkers could also provide valuable prognostic information. Some markers have already shown to be helpful in predicting the risk of an ischaemic stroke within 2 weeks. This could be useful to guide rapid referral to a neurologist and early initiation of intensive treatment of risk factors, including anticoagulation in patients with atrial fibrillation, and carotid endarterectomy in cases with clinically relevant narrowing of the carotid artery.

There is a growing list of biomarkers associated with different components of the ischaemic cascade in the brain. To be useful in the diagnosis of TIA, a biomarker should be sensitive to early ischaemia and specific for the brain.[12-14] The biomarker should preferably be released in blood immediately after the ischaemic event and remain detectable for several days because it is then also applicable to patients who have a substantial patient delay. Based on a systematic review of the literature we selected seven biomarkers that potentially meet these criteria and showed to have diagnostic potential (table 1). The selection of markers is not definite and will be updated prior to our actual measurements. Previous biomarker studies in the field of cerebral ischemia up to now mainly focused on major stroke and showed methodological limitations which we want to overcome in the present study. To our knowledge, this study, Markers in the Diagnosis of TIA (MIND-TIA), is the first to evaluate the value of serum biomarkers in patients suspected of TIA in addition to history taking. This paper presents the MIND-TIA study protocol.

### Primary objective

To assess the added diagnostic value of serum biomarkers beyond symptoms and signs in patients suspected of TIA.

### Secondary objective

To assess the short-term prognostic value of serum biomarkers in patients with TIA.

**Table 1.** Main characteristics of potential diagnostic biomarkers for TIA.

| Biomarker (abbreviation) | Full name | Main biological action | Main study reference |
|---|---|---|---|
| **B-FABP** | Brain-type fatty acid binding protein | Protein involved in the intracellular transport and oxidation of fatty acids, and membrane lipid trafficking, expressed in glial cells | Wunderlich, et al.[20] |
| **H-FABP** | Heart-type fatty acid binding protein | Protein involved in the intracellular transport and oxidation of fatty acids, and membrane lipid trafficking, expressed in myocardium but also in neuronal cell bodies in the central nervous system | Wunderlich, et al.[20] |
| **PARK7** | Parkinson protein 7 | RNA binding protein regulatory subunit, protects neurons against oxidative stress and cell death | Allard, et al. [21] |
| **NDKA** | Nucleoside diphosphate kinase A | Enzyme catalysing transfer of phosphate groups between nucleoside tri-phosphates and nucleoside diphosphates (e.g. ATP to GDP), expressed in neurons | Allard, et al. [21] |
| **UFDP** | Ubiquitin fusion degradation protein 1 | Enzyme in the pathway for degrading ubiquitin-protein conjugates, involved in protein degradation in cell damage | Allard, et al. [22] |
| **NR2A/2B** | N-Methyl-D-aspartate (NMDA) receptor subunits | Product of the proteolytic degradation of NMDA receptors (part of the ischaemic cascade in the brain) | Dambinova, et al.[23] |
| **NR2A/2B Ab** | N-Methyl-D-aspartate (NMDA) receptor antibodies | Antibodies to NMDA receptor fragments | Weismann, et al.[24] |

## METHODS/DESGIN

### Study design

A cross-sectional diagnostic accuracy study with an additional 6 months follow-up period. Participants are patients suspected of a TIA by their GP. In all participants we will perform a biomarker assessment (index test) and the 'definite' diagnosis of TIA will be determined by an expert panel diagnosis (reference standard). A panel of three neurologists will evaluate all available diagnostic information, including

imaging of the brain and additional 'diagnostic' information that became available in the 6 months of follow-up after the 'event' (so called delayed verification).

## Study population and setting

The study population will consist of patients suspected of a new (not necessarily first) possible TIA by the GP. Patients are recruited within 72 h after symptom onset and either directly after their GP consultation or at the time they visit the TIA outpatient clinic after referral by the GP. We will use the following inclusion and exclusion criteria:

*Inclusion criteria*

- Age 18 years and older.
- A new episode of symptoms or signs suspected of TIA for which the GP considers referral to the TIA outpatient clinic for further investigations to confirm or exclude TIA, or for additional treatment.
- A blood sample can be collected within 72 h after onset of symptoms.
- Written informed consent.

*Exclusion criteria*

- Patients that still have active symptoms or signs at the time of recruitment (i.e. during consultation of the GP), and thus are suspected of an ongoing stroke.
- If valid history taking is impossible because of severe cognitive impairment or insufficient knowledge of the Dutch language.
- Patients with a life expectancy of less than 6 months.

We aim to include 350 patients suspected of TIA, targeting at 250 patients who show to have a definite diagnosis of TIA according to the panel. Following the sample size calculation below, we need at least 200 recruiting GPs in the catchment area of four to five hospitals with a TIA outpatient clinic to complete inclusion within 2 years. Geographically, the study region in the centre of the Netherlands contains around 900 GPs and seven TIA outpatient clinics.

## Recruitment and consent

Patients suspected of TIA will be recruited (not included) by the participating GP or at the time they visit the TIA outpatient clinic after GP referral. The GP or TIA outpatient clinic personnel will ask if the patient agrees to be contacted by the researcher by telephone to explain the study and discuss possible participation.

The researcher will check whether the patient is eligible and still willing to participate. If so, a home visit by a research nurse is arranged and after the patient has signed informed consent, he/she is included in the study and further study procedures are initiated.

## Outcome measures

*Diagnosis of TIA*
Main study endpoint is the diagnosis of TIA (or minor stroke). The expert panel classifies subjects into (i) TIA, (ii) minor (or even major) ischaemic stroke, or (iii) other diagnoses (haemorrhagic cerebrovascular disease or non-cerebrovascular disease). In the analysis we will use a composite endpoint of TIA and minor ischaemic stroke.

*Endpoints after six months of follow-up*
In order to improve the final diagnosis by the panel and to evaluate the short-term prognostic value of the set of biomarkers we will assess the occurrence of (ischaemic) cerebrovascular events and (ischaemic) cardiovascular events, and mortality during six months of follow-up.

The primary prognostic endpoint will be a composite endpoint of ischaemic stroke and (all- cause) mortality within the 6 months follow-up period. This outcome is most often used in prognostic studies concerning cerebrovascular disease.

Secondary endpoint(s) are: the composite of recurrent TIA or ischaemic stroke, all-cause mortality, and high-risk stroke mechanism requiring specific early intervention (the latter defined as the presence of a treatment-emergent mechanism for which a specific therapy other than antiplatelet therapy is indicated, i.e. stenosis of the carotid artery necessitating carotid endarterectomy or a cardioembolic source warranting anticoagulation)

## Study procedures

Our study design aims to mimic the routine diagnostic routing of TIA as much as possible, as is common for diagnostic studies. For study reasons, a research nurse will visit the participant at home to draw an extra blood sample as soon as possible after inclusion for assessment of the biomarkers. After blood sampling participants complete a health-related questionnaire and the research nurse will fill out a standardised case record form (CRF) with items on history taking.

Following routine care, the GP will refer participants to the regional TIA outpatient clinic for further investigations and (additional) treatment. The neurologist

will determine, in accordance with common practice, which additional tests should be performed. In the Netherlands the diagnostic evaluation at TIA outpatient clinics is organized according to national guidelines and is similar among hospitals. Brain imaging is performed in all patients suspected of TIA/minor stroke at the TIA outpatient clinics, nearly always CT scanning but increasingly next to this also MRI.

We will collect data on the following tests/assessments:

1. The findings during medical history taking and the physical examination by the GP. This will be done retrospectively when patients are included.
2. Venous blood sampling (20 ml of blood) for assessment of a set of biomarkers blinded to other results.
3. Case record form (CRF) with standardised history taking, completed by the research nurse and including a narrative account back-upped on tape of the signs and symptoms by the patient.
4. Findings during the clinical assessment of the neurologist at the TIA outpatient clinic, including electrocardiography, and if performed, carotid duplex scan and CT (or MRI) of the brain.
5. Follow-up assessment of the six months following the event by scrutinising the electronical medical files of the participating GPs, with collection of data on all endpoints.

**Biomarker assessment**

We will assess the levels of a set of biomarkers in a sample of blood taken within 72 h after onset of symptoms.

We will collect 20 ml of venous blood by venepuncture. The whole blood samples will be transported immediately to Saltro Diagnostic Center (an accredited primary care diagnostic facility in the Utrecht region) in a Cool Transport container. Pre-analytical processing will be performed within 3 h after collection. Serum will be separated by centrifugation at 2500 g for 10 min. The serum samples will then be stored in 0.5 ml aliquots at −80 °C and transported to the University Medical Center of Utrecht Biobank for long-term storage.

We plan to assess the following biomarkers by sandwich enzyme-linked immunosorbent assay (ELISA) procedures: B-FABP, H-FABP, PARK-7, NDKA, UFDP, NR2 and NR2Ab. These measurements will be performed at the end of the study in one single batch, and blinded to other results and outcomes.

The surplus of serum and a buffy coat will be stored to facilitate future (biomarker) investigations in (suspected) TIA patients.

## Panel diagnosis

An expert panel consisting of three neurologists will evaluate paper-based summaries of all case record forms (including medical history, initial signs and symptoms, the patient's own narrative account of symptoms), reports of the neurologist, radiological imaging reports on brain imaging and carotid artery function, and six months of follow-up.

The panel will classify whether the patient has had a TIA, a minor (or even major) ischaemic stroke, or any other diagnosis. They will follow the definitions from the scientific statement of the American Heart Association 'Definition and evaluation of TIA' (2009).[2] Within the group of TIA or minor strokes, the panel will also determine the aetiology of the ischaemic event, i.e. cardioembolic, large artery atherosclerotic, lacunar, other or undetermined aetiology. The panel judgement is made without knowledge of the biomarker values.

Every panel member will first assess the cases individually. Cases in which the panel members disagree will be discussed in a plenary meeting and a final decision will be made by voting, with the majority of votes counting. Panel meetings will be led by the researcher, who is responsible for providing all necessary data, but who will not participate in the consensus discussions.

Reproducibility of the panel diagnosis will be evaluated by calculating the inter-rater agreement with kappa statistics and by assessment of the reproducibility of the plenary decision process by reassessing a sample of around 10 % of the patients.

*Sample size calculation*

Our sample size calculation is based on the primary research question to be able to answer whether any of the biomarkers has added diagnostic value beyond the clinical assessment. We applied Harrell's rule of thumb[15] that may be used for power calculations in diagnostic and prognostic studies. This rule states that for every determinant considered for multivariate logistic regression analysis at least ten subjects are needed in the smallest category of the outcome variable.

On a TIA service the diagnosis of TIA is confirmed by the neurologist in around 70 % of patients referred by the GP.[11,16] About 30 % of patients will be diagnosed as non-TIA (the latter being the smallest outcome category).

Following these proportions and because we evaluate up to 10 potential diagnostic determinants, 100 non-TIA patients are required. This means that we need a total of (100 x (1/0.3)=) 333 patients suspected of TIA. To be on the safe side and to allow for some 'loss to follow-up' and missing of essential endpoints, we aim to include 350 patients.

In case the proportion of non-TIA patients is higher than 30 %, less than 350 suspected TIA will suffice: we will stop inclusion after a total of 100 non-TIA patients have been verified by the panel and included in the study.

We realize that the power is insufficient for answering the secondary research question on prognosis based on an expected incidence of 20–30 follow-up events in six months. At the best, two or three predictors could be evaluated in multivariable regression analysis. The results on prognosis will therefore be hypothesis generating rather than hypothesis testing.

## Data analysis

*Diagnostic study*

The final TIA diagnosis will be presented as frequencies of the composite of TIA or minor stroke versus other diagnoses. The parameters of routine clinical assessment (symptoms and signs) of the GP and the mean biomarker values will be presented for subjects with a TIA/minor stroke and subjects with other diagnoses. First, the positive and negative predictive value and sensitivity and specificity will be assessed as test characteristics of all diagnostic tests/biomarkers.

Multiple logistic regression analyses with and without biomarker test results will be performed after multiple imputation of missings, to quantify the diagnostic accuracy of the routine clinical assessment by the GP (first model) and the improvement of diagnostic accuracy by adding biomarker assessment to this clinical assessment (additional models). Overall diagnostic accuracy of the models (after adjustment for over-optimism using bootstrapping techniques) will be quantified by assessing and comparing their calibration (applying the Hosmer-Lemeshow test) and discrimination (using ROC area or c-statistics) and classification across various probability cut-offs (e.g. using the integrated discrimination index and the net reclassification improvement).

*Prognostic study*

The nowadays advocated prognostic ABCD2-score (Age ≥ 60, Blood pressure ≥140/90 mmHg, Clinical features, Duration of symptoms, Diabetes) will be assessed in each subject. Because we expect a low number of short-term events, we will only explore the predictive ability of the ABCD2-score, the biomarkers, and ABCD2 plus biomarkers(s).

### Regulation statement

This study is conducted according to the principles of the current version of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO).

### Ethics committee approval

Ethical approval was given by the Medical Research Ethics Committee of the University Medical Center of Utrecht, the Netherlands, on September 5th 2013.

## DISCUSSION

In the MIND-TIA study we hope to find novel biomarkers that improve the accuracy of the GP's diagnosis in patients suspected of TIA. This would result in a more appropriate assessment of patients suspected of TIA and timely treatment, and thus improved prognosis of TIA patients.

The study will follow clinical practice. This will help future implementation of the results in daily practice. Early blood sampling is necessary because some (potential) markers of brain ischaemia can no longer be detected 72 h after the onset of symptoms and because early treatment of TIA is essential to optimize prognosis. Diagnostic research should involve patients suspected of a certain disease, and results of tests should be considered in addition to already available test results from the clinical assessment, thus following the natural diagnostic hierarchy. In our study we thus aim to evaluate the added value of biomarkers beyond the clinical assessment of the GP.

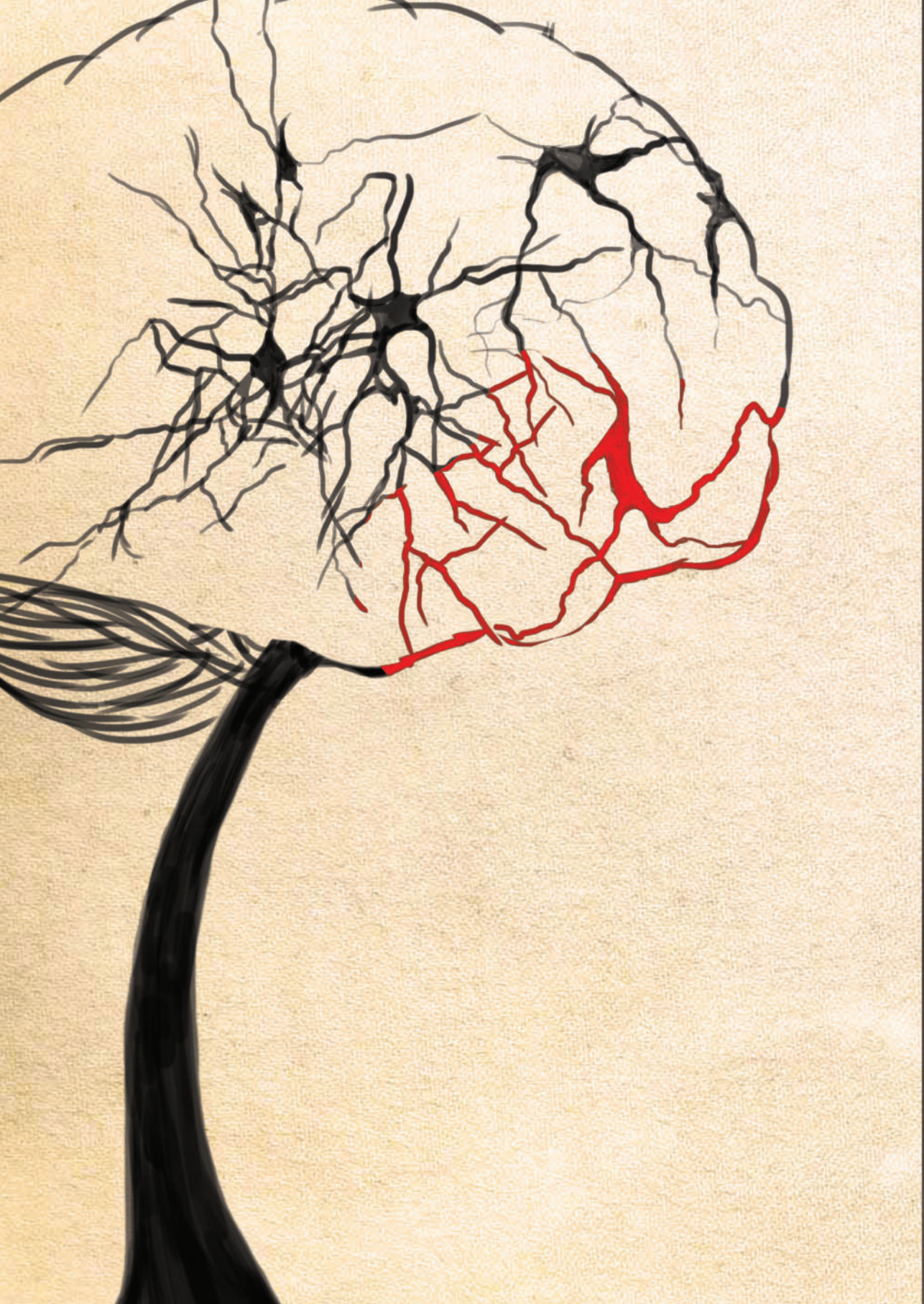
The success of our study depends on the shared effort of a large number of GPs. To improve participation, we facilitate the inclusion process by involving trained research nurses who do the home visits including the informed consent procedure.

In diagnostic accuracy studies creating a valid reference standard is of a major concern. Specifically in the case of TIA, an acceptable reference standard diagnosis is challenging. In lack of a single reference test or the possibility of a composite reference standard, panel diagnosis is the only acceptable method for obtaining a final TIA diagnosis.[17,18] Our panel will evaluate diagnostic information collected through various sources (GP, research nurse and neurologist), including a clinical follow-up period of six months.[19] We aim for transparent reporting of the decision making process of the panel, including assessing its reproducibility.

## REFERENCES


1. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, et al. European Heart Network. Brussels, Sophia Antipolis: European Society of Cardiology; 2012.
2. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke. 2009;40:2276–93.
3. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007;6:1063–72.
4. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med. 2007;167:2417–22.
5. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370:1432–42.
6. Kappelle LJ. A transient ischaemic attack (TIA) is an emergency. Ned Tijdschr Geneeskd. 2007;151:2761–3.
7. Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. Lancet Neurol. 2009;8:235–43.
8. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk M, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet. 2007;369:293–8.
9. Amarenco P, Labreuche J, Lavallee PC. Patients with transient ischemic attack with ABCD2<4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD2 >/=4. Stroke. 2012;43:863–5.
10. Amort M, Fluri F, Schafer J, Weisskopf F, Katan M, Burow A, et al. Transient ischemic attack versus transient ischemic attack mimics: frequency, clinical characteristics and outcome. Cerebrovasc Dis. 2011;32:57–64.
11. Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J Neurol. 2011;18:644–8.
12. Jensen MB, Chacon MR, Sattin JA, Aleu A, Lyden PD. The promise and potential pitfalls of serum biomarkers for ischemic stroke and transient ischemic attack. Neurologist. 2008;14:243–6.
13. Kernagis DN, Laskowitz DT. Evolving role of biomarkers in acute cerebrovascular disease. Ann Neurol. 2012;71:289–303.
14. Maas MB, Furie KL. Molecular biomarkers in stroke diagnosis and prognosis. Biomark Med. 2009;3:363–83.
15. Harrell Jr FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med. 1984;3:143–52.
16. Lavellee PC, Mesequer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6:953–60.

17. Castle J, Mlynash M, Lee K, Caulfield AF, Wolford C, Kemp S, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. Stroke. 2010;41:1367–70.
18. Moons KG, Grobbee DE. When should we remain blind and when should our eyes remain open in diagnostic studies? J Clin Epidemiol. 2002;55:633–6.
19. Reitsma JB, Rutjes AW, Khan KS, Coomarasamy A, Bossuyt PM. A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. J Clin Epidemiol. 2009;62:797–806.
20. Wunderlich MT, Hanhoff T, Goertler M, Spener F, Glatz J, Wallesch CW, et al. Release of brain-type and heart-type fatty acid-binding proteins in serum after acute ischaemic stroke. J Neurol. 2005;252:718–24.
21. Allard L, Burkhard PR, Lescuyer P, Burgess JA, Walter N, Hochstrasser DF, et al. PARK7 and nucleoside diphosphate kinase A as plasma markers for the early diagnosis of stroke. Clin Chem. 2005;51:2043–51.
22. Allard L, Turck N, Burkhard PR, Walter N, Rosell A, Gex-Fabry M, et al. Ubiquitin fusion degradation protein 1 as a blood marker for the early diagnosis of ischemic stroke. Biomark Insights. 2007;2:155–64.
23. Dambinova SA, Bettermann K, Glynn T, Tews M, Olson D, Weissman DJ, et al. Diagnostic potential of the NMDA receptor peptide assay for acute ischemic stroke. PLoS One. 2012;7:e42362.
24. Weissman JD, Khunteev GA, Heath R, Dambinova SA. NR2 antibodies: risk assessment of transient ischemic attack (TIA)/stroke in patients with history of isolated and multiple cerebrovascular events. J Neurol Sci. 2011;300:97–102.



# Chapter 6

# Candidate biomarkers for the diagnosis of TIA: a systematic review

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*Cerebrovascular Diseases 2019*

## ABSTRACT

### Background and purpose

A rapid serum biomarker that confirms or rules out a transient ischemic attack (TIA) would be of great value in clinical practice. We aimed to systematically review current evidence for the diagnostic accuracy of blood biomarkers in the early diagnosis of TIA.

### Methods

Systematic review with quality appraisal of individual studies using the QUADAS-2 tool. MEDLINE and EMBASE databases were searched up to May 1, 2017, to select primary diagnostic accuracy studies evaluating potential biomarkers in blood for the diagnosis of TIA or ischemic stroke.

### Results

Of 4,215 studies retrieved, 78 met our eligibility criteria. Forty-five studies restricted their population to ischemic stroke patients, 32 included both TIA and ischemic stroke patients, and only one study was restricted to TIA patients. In total 62/78 (79.5%) studies had a case-control design comparing TIA or stroke patients with healthy subjects. Overall, 125 single biomarkers and five biomarker panels were studied, with a median number of participants per study of 92.0 (IQR 44.8-144.5), varying from 8 to 915. Sufficient information to extract 2x2 tables was available for 35 (44.9%) articles, and for 60 (48.0 %) biomarkers. Several markers, such as NR2A/B(antibodies), PARK7, NDKA, UFD-1 and H-FABP, have shown moderate to high diagnostic accuracy in multiple studies.

### Conclusions

Although overall the methodological quality of studies evaluating biomarkers of brain ischemia was poor, several biomarkers have shown the potential to detect transient brain ischemia in an early phase. Diagnostic accuracy studies in suspected cases of TIA are needed to determine their true clinical value.

## INTRODUCTION

The clinical diagnosis of Transient Ischemic Attack (TIA) can be difficult for both general practitioner (GP) and neurologist. Timely recognition of TIA is important, since the risk of a subsequent ischemic stroke is especially high in the first days after a TIA and early initiation of treatment substantially reduces this risk.[1,2] A rapid serum biomarker that confirms or rules out a TIA would be of great value in clinical practice.

To date, the diagnosis of TIA still mainly relies on precise history taking. The initial evaluation of patients suspected of TIA is often performed by a GP, without further additional testing at that point. Establishing or excluding TIA can be difficult for several reasons. TIAs may (i) present atypically, (ii) the symptoms are often short-lasting and resolved at consultation and (iii) there is a broad differential diagnosis, e.g. migraine, seizures (pre)syncope and vestibular syndromes. An early detectable biomarker could help clinicians to diagnose TIA more accurately within a shorter time frame. Rapid and correct exclusion of TIA would save costly referrals to a TIA outpatient clinic, while confirmation of TIA facilitates early (anti-thrombotic) treatment and can reduce the risk of subsequent stroke.

A rapidly growing range of biomarkers associated with brain ischemia has been tested, especially in patients with a possible stroke for purposes of diagnosis, and early prognosis. Yet, no diagnostic biomarkers are used in everyday clinical practice for detection or exclusion of TIA or stroke. Previous reviews on stroke biomarkers emphasized the difficulties concerning biodynamic aspects (such as the influence of the specific region of ischemia, and the role of the blood-brain barrier delaying the release of proteins), and also the methodological limitations of biomarker studies.[3,4]

TIA and ischemic stroke must be regarded as a continuum, both initiating the same ischemic cascade, but with a different level of severity. Biomarkers of TIA reflect this ischemic cascade and not (necessarily) cell necrosis. Because of the difference in degree of brain ischemia, biomarker values will often be lower and closer to normal values in TIA patients than in stroke patients. Moreover, because in TIA symptoms and signs relieve fast, there is often more delay in seeking medical attention by patients with a TIA than in the case of severe and/or persisting clinical features as in stroke.

A useful diagnostic biomarker for TIA must first of all be sensitive to low grades of ischemia, and detectable in blood from the first hour till several days after symptoms. Furthermore, the biomarker must differentiate TIAs from a heterogeneous group of alternative diagnoses to be of use in clinical practice. To evaluate clinical relevance, diagnostic accuracy studies among *suspected* patients are needed, as opposed to

studies that compare cases with healthy subjects.[5] These latter studies are a logical first step in the evaluation of new markers that provide a sense of their potential value, but typically overestimate the diagnostic performance when measured in suspected patients in whom the markers will be used in practice.

We aimed to systematically review current evidence for the use of blood biomarkers in the early diagnosis of TIA.

## METHODS

A literature search was conducted following PRISMA guidelines and using the MEDLINE and EMBASE databases, last updated May 1, 2017.[6] We used the key terms shown in Box 1 to find papers evaluating potential biochemical markers for the diagnosis of TIA. Although our actual domain of interest was patients with transient symptoms suspected of TIA, we broadened our search to the whole spectrum of brain ischemia, instead of restricting to TIA only, as a pilot search showed that most published studies tested biomarkers in a population with both ischemic stroke and TIA cases. To narrow our search to diagnostic studies we used a set of diagnostic terms.

Two reviewers screened titles and abstracts for relevance (LD and NK). A first sample of articles was used to cross-check the selection process. Full texts of selected articles were reviewed independently by both reviewers. Primary studies on the diagnostic value of blood biomarkers in patients with (suspected of) TIA or ischemic stroke were included. Animal studies, prognostic studies, conference abstracts and non–English publications were excluded. We also screened reference lists of included articles.

Data were extracted with a standardized data extraction form, which we included as a supplementary file. The quality of included studies was assessed with the modified QUADAS-2 tool.[7] Disagreements between the two reviewers were resolved by discussion. The most important aspects of data extraction were:

- Relevance to clinical domain: (to what extent) is the biomarker tested in TIA (instead of stroke) patients? Most relevant to our domain is a study population of patients *suspected of* TIA, as opposed to studies using a case-control design.
- Timing of blood sampling: is it reported and does it match an early diagnosis of TIA, i.e. the usual time window of diagnostic assessment is from the same day up to several days after the event?
- Adequate reference standard: diagnostic assessment by a neurologist with the use of neuroimaging was the minimum requirement. Ideally a panel of

neurologists using such information and detailed history taking represented the reference standard.[8]

- Relevant measures of diagnostic accuracy: is a cut-off used and was it pre-defined? Most relevant measures considered were predictive values calculated from a 2x2 table in univariate analysis, and ORs and the area under the receiver operating characteristics (ROC) curve (AUC) or c-statistic in multivariate analysis. Ideally the added value of a biomarker was calculated in addition to relevant items of history taking or clinical judgment, and results were validated in a second group of suspected patients.

### Definition of TIA

In the data extraction we also assessed the applied definitions of TIA and minor stroke. The original time-based definition of TIA is based on a maximum duration of symptoms of 24 hours. The new tissue-based definition of TIA was introduced in 2009 following advancements in neuroimaging techniques and includes the criterion of absence of infarction on brain imaging.[9] Around 30-40% of those classified as TIA with the old definition would be classified as minor stroke with the new definition, when using high resolution MRI.[10,11] Currently, the tissue-based definition is most widely endorsed because differentiating minor strokes yields prognostic information. However, the time-based definition is still often being used by neurologists and researchers, certainly when a high resolution MRI scan is not routinely available in the clinical setting.



### Estimation of AUC

Many studies did not report measures of diagnostic accuracy. To estimate the discriminative ability of the markers in these studies, we used methods to derive an AUC from reported (absolute) biomarker values. From the mean values and standard deviations (SD) of diseased (i.e. TIA/stroke) and non-diseased patients an AUC can be estimated.[12] If medians and interquartile ranges (IQR) were reported, we first converted these into means and SD by fitting a lognormal distribution. We used the approach of Hanley and McNeil to compute a confidence interval (CI) for the AUC, based on the number of diseased and non-diseased cases.[13] The latter was also done for studies that reported an AUC without CI. In this way we were able to give an illustrative overview of both reported and estimated AUCs for different markers in a forest plot.

### Data synthesis

Because of the expected heterogeneity of the results we did not aim for data pooling or meta-analysis. First, we will present an overview of the quality assessments of the identified studies, and the total number of biomarkers evaluated. Second, study results of individual potential biomarkers will be described. This concerns a selection of markers that best comply with our clinical domain and the criteria described above, thus based on a combination of applicability, methodological quality of (current) evidence and the diagnostic accuracy of markers. Because of the limited number of studies with clinical populations of patients suspected of TIA (or stroke), we also (shortly) discuss studies that used a case-control design comparing TIA (or stroke) patients with healthy subjects (*not* suspected of TIA).

## RESULTS

Our search identified in total 4,215 studies. A flowchart of the review process is supplemented as appendix (Figure 1). All abstracts were read, 198 articles were read in full, and 78 studies met our eligibility criteria.

These studies included a total of 17,216 participants, of which 9,391 (54.5%) were patients diagnosed with a cerebrovascular event, and 7,825 (45.5%) were either patients with stroke mimicking diagnoses (N=1,399) or 'healthy' volunteers (N=6,426). The total number of patients with a TIA was 1,141 (12.1% of 9,391 cerebrovascular events) . The median number of TIA or stroke patients per study was 92.0 (IQR 44.8-144.5), varying from 8 to 915 patients.

### Quality assessment

An overview of the results of the (modified) QUADAS-2 assessment is given in figure 2. None of the studies restricted the study population to *suspected* TIA patients only. One study (1.3%) included only established TIAs in a case-control design, comparing cases with TIA with healthy volunteers as controls. In 45 (57.7%) studies biomarkers were examined in stroke patients only, excluding patients with TIA. In the remaining 32 (41.0%) studies the population was mixed, with both TIA and stroke patients. Patients *suspected of* stroke or TIA were included in 16 (20.5%) studies.

A predefined cut-off value was mentioned in four (5.1%) studies. In 37 (47.4%) studies an optimal cut-off was derived from the examined cohort, of which 3 (8.1%) were externally validated in a different cohort. Twenty-three (29.5%) studies compared mean values of the biomarkers between those who eventually showed to have a stroke or TIA versus those without stroke or TIA.

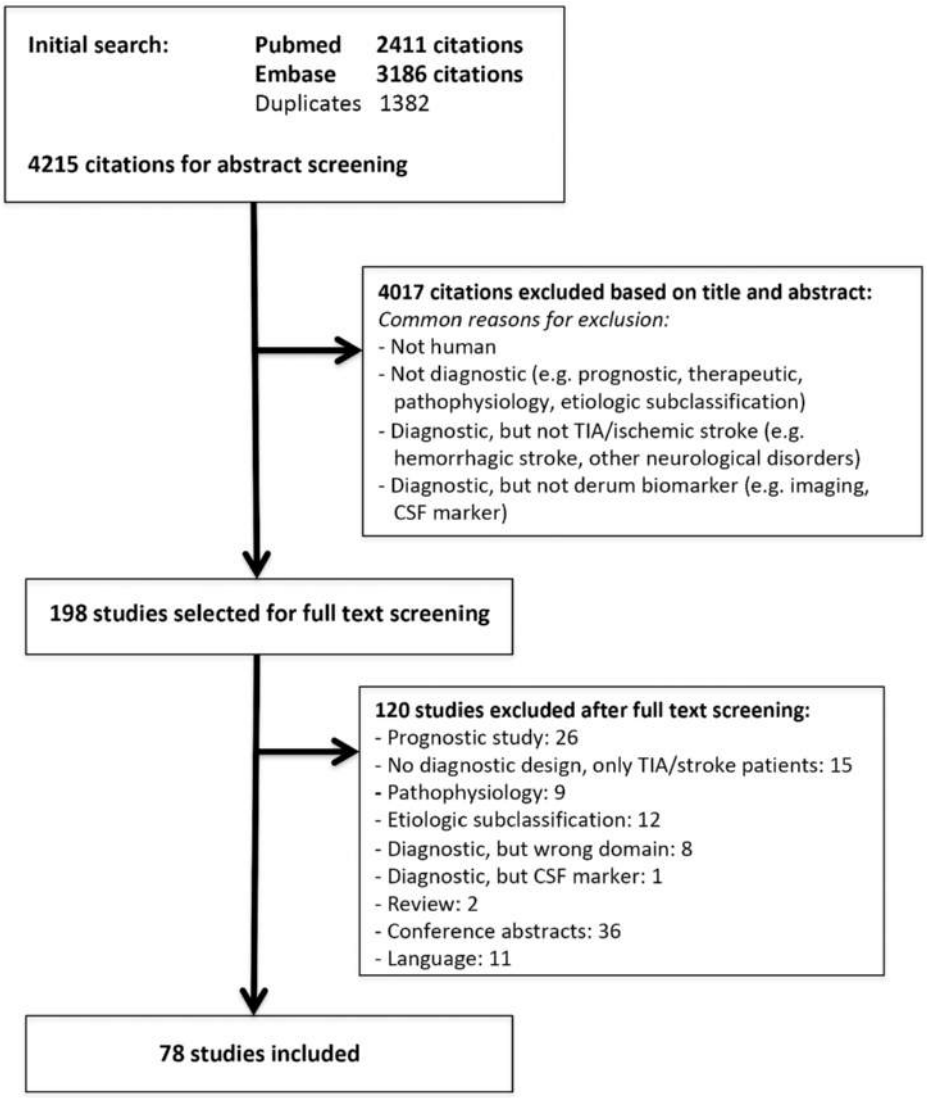



**Figure 1.** Flowchart of the systematic review search strategy.
TIA, Transient Ischemic Attack; CSF, cerebrospinal fluid.

Most studies used the evaluation of the attending neurologist as the reference standard for the diagnosis of TIA or stroke. In 5 (6.4%) studies a panel diagnosis was used (two or three panel members). Classification of ischemic cerebrovascular disease according to the tissue-based definition of TIA was reported in only one study. The remaining studies all used the time-based definition for TIA or did not report the applied definition of TIA. Some studies (12/32 [37.5%]) clearly distinguish

TIA from stroke as a separate entity in their main analysis. Three studies (9.4%) classified TIA as a non-stroke diagnosis. Most often (17/32 [53.1%]) TIA and (minor) stroke were combined as ischemic cerebrovascular diagnoses.

Most studies described the time window of blood sampling for biomarker assessment in relation to the onset of symptom or signs, 17 (21.8%) studies reported the actual time (median or mean) to blood sampling.

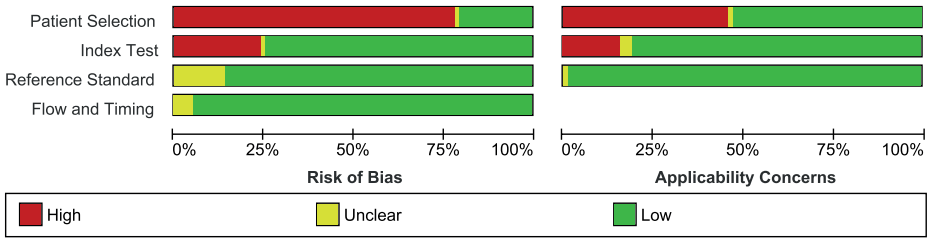



**Figure 2.** Risk of bias and applicability concerns summary about each QUADAS-2 domain presented as percentages across the 78 included studies.

## Biomarkers identified

A total of 124 single biomarkers and five biomarker panels were studied. Of the single biomarkers, 91 (73.4%) were only evaluated in a case-control design, of which 74 in a single study and 17 in two or more studies. The remaining 33 (26.6%) markers were evaluated in at least one study among patients suspected of TIA or stroke, of which 24 markers were evaluated in multiple studies (including case-control studies). The number of biomarkers tested per study varies from 1 to 17. Sufficient information to extract 2x2 tables was reported in 35 (44.9%) articles, and for 60 (48.4 %) biomarkers. Of these markers only one was examined in a second cohort using the same cut-off. Of the biomarker panels, one was evaluated among suspected cases, and four in a single case control study.

In the next section we will discuss results of several candidate biomarkers that showed potential as an early marker of TIA. Figure 3 presents a forest plot with both reported and estimated AUCs per study of these markers. Additionally, a scoping plot (figure 4) depicts to what extent the same markers have been evaluated in the domain of interest, i.e. patients suspected of TIA.

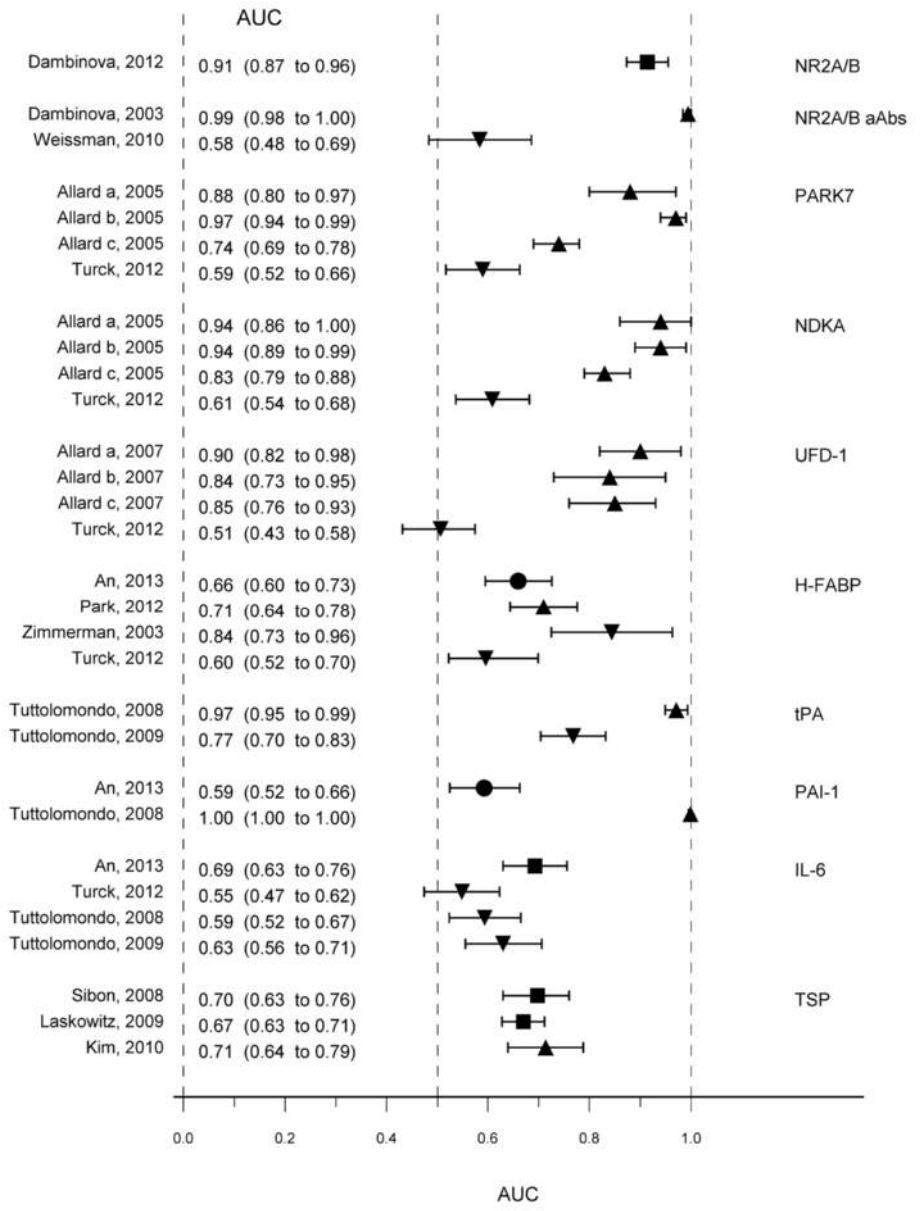



**Figure 3.** Forest plot with both reported and estimated AUCs per study, of candidate biomarkers that showed potential to be an early marker of TIA.
AUC, area under the ROC curve; NR2A/B, N-Methyl-D-aspartate receptor subunit; NR2A/B Abs, antibodies to NR2A/B; PARK-7, Parkinson 7; NDKA, Nucleoside Diphosphate Kinase A; UFD-1, Ubiquitin Fusion Degradation protein 1; H-FABP, heart-type fatty acid binding protein; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; IL-6, interleukin-6; TSP, Triage Stroke Panel.
■ = cohort of suspected cases, reported AUC; ● = cohort of suspected cases, estimated AUC; ▲ = case-control design, reported AUC; ▼ = case-control design, estimated AUC.

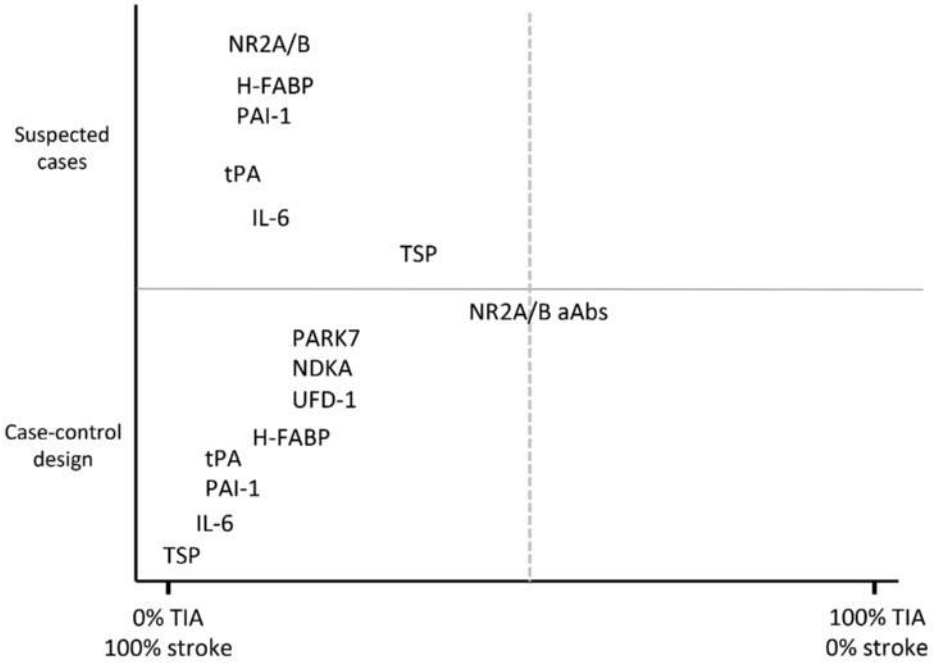



**Figure 4.** Scoping plot depicting to what extent candidate markers have been evaluated in the domain of interest, i.e. patients suspected of TIA.
TIA, transient ischemic attack; NR2A/B, N-Methyl-D-aspartate receptor subunit; NR2A/B Abs, antibodies to NR2A/B; H-FABP, heart-type fatty acid binding protein; PAI-1, plasminogen activator inhibitor 1; tPA, tissue plasminogen activator; IL-6, interleukin-6; TSP, Triage Stroke Panel; PARK-7, Parkinson 7; NDKA, Nucleoside Diphosphate Kinase A; UFD-1, Ubiquitin Fusion Degradation protein 1.

## Individual biomarkers

*NR2A/2B and NR2A/2B antibodies*

NR2A/2B is a peptide fragment produced by the cleavage of synaptic N-Methyl-D-aspartate (NMDA) receptors. The excitatory NMDA receptor is one of the key regulators in the ischemic cascade of the brain. The NR2A/2B fragments can pass the blood-brain-barrier and enter the bloodstream immediately after an episode of brain ischemia. These peptide fragments may act as foreign antigens and abnormally high concentrations initiate an immune response which generates measurable autoantibodies (aAbs) in the blood.[14] Both NR2A/B and NR2A/B aAbs are measured by enzyme-linked immunosorbent assay (ELISA); NR2A/B is also available as a point-of-care test (POCT).

NR2A/2B was tested as a single marker in a population of 192 patients suspected of ischemic stroke (ischemic stroke diagnosis N=101, non-stroke diagnosis N=91). Dambinova et al (2012) reported a negative predictive value (NPV) of 96.0% (95%CI 92.3 - 98.3) and positive predictive value (PPV) of 93.0% (95%CI 86.1 - 97.1) for NR2A/2B applying the cut-off value of 1.0 µg/L in this population.[15] Two previous studies of the same research group evaluating NR2A/2B aAbs were designed as case-control study. In the first study NR2A/2B aAbs values did not differ significantly between 56 TIA and 31 ischemic stroke patients. A comparison with healthy volunteers resulted in a high c-statistic of 0.99 (no 95% CI given) at an optimal cut-off value of 2.0 g/L.[14] In the second study, interestingly, levels of NR2A/2B aAbs were higher in patients with prior TIA or stroke than in patients with a first acute TIA or stroke.[16]

*PARK7, NDKA and UFD-1*

Parkinson 7 (PARK7), Nucleoside Diphosphate Kinase A (NDKA) and Ubiquitin Fusion Degradation protein 1 (UFD-1), all three ELISA tests, were first identified in postmortem cerebrospinal fluid of stroke patients and later validated as early plasma markers of stroke by a research group from Switzerland. Allard et al reported results of these markers in blood in three different cohorts, comparing stroke patients (total stroke N=622, TIA N=153) to healthy controls. NPVs ranged from 57% to 92% and PPVs from 82% to 97%, depending on the cut-off value applied.[17,18] Relevant to our review question is that these markers were equally increased in TIA patients and ischemic stroke patients. Also, all three markers seem to fit the clinically relevant time window, as increased biomarkers levels within 3 hours after onset did not differ from levels after 3 hours (ranging till 5 days after onset).

A recent publication (2012) of the same research group showed an assessment of 29 biomarkers in a new cohort (103 strokes (19 TIA) and 132 healthy controls). The main objective of this study was to determine if biomarkers can act as a time indicator, detecting very early stroke patients within the therapeutic window for thrombolysis. Accuracy data for differentiating strokes from healthy subjects are not given, but PARK7 and NDKA (and not UFD1) belong to the 5 markers that show the largest differences between cases and controls.[19] A study in a clinical population suspected of cerebrovascular disease is lacking.

*H-FABP*

Heart-type fatty acid binding protein (H-FABP) is a small protein involved in the intracellular transport and oxidation of fatty acids. It was named after its first

detection in myocardium, but it is also enriched in neuronal cell bodies in the central nervous system, and is rapidly released from tissue to peripheral blood following an ischemic event. Besides a marker for cardiac ischemia, H-FABP has also shown to be a marker for stroke.[20] Both H-FABP ELISA kits and POCT are available.

All four studies identified that evaluated H-FABP found positive associations with ischemic stroke.[19-22] Two studies report accuracy measures, both from a case-control comparison with primarily strokes as cases. In 2004 a 'pilot study' with a small sample size of 22 cases (11 ischemic stroke, 6 intracerebral hemorrhage, 5 TIA) and 22 controls, reported 68.8% sensitivity and 100% specificity.[21] However, in a larger population (111 ischemic strokes and 127 controls with other neurologic diagnoses) lower accuracy was found at a newly defined cut-off: 59.5% sensitivity and 79.5% specificity.[20] Based on these data the authors concluded that H-FABP appears to be unfit for use as a single marker because of limited sensitivity, but might add value in a panel of markers.

*tPA and PAI-1*

Tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1), both measured by ELISA, are markers of thrombotic/fibrinolytic mechanisms. tPA is an enzyme involved in the breakdown of a blood clot by catalyzing the conversion of plasminogen to plasmin. We know recombinant tPA as thrombolytic drug in the early treatment of stroke. PAI-1 is a principal inhibitor of tPA.

Tuttolomondo et al first evaluated both markers in a case-control design with only ischemic stroke patients (N=120); the reported discriminative characteristics were remarkably high (AUC of tPA 0.97, and of PAI-1 0.99).[23]

Both markers have also shown diagnostic potency, however limited, in patients suspected of stroke or TIA. tPA was an independent predictor of stroke diagnosis (OR 1.63 [95%CI 1.20-2.21] for the 75th versus the 25th centile of the marker distribution) in a study with 405 suspected stroke patients (40/285 cerebrovascular events were TIAs).[24] The authors also showed a modest yet non-significant improvement of the AUC by the addition of tPA to the Face Arm Speech Test (FAST) (from 0.60 [95% CI 0.55–0.65] to 0.66 [95% CI 0.60–0.72]). PAI-1 was evaluated by An et al in addition to a clinical model in a population of 278 suspected strokes. PAI-1 was an independent predictor of stroke in a model with age, sex, cardiovascular risk factors and serum creatinine. However, PAI-1 did not remain as an independent variable in the best diagnostic model consisting of age, FAST, atrial fibrillation and three other serum markers (S100B, MMP-9 and IL-6).[22]

*IL-6*

Interleukin-6 (IL-6) is a cytokine involved in inflammation and infection responses but also in the regulation of metabolic, regenerative, and neural processes. IL-6 expression is increased in the brain following ischemia, and damaged neurons may contribute to its increased levels. IL-6 is one of the markers of inflammation most studied as stroke biomarker.[25]

Various case-control studies demonstrate that plasma IL-6 is elevated in the acute phase of ischemic stroke.[19,23,26] Two studies have evaluated IL-6 in a clinical population of suspected stroke patients. In the previously mentioned Korean study by An et al IL-6 is among the three (out of ten) markers that are independent predictors in multivariate regression analyses including clinical variables (OR 1.77, 95% CI 1.31–2.38, p<0.001). In this population with 175 ischemic stroke and 13 TIA patients the panel IL-6/S100B/MMP-9 showed added value beyond age, atrial fibrillation and FAST symptoms (AUC: 0.865 vs. 0.837, p=0.069).[22] In the second study with 405 patients suspected of stroke, IL-6 was associated with stroke but had no added value beyond FAST in bivariate logistic regression analysis.[24]

*Triage Stroke Panel*

The Triage Stroke Panel (TSP) is a rapid, point-of-care fluorescence immunoassay. It simultaneously measures four biomarkers (B-type natriuretic peptide, D-dimer, matrix metalloproteinase-9, and S100B) resulting in a single composite result, the Multimarker Index (MMX).[27]

The MMX was developed by the BRAIN study group in a population of 1,146 patients suspected of stroke recruited at 17 different hospitals in the USA.[28] The model was created to discriminate between all stroke diagnoses (including TIA) and non-stroke diagnoses. Temporal validation was performed in a set of 343 patients recruited in the same hospitals after completion of the primary study, showing virtually identical discriminative characteristics. For all stroke diagnoses the AUC was 0.69 (no 95% CI given). The chosen optimal cut-off had a sensitivity of 90% and a specificity of 47%. A sub-analysis showed that the discriminative capacity was poor for identifying TIA beyond three hours after onset (0-3 hours; AUC 0.69, 3-24 hours; AUC 0.43-0.48).

The commercial TSP was evaluated in emergency department settings by two different research groups. Sibon et al. (2009) found discriminative characteristics for all strokes (including TIA) comparable to the BRAIN study (AUC 0.70 [95% CI 0.63-0.76], sensitivity 94%, specificity 24%). Although there was no subgroup analysis for TIA (33 of 131 strokes), descriptive results show that the probability of TIA is virtually equal for MMX scores higher and lower than the MMX cut-off score

of 1.3.[29] Vanni et al. (2011) evaluated TSP in 155 patients suspected of stroke, but they considered TIA as a non-stroke diagnosis in their analysis. Therefore, these results were not useful in answering our research question.[27]

*miRNA*

MicroRNAs (miRNAs) are non-protein-coding short RNA molecules that regulate gene expression, and divided into intracellular and extracellular, or circulating, miRNAs.[30] The usefulness of miRNAs is now being evaluated for various diseases including ischemic stroke. Test methods for miRNA are more complex and part of an actively developing field. The studies on miRNAs we found with our search report high accuracy, but all had major methodological limitations. Most studies generated new potential markers with a strategy of first selecting miRNAs with the largest difference between stroke and healthy subjects by miRNA profiling and then present diagnostic accuracy for those miRNAs in the same patients. All studies had a case-control design, and validation studies are lacking.

## DISCUSSION

With our systematic literature review on blood biomarkers for the diagnosis of TIA we show that not a single biomarker study evaluated the performance in the intended population of interest: patients suspected of TIA. There are studies providing accuracy data on detecting or excluding ischemic stroke, but most had methodological shortcomings. Small sample sizes, a case-control design comparing TIA(/stroke) patients with healthy controls, data-derived thresholds, and not externally validating the performance in new patients all lead to a difficult to interpret and questionable evidence base for the role of these biomarkers in daily practice.

We identified a total of 124 different biomarkers being studied. They form a heterogeneous group of markers originating from various cell types and involved in very diverse cellular processes, many of which are not restricted to the brain. Some have a theoretical basis and were developed in animal or in vitro models, while others have been identified by comparing plasma or liquor of stroke patients with that of healthy subjects.

Although evidence is limited, some markers might have added value beyond the clinical assessment in diagnosing brain ischemia, and specifically in TIA suspected cases. NR2A/B was the only single marker that had both high negative and positive predictive values in a population of suspected stroke (N=192, with 101

ischemic strokes and 91 non-stroke diagnoses). Predictive values of PARK7 and NDKA were also high, but these data were all derived from case-control design studies thus overestimating the real diagnostic accuracy that should be calculated from the domain of suspected cases and then comparing cases with non-cases.[5] Other shortcomings are the small sample sizes of the separate cohorts and that different cut-offs were applied. Markers H-FABP, tPA, PAI-1 and IL-6 seem to be unfit as a single marker, but may add value in a combination of markers. TSP (Triage Stroke Panel), the first commercial panel of stroke markers, showed to have poor discriminative capacity in subgroups of suspected TIA patients. MiRNAs are a relatively new source of biomarkers and many new miRNAs are proposed by profiling studies, but to date the usefulness for TIA/stroke diagnosis remains uncertain because of a lack of reliable data.

Whiteley et al performed a systematic review of blood biomarkers in the diagnosis of ischemic stroke in 2007. They similarly concluded that design and reporting of many biomarker studies was poor.[4] The 58 markers they identified largely correspond with the markers identified by our review as a result of the overlapping study domains. However, ten years of research yielded many new proposed biomarkers and also new data on existing markers. Fifty-five of our 78 included studies were published after 2007.



Strength of our review is the clear focus on diagnostic markers for TIA, however, with a broad search as a starting point including studies that evaluated biomarkers for all-type brain ischemia. TIA and ischemic stroke are similar in that they are clinical expressions (of different degrees) of brain ischemia, thus in principle they largely share the same markers, except for markers of cell necrosis. A broad search was required to also identify biomarkers that showed potential as a diagnostic marker of ischemic stroke, but have not been evaluated for suspected TIA yet. The complete review process was performed by two reviewers who applied a modified QUADAS2 tool to evaluate the quality of diagnostic studies.

Limitations must also be considered. We had to assess the performance of a large number of different markers in studies with much heterogeneity in design and reporting, and on average poor quality. It was therefore impossible to adequately compare the diagnostic potential of the various markers or even provide a summary odds ratio. The ‘selection’ of the most promising markers based on this review is still sensitive to subjectivity. Considering the various utilities of biomarkers we decided to narrow our search by a broad set of diagnostic terms as a filter because a validated diagnostic filter is lacking.[31] We may have missed potential biomarkers using this filter, although in our opinion it is unlikely that studies lacking our diagnostic terms would add biomarkers with supporting

evidence of diagnostic value. A final concern is the possible effect of publication bias with underreporting of negative results.

A large study in patients suspected of TIA is needed to get a valid estimate of the accuracy of blood biomarkers. At present it is doubtful whether a single marker would have add substantial diagnostic value beyond the clinical assessment. A multimarker panel such as the Triage Stroke Panel (TSP) may produce higher accuracy, but other combinations than TSP need to be evaluated.

## Conclusions

Currently, none of the evaluated biomarkers can be recommended for diagnosing TIA in suspected cases. Adequately performed diagnostic studies are needed that evaluate some of the promising markers in the domain of patients suspected of TIA.

## REFERENCES


1. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007;6(12):1063-72.
2. Rothwell PM, Algra A Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016;388(10042):365-375.
3. Kernagis DN, Laskowitz DT. Evolving role of biomarkers in acute cerebrovascular disease. Ann Neurol. 2012;71(3):289-303.
4. Whiteley W, Tseng MC, Sandercock P. Blood biomarkers in the diagnosis of ischemic stroke: a systematic review. Stroke. 2008;39(10):2902-9.
5. Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM. Evidence of bias and variation in diagnostic accuracy studies. CMAJ. 2006;174(4):469-76.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
7. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
8. Bertens LC, Broekhuizen BD, Naaktgeboren CA, Rutten FH, Hoes AW, van Mourik Y, et al. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. PLoS Med. 2013;10(10):e1001531.
9. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-93.
10. Moreau F, Asdaghi N, Modi J, Goyal M, Coutts SB. Magnetic Resonance Imaging versus Computed Tomography in Transient Ischemic Attack and Minor Stroke: The More You See the More You Know. Cerebrovasc Dis Extra. 2013;3(1):130-6.
11. Förster A, Gass A, Kern R, Ay H, Chatzikonstantinou A, Hennerici MG, et al. Brain Imaging in Patients with Transient Ischemic Attack: A Comparison of Computed Tomography and Magnetic Resonance Imaging. Eur Neurol. 2012;67(3):136-41.
12. Faraggi D, Reiser B. Estimation of the area under the ROC curve. Stat Med. 2002;21(20):3093-106.
13. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29-36.
14. Dambinova SA, Khounteev GA, Izykenova GA, Zavolokov IG, Ilyukhina AY, Skoromets AA. Blood test detecting autoantibodies to N-methyl-D-aspartate neuroreceptors for evaluation of patients with transient ischemic attack and stroke. Clin Chem. 2003;49(10):1752-62.
15. Dambinova SA, Bettermann K, Glynn T, Tews M, Olson D, Weissman JD, et al. Diagnostic potential of the NMDA receptor peptide assay for acute ischemic stroke. PLoS One. 2012;7(7):e42362.

16. Weissman JD, Khunteev GA, Heath R, Dambinova SA. NR2 antibodies: risk assessment of transient ischemic attack (TIA)/stroke in patients with history of isolated and multiple cerebrovascular events. J Neurol Sci. 2011;300(1-2):97-102.
17. Allard L, Burkhard PR, Lescuyer P, Burgess JA, Walter N, Hochstrasser DF, et al. PARK7 and nucleoside diphosphate kinase A as plasma markers for the early diagnosis of stroke. Clin Chem. 2005;51(11):2043-51.
18. Allard L, Turck N, Burkhard PR, Walter N, Rosell A, Gex-Fabry M, et al. Ubiquitin fusion degradation protein 1 as a blood marker for the early diagnosis of ischemic stroke. Biomark Insights. 2007;2:155-64.
19. Turck N, Robin X, Walter N, Fouda C, Hainard A, Sztajzel R, et al. Blood glutathione S-transferase-pi as a time indicator of stroke onset. PLoS One. 2012;7(9):e43830.
20. Park SY, Kim MH, Kim OJ, Ahn HJ, Song JY, Jeong JY, et al. Plasma heart-type fatty acid binding protein level in acute ischemic stroke: comparative analysis with plasma S100B level for diagnosis of stroke and prediction of long-term clinical outcome. Clin Neurol Neurosurg. 2013;115(4):405-10.
21. Zimmermann-Ivol CG, Burkhard PR, Le Floch-Rohr J, Allard L, Hochstrasser DF, Sanchez CJ. Fatty acid binding protein as a serum marker for the early diagnosis of stroke: a pilot study. Mol Cell Proteomics. 2004;3(1): 66-72.
22. An SA, Kim J, Kim OJ, Kim JK, Kim NK, Song J, et al. Limited clinical value of multiple blood markers in the diagnosis of ischemic stroke. Clin Biochem. 2013;46(9):710-5.
23. Tuttolomondo A, Pinto A, Corrao S, Di Raimondo D, Fernandez P, Di Sciacca R, et al. Immuno-inflammatory and thrombotic/fibrinolytic variables associated with acute ischemic stroke diagnosis. Atherosclerosis. 2009;203(2):503-8.
24. Whiteley W, Wardlaw J, Dennis M, Lowe G, Rumley A, Sattar N, et al. Blood biomarkers for the diagnosis of acute cerebrovascular diseases: a prospective cohort study. Cerebrovasc Dis. 2011;32(2):141-7.
25. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta. 2011;1813(5):878-88.
26. Lynch JR, Blessing R, White WD, Grocott HP, Newman MF, Laskowitz DT. Novel diagnostic test for acute stroke. Stroke. 2004;35(1):57-63.
27. Vanni S, Polidori G, Pepe G, Chiarlone M, Albani A, Pagnanelli A, et al. Use of biomarkers in triage of patients with suspected stroke. J Emerg Med. 2011;40(5):499-505.
28. Laskowitz DT, Kasner SE, Saver J, Remmel KS, Jauch EC. Clinical usefulness of a biomarker-based diagnostic test for acute stroke: the Biomarker Rapid Assessment in Ischemic Injury (BRAIN) study. Stroke. 2009;40(1):77-85.
29. Sibon I, Rouanet F, Meissner W, Orgogozo JM. Use of the Triage Stroke Panel in a neurologic emergency service. Am J Emerg Med. 2009;27(5):558-62.
30. Long G, Wang F, Li H, Yin Z, Sandip C, Lou Y, et al. Circulating miR-30a, miR-126 and let-7b as biomarker for ischemic stroke in humans. BMC Neurol. 2013;13:178.
31. Beynon R, Leeflang MM, McDonald S, Eisinga A, Mitchell RL, Whiting P. et al. Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE. Cochrane Database Syst Rev. 2013;(9):Mr000022.

**Box 1. Search terms used**

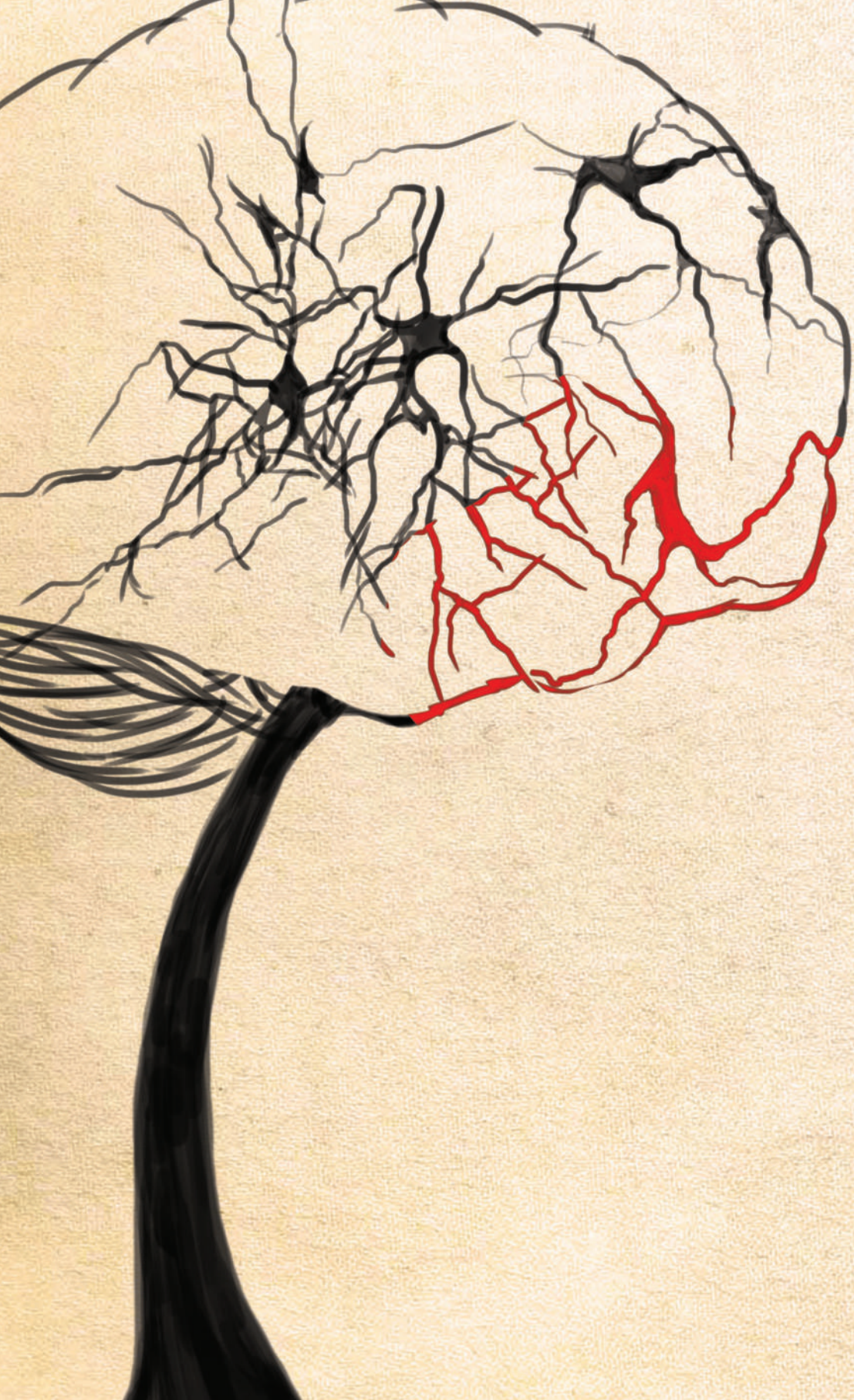
**PubMed search terms**

((((((((((((biological markers[MeSH Terms]) OR diagnostic marker*[Title/Abstract]) OR biomarker[Title/Abstract]) OR marker*[Title/Abstract]) OR antibody[Title/Abstract]) OR antibodies[Title/Abstract]) OR antigen*[Title/Abstract]) OR laboratory test[Title/Abstract]) OR blood test[Title/Abstract]) OR *RNA[Title/Abstract]) OR microRNA[Title/Abstract])) AND ((((((((((((((((((((((((((((ischemic attack, transient[MeSH Terms]) OR Transient ischemic attack*[Title/Abstract]) OR Transient ischaemic attack*[Title/Abstract]) OR TIA[Title/Abstract]) OR TIAs[Title/Abstract]) OR attack* AND , transient ischemic[Title/Abstract]) OR attack* AND , transient ischaemic[Title/Abstract]) OR Ischemic attack* AND , transient[Title/Abstract]) OR ischaemic attack* AND , transient[Title/Abstract]) OR cerebral ischemia*[Title/Abstract]) OR cerebral ischaemia*[Title/Abstract]) OR brain ischemia*[Title/Abstract]) OR brain ischaemia*[Title/Abstract]) OR Stroke*[Title/Abstract]) OR stroke[MeSH Terms]) OR CVA[Title/Abstract]) OR CVAs[Title/Abstract]) OR Cerebrovascular accident*[Title/Abstract]) OR brain vascular accident*[Title/Abstract]) OR vascular accident* AND , brain[Title/Abstract]) OR brain infarction[Title/Abstract]) OR cerebral infarction[Title/Abstract]) OR ischemic brain[Title/Abstract]) OR ischaemic brain[Title/Abstract]) OR ischemic neuronal[Title/Abstract]) OR ischaemic neuronal[Title/Abstract]) OR neuronal ischemia[Title/Abstract]) OR neuronal ischaemia[Title/Abstract]) OR ischemic encephalopathy[Title/Abstract]) OR ischaemic encephalopathy[Title/Abstract])) AND ((((((((((sens[Title/Abstract]) OR spec[Title/Abstract]) OR sensitiv*[Title/Abstract]) OR specific*[Title/Abstract]) OR diagno*[Title/Abstract]) OR area[Title/Abstract]) OR auc[Title/Abstract]) OR roc[Title/Abstract]) OR false[Title/Abstract])

*Animal studies filtered out*

**Embase search terms**

('biological marker'/exp OR 'biochemical marker'/exp OR 'molecular marker'/exp OR biomarker*:ab,ti OR 'laboratory test':ab,ti OR 'laboratory tests':ab,ti OR 'blood test':ab,ti OR 'blood tests':ab,ti OR rna:ab,ti OR microrna:ab,ti) AND ('brain infarction'/exp OR 'brain ischemia'/exp OR 'cerebrovascular accident'/exp OR 'transient ischemic attack':ab,ti OR 'transient ischaemic attack':ab,ti OR tia:ab,ti OR tias:ab,ti OR 'cerebral ischemia':ab,ti OR 'cerebral ischaemia':ab,ti OR 'brain ischaemia':ab,ti OR stroke*:ab,ti OR cva:ab,ti OR cvas:ab,ti OR 'cerebrovascular accidents':ab,ti OR 'cerebral infarction':ab,ti OR 'ischemic brain':ab,ti OR 'ischaemic brain':ab,ti OR 'ischemic encephalopathy':ab,ti OR 'ischaemic encephalopathy':ab,ti) AND (sens:ab,ti OR spec:ab,ti OR sensitiv*:ab,ti OR specific*:ab,ti OR diagno*:ab,ti OR area:ab,ti OR auc:ab,ti OR roc:ab,ti OR false:ab,ti) AND [humans]/lim AND [embase]/lim



# Chapter 7

# No added value of serum biomarkers in suspected TIA: results of the MIND-TIA study

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## ABSTRACT

### Objective

The diagnosis of TIA based on symptoms and signs can be challenging and would greatly benefit from a rapid serum biomarker of brain ischaemia. We aimed to quantify the added diagnostic value of serum biomarkers in patients suspected of TIA beyond symptoms and signs.

### Methods

A cross-sectional diagnostic accuracy study with a six-month follow-up period. Participants were patients suspected of TIA by the general practitioner (GP), in whom a blood sample could be collected within 72 hours from symptom onset. A research nurse visited the participant for the blood sample and a standardised interview. The GP referred participants to the regional TIA service. An expert panel of three neurologists classified cases as TIA, minor stroke or any other diagnosis, based on all available diagnostic information including the GP's and neurologist's correspondence and the follow-up period. We used multivariable logistic regression analyses to quantify the diagnostic accuracy of clinical predictors, and the improvement of accuracy by seven biomarkers (NR2, NR2Abs, PARK7, NDKA, UFD-1, B-FABP, H-FABP).

### Results

206 patients suspected of TIA participated, of whom 126 (61.2%) were diagnosed with TIA (n=104) or minor stroke (n=22) by the expert panel. Median time from symptom onset to the blood sample collection was 48.0 (IQR 28.3-56.8) hours. None of the seven biomarkers had discriminative value in the diagnosis of TIA, with c-statistics ranging from 0.45 to 0.58. The final multivariable model (c-statistic 0.83 [0.78-0.89]) consisted of eight clinical predictors of TIA/minor stroke: increasing age, a history of coronary artery disease, sudden onset of symptoms, occurrence of symptoms in full intensity, dysarthria, no history of migraine, absence of loss of consciousness, and absence of headache. Addition of the individual biomarkers did not further increase the c-statistic.

### Conclusion

Currently available blood biomarkers have no added diagnostic value in suspected TIA.

## INTRODUCTION

Symptoms suggestive of a transient ischaemic attack (TIA) often pose a diagnostic dilemma, and at the same time warrant urgency as the risk of a subsequent ischaemic stroke is highest during the first hours and days following a TIA.[1,2] A rapid and complete diagnostic assessment and urgent start of adequate treatment to prevent subsequent ischaemic stroke substantially decreases this risk, with the early initiation of an antithrombotic as the key intervention.[3-5]

Symptoms and signs of a TIA are typically short-lasting (5-30 minutes), and have often disappeared by the time the patient consults a physician, which is often a general practitioner (GP). The diagnosis of TIA is mainly based on careful history taking, and can be notoriously difficult for physicians. The differential diagnosis is broad and depends on symptoms and setting, with migraine and epileptic seizures as important TIA mimics. Especially, TIAs originating from the vertebrobasilar artery territory are often hard to distinguish from benign entities such as peripheral vestibular syndromes. MRI is recommended as imaging modality to confirm novel ischaemic lesions with diffusion weighted imaging,[6, 7] but referral of every patient presenting with any symptom of TIA for MRI is impossible. Moreover, MRI is less widely available than CT, and still a minority of suspected TIA patients has relevant lesions on MRI (30-40%).[6,7] In primary care, the GP has the difficult task to decide, based on history taking only, whether the patient should be referred to the neurologist.

In patients referred by the GP to a TIA service, the diagnosis of TIA is confirmed by neurologists in around 70% of cases.[8-10] However, also the neurologist is not always sure; in about a quarter of cases the definite diagnosis by the neurologist holds a degree of uncertainty, i.e. the neurologist concludes that a TIA is probable or possible.[11] Even among experienced neurologists there is substantial interobserver disagreement in TIA diagnosis with Cohen's kappa statistics varying from 0.65 to 0.78.[8]

A possible solution to these diagnostic difficulties would be a serum biomarker that can reliably detect (transient) brain ischaemia in an early phase after symptom onset. This would enable a more accurate diagnosis within a short time frame. We designed the MIND-TIA (Markers in the Diagnosis of TIA) study to evaluate markers of brain ischaemia for this purpose.[12] We performed a systematic review to select candidate markers that can be detected in blood immediately after a TIA and remain detectable until several days after.[12] Previous clinical biomarker studies in the field of cerebral ischaemia focused on (major) stroke, and most studies compared

stroke patients with healthy volunteers, and thus did not evaluate the biomarkers in patients *suspected* of cerebral ischaemia, the domain of clinical interest.

In the current study we aimed to assess the added diagnostic value of serum biomarkers in addition to symptoms and signs in patients suspected of TIA.

## METHODS

We described the design and methods of the MIND-TIA study in detail elsewhere.[12] In short, the MIND-TIA study was a cross-sectional diagnostic study, with an additional follow-up period of six months. Participants were patients suspected of a TIA by their GP who were referred to a TIA service. In all participants we performed a biomarker assessment (index test) and the 'definite' diagnosis of TIA was determined by a panel of three experienced stroke neurologists (the reference standard), who based their consensus opinion on all available diagnostic information, including imaging of the brain and the 6 months of follow-up, but without the information from the biomarkers.

### Study population

From September 2013 till September 2016 we included patients with a new (not necessarily first) episode of symptoms or signs suspected of a TIA by their GP. Patients were eligible if a blood sample could be collected within 72 hours of symptom onset. Patients were recruited immediately after GP consultation, or during their visit at the TIA outpatient clinic. Over 350 GPs and 11 TIA outpatient clinics in the region of Utrecht (The Netherlands) participated. Patients were excluded if (i) they still had active symptoms or signs at the time of recruitment (i.e. during consultation of the GP) and therefore were suspected of an ongoing stroke, (ii) blood could not be drawn within 72 hours, (iii) valid history taking was impossible because of severe cognitive impairment or insufficient knowledge of the Dutch language, or (iv) life expectancy was less than six months.

### Main study procedures

A research nurse visited the participant at home or at the TIA outpatient clinic, to draw a blood sample as soon as possible after inclusion. Additionally, the research nurse interviewed the patient and filled out a standardised case record form (CRF) on symptoms and signs. Following routine care, the GP referred participants to the regional TIA outpatient clinic. We collected all correspondence of the GP and the neurologist at the TIA service, including the results of additional investigations such

as carotid duplex scan, (holter) ECG and CT or MRI of the brain. After six months we scrutinized the electronical medical files of the GP for recurrent cerebro- and cardiovascular events, and other episodes of symptoms relevant to the diagnosis of the initial event.

### Panel diagnosis

An expert panel of three vascular neurologists evaluated standardised case summaries based on the CRF (including medical history, initial signs and symptoms, and the patient's own narrative account of symptoms), GP's and neurologist's correspondence, and the six months of follow-up. Without knowledge of the biomarker values, cases were classified as a TIA, a minor ischaemic stroke, or any other diagnosis. The panel primarily applied the time-based definition of TIA (symptoms lasting < 24 hours).[13] However, for each case the panel also determined whether neuroimaging (CT and/or MRI) showed ischaemic lesions corresponding with this symptom episode.

The panel members assessed all cases individually, providing both their most likely diagnosis and their estimation of the chance of a TIA on a visual analogue scale (VAS). Consensus on the diagnosis of TIA was assumed if all three neurologists similarly scored the chance of TIA ≤ 20% or ≥ 80 %. All other cases were discussed during a panel meeting and a final judgement was based on a majority of votes. At the end of the study we informed the treating GP about the panel diagnosis.



### Biomarker assessment

We assessed the following biomarkers in serum: NR2, NR2 antibodies (NR2Ab), B-FABP, H-FABP, NDKA, UFD1 (all by sandwich enzyme-linked immunosorbent assay (ELISA) procedures), and PARK-7 (by Luminex assay procedure). See *Supplementary file* for main characteristics of these biomarkers. The Laboratory of Clinical Chemistry and Haematology of the University Medical Center Utrecht performed the measurements, without knowledge of the panel outcome.

NR2 and NR2 antibody were measured using the Gold Dot NR2 Peptide Test and Gold Dot NR2 Antibody Test (CIS Biotech, Inc., Decatur, USA). The lower limits of detection (LOD) were 0.1 ng/mL and 0.8 ng/mL, respectively.

B-FABP, NDKA and UFD1 were measured with the FABP7 ELISA (EKU04045), NME1 ELISA (EKC34865) and UFD1L ELISA (EKC35975) from Biomatik, Cambridge, Ontario. For B-FABP the LOD was 0.2 ng/mL and inter-assay variation at 0.40 ng/mL 11.0%. For NDKA, the LOD was 10 pg/mL, and inter-assay variation at 40 pg/mL was 10.1%. For UFD1, the lower limit of detection was 62.5 pg/mL, and inter-

assay variation <14%.H-FABP was measured using the FABP3 ELISA (RAB0657), from Merck Sigma-Aldrich, Saint Louis, Missouri, USA. The LOD was 8 ng/mL, and inter-assay variation <11.5%.

Park7 was measured using a beads-based multiplex-immunoassay. The Bio-Plex® 200 Systems (Bio-Rad#171–000201) were used for measurement and data analysis. Limit of quantitation for Park7 was 100 pg/mL. Inter-assay variation was <5.3%.

### Data analysis

All diagnostic variables of routine clinical assessment (symptoms and signs) of the GP and the (mean and median) biomarker values are presented for subjects with a TIA or minor stroke and subjects with other diagnoses. Biomarker levels of both groups were compared using Mann-Whitney U tests. Three biomarkers showed test results below the detection range. In these cases, we assigned a biomarker level fixed at 50% of the lower limit of detection in our database, and the mean and median values of only those patients with values within the detection range are presented in a separate table.

Diagnostic accuracy measures were assessed for both clinical characteristics and biomarkers. We created ROC curves and used the Youden index to determine the cut-off of maximum potential effectiveness of the biomarkers in our population, and we present corresponding accuracy data.

We performed multivariable logistic regression analyses to quantify the diagnostic accuracy of the strongest predictors of the clinical assessment (excluding additional examinations), and aimed to determine the improvement of diagnostic accuracy by adding biomarker assessment to these clinical determinants. Harrell's rule of thumb was applied to determine the maximum number of determinants in our final multivariate model, i.e. one determinant per ten subjects in the smallest category of the outcome value (in our situation patients without TIA/minor stroke).[14] In the multivariable analysis, we used stepwise backwards selection of variables, with a cut-off of $p<0.10$.

### Patient and public involvement

There were no patients or public involved in the design or conduct of this study.

The participants of the study will be informed about the main findings of the MIND-TIA study in general (those who signed up for this).

## RESULTS

A total of 242 potentially eligible patients were announced to the research team by telephone by the GP or via TIA services. Fifteen patients needed to be excluded, because of (i) onset of symptoms more than 72 hours ago (n=7), (ii) ongoing symptoms (n=6), or (iii) severe cognitive impairment (n=2). Eight patients decided not to participate after receiving detailed study information. In thirteen additional patients it was not possible to plan a visit by the research nurse within the 72 hours from symptom onset due to logistical reasons. Characteristics of the 206 included patients are shown in Table 1.

**Table 1.** Characteristics of the 206 participants suspected of TIA by the GP, divided by the final diagnosis of the expert panel.

| Characteristic | Total (n=206) | TIA/Minor stroke (n=126) | No TIA/minor stroke (n=80) | *P* |
|---|---|---|---|---|
| **Demographic characteristics** | | | | |
| Mean age in years (SD) | 67.7 (13.7) | 71.4 (12.0) | 62.0 (14.2) | <0.001 |
| Male sex | 112 (54.4%) | 69 (54.8%) | 43 (53.8%) | 0.89 |
| **Cardiovascular risk factors** | | | | |
| BMI in kg/m$^2$ (SD) | 25.7 (4.0) | 25.7 (4.2) | 25.6 (3.8) | 0.85 |
| Smoking status | | | | |
| Current smoker | 38 (18.5%) | 18 (14.3%) | 20 (25.0%) | 0.05 |
| Former smoker | 87 (42.2%) | 58 (46.0%) | 29 (36.3%) | 0.17 |
| Never smoked | 81 (39.3%) | 50 (39.7%) | 31 (38.7%) | 0.89 |
| Alcohol consumption | (n=205) | (n=125) | (n=80) | |
| 0-7 units/week | 143 (69.8%) | 89 (71.2%) | 54 (67.5%) | 0.63 |
| 8-14 units/week | 37 (18.0%) | 22 (17.6%) | 15 (18.8%) | 0.83 |
| >14 units/week | 25 (12.2%) | 14 (11.2%) | 11 (13.7%) | 0.59 |
| First degree relatives with CVD below 65 years | (n=204) | (n=125) | (n=79) | |
| 0 | 127 (62.3%) | 84 (67.2%) | 43 (54.4%) | 0.07 |
| 1 | 59 (28.9%) | 29 (23.2%) | 30 (38.0%) | 0.02 |
| ≥2 | 18 (8.8%) | 12 (9.6%) | 6 (7.6%) | 0.62 |
| Hypertension | 121 (59%) | 84 (66.7%) | 36 (45.0%) | 0.002 |
| Diabetes mellitus | 27 (13%) | 18 (14.3%) | 8 (10.0%) | 0.37 |
| Hyperlipidaemia | 85 (42%) | 58 (46.0%) | 27 (33.8%) | 0.08 |
| **Medical history** | | | | |
| Prior cerebrovascular disease | 51 (24.8%) | 35 (27.8%) | 16 (20.0%) | 0.21 |
| TIA | 31 (15.0%) | 22 (17.5%) | 9 (11.3%) | 0.22 |
| Ischaemic stroke | 22 (11%) | 15 (11.9%) | 7 (8.8%) | 0.48 |

**Table 1.** Continued.

| Characteristic | Total (n=206) | TIA/Minor stroke (n=126) | No TIA/minor stroke (n=80) | *P* |
|---|---|---|---|---|
| **Medical history** | | | | |
| Haemorrhagic stroke | 7 (3%) | 5 (4.0%) | 2 (2.5%) | 0.57 |
| Prior cardiovascular disease | 54 (26%) | 43 (34.1%) | 11 (13.8%) | 0.001 |
| Angina pectoris | 13 (6%) | 12 (9.5%) | 1 (1.3%) | 0.02 |
| Myocardial infarction | 13 (6%) | 13 (10.3%) | 0 (0.0%) | 0.003 |
| Peripheral artery disease | 5 (2%) | 4 (3.2%) | 1 (1.3%) | 0.38 |
| Vascular surgery | 23 (11%) | 19 (15.1%) | 4 (5.0%) | 0.03 |
| Atrial fibrillation | 21 (10%) | 15 (11.9%) | 6 (7.5%) | 0.31 |
| Renal insufficiency | 16 (8%) | 11 (8.7%) | 5 (6.3%) | 0.52 |
| History of migraine | 23 (11%) | 9 (7.1%) | 14 (17.5%) | 0.02 |
| History of epilepsy | 2 (1%) | 2 (1.6%) | 0 (0.0%) | 0.26 |

TIA, transient ischaemic attack; BMI, body mass index; CVD, cardiovascular disease.

The expert panel diagnosed 126/206 (61.2%) patients with a TIA (n=104) or minor stroke (n=22). Five of the 104 TIA patients (according to the criterion of symptoms lasting < 24 hours) had (corresponding) ischaemic lesions proven with brain imaging. Among the 80 patients with alternative diagnoses, most were labelled as migraine (n=24, 30.0%), stress-related or somatoform symptoms (n=16, 20.0%), and syncope (n=9, 11.3%) (Table 2).

**Table 2.** Overview of final diagnoses in the 80 patients with no TIA or minor stroke according to the expert panel.

| Diagnoses | N (%) |
|---|---|
| Migraine with aura | 24 (30.0) |
| Stress-related/functional/somatoform | 16 (20.0) |
| Syncope (reflex syncope/orthostatic hypotension) | 9 (11.2) |
| Transient neurological attack (TNA) | 7 (8.8) |
| Vestibular syndrome | 5 (6.2) |
| Peripheral neuropathy | 2 (2.5) |
| Cranial nerve palsy | 2 (2.5) |
| Ocular disease | 2 (2.5) |
| Other diagnoses | 7 (8.8) |
| Epileptic seizure; subdural haematoma; pituitary adenoma; encephalopathy; retinal spasms; sleep phenomena; amyloid spell in cerebral amyloid angiopathy. | |
| Unclear | 6 (7.5) |
| Total | 80 |

In 87/206 (42.2%) cases the individual assessments by the panel members resulted in consensus on the presence (three VAS estimates of ≥ 80%) or absence (three VAS estimates of ≤ 20%) of TIA/minor stroke. The remaining 119 cases were discussed during panel meetings. In 51/119 cases the initial individual judgements on the most likely diagnosis were incongruent. In 14 cases disagreement remained after the panel discussion, and the majority vote (two against one) was decisive. The Fleiss kappa was 0.90 for the complete expert panel process. We resampled 20 cases for blinded re-assessment by the panel, and in 18 cases they decided uniformly while in two cases their final panel judgment was inconsistent with the original diagnosis. Table 3 compares the panel diagnosis with the diagnosis of the treating neurologist.

**Table 3.** Panel diagnosis versus the diagnosis of the treating neurologist

| | | **Diagnosis treating neurologist** | |
|---|---|---|---|
| | | **(Possible) TIA/minor stroke - *Treated as such*** | **Other diagnosis** |
| **Panel diagnosis** | **TIA/minor stroke** | 125 | 1 |
| | **Other diagnosis** | 30 | 50 |

TIA, transient ischaemic attack.



The median time from symptom onset to the blood sample collection was 48.0 (IQR 28.3-56.8) hours. Subsequently, the time until the start of sample preparation and sample storage was 1.4 (1.2-1.7) hours and 2.6 (2.5-2.7) hours respectively. In one patient we were (technically) unable to draw a blood sample.

Table 4 shows the mean and median values of all biomarkers tested, in TIA or minor stroke patients and those with alternative diagnoses. Only H-FABP showed on average higher levels in TIA/minor stroke patients. For three biomarkers a high number of patients showed biomarker values below the detection range: NR2ab (47.8%), NR2 (80.0%), and B-FABP (93.7%). In a separate table (Table 5) we give an overview of the mean and median values of these three markers selectively in those with detectable values.

**Table 4.** Mean and median values of the seven biomarkers in those with and without a TIA or minor stroke

| **Biomarker*** | | **TIA/minor stroke** | **No TIA/minor stroke** | ***P*** |
|---|---|---|---|---|
| **(unit of measurement)** | | **N= 125** | **N= 80** | |
| **NR2** | Mean (95%CI) | 0.25 (0.03-0.46) | 0.34 (0.04-0.64) | 0.95 |
| (ng/ml) | Median (IQR) | *0.05 (0.05-0.05)* | *0.05 (0.05-0.05)* | |
| **NR2Ab** | Mean (95%CI) | 1.48 (1.15-1.82) | 1.74 (1.29-2.18) | 0.21 |
| (ng/ml) | Median (IQR) | 0.90 (0.40-1.70) | 1.0 (0.40-2.10) | |
| **PARK7** | Mean (95%CI) | 16.91 (15.95-17.87) | 18.11 (16.63-19.59) | 0.37 |
| (ng/ml) | Median (IQR) | 16.61 (13.42-19.77) | 16.83 (13.87-21.08) | |
| **NDKA** | Mean (95%CI) | 68.64 (60.19-77.08) | 64.75 (53.75-75.44) | 0.47 |
| (pg/m) | Median (IQR) | 52.70 (35.80-82.33) | 48.55 (34.30-80.35) | |
| **UFD1** | Mean (95%CI) | 203.27 (168.24-238.29) | 211.70 (168.03-255.37) | 0.72 |
| (pg/ml) | Median (IQR) | 153.00 (30.00-307.00) | 173.50 (30.00-304.75) | |
| **B-FABP** | Mean (95%CI) | 0.11 (0.10-0.12) | 0.11 (0.10-0.13) | 0.95 |
| (ng/ml) | Median (IQR) | *0.10 (0.10-0.10)* | *0.10 (0.10-0.10)* | |
| **H-FABP** | Mean (95%CI) | 20.98 (18.85-22.79) | 20.21 (15.53-24.77) | 0.05 |
| (ng/ml) | Median (IQR) | 19.70 (13.83-27.00) | 17.40 (11.80-23.00) | |

TIA, transient ischaemic attack; ng/ml, nanogram per milliliter; pg/ml, picogram per milliliter; CI, confidence interval; IQR, interquartile range.
***** NR2, NR2ab and B-FABP showed test results below the detection range. These cases were assigned with a biomarker level fixed at 50% of the lower limit of detection.
****** Biomarker levels of both groups were compared using Mann-Whitney U tests.

**Table 5.** Mean and median biomarker values of only those patients with detectable levels, for the three markers that showed marker levels below limit of detection.

| **Biomarker** | | **TIA/minor stroke** | **No TIA/minor stroke** |
|---|---|---|---|
| **NR2** | N (%) | 25 (61.0) | 16 (39.0) |
| N=41 | Mean (SD) | 1.03 (2.60) | 1.48 (2.78) |
| | Median (IQR) | 0.36 (0.18-0.72) | 0.36 (0.13-1.50) |
| **NR2ab** | N (%) | 61 (57.0) | 46 (43.0) |
| N=107 | Mean (SD) | 2.14 (1.47) | 2.31 (1.51) |
| | Median (IQR) | 1.60 (1.15-2.70) | 1.70 (1.10-3.60) |
| **B-FABP** | N (%) | 8 (57.1) | 6 (42.9) |
| N=14 | Mean (SD) | 0.31 (0.10) | 0.30 (0.11) |
| | Median (IQR) | 0.28 (0.25-0.36) | 0.26 (0.22-0.41) |

TIA, transient ischaemic attack.

ROC curve analyses (Table 6) and univariable regression analyses confirm that none of the seven markers has sufficient discriminative value in the diagnosis of TIA, with c-statistics ranging from 0.45 to 0.58.

Table 7 shows the results of univariable logistic regression analyses assessing the diagnostic value of separate clinical characteristics. The biomarkers proved to have no predictive value in the multivariable analyses, and therefore we subsequently created an optimal clinical model with eight clinical determinants. The final multivariable model is shown in Table 8, and had a c-statistic of 0.83 (0.78-0.89). Predictors of a diagnosis of TIA or minor stroke are: (i) a higher age; (ii) a history of coronary artery disease (angina or myocardial infarction); (iii) a sudden onset of symptoms; (iv) occurrence of symptoms in full intensity; (v) dysarthria; (vi) no history of migraine; (vii) absence of loss of consciousness; (viii) absence of headache. As expected in view of the univariable analyses, adding the individual biomarkers, or a combination of biomarkers, to the clinical model did not improve the c-statistic.

**Table 6.** C-statistic of each biomarker, and optimal sensitivity and specificity using the Youden index.

| Biomarker | C-statistic (95%CI) | Sensitivity | Specificity | Cut-off |
|---|---|---|---|---|
| **NR2** | 0.50 (0.42-0.58) | 0.18 | 0.85 | 0.13 ng/ml |
| **NRab** | 0.45 (0.37-0.53) | 0.05 | 0.96 | 4.45 ng/ml |
| **PARK7** | 0.46 (0.38-0.54) | 0.64 | 0.39 | 15.23 ng/ml |
| **NDKA** | 0.53 (0.45-0.61) | 0.37 | 0.75 | 74.90 pg/ml |
| **UFD1** | 0.49 (0.40-0.57) | 0.24 | 0.78 | 313.50 pg/ml |
| **B-FABP** | 0.50 (0.42-0.58) | 0.06 | 0.96 | 0.22 ng/ml |
| **H-FABP** | 0.58 (0.50-0.66) | 0.35 | 0.65 | 19.15 ng/ml |

CI, confidence interval; ng/ml, nanogram per milliliter; pg/ml, picogram per milliliter.

**Table 7.** Univariable logistic regression analyses assessing the value of clinical characteristics in the diagnosis of TIA.

| Variables | OR (95%CI) | *P* |
|---|---|---|
| **Demographic characteristics** | | |
| Age per year | 1.06 (1.03-1.08) | <0.001 |
| Male sex | 1.04 (0.59-1.83) | 0.89 |
| **Medical history** | | |
| Prior cerebrovascular disease | 1.54 (0.79-3.01) | 0.21 |
| TIA | 1.67 (0.73-3.84) | 0.23 |
| Ischaemic stroke | 1.41 (0.55-3.62) | 0.48 |
| Haemorrhagic stroke | 1.61 (0.31-8.51) | 0.57 |
| Prior cardiovascular disease | 3.25 (1.56-6.78) | 0.002 |
| Angina pectoris | 8.32 (1.06-65.25) | 0.04 |
| Myocardial infarction | 19.15 *** | 0.002 |
| Peripheral artery disease | 2.60 (0.28-23.60) | 0.40 |
| Vascular surgery | 3.37 (1.10-10.32) | 0.03 |
| Renal insufficiency | 1.44 (0.48-4.30) | 0.52 |
| Atrial fibrillation | 1.67 (0.62-4.50) | 0.31 |
| History of epilepsy | 3.23 *** | 0.52 |
| History of migraine | 0.36 (0.15-0.88) | 0.03 |
| **Cardiovascular risk factors** | | |
| BMI per unit increase in kg/m2 | 1.01 (0.94-1.08) | 0.85 |
| Smoking (ever vs. never) | 1.04 (0.59-1.85) | 0.89 |
| Alcohol consumption per unit/week | 0.99 (0.96-1.03) | 0.62 |
| Positive family history of CVD* | 0.58 (0.33-1.04) | 0.07 |
| Hypertension | 2.44 (1.38-4.35) | <0.001 |
| Diabetes Mellitus | 1.50 (0.62-3.63) | 0.37 |
| Hyperlipidaemia | 1.67 (0.94-2.99) | 0.08 |
| **Course of symptoms** | | |
| Duration of symptoms ** | 1.08 (0.93-1.25) | 0.31 |
| Sudden onset of symptoms | 2.43 (0.89-6.67) | 0.09 |
| Preceding symptoms | 0.69 (0.38-1.25) | 0.23 |
| Occurrence of symptoms in full intensity | 2.00 (0.95-4.19) | 0.07 |
| **Type of symptoms** | | |
| Motor symptoms | 2.33 (1.28-4.23) | 0.01 |
| Sensory symptoms | 1.45 (0.82-2.58) | 0.20 |
| Vision problem | 0.53 (0.29-0.97) | 0.04 |
| Blurred vision | 0.29 (0.12-0.73) | 0.008 |
| Diplopia | 0.46 (0.17-1.30) | 0.14 |
| Hemianopia | 0.84 (0.28-2.51) | 0.75 |
| Amaurosis fugax | 3.36 (0.72-15.76) | 0.12 |

**Table 7.** Continued.

| Variables | OR (95%CI) | *P* |
|---|---|---|
| **Type of symptoms** | | |
| Communication problem | 1.35 (0.77-2.38) | 0.29 |
| Dysphasia | 0.99 (0.53-1.84) | 0.98 |
| Dysarthria | 1.71 (0.80-3.68) | 0.17 |
| Positive visual phenomena | 0.25 (0.10-0.61) | 0.002 |
| Vertigo | 0.77 (0.39-1.54) | 0.46 |
| Disturbed balance or gait | 1.14 (0.57-2.28) | 0.71 |
| Headache | 0.33 (0.18-0.60) | <0.001 |
| Lightheadedness | 0.66 (0.37-1.16) | 0.15 |
| Palpitations | 0.31 (0.11-0.87) | 0.03 |
| Presyncope | 0.44 (0.19-1.07) | 0.07 |
| Loss of consciousness | 0.12 (0.01-1.05) | 0.06 |

OR, odds ratio; CI, confidence interval; TIA, transient ischaemic attack; CVD, cardiovascular disease.

* A positive family history was defined as ≥1 first grade family member with myocardial infarction, ischaemic stroke or peripheral artery disease < 65 years of age.

** Duration of symptoms in minutes was naturally log-transformed.

*** A Fisher's exact test was used in case of observed values of zero.



**Table 8.** Final multivariable logistic regression model of predictors of the diagnosis of TIA

| Variables | OR (95%CI) | *P* |
|---|---|---|
| Age per year | 1.06 (1.03-1.09) | <0.001 |
| History of coronary artery disease* | 34.16 (3.39-344.03) | 0.003 |
| Sudden onset of symptoms | 2.72 (0.83-8.86) | 0.098 |
| Onset of symptoms in full intensity | 2.51 (0.94-6.71) | 0.066 |
| Dysarthria | 4.08 (1.42-11.73) | 0.009 |
| History of migraine | 0.24 (0.07-0.83) | 0.024 |
| Loss of consciousness | 0.03 (0.01-0.31) | 0.003 |
| Headache | 0.23 (0.11-0.48) | <0.001 |

C-statistic: 0.83 (0.78-0.89).

Backward selection of variables was applied, using a cut-off of P <0.10.

OR, odds ratio; CI, confidence interval.

* A history of stable or unstable angina and/or myocardial infarction.

## DISCUSSION

Currently available blood biomarkers have no value in addition to clinical symptoms and signs in the diagnosis of TIA. A multivariate diagnostic model consisting of clinical determinants only had good diagnostic accuracy with a c-statistic of 0.83 (0.78-0.89).

Our study was the first to evaluate potential diagnostic serum biomarkers in a large clinical population of patients suspected of TIA. Evidence for the potential of our set of biomarkers was mainly based on studies comparing early biomarker levels in major ischaemic stroke patients with levels in healthy individuals.[12] Obviously, however, the value of diagnostic tests should be assessed in the relevant domain, i.e. patients suspected of the disease of interest in daily practice. A comparison of biomarker levels in patients with a severe manifestation of the disease with the levels in healthy volunteers is both clinically less relevant and bound to overestimate the diagnostic value in day to day clinical practice. For the interpretation of our results it is important to realise that it is a much more challenging task for a biomarker to discriminate TIA/minor stroke (lower grades of ischaemia) from TIA mimicking entities, because the tissue damage is less than in major stroke patients and because the time to first medical consultation (and thus biomarker assessment) is in general much longer in patients suspected of TIA. Moreover, some of the biomarkers are more likely to show increased values in TIA mimics than in healthy volunteers.

The diagnostic value of NR2 was previously evaluated in a population of suspected stroke patients. In this study among 192 patients in whom 53% indeed had a stroke, the negative and positive predictive value were 96.0% (95%CI 92.3 - 98.3) and 93.0% (95%CI 86.1 - 97.1), respectively.[15] In our patient population of patients suspected of TIA/minor stroke (61% TIA/minor stroke), 80.0% of patients had a NR2 value below the border of detection. Importantly, we measured NR2 in serum and not in plasma as is preferred because of degradation of NR2 by proteases during a longer pre-analytic phase. However, this could only partly explain these results as it is estimated that serum measurements lead to approximately 30% lower values. Another difference is the total time to sample storage; a median of 2.6 hours in our study, and a maximum of 30 minutes in the aforementioned study.[15] Blood samples with the highest NR2 values (from TIA as well as non-TIA patients), however, also had a time to storage of three hours. Overall, we could not detect a correlation between time to storage and the value of NR2. Sensitivity analysis of the subsample of patients with NR2 values above the detection level also showed that NR2 had no diagnostic value in our

population (c-statistic 0.50). Unlike NR2, NR2ab levels do not increase early after acute ischaemia. Previous studies suggested that NR2ab levels rather reflect a history of (multiple) ischaemic cerebrovascular events.[16] However, in our study we were unable to find a correlation between NR2ab levels and either previous ischaemic cerebrovascular events or current TIA.

H-FABP was the only marker with on average higher values in patients with TIA/minor stroke compared to those with an alternative diagnosis. Still, with a c-statistic of 0.58 the overall diagnostic accuracy of HFABP was very low. As a comparison, the c-statistic of the variable age was 0.69. Neither in univariable nor multivariable logistic regression analyses H-FABP was a predictor of TIA/minor stroke.

B-FABP had only been evaluated as an early marker in stroke patients in a study with serial measurements of both B-FABP and H-FABP in 42 stroke patients and a comparison with a control group (ideally patents suspected of stroke but who did not have the disease) was lacking.[17] This study showed peak concentrations of both markers several hours after stroke, but also indicated B-FABP to be the least sensitive of the two. In our study the levels of B-FABP were below the detection level in the large majority of patients. Although the numbers are small, results in those with values in the detection range gave no indication of any discriminative value of B-FABP.

Previous studies evaluating the markers PARK7, NDKA and UFD-1 suggested that levels equally increase in TIA patients and in major stroke patients, and that levels stay elevated for days.[18,19] Both high positive and negative predictive values were reported, however, with three rather divergent cut-offs used and in case-control studies with healthy volunteers as controls. In our clinical population the levels of all three biomarkers in patients with TIA/minor stroke were comparable to those in TIA suspected patients with an alternative diagnosis.

The Dawson score and the Diagnosis of TIA (DOT) score have been proposed as diagnostic scores for TIA, but did not find their way to clinical practice.[20,21] They were derived from logistic regression analyses, and consist of 9 and 17 clinical determinants, respectively. The Dawson score showed poor results when applied by GPs (c-statistic 0.70).[22] Similar to the Dawson and the DOT-score our final multivariable diagnostic model includes age, previous cardiovascular disease and individual symptoms that are positively or negatively associated with TIA (e.g. loss of consciousness and headache are negative predictors of TIA in all three models). We also included variables on the course of symptoms in our analyses, and we show that a sudden onset of symptoms and an onset in full intensity (i.e. no gradual progression of symptoms) are important predictors of a TIA. This once

more underlines that careful history taking on the course of symptoms is crucial, and that such items should be included in attempts to create a useful diagnostic tool.

Main strengths of our study are the extensive information gathered per patient, and the expert panel establishing the final diagnosis in a standardised manner. An expert panel procedure with consensus meetings is considered to be the best option to confirm a diagnosis if an objective reference standard is lacking. The standardised interview by the research nurse provided detailed history taking of experienced symptoms and signs, that was verified in the GP's and neurologist's correspondence. This detailed information per case, including a narrative of the patient him or herself, was crucial in the expert panel procedure.

Because we recruited patients in the home setting, we had blood transportation delay. This may have caused degradation by proteases of some biomarkers such as NR2 and therefore artificially overall lower values. On the other hand, when such biomarkers are applied in out-of-hospital settings, similar delays will occur.

Although the results of this study do not favour the use of biomarkers, the idea of a blood test providing evidence for transient cerebral ischaemia remains appealing. Translational research will bring new biomarkers and perhaps also new sources of biomarkers. With this cohort we built a valuable biobank that gives the opportunity to easily evaluate such new markers. Future studies evaluating biomarkers that are influenced by early degradation, like NR2, should consider immediate measurement by point-of-care tests in the outpatient setting. Furthermore, serial measurements in TIA patients could gain more insight in the course of biomarker levels within the first days.

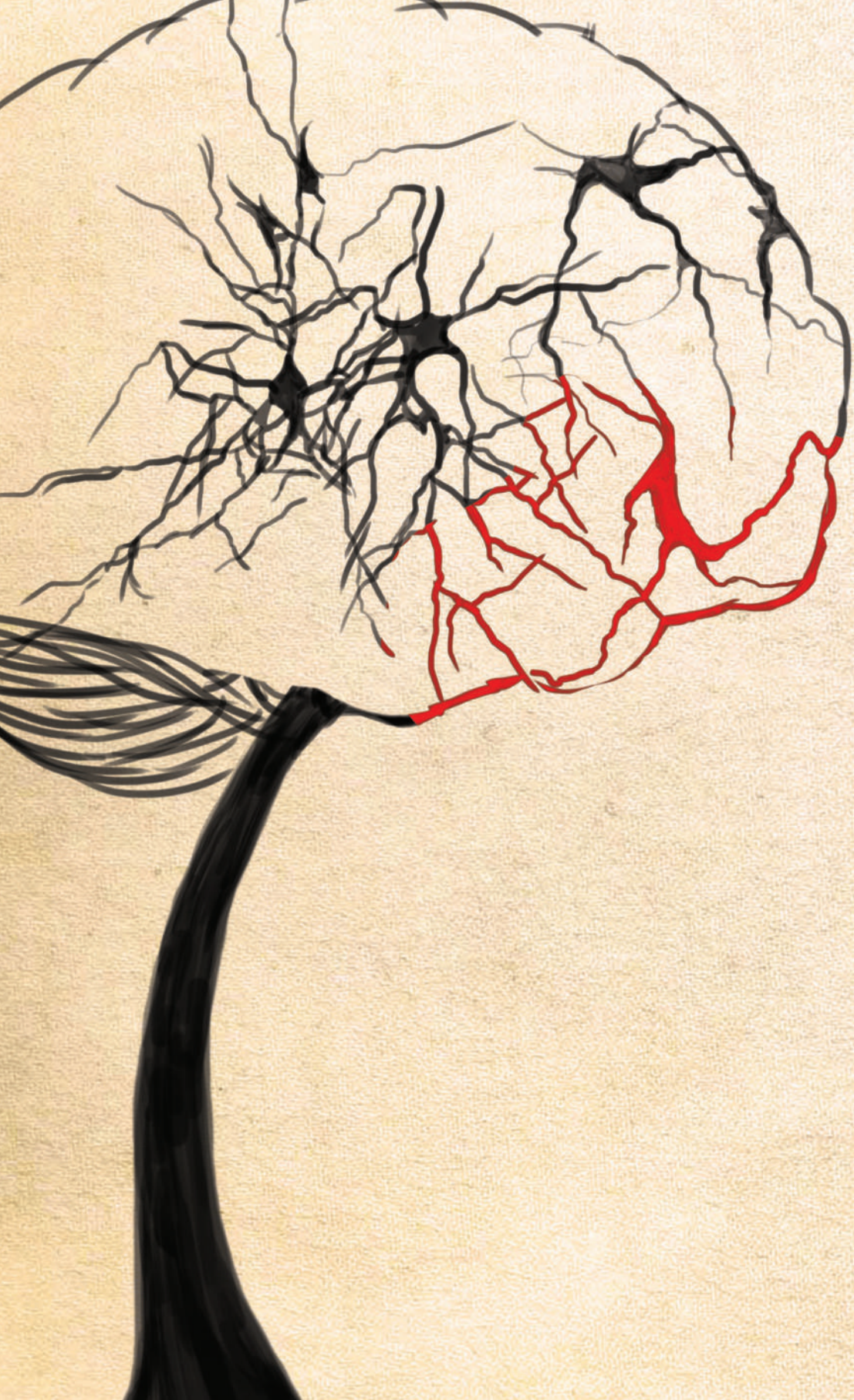
## CONCLUSION

Our study shows that current blood biomarkers have no value in patients suspected of TIA. Among the most important clinical predictors of a TIA or minor stroke are a sudden onset of symptoms and an onset in full intensity.

## REFERENCES


1. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007;6(12):1063-72.
2. Wu CM, McLaughlin K, Lorenzetti DL. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med. 2007;167(22):2417-22.
3. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370:1432–42.
4. Lavellee PC, Mesequer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6:953–60.
5. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016;388(10042):365-75.
6. Moreau F, Asdaghi N, Modi J, Goyal M, Coutts SB. Magnetic Resonance Imaging versus Computed Tomography in Transient Ischemic Attack and Minor Stroke: The More You See the More You Know. Cerebrovasc Dis Extra. 2013;3(1):130-6.
7. Förster A, Gass A, Kern R, Ay H, Chatzikonstantinou A, Hennerici MG, et al. Brain Imaging in Patients with Transient Ischemic Attack: A Comparison of Computed Tomography and Magnetic Resonance Imaging. Eur Neurol. 2012;67(3):136-41.
8. Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J of Neurol. 2011;18(4):644-8.
9. Amarenco P, Labreuche J, Lavallee PC. Patients with transient ischemic attack with ABCD2 <4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD2 >/=4. Stroke. 2012;43(3):863-5.
10. Amort M, Fluri F, Schafer J, Weisskopf F, Katan M, Burow A, et al. Transient ischemic attack versus transient ischemic attack mimics: frequency, clinical characteristics and outcome. Cerebrovasc Dis. 2011;32:57–64.
11. Dolmans LS, Kappelle LJ, Bartelink ME, Hoes AW, Rutten FH. Delay in patients suspected of transient ischaemic attack: a cross-sectional study. BMJ Open. 2019;9(2):e027161.
12. Dolmans LS, Rutten FH, Bartelink ML, Seppenwoolde G, van Delft S, Kappelle LJ, et al. Serum biomarkers for the early diagnosis of TIA: The MIND-TIA study protocol. BMC Neurol. 2015;15:119.
13. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-93.
14. Harrell FE, Jr., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med. 1984;3(2):143-52.

15. Dambinova SA, Bettermann K, Glynn T, Tews M, Olson D, Weissman DJ, et al. Diagnostic potential of the NMDA receptor peptide assay for acute ischemic stroke. PLoS One. 2012;7:e42362.
16. Weissman JD, Khunteev GA, Heath R, Dambinova SA. NR2 antibodies: risk assessment of transient ischemic attack (TIA)/stroke in patients with history of isolated and multiple cerebrovascular events. J Neurol Sci. 2011;300(1-2):97-102.
17. Wunderlich MT, Hanhoff T, Goertler M, Spener F, Glatz J, Wallesch CW, et al. Release of brain-type and heart-type fatty acid-binding proteins in serum after acute ischaemic stroke. J Neurol. 2005;252:718–24.
18. Allard L, Burkhard PR, Lescuyer P, Burgess JA, Walter N, Hochstrasser DF, et al. PARK7 and nucleoside diphosphate kinase A as plasma markers for the early diagnosis of stroke. Clin Chem. 2005;51:2043–51.
19. Allard L, Turck N, Burkhard PR, Walter N, Rosell A, Gex-Fabry M, et al. Ubiquitin fusion degradation protein 1 as a blood marker for the early diagnosis of ischemic stroke. Biomark Insights. 2007;2:155–64.
20. Dutta D. Diagnosis of TIA (DOT) score--design and validation of a new clinical diagnostic tool for transient ischaemic attack. BMC Neurol. 2016;16:20.
21. Dawson J, Lamb KE, Quinn TJ, Lees KR, Horvers M, Verrijth MJ, et al. A recognition tool for transient ischaemic attack. QJM. 2009;102:43-9.
22. Lasserson DS, Chandratheva A, Giles MF, Mant D, Rothwell PM. Influence of general practice opening hours on delay in seeking medical attention after transient ischaemic attack (TIA) and minor stroke: prospective population based study. BMJ. 2008;337:a1569.



# Chapter 8

# Diagnostic accuracy of the Explicit Diagnostic Criteria for TIA: a validation study

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*Stroke 2019; 50: 2080–2085*

## ABSTRACT

### Background and purpose

The clinical diagnosis of a transient ischemic attack (TIA) can be difficult. Evidence based criteria hardly exist. We evaluated if the recently proposed 'Explicit Diagnostic Criteria for TIA' (EDCT), an easy to perform clinical tool focusing on type, duration and mode of onset of clinical features, would facilitate the clinical diagnosis of TIA.

### Methods

We used data from patients suspected of a TIA by a general practitioner (GP) and referred to a TIA service in the region of Utrecht, The Netherlands, who participated in the 'Markers in the Diagnosis of TIA' (MIND-TIA) study. Information about the clinical features was collected with a standardized questionnaire within 72 hours after onset. A panel of three experienced neurologists ultimately determined the definite diagnosis based on all available diagnostic information including a 6-month follow-up period. Two researchers scored the EDCT. Sensitivity, specificity, and predictive values of the EDCT were assessed using the panel diagnosis as reference. A secondary analysis was performed with modified subcriteria of the EDCT.

### Results

Of the 206 patients, 126 (61%) had a TIA (n=104) or minor stroke (n=22), and 80 (39%) an alternative diagnosis. Most common alternative diagnoses were migraine with aura (n=24, 30.0%), stress related or somatoform symptoms (n=16, 20.0%), and syncope (n=9, 11.3%). The original EDCT had a sensitivity of 98.4% (95%CI: 94.4 – 99.8), and a specificity of 61.3% (49.7 – 71.9). Negative and positive predictive values were 96.1% (86.0 – 99.0) and 80.0% (75.2 – 84.1) respectively. The modified EDCT showed a higher specificity of 73.8% (62.7 – 83.0) with the same sensitivity, and a similar negative predictive value of 96.7%, but a higher positive predictive value of 85.5% (80.3 – 89.5).

### Conclusions

The EDCT has excellent sensitivity and negative predictive value, and could be a valuable diagnostic tool for the diagnosis of TIA.

## INTRODUCTION

The diagnosis of transient ischemic attack (TIA) can be notoriously difficult, mainly because it is often solely based on history taking. Patients suspected of a TIA require an urgent assessment with timely start of antithrombotic therapy to reduce the risk of an early ischemic stroke.[1] However, even after careful evaluation at a TIA service the final diagnosis made by the neurologist often holds a degree of uncertainty.[2] Both excluding and confirming a TIA can be difficult, and therefore underdiagnosis as well as overdiagnosis are common.

Strict criteria for the diagnosis of TIA do not exist. In clinical practice and research, the diagnosis is usually at the discretion of the treating physician without specific requirements with respect to the type of neurological symptoms and deficits. Attempts have been made to facilitate the diagnosis of TIA by creating a diagnostic score based on multivariable logistic regression modelling.[3,4] Yet, these scores did not find their way to the clinic, probably because they are not feasible in clinical practice considering the large number of items included in the scores. Most importantly, these scores are not sufficiently accurate to confirm or rule out TIA.[5]

Skeptics state that possible symptoms and signs of a TIA are too heterogeneous to create a useful diagnostic score. Still, recently, two of us (ERL and JO) developed a set of Explicit Diagnostic Criteria for TIA (EDCT) based on clinical practice and experience instead of statistical methods.[6] The criteria were originally developed with a focus on the discrimination between TIA and migraine with aura, one of its most common mimics. As a first step the performance of these criteria was evaluated in separate cohorts of patients with TIA or with migraine with aura. EDCT correctly classified 99% of TIAs and 95% of migraine with aura cases (as non-TIA). The criteria have, however, not been validated in the clinically relevant domain of patients suspected of TIA. In case the EDCT correctly classifies those with and without TIA, diagnostic management of these patients could be improved considerably. Thus, we evaluated the diagnostic value of EDCT criteria in patients with suspected TIA.



## MATERIALS AND METHODS

The authors declare that all supporting data are available within the article.

The criteria of the EDCT are summarized in Table 1. We used the MIND-TIA (Markers in the Diagnosis of TIA) cohort to validate the accuracy of the EDCT.[7] This cohort consists of 206 patients suspected of a TIA by their general practitioner (GP) who were evaluated between September 2013 and September 2016, in the

region of Utrecht, The Netherlands. All participants were referred by their GP to a regional TIA service for evaluation by a neurologist and ancillary investigations, including brain imaging. Signs and symptoms were recorded with a standardized questionnaire filled out by a research nurse within 72 hours after onset (see Supplemental material). In addition, a taped narrative of the patient was collected. Thus, a predefined set of variables could be obtained per participant.

### Assessment of the EDCT

The data gathered in the MIND-TIA study provided all necessary information for classification according to the criteria of the EDCT. For each participant we double-checked the data retrieved from the standardized questionnaire with the correspondence of the consulting neurologist and the GP (DV). In case of any doubt about the scoring, or discrepancy between the results of the research nurse's interview and the correspondence, a second researcher (LSD) also made a judgment. If there was discrepancy between the two researchers, a third researcher (LJK) was asked for the majority vote. Also, one of us (LSD) checked the scoring of (i) all cases in which the EDCT came to another diagnosis than the expert panel standard, and (ii) a random sample of 20% of all cases.

We also included the cases that had a final diagnosis of minor disabling stroke. These cases of minor strokes had to fulfill the essential criteria A, C and D, but were allowed to not fulfill criteria B (duration < 24 hours) and/or E (absence of infarction on imaging; Table 1).

### Panel diagnosis

An expert panel consisting of three experienced stroke neurologists (PJN, EJD, LJK) determined the definite diagnosis, using all information from: (i) the standardized questionnaire (ii) a taped patient's narrative of the event, (iii) the correspondence of the GP; (iv) the discharge letters from the treating neurologist, and other specialists if attended; (v) the results of the ancillary investigations, including brain imaging (CT and/or MRI); (vi) a 6-month follow-up period.

The expert panel determined whether patients had a TIA or minor disabling stroke, or an alternative diagnosis, applying the time-based definition of TIA.[8] The panel members first assessed all cases individually, and estimated the probability of a TIA on a visual analogue scale (VAS). Consensus on the diagnosis of TIA was assumed if all three neurologists similarly scored the probability of TIA ≤ 20% or ≥ 80%. All other cases were discussed in a panel meeting, and a final judgement was based on a majority of votes.

## Data analysis

We assessed the diagnostic accuracy of the EDCT (sensitivity, specificity, predictive values and c-statistic, with 95% confidence intervals), with the panel diagnosis as reference standard.

During the process of scoring we recognized certain patterns in the assessment of the C-criterion that led to cases falsely identified as TIA. Therefore, and also to reduce the chance of misinterpretation by the user, we rephrased the original subcriteria C1-C3 (describing an onset in full intensity [C1], symptoms occurring simultaneously [C2], and the presence of actual neurological deficits), so that these apply to all symptoms instead of one or some of the symptoms (see Table 1). As a secondary analysis we also assessed the performance of this modified EDCT.

**Table 1.** Original explicit diagnostic criteria for TIA (EDCT), and the modified subcriteria C1, C2 and C3.(6)

| | |
|---|---|
| A. | Sudden onset of fully reversible neurological or retinal symptoms (typically hemiparesis, hemihypesthesia, aphasia, neglect, amaurosis fugax, hemianopsia or hemiataxia) |
| B. | Duration < 24 hours |
| C. | At least two of the following:<br>1. At least one symptom is maximal in < 1 minute (no gradual spread)<br>2. Two or more symptoms occur simultaneously<br>3. Symptoms in the form of deficits (no irritative symptoms such as photopsias, pins and needles, etc)<br>4. No headache accompanies or follows the neurological symptoms within one hour |
| C.* | *At least two of the following:*<br>*1.* All symptoms are maximal in < 1 minute (no gradual spread)*<br>*2.* All symptoms occur simultaneously*<br>*3.* All symptoms are deficits (no irritative symptoms such as photopsia's, pins and needles, etc)*<br>*4. No headache accompanies or follows the neurological symptoms within one hour* |
| D. | None of the following isolated symptoms (can occur together with more typical symptoms): shaking spells, diplopia, dizziness, vertigo, syncope, decreased level of consciousness, confusion, hyperventilation associated paraesthesia's, unexplained falls, amnesia. |
| E. | No evidence of acute infarction in the relevant area on neuroimaging |

*: modified criteria.

## Ethical approval

The MIND-TIA study has been approved by the Medical Research Ethics Committee of the University Medical Center of Utrecht, the Netherlands. All participants gave written informed consent.

## RESULTS

Of the 206 patients suspected of TIA by their GP, 126 (61%) participants had a TIA (n=104) or minor disabling stroke (n=22), and 80 (39%) patients had an alternative diagnosis according to the expert panel. Mean (SD) age was 67.7 (13.7) years and was higher among those with TIA/minor stroke than in those with an alternative diagnosis (71.4 (12.0) versus 62.0 (14.2); Table 2).

**Table 2.** Characteristics of 206 patients suspected of TIA by the general practitioner, according to those with a final diagnosis of TIA or minor stroke and those with an alternative diagnosis.

| Characteristic | Total (n=206) | TIA/minor stroke (n=126) | Alternative diagnosis (n=80) | P-value |
|---|---|---|---|---|
| Mean age in years (SD) | 67.7 (13.7) | 71.4 (12.0) | 62.0 (14.2) | <0.01 |
| Male gender, n (%) | 112 (54.4) | 69 (54.8) | 43 (53.8) | 0.89 |
| **Cardiovascular risk factors** | | | | |
| Mean BMI in kg/m$^2$ (SD) | 25.7 (4.0) | 25.7 (4.2) | 25.6 (3.8) | 0.85 |
| Smoking, n (%) | | | | |
| Current smoker | 38 (18.5) | 18 (14.3) | 20 (25.0) | 0.05 |
| Former smoker | 87 (42.2) | 58 (46.0) | 29 (36.3) | 0.17 |
| Never smoked | 81 (39.3) | 50 (39.7) | 31 (38.7) | 0.89 |
| First degree relatives with CVD <65 years, n (%) | (n=204) | (n=125) | (n=79) | |
| 0 | 127 (62.3) | 84 (67.2) | 43 (54.4) | 0.07 |
| 1 | 59 (28.9) | 29 (23.2) | 30 (38.0) | 0.02 |
| ≥2 | 18 (8.8) | 12 (9.6) | 6 (7.6) | 0.62 |
| Hypertension, n (%) | 121 (59) | 84 (66.7) | 36 (45.0) | <0.01 |
| Diabetes mellitus, n (%) | 27 (13) | 18 (14.3) | 8 (10.0) | 0.37 |
| Hyperlipidemia, n (%) | 85 (42) | 58 (46.0) | 27 (33.8) | 0.08 |
| **Medical history** | | | | |
| Previous cerebrovascular event, n (%) | 51 (24.8) | 35 (27.8) | 16 (20.0) | 0.21 |
| TIA | 31 (15.0) | 22 (17.5) | 9 (11.3) | 0.22 |
| Ischemic stroke | 22 (11) | 15 (11.9) | 7 (8.8) | 0.48 |
| Hemorrhagic stroke | 7 (3) | 5 (4.0) | 2 (2.5) | 0.57 |
| Previous cardiovascular disease, n (%) | 54 (26) | 43 (34.1) | 11 (13.8) | <0.01 |
| Angina pectoris | 13 (6) | 12 (9.5) | 1 (1.3) | 0.02 |
| Myocardial infarction | 13 (6) | 13 (10.3) | 0 (0.0) | <0.01 |
| Peripheral artery disease | 5 (2) | 4 (3.2) | 1 (1.3) | 0.38 |
| Previous vascular surgery | 23 (11) | 19 (15.1) | 4 (5.0) | 0.03 |
| Renal insufficiency | 16 (8) | 11 (8.7) | 5 (6.3) | 0.52 |
| Atrial fibrillation | 21 (10) | 15 (11.9) | 6 (7.5) | 0.31 |
| History of migraine, n (%) | 23 (11) | 9 (7.1) | 14 (17.5) | 0.02 |
| History of epilepsy, n (%) | 2 (1) | 2 (1.6) | 0 (0.0) | 0.26 |

TIA, transient ischemic attack; BMI, Body Mass Index; SD, standard deviation; CVD, cardiovascular disease. P-values were calculated using T-tests for continuous variables, and Chi-square tests for categorical variables.

Migraine with aura was the most common alternative diagnosis (n=24, 30.0%), followed by stress-related or somatoform symptoms (n=16, 20.0%), and syncope (n=9, 11.3%; Table 3).

The EDCT classified 155 (75.2%) as TIA or minor stroke. There were two false negative cases (1.6% of TIA/minor stroke), i.e. cases that had no TIA/minor stroke according to the EDCT but were classified as a TIA by the panel. Both cases had diplopia as the primary symptom. These two participants with a false negative EDCT did not suffer from a recurrent cerebrovascular event (TIA nor stroke) during the six-month follow-up period. Thirty-one cases (38.8% of those with an alternative diagnosis) were false positive, i.e. cases that fulfilled the EDCT criteria, but were judged as no TIA (or minor stroke) by the panel. The diagnoses among these 31 false positive patients are shown in Table 4.

**Table 3.** Definite diagnoses in 80 patients with no TIA or minor stroke according to the expert panel

| **Diagnoses** | **N (%)** |
|---|---|
| Migraine with aura | 24 (30.0) |
| Stress related/somatoform | 16 (20.0) |
| Syncope (reflex syncope/orthostatic hypotension) | 9 (11.2) |
| Transient neurological attack (TNA)* | 7 (8.8) |
| Vestibular syndrome | 5 (6.2) |
| Peripheral neuropathy | 2 (2.5) |
| Cranial nerve palsy | 2 (2.5) |
| Ophthalmic | 2 (2.5) |
| Other diagnoses | 7 (8.8) |
| Epileptic seizure; subdural hematoma; pituitary adenoma; encephalopathy; retinal spasms; sleep phenomena; amyloid spell in cerebral amyloid angiopathy. | |
| Unclear | 6 (7.5) |
| Total | 80 |

*Transient neurological attack (TNA): transient episode of nonfocal neurological symptoms not fulfilling criteria for a TIA but lacking a clear alternative diagnosis.

**Table 4.** Final diagnosis in those patients with a false positive test outcome of the original EDCT, and the modified EDCT.

| | EDCT | Modified EDCT |
|---|---|---|
| **Diagnosis** | **N (%)** | **N (%)** |
| Migraine with aura | 13 (41.9) | 4 (19.0) |
| Stress related/somatoform | 8 (25.8) | 7 (33.3) |
| Peripheral neuropathy | 2 (6.5) | 2 (9.5) |
| Transient neurological attack (TNA) | 1 (0.4) | 1 (4.8) |
| Epilepsy | 1 (0.4) | 1 (4.8) |
| Syncope | 1 (0.4) | 1 (4.8) |
| Unclear | 1 (0.4) | 1 (4.8) |
| Other diagnoses* | 4 (12.9) | 4 (19.0) |
| Total | 31 | 21 |

* including: abducens nerve palsy (n=1); encephalopathy (n=1); subdural hematoma (n=1); vasospastic amaurosis fugax (n=1).
EDCT, explicit diagnostic criteria for TIA.

Table 5 shows an overview of the diagnostic accuracy of the EDCT. The original EDCT had a sensitivity of 98.4% (95%CI: 94.4 – 99.8), and a specificity of 61.3% (95%CI: 49.7 – 71.9). Negative and positive predictive value were 96.1% (95%CI: 86.0 – 99.0) and 80.0% (95%CI: 75.2 – 84.1), respectively.

**Table 5.** Diagnostic accuracy of the original EDCT, and the modified EDCT.

| | EDCT | Modified EDCT |
|---|---|---|
| | **Value (95% CI)** | **Value (95% CI)** |
| Sensitivity | 98.4% (94.4 – 99.8) | 98.4% (94.4 – 99.8) |
| Specificity | 61.3% (49.7 – 71.9) | 73.8% (62.7 – 83.0) |
| Positive predictive value | 80.0% (75.2 – 84.1) | 85.5% (80.3 – 89.5) |
| Negative predictive value | 96.1% (86.0 – 99.0) | 96.7% (88.1 – 99.2) |
| Positive likelihood ratio | 2.54 (1.93 – 3.35) | 3.75 (2.59 – 5.42) |
| Negative likelihood ratio | 0.03 (0.01 – 0.10) | 0.02 (0.01 – 0.09) |
| Accuracy | 84.0% (78.2 – 88.7) | 88.8% (83.7 – 92.8) |
| C-statistic | 0.80 (0.73 – 0.87) | 0.86 (0.80 – 0.92) |

CI, confidence interval; EDCT, explicit diagnostic criteria for TIA.

Reassessment of the EDCT after modification of the C-criterion resulted in 10 less false positive patients (21 instead of 31). These included nine patients

diagnosed with migraine with aura, and one with stress-related/somatoform symptoms. The number of two false negative patients remained unchanged. The modified EDCT had a specificity of 73.8% (95%CI: 62.7 – 83.0), and a sensitivity of 98.4% (95%CI: 94.4 – 99.8). The negative and positive predictive value were 96.7% (95%CI: 86.0 – 99.0) and 85.5% (95%CI: 80.3 – 89.5), respectively.

Separate analyses of the 22 patients with a minor disabling stroke did not substantially change the results (data not shown).

To assess interobserver variability, a second researcher (LSD) also scored the EDCT for all false positive and negative cases (according to the assessment of the first researcher, DV), and a 20% random sample of all 206 patients. For the modified EDCT there was agreement on the two false negative cases and the random sample, and disagreement on 1/22 false positive cases. A third researcher (LJK) assessed the modified EDCT of the false positive and negative cases and came to the same results (100% agreement) as the second researcher.

## DISCUSSION

This first evaluation of the diagnostic accuracy of the explicit diagnostic criteria for TIA (EDCT) in patients *suspected of TIA* demonstrates that the criteria have an excellent sensitivity (98.4%) and negative predictive value (96.1%). Moreover, modification of the EDCT by rephrasing the C-criteria resulted in a similar negative predictive value, but in an increase in positive predictive value.



In the primary care setting it is most valuable if a tool can safely exclude a TIA, which requires a high negative predictive value. If a GP would use the modified EDCT in 100 patients suspected of TIA (with a prior chance of a TIA/minor stroke of 61%), 71 patients would be referred to a TIA service and as a result 60 confirmed as TIA and 11 would receive another final diagnosis after evaluation by the neurologist. Among the 29 patients in whom the GP would make another diagnosis, only one patient would wrongly *not* receive the diagnosis TIA. Both false negative cases in our study had diplopia, which could mean that the EDCT is more reliable to diagnose a TIA in the anterior than in the posterior circulation.

Two previous diagnostic scores that aim to facilitate clinicians were developed based on regression analysis. The Dawson score consists of 9 determinants, including age and history of hypertension, supplemented with 7 symptoms.[3] The Diagnosis of TIA (DOT) score consists of 17 determinants, including age, history of hypertension, history of or actual atrial fibrillation, supplemented with 14 specific symptoms.[4] Both the Dawson and the DOT are not widely used and have not

been established as a useful tool in clinical practice nor in research. The Dawson score had poor diagnostic value when applied by GPs (c-statistic 0.70).[5] The DOT score performed better in a direct comparison with the Dawson score in a cohort of 525 suspected TIA patients seen at a British TIA service (c-statistic 0.89 [0.85-0.92] versus 0.83 [0.79-0.87]).[4] However, this comparison was performed in the derivation cohort of the DOT score and therefore very likely overestimates the performance of the DOT score. Comparing our results with these studies and considering that the EDCT is just based on clinical experience, the overall discriminative ability of the EDCT in this external validation is remarkably high.

One might argue that a purely clinical score is not necessary anymore in the modern era of sensitive neuroradiological methods such as diffusion-weighted MRI or perfusion CT-scanning.[9,10] This is true in a hospital setting in developed countries, but imaging cannot always help to distinguish between TIA and the most common mimics. In addition, it does not apply at all in a primary care setting or in non-Western countries.

In the current study we found a lower specificity of the EDCT than in the first study in which he EDCT was tested in separate cohorts of patients with migraine with aura or with a TIA. Testing EDCT in a large cohort of patients with migraine with aura including many who had aura without headache showed a specificity of 95%, whereas in the present study migraine was the most common false positive diagnosis. This difference can be explained by the fact that the patients with migraine in the MIND-TIA study were all initially suspected of a TIA by the GP, and could therefore be considered to be more profound mimics of TIA. The quality of the collected information about characteristics of migraine might have been better if the investigator would have had the EDCT at hand during data collection. This should be tested in further prospective studies. In the current form EDCT is excellent for screening patients for research projects because of a very high sensitivity. Before inclusion in TIA trials, the diagnosis must, however, be refined by expert evaluation.

Our study is the first to assess the EDCT among patients suspected of TIA by their GP. Strong points are the standardized way of collecting the required information and the completeness of data and the standardized way in which we assessed the TIA diagnosis by an expert panel. The use of an expert panel as the reference standard can, however, also be criticized. Although the panel consisted of experienced neurologists, they had to make a diagnosis on the basis of written information and did not speak to the patients themselves. One might also argue that neurologists on a regular basis disagree about the diagnosis of TIA.[2] However, in the absence of better alternatives, we feel that the use of consensus meetings

by a panel of experts is the best available option for the reference standard. Initial history taking was performed by a trained nurse and not by a medical specialist. This is different from most clinical practices, but a standardized questionnaire guaranteed objective and straightforward information about the symptoms and signs of the patients. Another limitation of our study is that the modification of EDCT was based on our MIND-TIA data and that we also validated that score in the same dataset. Thus, another external validation in a larger cohort is needed.

Finally, the actual usability in clinical practice and the performance of the score, and the modified score, when applied by GPs or physicians at an emergency department (ED) is unknown at this point. There may be differences between a structured nurse interview and everyday history taking by a GP or emergency physician. We therefore recommend to perform an implementation study in the primary care and ED setting as the final step before use in everyday practice by GPs.

In conclusion, this study showed that the original, and especially the proposed modified EDCT are easy to apply, and have excellent diagnostic properties in patients suspected of TIA in primary care. They could be a valuable diagnostic tool for use in primary care and emergency departments as well as being a valuable supplement in TIA clinics.

## REFERENCES


1. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370:1432-42.
2. Castle J, Mlynash M, Lee K, Caulfield AF, Wolford C, Kemp S, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. Stroke. 2010;41:1367–70.
3. Dawson J, Lamb KE, Quinn TJ, Lees KR, Horvers M, Verrijth MJ, et al. A recognition tool for transient ischaemic attack. QJM. 2009;102:43-9.
4. Dutta D. Diagnosis of TIA (DOT) score--design and validation of a new clinical diagnostic tool for transient ischaemic attack. BMC Neurol. 2016;16:20.
5. Lasserson DS, Mant D, Hobbs FDR, Rothwell PM. Validation of a TIA recognition tool in primary and secondary care: implications for generalizability. Int J Stroke. 2015;10:692–6.
6. Lebedeva ER, Gurary NM, Gilev DV, Christensen AF, Olesen J. Explicit diagnostic criteria for transient ischemic attacks to differentiate it from migraine with aura. Cephalalgia. 2018;38:1463-70.
7. Dolmans LS, Rutten FH, Bartelink ML, Seppenwoolde G, van Delft S, Kappelle LJ, et al. Serum biomarkers for the early diagnosis of TIA: The MIND-TIA study protocol. BMC Neurol. 2015;15:119.
8. Degan D, Ornello R, Tiseo C, De Santis F, Pistoia F, Carolei A, et al. Epidemiology of Transient Ischemic Attacks using time- or tissue-based definitions: A population-based study. Stroke. 2017;48:530-6.
9. Cereda CW, George PM, Inoue M, Vora N, Olivot JM, Schwartz N, et al. Inter-rater agreement analysis of the Precise Diagnostic Score for suspected transient ischemic attack. Int J Stroke. 2016;11:85-92.
10. Grams RW, Kidwell CS, Doshi AH, Drake K, Becker J, Coull BM, et al. Tissue-Negative Transient Ischemic Attack: Is there a role for perfusion MRI? AJR. 2016;207:157-62.

## SUPPLEMENTAL MATERIAL

### Standardized questionnaire by the research nurse

This concerns a translated version of the subpart of the case report form on signs and symptoms. Items such as relevant past medical history, cardiovascular risk factors and current medication are excluded here.

For the assessment of the Explicit Diagnostic Criteria for TIA (EDCT) the researchers used the data from this questionnaire, but also the correspondence of the GP and neurologist.

**Patient's narrative of signs and symptoms**

'Can you describe in your own words the symptoms for which you consulted the GP?'

***--- The response to (only) this question will be recorded ---***

**Course of symptoms**

- The start of symptoms was: ☐ sudden ☐ gradually
- Total duration of symptoms: ☐☐ h ☐☐ min
- Did the participant feel the symptoms coming or did they come unexpectedly?
  ☐ He/she felt symptoms coming
  ☐ Symptoms came unexpectedly
- Were there any signs or symptoms preceding the (possible) neurological deficits?
  ☐ No
  ☐ Yes, namely:_____
- Were symptoms immediately there in full intensity or did they get worse over time?
  ☐ Onset of symptoms in full intensity
  ☐ Symptoms got worse over time
- Does the participant fully remember the signs and symptoms?
  ☐ YES ☐ NO
- Had the participant experienced the symptoms (suspected of a TIA) before?
  ☐ YES ☐ NO

  If yes, when?_____

  How many times? ☐☐☐

**Were the following signs and symptoms present?**

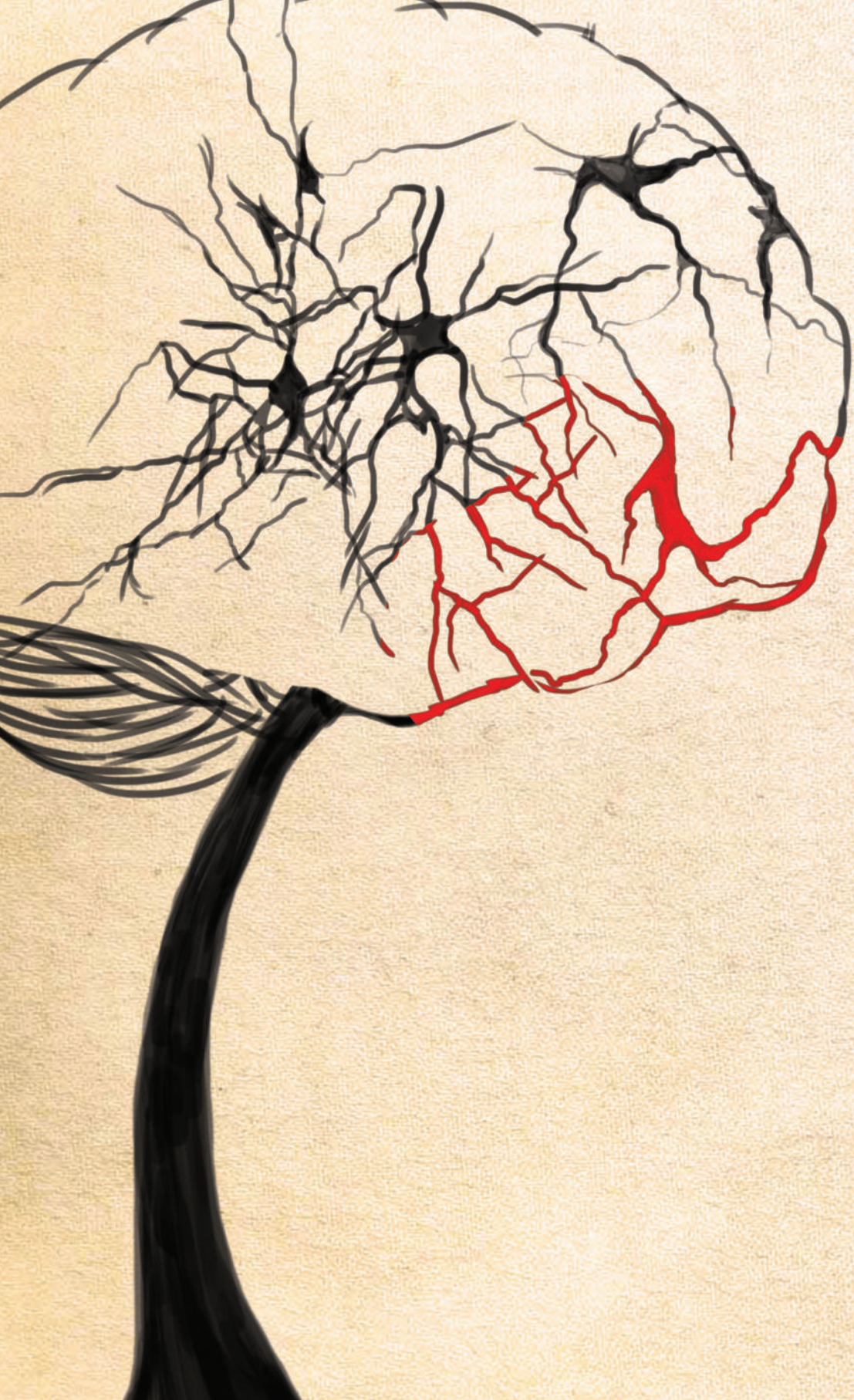
| | |
|---|---|
| Total or partial loss of strength (motor deficit) in arm/hand, leg/foot or face | ☐ Yes ☐ No |
| If yes: Unilateral<br>Bilateral | ☐<br>☐ |
| Numbness/tingling sensation (sensory deficit) in arm/hand, leg/foot, or face | ☐ Yes ☐ No |
| If yes: Unilateral<br>Bilateral | ☐<br>☐ |
| Vision problem/impaired vision | ☐ Yes ☐ No |
| If yes; this concerned:<br>❖ Diplopia<br>❖ Blurred vision (both eyes)<br>❖ Loss of vision/blindness in one part of visual field (both eyes)<br>❖ Loss of vision/blindness in one eye (amaurosis fugax); as a shade coming down over the eye | <br>☐<br>☐<br>☐<br>☐ |
| Seeing flashes, sparkles, stars or other visual phenomena | ☐ Yes ☐ No |
| Communication problem | ☐ Yes ☐ No |
| If yes; this concerned:<br>❖ Incoherent language, trouble finding words, strange sentences or words, trouble understanding language (dysphasia)<br>❖ Problems with articulation and pronouncing words (dysarthria) | <br>☐<br>☐ |
| Spinning sensation/true vertigo | ☐ Yes ☐ No |
| Lightheadedness | ☐ Yes ☐ No |
| Feeling like one might black-out/faint (presyncope) | ☐ Yes ☐ No |
| Loss of consciousness | ☐ Yes ☐ No |
| Loss of short-term memory, without loss of consciousness | ☐ Yes ☐ No |
| Being adrift, unsteady gait, disturbed coordination (ataxia) | ☐ Yes ☐ No |
| Swallowing problem/choking | ☐ Yes ☐ No |
| Needs to be distinguished from: | |
| Globus sensation | ☐ Yes ☐ No |
| Muscle contractions or spasms | ☐ Yes ☐ No |
| Sudden fall to the ground (drop attack) | ☐ Yes ☐ No |
| Headache | ☐ Yes ☐ No |
| Nausea and/or vomiting | ☐ Yes ☐ No |
| Pain or tightness on the chest | ☐ Yes ☐ No |
| Shortness of breath | ☐ Yes ☐ No |
| Palpitations, irregular heartbeat | ☐ Yes ☐ No |
| Other relevant symptoms? | ☐ Yes ☐ No |

_____

_____

_____

_____



# Chapter 9

## General discussion

This thesis focuses on the difficulties in accurately diagnosing TIA and barriers to a timely diagnosis. In this chapter I will firstly summarize the main findings of the thesis. Secondly, I will put these findings in a broader context, and provide recommendations aimed at reducing the delay to the diagnosis of TIA and the start of stroke-preventive treatment, and how to avoid under- but also overdiagnosis. Awareness and education of general practitioners (GPs), patients and lay people are crucial, as is optimization of the health care trajectory of patients with suspected TIA.

## MAIN FINDINGS OF OUR STUDIES

Our literature review (Chapter 2) and our survey (Chapter 3) on patient delay showed that irrespective of previous public campaigns aimed at improving recognition of signs of stroke, patients with a (possible) TIA still tend to delay reporting their symptoms to the GP or primary care out-of-hours services. In around one third of patients this delay (between onset of symptoms and first contact) is longer than 24 hours.

Delays are even substantially longer after an onset of symptoms during out of office hours, also in the Dutch healthcare system with 24 hours availability of primary care services (Chapter 4). Patients and lay people, but also GPs, still seem insufficiently aware that a TIA is a medical urgency with the risk of a subsequent stroke being highest in the first hours to two weeks after a TIA. Thus, in case of a possible TIA immediate secondary prevention with antiplatelet agents is indicated given that the time to the assessment at a TIA service is often more than 24 hours. Our data show that only 43% of patients with a possible TIA who were naive to antithrombotics, received aspirin or clopidogrel to bridge the time to further diagnostic assessment.

Another literature review (Chapter 5) identified several candidate serum biomarkers for the diagnosis of TIA. However, to date most of these studies included only or mainly stroke patients, and compared them to healthy controls. There were no studies with biomarkers in the clinically much more relevant domain of patients suspected of a TIA.

In Chapter 7 we showed in our MIND-TIA cohort of 206 patients suspected of a TIA by their GP (of which 61% actually had a TIA or minor stroke according to an expert panel) that seven promising blood biomarkers had no value in distinguishing those with from those without a TIA. C-statistics ranged from 0.45 to 0.58. Therefore, we derived the optimal diagnostic prediction model based on clinical items only. With multivariable regression eight determinants were identified

as independent predictors of TIA or minor stroke (higher age, history of angina pectoris or myocardial infarction, a sudden onset of symptoms, occurrence of symptoms in full intensity, dysarthria, no history of migraine, absence of loss of consciousness, absence of headache), and the c-statistic of the model was good with 0.83 (0.78-0.89).

In Chapter 8 we validated in the same cohort the recently proposed 'explicit diagnostic criteria for TIA' (EDCT), which showed a good overall accuracy; c-statistic 0.80 (0.73-0.87), with especially a high negative predictive value (96.1%). Minor modification of the original criteria resulted in a higher positive predictive value (from 80.0% to 85.5%) and c-statistic (0.86), with only a small increase in negative predictive value (96.7%).

We compared the diagnosis of our expert panel consisting of three experienced vascular neurologists with that of the consulting neurologist (Chapter 7). The expert panel classified 30 cases as no TIA, while the patient was diagnosed with a TIA (n=10) or possible TIA (n=20) by the consulting neurologist and was treated accordingly. Vice versa, the expert panel classified a single case as a TIA, while the consulting neurologist concluded it was no TIA. However, this patient was already on stroke preventive medication. These results indicate that next to underdiagnosis and delay to stroke preventive treatment, there is also a problem of overdiagnosis of TIA, and thus overtreatment with antithrombotics.

## REDUCING DELAY TO DIAGNOSIS AND STROKE PREVENTIVE TREATMENT



***Case***

*Mr. T., a 75-year-old-man who lives alone, is reading the paper in the late afternoon when he suddenly notices that his right arm feels numb. He tries to shake his arm because it is quite similar to the feeling of a dead arm. Moving his hand and wrist feels more heavy than usual. Several minutes later, the arm feels just normal again. He has a bit of a strange feeling about it, but is comforted by the fact that the symptoms quickly resolved.*

*Next morning he meets a friend and tells about what he experienced. His friend, however, is more alarmed and suggests to contact the GP because it could have been a TIA. Mr. T. follows his friend's advice and gets an appointment the same day at 3 pm.*

## Educating patients and lay people

Despite the growing attention for the required urgency in case of stroke-like symptoms, lay people still not always act upon it by contacting a health care professional immediately. Patient delay is still a big problem, and the major contributor to the total time delay to diagnosis and treatment in patients suspected of a TIA. The patient delay in our Dutch cohort was comparable with the delays found in previous UK studies from 2002 to 2007.[1-3] In the past decennium, also in the Netherlands, there have been public campaigns using the acronym 'FAST' (Face drooping, Arm weakness, Speech difficulties, Time to call emergency service) aimed at better recognition of stroke-like symptoms and a quick response to such symptoms. However, a before and after evaluation of the British ACT FAST campaign pointed out that it had resulted in an improvement of patient delay in stroke patients, but not in patients with a TIA or minor stroke.[4] Patients with a stroke and patients with a TIA have similar neurological symptoms, but in case of a TIA these quickly resolve within minutes to hours while they persist in stroke. This suggests that more attention and specific education is needed to emphasize that also in case symptoms are resolving or already gone, patients should contact a health care service as soon as possible, in order to facilitate a rapid start of stroke preventive treatment.

Data on patient delay within the clinical domain of TIA are limited. With our surveys we aimed to better explore the determinants of this delay in order to give direction to public education. In our cohort, 87% of patients were familiar with the term TIA, and 57% knew key symptoms of TIA. When directly asking patients for the reason for their delay, the main reasons were (i) disappearance of symptoms, and (ii) considering the symptoms as not threatening. We showed that patients still tend to wait till GP office hours to report their TIA symptoms, despite 24/7 availability of GP care. Previous quantitative studies that explored determinants of patient delay used only univariable analyses, and showed conflicting results with respect to the role of recognition of symptoms. Our results showed that suspicion of a TIA by patients, or general knowledge about TIA symptoms, did not necessarily lead to shorter delay. Surprisingly, those who considered the possibility of a TIA (or stroke) as a cause of their symptoms, even less often considered their symptoms to be a medical emergency than those who did not. Of the typical symptoms, only speech difficulties, and more specifically dysarthria, were independently related to a shorter patient delay.

To reduce delay, lay people should be better educated about the characteristics of a TIA and its relation to stroke, but most importantly that also mild and short-lasting symptoms have to be reported to a medical service as soon as possible,

also outside office hours. In 2014 the British Stroke Association published a campaign briefing entitled 'Not just a funny turn; the real impact of TIA', in which they ask special attention for TIA as an important warning sign for stroke.[5] The document is addressed to health care providers and planners, and arrives at a list of calls for action, including the recommendation to ensure more prominent and tailored messages on TIA features in national and local stroke-awareness campaigns.

The FAST test (acronym for Facial drooping, Arm weakness, Speech difficulties, Time to call emergency services) has shown to improve the response after major stroke, however the sensitivity of FAST appears to be much lower in patients with a TIA or minor stroke. In the population-based OXVASC cohort 89.7% of major stroke patients had at least one FAST symptom, as opposed to 63.1% of TIA patients and 61.4% of minor stroke patients.[4] It can even be hypothesized that people may be falsely reassured when their symptoms do not match the more severe and typical symptoms depicted in the public FAST advertisements. Therefore, public education about TIA should include a broader scope of transient symptoms, such as loss of vision, diplopia, clumsiness and sensory disturbances.

Most importantly, lay people have to understand the link between these mild and quickly resolving symptoms and the risk of subsequent major stroke. TIA needs to lose its image as a benign condition. To conclude, tailored public education should on the one hand ensure that TIA and stroke are one continuum, and that similarly to a major stroke, a TIA is a medical emergency. On the other hand educating patients on TIA really asks for a different perspective, with also a different way of communicating symptomatology. A public awareness campaign focused on TIA, apart from the FAST campaigns focusing on major stroke is urgently needed.

***Continuation of the case***

*Mr. T. tells the GP about the short-lasting numbness of his arm. The GP tries to specify more exactly what he experienced, how these symptoms started and under what circumstances. Based on Mr. T.'s description, it seems that he experienced numbness together with weakness, rather than tingling or pins and needles alone. Most likely, there were no other neurological deficits; he experienced nothing unusual in the face or leg, no visual impairment, and no problem with communication. The GP considers the possibility of a TIA, but also considers a (short-lasting) peripheral nerve entrapment to be the cause of the symptoms. The GP contacts the neurologist on call to present the patient for an assessment at the TIA service. The neurologist agrees, and tells the patient is expected the following morning at 8 am. The GP is satisfied with the appointment on such short notice, and completes the referral, but does not prescribe aspirin for stroke prevention.*

*The next day, after all additional investigations have been completed, the neurologist sits with Mr. T. to discuss the findings and final diagnosis. The additional investigations, including CT imaging of the brain did not show any abnormalities, but the neurologist concludes based on the information from history taking that a TIA must have caused the symptoms. He therefore initiates stroke preventive medication, in this case clopidogrel and a statin.*

*Mr. T. goes to the pharmacy and takes the medication when he arrives at home; about 48 hours after he had his TIA.*

## Education of general practitioners

The timely start of antiplatelets is considered to be the essential intervention in the prevention of early strokes after TIA.[6] In the Dutch healthcare system, it is usually the GP who is contacted first and thus first assesses patients with symptoms suggestive of TIA. Given the delay from the GP consultation to the assessment at the TIA service, the initiation of aspirin by the GP in suspected TIA cases is an easy and realistic option to ensure early stroke preventive treatment in those with TIA, while overtreating of those who do not have TIA for only one or two days is considered to be acceptable. Therefore this early start of treatment has become a key task of GPs.

Our survey among 93 suspected TIA patients recruited from two TIA services showed that there is still much room for improvement in this regard; 57% of patients naive to antithrombotics did not receive antiplatelet therapy from the GP prior to their TIA service visit, while the median delay time from GP consultation to TIA

service visit was 30.0 (IQR 22.3-141.0) hours. In this survey we could not ask the referring GPs for their reasons for not prescribing antiplatelets in patients naive to antithrombotics. In the MIND-TIA study, however, we did send a questionnaire to GPs including questions about starting protective medication. In total 95 of the 206 (46.1%) questionnaires were completed, and in 37 (53.6%) of the 69 patients suspected of TIA and naive to antithrombotics the GP had prescribed antiplatelet medication prior to the TIA service visit. In 12 (37.5% of 32) patients the GP did not start such treatment because the neurologist's consultation could take place the same day. In the remaining 20 (62.5%) patients, the GPs had no valid argument not to start; 13 GPs responded that the assessment at the TIA service could be awaited, six considered the diagnosis of TIA too uncertain, and one considered initiating treatment a task of the neurologist.

The 2013 revised version of the Dutch GP guidelines for TIA and stroke included as a new recommendation to start with antiplatelets (i.e. aspirin) in any patient suspected of TIA, unless the patient will be seen by the neurologist the same day.[7] Our results indicate that a substantial proportion of GPs does not follow this recommendation, and seems to be insufficiently aware of the high risk of stroke early after TIA, and the crucial preventive role of timely initiated antiplatelet therapy. Therefore, implementation efforts are needed to increase the number of GPs that indeed start prescribing aspirin in 'any' patient suspected of TIA.

Multiple ways of changing the attitude of GPs on this issue can be considered, such as online practical training or a poster campaign at GP out-of-hours services. Furthermore, neurologists could help by advocating the immediate start with aspirin by the GPs during telephone referrals. Finally, in an update of the GP guidelines, the importance of the immediate start of aspirin by the GP could be emphasized more strongly, and should have a more prominent place in the summary. As an example, the UK guidelines recommend GPs to start such treatment in any patient suspected of TIA, even if an assessment by the neurologist would be possible the same day. A similar clear-cut recommendation should be included in the next GP guideline update in the Netherlands.



**Is the current health care trajectory of suspected TIA patients optimal?**

We have shown that there is considerable delay to diagnosis and start of treatment, both by the patient and by the physician. A prominent question is whether the current health care trajectory of suspected TIA patients could be improved. The Dutch health care system is characterized by a strong primary care. The gatekeeper's function of the GPs has beneficial effects on the selection of referrals and health care budgets, but it may cause undesirable delays in patients with

a TIA. Our study showed that assessment by the neurologist within 24 hours following from GP consultation is often not met (in our cohort in about 70% of cases). This delay, however, would not cause serious problems if GPs would initiate antiplatelet therapy in any case of suspected TIA.

An alternative model of care is one in which every suspected TIA patient presents directly to an emergency service. The French SOS-TIA study evaluated for the first time the implementation of a round-the-clock access TIA service.[8] A total of 1,085 patients suspected of TIA were assessed (65% could be confirmed as TIA/minor stroke, and 13% as possibly TIA). In total, 53% visited the clinic within 24 hours from symptom onset (this was 12% in our cohort of 93 patients recruited from two TIA services). The SOS-TIA study did not include a comparison with a 'care as usual' group, but the 90-day stroke risk was very low (1.2%). However, assessment of every suspected TIA patient immediately at a TIA emergency service would create a substantial workload for such services, and is very costly, while the benefits in terms of lowering recurrent stroke risk is primarily caused by the more timely start of antiplatelet therapy.

In the Netherlands, the Radboud University Medical Center launched a 24/7 TIA service in 2010 as part of their stroke center.[9] Their concept is different from the SOS-TIA model, and not that different from the regular Dutch model of care. Most patients are still referred by GPs, but the organization of care has put more emphasis on a rapid start of antiplatelet treatment and a rapid full diagnostic assessment. Patients suspected of a TIA nowadays can be examined the next morning in hospital if symptoms occur out of office hours. Exceptions are patients suspected of multiple episodes of TIA who are seen immediately at the stroke center. Furthermore, in any suspected TIA patient, the neurologist recommends the GP to already start with antiplatelet therapy. To our knowledge the cost-effectiveness of this 24/7 TIA service at the Radboud University Medical Center is not assessed until now.

Reorganization of the already existing TIA outpatient clinics to warrant the capacity and the personnel to offer a rapid complete diagnostic assessment for every suspected TIA, would be an important step in the prevention of early recurrent stroke. Also, these initiatives of '24/7 TIA services' as part of stroke centers may further increase awareness among lay people and GPs. Yet, at least for our Dutch healthcare system, we consider enforcing the early start of treatment by GPs as the crucial step forward, and also the most cost-effective strategy.

## BIOMARKERS FOR THE DIAGNOSIS OF TIA: CONTINUE THE SEARCH?

In analogy with the acute coronary syndrome, where (high sensitivity) troponin and other biomarkers are crucial to assess suspected patients, we were hopeful that blood biomarkers could have additional value in the early diagnosis of TIA. The more so because some biomarkers were promising in that earlier studies showed that some markers could discriminate ischemic stroke patients from 'healthy' controls. For the MIND-TIA study we selected based on a systematic literature review a set of such candidate biomarkers, specifically focusing on the diagnosis of TIA. Obviously, we were focusing on biomarkers that could be helpful in the clinically relevant domain of patients suspected of TIA, and thus could discriminate patients with TIA from patients with similar symptoms but no TIA. Moreover, we focused on biomarkers that remained elevated in blood for several days after an event, because of the well-known time delay between symptom onset and seeking medical advice in these patients. However, none of the selected markers had (added) diagnostic value in our cohort of patients suspected of a TIA by the GP, with c-statistics of each marker not exceeding 0.58.

Evidence for the potential of our set of biomarkers was still mainly based on studies among patients with major ischemic stroke making a case-control comparison, and thus comparing early biomarker levels of stroke patients with those of healthy individuals. The lack of discriminative value of the biomarkers in our MIND-TIA cohort in contrast with these previous studies is probably for the largest part explained by (i) the lower degree of brain ischemia (with no/nearly no necrosis) in our 'cases', (ii) applying the (clinically more relevant) comparison of patients suspected of TIA, thus with patients with events mimicking a TIA instead of healthy controls in the sample, and (iii) the longer time from symptom onset to blood sample collection of (median) 48 hours in MIND-TIA, compared to the previous studies in which patients were recruited in an emergency department setting.

The concept of an accurate blood biomarker that supports the diagnosis of already resolved symptoms suggestive of TIA remains attractive, irrespective of the fact that our study clearly showed that currently available biomarkers do not fulfill the expectations. A complicating factor of the clinical domain of TIA is the wide time interval of presentation to medical services. Symptoms often resolve very fast which easily results in delay and inertia. Therefore, a useful biomarker of TIA should show increased levels rapidly after TIA onset, with elevated levels persisting for several days. From biomarker dynamics in other fields such as myocardial ischemia we know that biomarkers with early peak levels, often also rapidly decrease. The use of a single diagnostic marker that covers the first days after a TIA may thus be

unlikely, and a possible solution may be a combination of biomarkers; including markers with a rapid increase and those with increased levels lasting several days. Another possibility may be the use of a biomarker that instead of showing peak levels after a TIA reflects underlying pathology. Problem here is that the exact etiology of brain ischemia is diverse, varying from cardioembolism to large artery atherosclerosis and thrombotic occlusion of small penetrating arteries affected by lipohyalinosis. It was hypothesized that NR2A/B antibodies (NR2A/B Abs) reflect previous episodes of (silent) ischemia.[10] However, in our cohort we did not find an association of NR2A/B Abs with a history of stroke or TIA.

Translational research will without doubt provide new biomarkers and perhaps also new sources of biomarkers. MiRNAs are a relatively new source of biomarkers in a rapidly developing field of research, and the coming years will learn if this in the end will lead to useful tools for clinical practice. With the MIND-TIA cohort we built a valuable biobank that provides the opportunity to easily evaluate such new markers.

## BACK TO THE CLINICAL ASSESSMENT: CAN DIAGNOSTIC PREDICTION MODELS SUPPORT CLINICIANS?

Previous attempts to facilitate clinicians with a diagnostic score or tool for TIA resulted in two scores that were based on regression analysis: the Dawson score (consisting of 9 determinants), and the Diagnosis of TIA (DOT) score (17 determinants).[11,12] The DOT score performed better in a direct comparison with the Dawson score in a cohort of 525 suspected TIA patients from a British TIA service (c-statistic 0.89 vs 0.83).[12] However, this was evaluated in the derivation cohort of the DOT score. The Dawson score had poor diagnostic value when applied by GPs (c-statistic 0.70).[11] Both the DOT and the Dawson are not used in clinical practice nor in research, probably because they are not practical because of the large number of determinants, and moreover considered not sufficiently accurate.

Recently, two neurologists developed the ‘explicit diagnostic criteria for TIA’ (EDCT) based on clinical practice and experience instead of statistical methods.[13] All criteria have to be fulfilled to classify a suspected event as a TIA. These include the key characteristics of a TIA, i.e. a sudden onset, an onset in full intensity without a gradual spread of symptoms, and the presence of neurological deficits instead of positive symptoms. The EDCT showed high diagnostic accuracy in our MIND-TIA cohort, with especially a remarkably high negative predictive value (96.1%). Moreover, we could demonstrate that positive predictive value was substantially higher after minor modification of the criteria. Our modification

was based on rephrasing of the subcriteria C1-C3 (describing an onset in full intensity (C1), symptoms occurring simultaneously (C2), and the presence of actual neurological deficits), so that these apply to all symptoms instead of one or some of the symptoms. Given the excellent diagnostic accuracy with high negative predictive value, the modified EDCT seems to be a useful tool that can fill the gap of existing diagnostic uncertainty in the primary care setting. With our study described in Chapter 7 we validated the EDCT in the domain of interest, i.e. patients suspected of a TIA by the GP. The EDCT criteria are easy to use, with (when including subcriteria) seven items that have to be assessed based on history taking. Given that patients suspected of a TIA are referred to the TIA service for further diagnostic and prognostic assessment, a clinical decision rule that can safely exclude TIA is most valuable. Considering that around 40% of patients referred to a TIA service receive an alternative definite diagnosis, the EDCT could potentially save many costly referrals. Furthermore, facilitating and empowering GPs with a diagnostic tool for TIA may also result in a higher prescription rate of antiplatelets in the GP office.

Critical in evaluating a diagnostic model in a research setting is the best possible certainty about the outcome and to let all participants have this reference test or "gold" standard. For the diagnosis of TIA this is a panel of expert neurologists using all available diagnostic information. With respect to this evaluation of the EDCT, it must be realized that we compared classification criteria composed by neurologists with the joint judgment of three neurologists who in the end use the same diagnostic criteria and strategies. Therefore, one could argue that the performance of the EDCT might be overestimated because of incorporation bias; symptoms considered to be useful show to be useful. To date, however, there is no better alternative reference test available, and we are thus unable to fully exclude this possible source of bias.

A final critical note must be considered. Although the EDCT seem practicable and easy to apply, it still contains items that are not purely objective (for example the judgment whether symptoms are neurological deficits). At this point the actual usability of the EDCT for clinical practice and the performance of the score when applied by GPs in everyday practice is still unknown. To determine whether the EDCT really is a useful diagnostic tool for GPs, a prospective study in patients suspected of a TIA is needed, in which one group of GPs provides care as usual and another group bases their diagnosis, referral and treatment decisions on the score of the EDCT.

## DIAGNOSTIC UNCERTAINTY AND THE RISK OF UNDERDIAGNOSIS BUT ALSO OVERDIAGNOSIS

Symptoms of a TIA can be hard to recognize for patients, but also for physicians. They can be mild or vague, and vary strongly depending on the area of ischemia. Especially TIAs originating from the vertebrobasilar system can be difficult to identify. A GP who considers the possibility of a TIA, will almost always refer a patient to a TIA service for additional investigations. However, the suspicion of a TIA does not always arise, and sometimes only after a second or third event, or worse after a full-blown stroke. Although data are lacking, unrecognized TIAs are considered to be common.

Next to underdiagnosis, also overdiagnosis is a clinical problem. The case in the introduction of this thesis is an example of the diagnostic dilemma a GP and ultimately the neurologist can be challenged with. As brain imaging and other additional investigations most often do not provide conclusive evidence, the neurologist in doubt usually weighs 'circumstantial evidence' such as the presence of cardiovascular risk factors, a positive family history of cardiovascular disease, or a history of migraine. After the diagnostic assessment at the TIA service, the neurologist has to make a decision, and it is one with high stakes. Concluding it was a TIA means lifelong treatment with comprehensive stroke preventive medication. On the other hand, if the neurologist incorrectly concludes it was no TIA, this means that the patient is at increased risk of a full-blown stroke in the absence of preventive treatment.

Because of the possibly severe consequences of not treating a TIA, in practice the tendency is to choose for continuing stroke preventive treatment in those cases in which a TIA cannot be ruled out. In the MIND-TIA study we were able to compare the diagnosis of the panel with the diagnosis of the consulting neurologist. A substantial number of cases was classified by the panel as no TIA, while the patient was diagnosed with a (possible) TIA by the consulting neurologist and was treated accordingly (30 [37.5%] of the 80 cases that were classified as no TIA by the panel). The opposite (panel determined it was a TIA, treating neurologist concluded no TIA) occurred in only one case, and this concerned a patient that was already on stroke preventive medication. Although we realize that the panel judgment is not the "gold" standard and thus not always correct, this comparison confirms the tendency of neurologists choosing for treatment in doubtful cases. In other words, neurologists intend to be rather safe than sorry. This seems logical and justifiable at least for the short term; however, how safe and desirable is this for the long term?

The bleeding risk of aspirin is an ongoing subject in the discussion on the balance of risk and benefits in primary prevention of cardiovascular disease. A systematic

review of observational studies on bleeding risk with long-term aspirin showed that the overall pooled estimate of the relative risk of both gastro-intestinal bleeding and intracerebral hemorrhage was 1.4 (1.2-1.7).[14] In the ASCEND trial more than 15,000 adults with diabetes but no evident cardiovascular disease were randomly assigned to aspirin at a dose of 100 mg daily or placebo during a mean follow-up period of 7.4 years.[15] The results were published recently (2018) and showed that the benefit of aspirin to reduce the risk of myocardial infarction or stroke is small, and is outbalanced by the increased risk of bleeding. A major bleed occurred in 4.1% of participants on aspirin and in 3.2% of participants receiving placebo, meaning that 9 of every 1,000 participants had a major bleed as a result of taking aspirin; 11 of every 1,000 participants avoided first myocardial infarction or stroke as a result of aspirin in this study population. These data show that on the long term the risk of bleeding as a result of antiplatelet therapy is a serious concern, which might well be underestimated by neurologists taking a decision on a TIA diagnosis.

Beyond the harmful effects of antiplatelets, overdiagnosis and overtreatment have more consequences. According to protocol, patients diagnosed with TIA should also receive a statin and antihypertensive treatment and they will also be assigned to lifelong follow-up as part of secondary prevention of cardiovascular disease. Moreover, receiving the diagnosis of TIA can have a big impact on patients, being aware that they are now at increased risk of having a stroke.

Considering that there is probably a substantial proportion of patients who are wrongly treated as TIA patients, and realizing the lifelong impact of this diagnosis, these doubtful cases may require more attention than is now the case in daily practice. Usually the diagnosis is made by the treating neurologist that day without further follow-up or a moment of reconsideration of the initial diagnosis. Firstly, it might be useful for neurologists to discuss difficult cases with colleagues on a more regular basis, for example in a regular meeting within their department. Secondly, it could be valuable to have a follow-up evaluation with patients after several months or after a year. This could be done by the neurologist, but maybe also by the GP during the regular follow-up of secondary prevention. It is a concept similar to the six months follow-up period we included in the data presenting to our expert panel, which could provide information that sheds another light on the initial event. A more controversial option would be to treat those patients in whom a TIA is unlikely (but cannot be ruled out) only for a fixed period, for example one year.

Regardless of the way in which this can be achieved, we feel that there should be more attention for follow-up of TIA patients and the impact of potential overtreatment. This thesis mainly focused on achieving timely diagnosis to ensure a rapid start of treatment, but at the end of the diagnostic process the problem of potential overtreatment cannot be overlooked.

## CONCLUDING RECOMMENDATIONS

- Lay people should be better educated about the characteristics of a TIA and its relation to stroke, and most importantly that a TIA is a medical emergency, and therefore also mild and short-lasting symptoms have to be reported to a medical service as soon as possible to be able to initiate stroke preventive treatment.

- New and ongoing tailored public awareness campaigns focusing on TIA are needed, apart from the FAST campaigns focusing on major stroke.

- GPs should bring their knowledge to action and follow the guidelines by an immediate start of antiplatelet therapy in any suspected TIA case.

- Neurologists should advocate and support the initiation of antiplatelet therapy by the GP, and realize they have an important task in the communication about this treatment.

- An update of the Dutch GP guidelines on TIA must contain a clear-cut recommendation about the prompt start with aspirin in every patient suspected of TIA, instead of the current recommendation to start unless the patient is seen by the neurologist the same day.

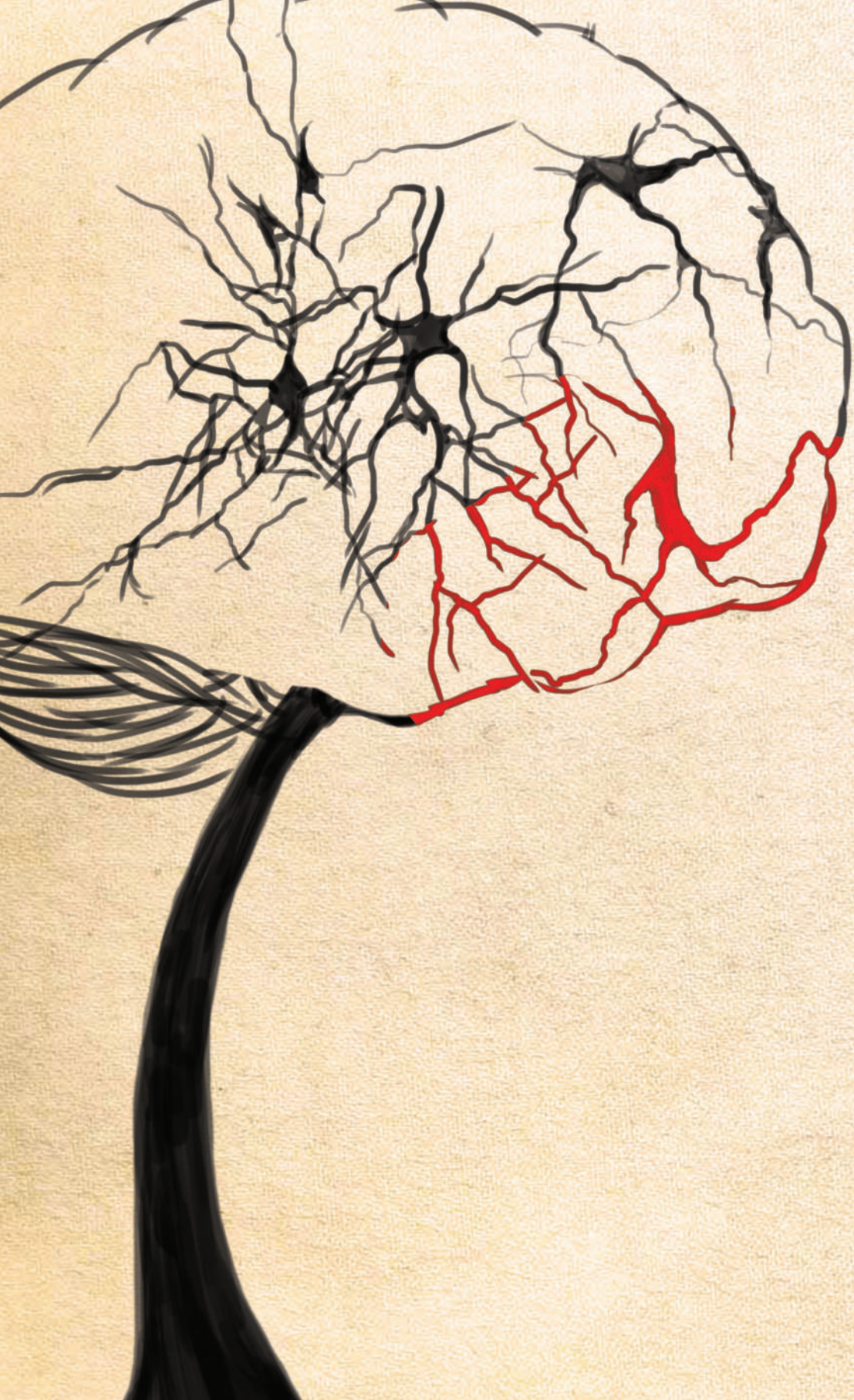
- Currently available blood biomarkers have no additional value in the diagnosis of TIA, but the search for (a combination of) biomarkers should continue.

- The modified 'explicit diagnostic criteria for TIA' (EDCT) are useful to support GPs and could be considered for adoption in the GP guidelines on TIA. First, however, an implementation study showing its effectiveness when used as a diagnostic strategy should be performed.

- Overdiagnosis of TIA and thus the risk of overtreatment is common. Follow-up of doubtful cases or discussion with colleagues to reconsider the diagnosis could prevent unnecessary lifelong treatment with antiplatelets and other cardiovascular medication.

## REFERENCES


1. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-42.
2. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behavior immediately after transient ischemic attack and minor stroke in 1000 consecutive patients: lessons for public education. Stroke. 2010;41(6):1108-14.
3. Giles MF, Flossman E, Rothwell PM. Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. Stroke. 2006;37(5):1254-60.
4. Wolters FJ, Li L, Gutnikov SA, Mehta Z, Rothwell PM. Medical attention seeking after transient ischemic attack and minor stroke before and after the UK Face, Arm, Speech, Time (FAST) public education campaign: Results from the Oxford Vascular Study. JAMA Neurol. 2018;75(10):1225-1233.
5. Stroke Association. Not just a funny turn; the real impact of TIA. 2014. Available from: https://www.stroke.org.uk/sites/default/files/sa-the_real_impact_of_tia-report-sp-v5_0.pdf.
6. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016;388(10042):365-75.
7. Verburg AF, Tjon ATMR, Verstappen WH, Beusmans GH, Wiersma T, Burgers JS. [Summary of the 'Stroke' guideline of the Dutch College of General Practitioners' (NHG)]. Ned Tijdschr Geneeskd. 2014;158(1):A7022.
8. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet neurol. 2007;6(11):953-60.
9. Van Rooij FG, Van Dijk EJ, De Leeuw FE. 24/7 TIA-service. Int J Integr Care. 2012;12(6):None.
10. Weissman JD, Khunteev GA, Heath R, Dambinova SA. NR2 antibodies: risk assessment of transient ischemic attack (TIA)/stroke in patients with history of isolated and multiple cerebrovascular events. J Neurol Sci. 2011;300:97–102.
11. Dawson J, Lamb KE, Quinn TJ, Lees KR, Horvers M, Verrijth MJ, et al. A recognition tool for transient ischaemic attack. QJM. 2009;102:43-9.
12. Dutta D. Diagnosis of TIA (DOT) score--design and validation of a new clinical diagnostic tool for transient ischaemic attack. BMC Neurol. 2016;16:20.
13. Lebedeva ER, Gurary NM, Gilev DV, Christensen AF, Olesen J. Explicit diagnostic criteria for transient ischemic attacks to differentiate it from migraine with aura. Cephalalgia. 2018;38:1463-70.
14. García Rodríguez LA, Martín-Pérez M, Hennekens CH, Rothwell PM, Lanas A. Bleeding risk with long-term low-dose aspirin: a systematic review of observational studies. PLoS One. 2016;11(8):e0160046.
15. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G. Effects of aspirin for primary prevention in persons with Diabetes Mellitus. N Engl J Med. 2018;379(16):1529-1539.



# Appendices

## SUMMARY

A Transient Ischemic Attack (TIA) is a short episode of neurological deficits due to acute brain ischemia, that resolves without remaining symptoms. However, a TIA is an important warning sign that a patient is at risk of a full stroke in the near future. Importantly, this risk is highest in the first days after a TIA. Timely diagnosis and initiation of stroke preventive treatment, most notably the start of antiplatelet therapy, drastically reduces the early risk of stroke.

The diagnosis of TIA can, however, be difficult for both general practitioners and neurologists. Symptoms may be mild or vague, and often last for only minutes. Multiple disorders can mimic a TIA, e.g. migraine with aura or seizures. Clinicians often need to rely on history taking, as symptoms have already disappeared. Moreover, even the best available brain imaging modality, diffusion-weighted magnetic resonance imaging (DW-MRI), does not show signs of acute ischemia in the majority of TIA patients. Both establishing and excluding the diagnosis can be difficult.

Another issue that hampers early diagnosis and timely intervention is patient delay. Symptoms of a TIA are easily misinterpreted or may be trivialized by patients and bystanders. Studies from the UK in the period 2002 till 2007 have indicated that 30-40% of TIA or minor stroke patients delay the first contact with a medical service for more than 24 hours.

An accurate blood biomarker of brain ischemia would solve some of these diagnostic difficulties. Previous studies provided preliminary evidence that certain biomarkers increase from the first hour after a stroke or TIA event until days or even a week after. A biomarker that rapidly and reliably detects brain ischemia in patients suspected of TIA would be extremely valuable, notably for general practitioners.

This thesis focused on (i) the value of tests or tools to support the clinical diagnosis of TIA, in particular blood biomarkers and clinical prediction models, and (ii) delay in the diagnosis and treatment of TIA, notably patient delay and its determinants.

## DELAY TO DIAGNOSIS AND TREATMENT OF TIA

We performed a systematic review to quantify patient delay in patients with suspected TIA, and to assess determinants related to such delay, using MEDLINE and EMBASE databases up to March 2017 (**Chapter 2**). Nine studies provided data on the time from onset of TIA symptoms to seeking medical help, published between 2006 and 2016, with 7/9 studies originating from the United Kingdom (UK). We only identified studies with established TIA or stroke patients. A total of

1103 time-defined TIA patients (no remaining symptoms > 24 h), and 896 minor stroke patients (i.e. mild remaining symptoms > 24 h) were included. Patient delay of more than 24 hours was reported in 33.1-44.4% of TIA patients, with comparable proportions for patients with minor stroke. Delays were on average much shorter in patients interviewed at the emergency department (ED) than those recruited at TIA outpatient clinics, underling the impact of the study setting; surveys at TIA outpatient clinics provide a better reflection of patient delay in the complete spectrum of TIA patients presenting via different health care routes. Three studies aimed to find determinants of patient delay, however, all used different statistical methods, and none of them performed multivariable analyses. It was therefore impossible to draw conclusions about which variables independently predict delay based on these data. Main conclusion from the review was that too many patients with TIA delay seeking medical attention for a substantial time period, and thus risk a delay in receiving appropriate treatment to prevent subsequent stroke.

In **chapter 3** we describe the results of our own survey on both patient and physician delay in 93 patients suspected of a TIA, recruited at two rapid access TIA services in Utrecht, The Netherlands. In a structured interview we assessed time delay to diagnosis and treatment, including the time to (i) patient's first contact with a medical service, (ii) consultation of the GP, and (iii) assessment at the TIA outpatient clinic. We used the diagnosis of the treating neurologist as the reference; 43 (46.2%) patients received a definite, 13 (14.0%) a probable, 11 (11.8%) a possible, and 26 (28.0%) no diagnosis of TIA. Median patient delay was 17.5 (IQR 0.8-66.4) hours, with a delay of more than 24 hours in 36 (38.7%) patients. The GP was first contacted in 76 (81.7%) patients. Although the actual GP consultation took place after a median time of only 2.8 (0.5-18.5) hours from the patient's first contact with the GP practice (GP delay), it took another 40.8 (IQR 23.1-140.7) hours before the patient was seen at the TIA service (referral delay). Of the 62 patients naïve to antithrombotic medication who consulted their GP, 27 (43.5%) received antiplatelet therapy, while Dutch GP guidelines recommend initiating an antiplatelet agent immediately unless the patient is assessed by a neurologist the same day. Our results emphasize the need for both patient and physician education, aimed at quick consultation at a TIA outpatient clinic and, even more important, to start early with secondary prevention in any case of a suspected TIA.

**Chapter 4** is on determinants of patient delay. In the 'Markers in the Diagnosis of TIA' (MIND-TIA) study, we included a standardized interview on patient delay. Participants were all referred by their GP to a TIA outpatient clinic within 72 hours from symptom onset. Next to the exact time to the patient's first contact with a medical service, we assessed (i) demographic and clinical characteristics, (ii)

patient's initial perception, and reaction to symptoms, and (iii) patient's knowledge about TIA. Of 202 participants, 123 (60.9%) received a definite diagnosis of a TIA or minor stroke by an expert panel. Of all patients, 119 (58.9%) considered a TIA (or stroke) as a possible cause of their symptoms. Among them, 30 (25.2%) thought it was a medical emergency. Remarkably, of the 83 patients not considering TIA as the cause of their symptoms, more patients thought of a medical emergency (45.8%). With multivariable linear regression analysis, independently related to increased delay were (i) symptom onset during out of office hours, (ii) absence of dysarthria, (iii) being unaware that a TIA requires urgent treatment, (iv) not considering the event an emergency, and (v) knowledge of TIA symptoms. Results for patients with a definite diagnosis of TIA/minor stroke and those with alternative diagnoses were similar. Our results show that suspicion of a TIA by patients, or general knowledge about TIA symptoms, do not necessarily lead to an urgent call for medical advice. A more important determining factor seems if patients are aware that a TIA requires urgent treatment. Delays are still substantially longer after an onset of symptoms during out of office hours, also in a healthcare system with 24 hours availability of GP care. Of typical TIA symptoms, only speech difficulties and specifically dysarthria were related to shorter delay.

## IMPROVING THE ACCURACY OF TIA DIAGNOSIS

**Chapter 5** describes the protocol of our main study 'Markers in the Diagnosis of TIA' (MIND-TIA). The primary aim was to quantify the added diagnostic value of serum biomarkers of brain ischemia in patients suspected of TIA. MIND-TIA is a cross-sectional diagnostic accuracy study with an additional six-month follow-up period, among patients suspected of a TIA in the primary care setting. Patients were recruited by more than 350 GPs in the catchment area of 11 TIA outpatient clinics in and around Utrecht, The Netherlands. In all patients a blood sample was drawn by a research nurse as soon as possible after the patient had consulted the GP, but at least within 72 h after onset of symptoms. Following routine care, participants were referred by the GP to the regional TIA outpatient clinic for additional investigations, including brain imaging. A panel consisting of three vascular neurologists was used to determine the 'definite' diagnosis (reference). Their decision was based on all available diagnostic information, including (i) standardized history taking by the research nurse, (ii) a taped patient's narrative of experienced symptoms, (iii) all clinical information from the assessment by the neurologist and other specialists, and (iv) information from the six-month follow-

up period. We aimed to assess the diagnostic accuracy, and value in addition to signs and symptoms of a set of candidate serum biomarkers, which we selected based on a review of literature.

We performed a systematic review on accuracy of biomarkers in the diagnosis of TIA, using MEDLINE and EMBASE databases up to May 1, 2017 (**Chapter 6**). We selected primary diagnostic accuracy studies evaluating potential biomarkers in blood for the diagnosis of TIA or ischemic stroke. Quality of individual studies was appraised using the QUADAS-2 tool. Our search identified 4,125 studies, of which 78 met our eligibility criteria. Forty-five studies restricted their population to ischemic stroke patients, 32 included both TIA and ischemic stroke patients, and only one study was restricted to TIA patients. The majority of studies (79.5%) had a case-control design, comparing TIA or stroke patients with healthy subjects. None of the biomarker studies evaluated the performance in the intended population of interest, that is patients *suspected of* a TIA. In total, 124 single biomarkers and five biomarker panels were studied. Overall the methodological quality of studies was poor. Sufficient information to extract 2x2 tables was available for 35 (44.9%) articles, and for 60 (48.0 %) biomarkers. Several markers, such as NR2A/B(antibodies), PARK7, NDKA, UFD-1 and H-FABP, have shown moderate to high diagnostic accuracy in multiple studies. However, the evidence base is fragile and adequately performed diagnostic studies are needed to determine the value of these markers in the clinical domain of suspected TIA.

**Chapter 7** presents the main results of the MIND-TIA study. A total of 206 patients suspected of TIA participated, of whom 126 (61.2%) were diagnosed with a TIA (n=104) or minor stroke (n=22) by the expert panel. Among the 80 patients with an alternative diagnosis, most frequent were migraine (n=24, 30.0%), stress related or somatoform symptoms (n=16, 20.0%), and syncope (n=9, 11.3%). The median time from symptom onset to the blood sample collection was 48.0 (IQR 28.3-56.8) hours. Of the seven biomarkers we assessed, none had discriminative value in the diagnosis of TIA, with c-statistics ranging from 0.45 to 0.58. However, a final multivariate diagnostic model consisting of eight clinical determinants had good diagnostic accuracy with a c-statistic of 0.83 (0.78-0.89). Age, a history of coronary artery disease, a sudden onset of symptoms, an onset with immediate full intensity, and dysarthria were independent positive predictors of a TIA or a minor stroke. A history of migraine, headache, and loss of consciousness were independent negative predictors. We showed that currently available blood biomarkers have no value in the diagnosis of TIA.

In **chapter 8** a recently proposed set of criteria for the diagnosis of TIA, the so-called 'explicit diagnostic criteria for TIA (EDCT)', is validated in our MIND-TIA

cohort. The EDCT is a clinical tool focusing on type, duration and mode of onset of clinical features, developed by two neurologists based on clinical practice and experience instead of statistical methods. All 206 participants of MIND-TIA (of whom 61% were diagnosed with TIA or minor stoke) were included. The data gathered in the MIND-TIA study provided all necessary information for classification according to the EDCT. Diagnostic accuracy of the EDCT was calculated with the panel diagnosis as reference standard. Additionally, we assessed the performance of the EDCT after minor modification of one of the subcriteria. The original EDCT had good overall accuracy (c-statistic 0.80 [0.73-0.87]), with especially a high negative predictive value (96.1%). The modification of the original criteria resulted in a higher positive predictive value (from 80.0% to 85.5%) and a small increase in negative predictive value (96.7%). Our study showed that the proposed EDCT was easy to apply, and could be a valuable diagnostic tool for the diagnosis of TIA in the primary care setting.

## MAIN CONCLUSIONS AND RECOMMENDATIONS

In **chapter 9** we discuss the main findings and conclusions of this thesis, and provide recommendations aimed at reducing delay in diagnosis and treatment of TIA, and how to avoid both under- and overdiagnosis of TIA. Education of general practitioners, patients and lay people are needed, as is optimization of the health care trajectory of patients with suspected TIA.

Lay people should receive better education about the characteristics of a TIA and its relation to stroke. Most importantly they should learn to consider a TIA as a medical emergency, and that also mild and short-lasting symptoms have to be reported to a medical service as soon as possible. Tailored public awareness campaigns focusing on TIA are needed, apart from the ‘FAST’ campaigns focusing on major stroke.

Awareness among GPs about the importance of a rapid start of antiplatelet therapy in suspected TIA is insufficient and should be improved. Also, neurologists should actively recommend immediate initiation of antiplatelet therapy when they are consulted by a GP. Furthermore, an update of GP guidelines should include a clear-cut recommendation on initiation of antiplatelets in every patient suspected of TIA, instead of the current more lenient recommendation to start unless the patient is seen by the neurologist the same day.

Currently available blood biomarkers have no additional value in the diagnosis of TIA. The modified ‘explicit diagnostic criteria for TIA (EDCT)’ may be a useful

tool for GPs to support the clinical diagnosis of TIA, in particular for excluding the diagnosis of TIA. Further research is needed to determine the actual usability of the criteria by GPs.

The results of the panel diagnosis in MIND-TIA indicated that overdiagnosis of TIA, and thus overtreatment, are common. Follow-up of doubtful cases or discussion with colleagues to reconsider the diagnosis could prevent unnecessary lifelong treatment with antiplatelets and other cardiovascular medication.

## NEDERLANDSE SAMENVATTING

Een Transient Ischemic Attack (TIA) is een korte episode van neurologische uitvalsverschijnselen ten gevolge van acute focale ischemie van de hersenen, die voorbijgaat zonder restverschijnselen. Een TIA is echter een belangrijk waarschuwingssignaal dat een patiënt risico loopt op een herseninfarct in de nabije toekomst. Dit risico is bovendien het grootst in de eerste dagen na een TIA. Een tijdige diagnose en start van behandeling gericht op beroertepreventie, in het bijzonder het opstarten van een plaatjesaggregatieremmer, kan het vroege risico op een herseninfarct drastisch verlagen.

De diagnose TIA kan echter lastig zijn, voor zowel huisartsen als neurologen. Symptomen kunnen mild of vaag zijn, en houden vaak slechts minuten aan. Diverse aandoeningen kunnen een TIA nabootsen, zoals migraine met aura en epilepsie. Artsen hebben vaak enkel de anamnese om zich op te baseren, omdat de klachten al voorbij zijn. Bovendien toont zelfs de best beschikbare vorm van beeldvorming, 'diffusion-weighted magnetic resonance imaging (DW-MRI)', in de meerderheid van de patiënten met een TIA geen tekenen van acute ischemie.

Een ander probleem dat vroegtijdige diagnose en behandeling belemmert is patiënt delay. De verschijnselen van een TIA kunnen gemakkelijk worden gemisinterpreteerd of getrivialiseerd door patiënten en omstanders. Britse studies in de periode 2002-2007 toonden dat 30-40% van de patiënten met een TIA of een minor stroke hun eerste contact met een medische instantie meer dan 24 uur uitstellen.

Een accurate biomarker van hersenischemie in bloed zou een oplossing kunnen zijn voor een deel van de knelpunten in de diagnostiek van TIA. Eerdere studies tonen bewijs van het bestaan van biomarkers die stijgen vanaf het eerste uur na een TIA en verhoogd blijven tot dagen en zelfs een week later. Een biomarker die snel en betrouwbaar hersenischemie detecteert in patiënten verdacht van een TIA, zou enorm waardevol zijn, vooral voor huisartsen.

Deze thesis richt zich op i) de waarde van testen of tools die de klinische diagnose van TIA ondersteunen, in het bijzonder biomarkers in bloed en klinische predictiemodellen, en ii) delay in de diagnose en behandeling van TIA, met een nadruk op patiënt delay en haar determinanten.

## DELAY IN DIAGNOSE EN BEHANDELING VAN TIA

We voerden een systematische review uit om patiënt delay in patiënten met verdenking op een TIA te kwantificeren en determinanten van dit delay te bepalen, met gebruik van MEDLINE en EMBASE databases tot maart 2017 (**Hoofdstuk 2**). Negen studies presenteerden data betreffende de tijd van begin van klachten tot het zoeken van medische hulp; ze werden gepubliceerd tussen 2006 en 2016, en 7/9 studies werden uitgevoerd in het Verenigd Koninkrijk. We vonden enkel studies met patiënten met een vastgestelde TIA of minor stroke. In totaal 1103 TIA-patiënten gedefinieerd volgens het tijdscriterium (geen restverschijnselen > 24 uur) en 896 minor stroke patiënten (milde restverschijnselen langer > 24 u) werden geïncludeerd. Patiënt delay van meer dan 24 uur werd gevonden in 33,1-44,4% van de TIA-patiënten, met vergelijkbare proporties voor patiënten met een minor stroke. Het delay was gemiddeld veel korter bij patiënten die werden geïnterviewd op de spoedeisende hulp dan bij patiënten die werden gerekruteerd op de TIA-polikliniek, wat de impact van de studiesetting benadrukt; steekproeven in de poliklinische setting geven een betere weergave van patiënt delay voor het complete spectrum van TIA-patiënten die zich presenteren via verschillende zorgkanalen. Drie studies richtten zich op determinanten van patiënt delay. Deze studies gebruikten echter elk andere statistische methoden en geen van alle multivariabele analyses. Het was daarom op basis van deze data niet mogelijk om te bepalen welke variabelen onafhankelijke voorspellers zijn van patiënt delay. De belangrijkste conclusie van het review was dat te veel patiënten met een TIA lang wachten met het zoeken van medische hulp en daarmee een verlate start van beroertepreventie riskeren.

In **hoofdstuk 3** beschrijven we de resultaten van onze eigen kwantitatieve interviewstudie naar delay door zowel patiënt als arts, onder 93 patiënten verdacht van een TIA gerekruteerd op twee TIA-services in Utrecht. Met een gestructureerd interview bepaalden we het delay tot diagnose en behandeling, waaronder de tijd tot i) het eerste contact van patiënt met een medische dienst, ii) consultatie van de huisarts, en iii) de beoordeling op de TIA-service. We gebruikten de diagnose van de behandelend neuroloog als referentiestandaard; 43 (46,2%) patiënten kregen een zekere, 13 (14,0%) een waarschijnlijke, 11 (11,8%) een mogelijke, en 26 (28,0%) geen diagnose TIA. Het mediane patiënt delay was 17,5 (IQR 0,8-66,4) uur, met een delay van 24 uur bij 36 (38,7%) patiënten. De huisarts werd als eerste zorgverlener gecontacteerd door 76 (81,7%) patiënten. Hoewel het daadwerkelijke huisartsconsult plaatsvond na slechts 2,8 (IQR 0,5-18,5) uur vanaf het eerste contact van de patiënt met de huisartspraktijk (huisarts delay), kostte

het nog eens 40,8 (IQR 23,1-140,7) uur tot de patiënt werd gezien op de TIA-service (delay van verwijzing). Van de 62 patiënten die nog geen antitrombotische medicatie gebruikten en een huisarts consulteerden, kregen 27 (43,5%) een plaatjesaggregatieremmer, terwijl de Nederlandse huisartsenrichtlijn voorschrijft om deze direct te starten tenzij de patiënt nog dezelfde dag wordt beoordeeld door een neuroloog. Onze resultaten benadrukken de noodzaak van educatie gericht op zowel patiënten als artsen, met als doel een spoedige beoordeling op een TIA-service en, als belangrijkste, een vroege start van secundaire preventie in elke patiënt verdacht van een TIA.

**Hoofdstuk 4** is gericht op determinanten van patiënt delay. In de 'Markers in the Diagnosis of TIA' (MIND-TIA) studie hebben we een gestandaardiseerd interview over patiënt delay opgenomen. Alle deelnemers werden door hun huisarts verwezen naar een TIA-polikliniek binnen 72 uur na start van klachten. Naast de exacte tijd tot het eerste contact van patiënt met een medische dienst, bepaalden we i) demografische en klinische karakteristieken, ii) de initiële perceptie van patiënt en reactie op klachten, en iii) de kennis van TIA. Van de 202 deelnemers, kregen 123 (60,9%) een uiteindelijke diagnose TIA of minor stroke van een expert panel. Van alle patiënten overwogen 119 (58,9%) de diagnose TIA (of beroerte) als mogelijke oorzaak van hun klachten. Onder hen beschouwden 30 (25,2%) de klachten als een medisch spoedgeval. Opvallend was dat onder de 83 patiënten die niet aan een TIA of beroerte dachten, significant meer van hen de klachten beschouwden als een spoedgeval (45.8%). In een multivariabele lineaire regressieanalyse waren de volgende variabelen onafhankelijk gerelateerd aan langer delay: i) begin van klachten tijdens kantooruren, ii) afwezigheid van dysartrie, iii) niet bewust zijn dat bij een TIA snelle behandeling nodig is, iv) de ervaren klachten niet als een spoedgeval zien, en v) het kennen van TIA-symptomen. De bevindingen voor patiënten met een definitieve diagnose TIA/minor stroke en patiënten met een alternatieve diagnose waren vergelijkbaar. Onze resultaten tonen dat de verdenking op een TIA door patiënten, of kennis van TIA-symptomen, niet per se leiden tot sneller inschakelen van medische hulp. Een meer bepalende factor lijkt te zijn of patiënten zich bewust zijn van het feit dat bij een TIA een snelle behandeling noodzakelijk is. Patiënt delay is nog steeds substantieel groter bij een begin van klachten buiten kantoortijden, ook in een zorgsysteem met 24-uurs beschikbaarheid van huisartsenzorg. Van de typische TIA-symptomen waren alleen spraakproblemen, en specifiek dysartrie, gerelateerd aan korter delay.

## OPTIMALISEREN VAN DE ACCURATESSE VAN DE DIAGNOSE TIA

**Hoofdstuk 5** beschrijft het protocol van onze hoofdstudie ' Markers in the Diagnosis of TIA' (MIND-TIA). Het belangrijkste doel was om de toegevoegde waarde te bepalen van serum biomarkers van hersenischemie in patiënten verdacht van een TIA. MIND-TIA is een cross-sectionele diagnostische accuratessestudie met een aanvullende follow-upperiode van zes maanden, onder patiënten die in de eerste lijn worden verdacht van een TIA. Patiënten werden gerekruteerd door meer dan 350 huisartsen in het verzorgingsgebied van 11 TIA-poliklinieken in en rondom Utrecht. Bij alle patiënten werd een bloedmonster afgenomen door een onderzoeksverpleegkundige. Dit gebeurde zo snel mogelijk nadat de patiënt de huisarts had geconsulteerd, maar in elk geval binnen 72 uur na het begin van klachten. Deelnemers werden via de standaardzorg door de huisarts verwezen naar een regionale TIA-poliklinieken voor aanvullende onderzoeken, inclusief beeldvorming van de hersenen. Een panel bestaande uit drie vasculair neurologen werd gebruikt om de 'definitieve' diagnose (referentie) te bepalen. Zij baseerden hun beslissing op alle beschikbare diagnostische informatie, onder meer i) een gestandaardiseerde anamnese door de onderzoeksverpleegkundige, ii) een bandopname van de patiënt zijn/haar eigen beschrijving van klachten, iii) alle klinische informatie verkregen bij de beoordeling door de neuroloog en andere specialisten, en iv) informatie voortkomend uit de follow-upperiode van zes maanden. Uiteindelijke doel was de diagnostische accuratesse te bepalen, en de toegevoegde waarde bovenop symptomen en verschijnselen, van een set van kandidaat-biomarkers die we selecteerden op basis van een literatuurreview.

We voerden een systematische review uit gericht op de accuratesse van biomarkers in de diagnostiek van TIA, met gebruik van MEDLINE en EMBASE databases tot 1 mei 2017 (**Hoofdstuk 6**). We selecteerden primaire diagnostische accuratessestudies die potentiële biomarkers in bloed voor de diagnose TIA of herseninfarct evalueerden. De kwaliteit van individuele studies werd beoordeeld middels de QUADAS-2 tool. Onze zoekopdracht identificeerde 4.125 studies, waarvan er 78 voldeden aan onze geschiktheidscriteria. 45 studies beperkten hun studiepopulatie tot patiënten met een herseninfarct, 32 includeerden zowel patiënten met een TIA als met een herseninfarct en slechts één studie includeerde alleen TIA-patiënten. De meerderheid van de studies (79,5%) had een case-control opzet, met een vergelijking van patiënten met een TIA of herseninfarct met gezonde personen. Geen van de studies evalueerde de biomarkers in de voorgenomen populatie van interesse, te weten patiënten *verdacht van* een TIA. In totaal werden 124 individuele biomarkers en vijf biomarker panels onderzocht. In het algemeen

was de methodologische kwaliteit van de studies matig. Voldoende informatie om 2x2 tabellen te extraheren was beschikbaar voor 35 (44,9%) artikelen en voor 60 (48,0%) biomarkers. Verscheidene markers, zoals NR2A/B(antilichamen), PARK7, NDKA, UFD-1 and H-FABP, hebben vrij hoge tot hoge accuratesse getoond in meer dan een enkele studie. Echter, het niveau van bewijskracht is laag en goed uitgevoerde diagnostische studies zijn nodig om de waarde van deze markers te bepalen in het domein van een klinische verdenking op een TIA.

**Hoofdstuk 7** presenteert de belangrijkste resultaten van de MIND-TIA-studie. Een totaal van 206 patiënten verdacht van een TIA namen deel, waarvan 126 (61,2%) door het expert panel werden gediagnosticeerd met een TIA (n=104) of minor stroke (n=22). Onder de 80 patiënten met een alternatieve diagnose waren migraine (n=24, 30,0%), stress-gerelateerde of psychosomatische klachten (n=16, 20.0%) en syncope (n=9, 11,3%) het meest frequent. De mediane tijd van begin van klachten tot de bloedafname was 48,0 (IQR 28,3-56,8) uur. Geen van de zeven biomarkers die we evalueerden had discriminerende waarde in de diagnose TIA, waarbij de c-statistiek varieerde van 0,45 tot 0,58. Daarnaast toonde een multivariaat diagnostisch model bestaande uit acht klinische determinanten goede diagnostische accuratesse met een c-statistiek van 0,83 (0,78-0,89). Leeftijd, een voorgeschiedenis van coronairlijden, een plots begin van klachten, klachten die direct in alle hevigheid beginnen en dysartrie waren onafhankelijke positieve voorspellers van een TIA of minor stroke. Een voorgeschiedenis van migraine, hoofdpijn en verlies van bewustzijn waren onafhankelijke negatieve voorspellers. We toonden dat de huidige beschikbare serum biomarkers geen waarde hebben in de diagnose TIA.

In **hoofdstuk 8** wordt een recent voorgestelde set van criteria voor de diagnose TIA, de zogenaamde 'explicit diagnostic criteria for TIA (EDCT)', gevalideerd in ons MIND-TIA cohort. De EDCT is een klinische tool die zich richt op type, duur en wijze van ontstaan van de klinische verschijnselen, ontwikkeld door twee neurologen en gebaseerd op de klinische praktijk en ervaring in plaats van op statistische methoden. Alle 206 deelnemers van MIND-TIA (waarvan 61% werden gediagnosticeerd met een TIA of minor stroke) werden geïncludeerd. De data die werden verzameld in de MIND-TIA-studie verschaften alle benodigde informatie voor classificatie volgens de EDCT. De diagnostische accuratesse van de EDCT werd berekend met de paneldiagnose als referentiestandaard. Hiernaast beoordeelden we de accuratesse van de EDCT na een geringe aanpassing van een van de subcriteria. De originele EDCT toonde in zijn geheel goede accuratesse (c-statistiek 0,80 [0,73-0,87]), met in het bijzonder een hoge negatief voorspellende waarde (96,1%). De modificatie van de originele criteria leidde tot een hogere positief voorspellende waarde (van 80,0% naar 85,5%) en

een kleine toename van de negatief voorspellende waarde (96,7%). Onze studie toonde dat de voorgestelde EDCT gemakkelijk toepasbaar is en een waardevolle diagnostische tool voor de diagnose TIA zou kunnen zijn in de eerstelijns setting.

## BELANGRIJKSTE CONCLUSIES EN AANBEVELINGEN

In **hoofdstuk 9** bespreken we de belangrijkste bevindingen en conclusies van deze thesis, en geven we aanbevelingen gericht op i) het verminderen van delay tot diagnose en behandeling van TIA en ii) hoe zowel onder- als overdiagnose te beperken. Educatie gericht op huisartsen, patiënten en leken zijn nodig, alsook optimalisatie van de zorgpaden voor patiënten verdacht van een TIA.

Leken zouden beter moet worden voorgelicht over de karakteristieken van een TIA en de relatie met een herseninfarct. Het belangrijkste is dat men leert een TIA als een medisch spoedgeval te zien, en dat ook milde en kortdurende klachten zo snel mogelijk aan een arts moeten worden gerapporteerd. Specifiek op TIA toegesneden publieke campagnes zijn nodig, los van de 'FAST' campagnes gericht op het herseninfarct.

Huisartsen zijn zich onvoldoende bewust van het belang van een snelle start van behandeling met een plaatjesaggregatieremmer in patiënten verdacht van een TIA, en dit bewustzijn moet worden verbeterd. Hierbij zouden neurologen de directe start van een plaatjesremmer expliciet moeten adviseren als zij door een huisarts geconsulteerd worden. Voorts zou een update van de Nederlandse huisartsrichtlijn een glasheldere aanbeveling moeten bevatten om plaatjesremming te starten in elke patiënt verdacht van een TIA, in plaats van de huidige meer gematigde aanbeveling om te starten tenzij de patiënt dezelfde dag door de neuroloog wordt beoordeeld.

De huidige beschikbare biomarkers hebben geen toegevoegde waarde in de diagnose TIA. De gemodificeerde 'explicit diagnostic criteria for TIA (EDCT)' zouden een nuttige tool voor huisartsen kunnen vormen om de klinische diagnose TIA te ondersteunen, vooral voor het uitsluiten van een TIA. Verder onderzoek is nodig om de daadwerkelijke bruikbaarheid van de criteria voor huisartsen te bepalen.

De resultaten van de paneldiagnose in MIND-TIA geven aan dat overdiagnose van TIA, en daarmee overbehandeling, veel voorkomt. Follow-up van twijfelachtige casus of bespreking van casus met collega's om een diagnose te heroverwegen, zouden onnodige levenslange behandeling met plaatjesaggregatieremmers en andere cardiovasculaire medicatie kunnen voorkomen.

## ABOUT THE AUTHOR

Faas Dolmans was born in Zoetermeer on September 21st, 1985. In 2003 he completed secondary school at Stedelijk Gymnasium Nijmegen, and started medical training at the University of Groningen. After graduating in 2009, he worked as a resident Internal Medicine at the Diakonessenhuis Utrecht. In 2011 he started General Practice vocational training at Utrecht University, and from 2012 he combined this training with a PhD project on the value of blood biomarkers in the diagnosis of TIA, supervised by prof dr. A.W. Hoes, prof dr. L.J. Kappelle, prof. dr. F.H. Rutten and dr. M.E.L. Bartelink. In the first year of the PhD track he completed a postgraduate master Epidemiology. Major part of his work as a PhD was the design and conduct of the “Markers IN the Diagnosis of TIA” (MIND-TIA) study. From 2017 Faas has been working as a general practitioner, currently in a practice in Bennekom. He lives in De Bilt with his wife Lisa and three children Jun, Mia and Sef.

## LIST OF PUBLICATIONS

1. Dolmans LS, Houwing RH, Vermeij CG. Screening op huidmaligniteiten na niertransplantatie. Ned Tijdschr Nefrol. 2011;1(4):20-3.

2. Dolmans LS, Rutten FH, El Bartelink ML, Seppenwoolde G, van Delft S, Kappelle LJ, et al. Serum biomarkers for the early diagnosis of TIA: The MIND-TIA study protocol. BMC Neurol. 2015;15:119.

3. Dolmans LS, Hoes AW, Bartelink MEL, Koenen NCT, Kappelle LJ, Rutten FH. Patient delay in TIA: a systematic review. J Neurol. 2019; 266(5):1051-1058.

4. Dolmans LS, Kappelle LJ, Bartelink ME, Hoes AW, Rutten FH. Delay in patients suspected of transient ischaemic attack: a cross-sectional study. BMJ Open. 2019;9(2):e027161.

5. Dolmans LS, Kappelle LJ, Bartelink, Hoes AW, Rutten FH. Determinants of patient delay in Transient Ischemic Attack. Eur Neurol. 2019;18:1-6.

6. Dolmans LS, Lebedeva ER, Veluponnar D, Van Dijk EJ, Nederkoorn PJ, Hoes AW, et al. Diagnostic accuracy of the Explicit Diagnostic Criteria for TIA: a validation study. Stroke. 2019;50:2080–2085.

7. Dolmans LS, Rutten FH, Koenen NCT, Bartelink MEL, Reitsma JB, Kappelle LJ, et al. Candidate biomarkers for the diagnosis of TIA: a systematic review. Cerebrovac Dis. 2019.

## DANKWOORD

Aan het begin van de huisartsopleiding sprak ik mijn wens uit om onderzoek te doen naast de opleiding. Dit leidde er uiteindelijk toe dat me vier mogelijke projecten werden voorgeschoteld. Vanwege een voorliefde voor neurologie was de keuze niet moeilijk. Het domein TIA sprak direct aan en dan het vinden van een diagnostische biomarker in bloed... Het kon haast niet beter. Tijdens een kennismakings-/sollicitatiegesprek bleek al snel dat dit ook het project was waar het minst al geregeld was. Eigenlijk niets.... Het was een idee op de plank, waar van voren af aan begonnen moest worden met het schrijven van een protocol, een METC aanvraag, het opzetten van de logistiek. Ik weet nog goed dat werd gezegd: 'Als je hiervoor kiest, moet je alles zelf doen.' Hier bleek geen woord aan gelogen, maar ik heb vanaf het begin genoten om je zo in een eigen project vast te bijten en iets te creëren. Precies dat wat ik zocht naast je werk als arts waar je de waan van de dag volgt. Ondanks dat ik inderdaad de kar geheel zelf moest op gang moest trekken, hebben een groot aantal mensen bijgedragen aan het slagen van de MIND-TIA studie, nevenstudies en dit proefschrift.

Allereerst wil ik uiteraard mijn directe promotieteam bedanken, dat door de promotie tot professor van mijn eerste co-promotor dr. Frans Rutten aan het einde van de rit verwarrend genoeg bestaat uit drie promotoren (naast Frans Rutten: prof. dr. Arno Hoes en prof. dr. Jaap Kappelle) en één co-promotor (dr. Marie-Louise Bartelink).

Beste 'nieuwbakken prof.' Rutten, beste Frans, wat geef jij een energie voor de wetenschap en voor het Julius Centrum. Je hebt een vanzelfsprekende toewijding in alles wat je doet. Altijd en voor iedereen sta je klaar. In mijn project was jij echt mijn eerste begeleider en hebben we de MIND-TIA studie opgetuigd en laten draaien. Ook al had en heb je een legertje aan promovendi, je neemt altijd de tijd om iets goed te bekijken, of te bespreken. Dat de tijd nemen is wel een dingetje, want je keuvelt soms graag wat af, en vrijwel altijd zit je bij een afspraak nog met je vorige afspraak van een uur geleden. Echter, ik weet ook altijd weer dat ik die tien minuten er aan het eind wel weer bij krijg. Je bent een hele mooie combinatie van relaxed en wat chaotisch, en toch scherp en precies als het moet. Onze studie was een flinke uitdaging en jouw bevlogenheid en het feit dat je er altijd was met even een snelle blik, een duwtje in de rug of een alternatieve oplossing, maakten dat we de lange inspanning voor die waardevolle buisjes bloed goed hebben kunnen afsluiten. Heel veel dank en waardering voor de tijd en energie die je in je drukke bestaan als huisarts hebt besteed aan mij en je andere promovendi.

Prof. dr. Hoes, beste Arno, onlangs nam je afscheid van het Julius Centrum, en werd je uitgebreid getypeerd en gelauwerd. Aan veren geen gebrek… en volkomen terecht! Als promovendi maakten we met een mini review een overzicht van alle dankwoorden van je 'oud-leerlingen'. Veel gehoord waren snel de vinger op de zere plek kunnen leggen, scherp, kritisch, dat je wat onbereikbaar kon lijken op je mooie kamer in de hoek van het Julius, maar je je juist een toegewijde begeleider toonde op de momenten dat het nodig was. Ook ik vond het in het begin lastig om je gedachten te peilen, maar op een borrel van het Julius zag ik al gauw meer van de prettige en humorvolle persoon die je bent. Je was de initiator van mijn project en de bewaker van de grote lijn. Ik vond het erg knap hoe je me maanden niet zag en bij een bijeenkomst zo weer bij was en wat aan de knoppen kon draaien voor de juiste koers. Aan het einde van de rit was je altijd snel met je opmerkingen bij mijn stukken om de vaart erin te kunnen houden. Dank voor alles, en veel succes en geluk in je nieuwe functie!

Prof. dr. Kappelle, beste Jaap, mijn dank voor jouw bijdrage aan ons project is erg groot. Niet alleen heb je inhoudelijk veel bijgedragen en met de panelprocedure een grote inspanning geleverd, ik heb vooral de manier van samenwerken en omgang met mij en anderen gewaardeerd. Je hebt een natuurlijke en vanzelfsprekende vriendelijkheid, en je zet je enorm in voor anderen, wat een verademing is in de grote fabriek die een ziekenhuis soms kan zijn. Je bent daarbij ook kritisch en direct op momenten dat het nodig is. In tijden dat onze studie vertraging op ging lopen, zocht jij naar speldenprikjes om de boel wel draaiende te houden. Je persoonlijke benadering was al snel duidelijk toen je bij de geboorte van onze zoon op kraambezoek kwam. Ik was verrast en vond het fantastisch dat de prof op de fiets op bezoek kwam met een Nijntje knuffeltje.

Dr. Bartelink, beste Marie-Louise, de enige vrouw in dit mannenteam. Ik heb minder intensief met je gewerkt dan met Frans, maar met name aan het begin van mijn traject was jouw input en begeleiding erg waardevol. Jij had soms een net andere kijk, en een voorgeschiedenis in dit project. Je bent flexibel en enthousiast, altijd bereid om mee te denken of snel naar een stuk te kijken. Op de huisartsopleiding zet je je in voor het 'evidence based medicine' onderwijs. Soms had ik met je te doen, als bij een goed voorbereide middag die haio's weer eens half meededen of opeens wat anders te doen hadden. De wetenschap is niet voor iedereen zo sappig. Ik hoop dat je je desondanks zo blijft inzetten als je doet, petje af ook daarvoor!

Heel veel credits gaan er naar Saltro en iedereen die zich vanuit Saltro direct voor onze studie heeft ingezet. Sanne van Delft en Gerdien Seppenwoolde, jullie hebben de best wel complexe logistiek feilloos op poten gezet en gecoördineerd.

Jullie hebben er voor gezorgd dat al die zeer waardevolle kleine bloedmonstertjes netjes op tijd van de arm van de patiënt in de diepvries en uiteindelijk in de Biobank van het UMC Utrecht terecht zijn gekomen. Nora, Gonny , Carlien, Lisette en Peggy, jullie hebben als onderzoeksverpleegkundigen al het werk verzet, door in diensten zo snel mogelijk naar deelnemers te rijden, het bloedmonster te nemen, maar ook de belangrijkste data te verzamelen in het CRF. Ik heb genoten van jullie inzet, en ik denk dat dit voor jullie ook een leuke en leerzame ervaring is geweest. Marjan en Marlijn, bedankt voor jullie regie naast Gerdien, en ten slotte nog een shout-out naar alle medewerkers op het lab die het bloed hebben verwerkt bij binnenkomst. Ik vind het echt heel bijzonder dat we deze logistiek drie jaar hebben kunnen laten draaien. Jullie waren geweldig!

Grote dank aan alle (ongeveer 350) huisartsen die aan MIND-TIA hebben deelgenomen! Ook jullie waren een zeer belangrijke schakel in ons project. We vroegen jullie ons altijd in jullie achterhoofd te hebben, en ons te bellen op een relatief weinig voorkomend moment suprême. Uiteindelijk hebben heel veel verschillende huisartsen een patiënt aangemeld en zo een bijdrage geleverd. Ook dank voor de hartelijke ontvangsten tijdens al mijn bezoeken aan praktijken om follow-upgegevens te verzamelen. Het is een enorm mooie gezamenlijke inspanning geweest.

Een kleiner groepje dat grootse daden heeft verricht is het expertpanel van neurologen, bestaande uit dr. Ewoud van Dijk (Radboud UMC), dr. Paul Nederkoorn (Amsterdam UMC) en prof. dr. Jaap Kappelle (UMC Utrecht). Eerst beoordeelden jullie elk afzonderlijk voor alle 206 deelnemers een uitgebreid papieren casusformulier. Vervolgens werd een meerderheid van de deelnemers besproken op een van vier panelbijeenkomsten. Jullie zijn ontzettend flexibel geweest en hebben flink gereisd voor dit nobele doel. Een enkele keer werd het een avond met pizza. Voor mij waren de bijeenkomsten heel leerzaam, en ik denk dat het voor jullie zelf ook bepaalde inzichten heeft gegeven, bijvoorbeeld de verschillen in werk- en denkwijze tussen centra. Jullie werk was een onmisbaar en zeer waardevol onderdeel van MIND-TIA.

Dr. Reitsma, beste Hans, dank voor jouw bijdrage in bepaalde onderdelen van mijn project, zoals de opzet van de panelprocedure en het biomarker review. Je bent bijzonder geduldig, optimistisch en hebt ideeën die anderen niet hebben. Ik heb met veel plezier met je gewerkt aan ons experimentele plot van geschatte AUC's, waarover overigens geen enkele reviewer gerept heeft, waarschijnlijk omdat het ze boven hun pet ging...

Dear prof. Jes Olesen and dr. Elena Lebedeva, thank you for our special collaboration on the validation of your 'explicit diagnostic criteria for TIA (EDCT)'.

You and Jaap did meet each other on a conference, but we actually never met. We operated by email communication, which worked out pretty fine! We were quite surprised by the accuracy of the EDCT, and are curious about its future impact.

Al met al heb ik heel wat jaren op het Julius rondgelopen, door de huisartsopleiding heen, en later naast mijn praktijkdagen als zelfstandig huisarts. Alle kamergenoten op kamer 6.104 waar ik de langste tijd heb doorgebracht, dank voor de gezelligheid tijdens lange dagen achter een computer waarna een borrel af en toe nodig was. Hetzelfde geldt voor alle mede-AIOTHO's en latere kamergenoten in het van Geunsgebouw. Namen ga ik niet noemen anders ga ik geheid mensen vergeten. De doorloop op het Julius is groot, maar ik heb genoten van de sfeer van zoveel jonge onderzoekers bij elkaar in een centrum.

Nog een speciaal bedankje aan de vele studentstagairs die me hebben geholpen binnen MIND-TIA of nevenprojecten. De patiëntinterviews op TIA poliklinieken (binnen de studie van hoofdstuk 3) zijn bijvoorbeeld gedaan door drie achtereenvolgende stagestudenten. Studenten hebben geholpen met de literatuureviews, dataverzameling en -verwerking, het scoren van de EDCT, noem maar op. Het was een leuke afwisseling om af en toe weer samen met een student in 12 weken naar iets concreets toe te werken.

Studentstagairs bleken ook nog voor andere dingen nuttig te zijn. Een van de biomarkertestkits kon door regelgeving niet naar Europa worden verscheept en het kwam er op neer dat ik deze dan zelf moest ophalen in Atlanta. Toevallig had stagiair Mara een broertje in New York, waar we de kits wel naar toe konden laten sturen. Dit leverde daardoor nog een veel leuker weekendje VS op. Bedankt overigens FedEx, dat jullie de kits 5 u voor de terugvlucht toch nog bezorgden. En bedankt douane op Schiphol dat jullie bij het nonchalant naar buiten wandelen wel mijn koffer met 6 dozen ELISA kits in een groot scanapparaat stopten, maar ik zonder enig woord mocht doorlopen.

Aan het einde van de rit konden dan eindelijk de biomarkers bepaald worden op het lab van het UMC Utrecht. Hier zaten de nodige haken, ogen en frustraties aan, maar uiteindelijk is alles gelukt na veel hard werk en een hoop toewijding om voor elke biomarker betrouwbare metingen te krijgen. Veel dank aan iedereen die zich hiervoor heeft ingezet, in het bijzonder Imo Hofer en Inge Maitimu-Smeele. Fokke Terpstra, ik ben erg tevreden over jouw begeleiding vanuit de Biobank. Je hulp was altijd snel en adequaat.

Ik dank de SBOH voor hun ondersteuning van AIOTHO's en de perfecte voorwaarden die ze zo scheppen voor huisartsen in opleiding met interesse voor wetenschappelijk onderzoek.

Elisa Calamita, jij verzorgde de vormgeving van mijn proefschrift inclusief de omslag. Je was vliegensvlug met het verwerken van mijn wensen en ideeën, en het resultaat is prachtig!

Douwe, Emmerik en Wouter, allemaal een ander vakgebied als arts, maar alle vier (bijna) gepromoveerd in Utrecht. We deelden klein onderzoeksleed, maar veel leuker liefde voor een drankje bij muziek. Ook mijn bijzonder goede vrienden vanuit mijn jaarclub en mijn studiegenoten uit Groningen, dank voor morele ondersteuning en vooral de nodige ontspanning op zijn tijd.

Sander en Kevin, van jullie allebei heb ik al de eer gehad jullie paranimf te zijn! Heel fijn, en om meerdere redenen vanzelfsprekend, om jullie aan mijn zijde te hebben tijdens mijn verdediging. Kevin, wij gaan terug naar zeer jeugdige jaren, en deden een groot deel van onze middelbare school en onze gehele studietijd alles samen. Sander, jij was mijn gehele promotietraject mijn maatje. Kamergenoot, we haalden samen onze epidemiologiepunten, en we vertegenwoordigden samen de mannelijke AIOTHO's. Bij jullie beiden ben ik benieuwd waar jullie carrière eindigt, en ik hoop dat we ondanks onze drukke levens contact houden!

Wordt dit dankwoord al te lang? Kan ik nog mijn ouders bedanken? Tja, het is bij zo'n proefschrift toch vaak het dankwoord dat als eerste (of enige) gelezen wordt om te kijken of men wordt genoemd... Pap en mam, ik wil jullie hier in elk geval bedanken voor het optimisme, doorzettingsvermogen en de nuchtere kijk op de wereld die jullie me hebben bijgebracht, die ik in dit hele verhaal goed heb kunnen gebruiken.

Lieve Lisa, wij vonden elkaar precies aan de start van mijn promotietraject. Om aan te geven hoeveel we sinds die tijd hebben meegemaakt, en ook hoe lang de rit bij elkaar is geweest: we zijn inmiddels bezig met het bouwen van ons tweede huis, en ten tijde van het schrijven van dit dankwoord ben je bevallen van onze derde. Ik vind het geweldig dat je me altijd de ruimte hebt gegeven om mijn ding te doen, ook al vond je dat onderzoekswerk eigenlijk maar een beetje saai en slecht betaald, en keek je me vaak een beetje lachend aan als ik enthousiast begon over een analyse zus of zo.

Ik sluit een hele mooie tijd af.