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Is the time of calling helpful for differentiating transient ischaemic attack and stroke from mimics in primary care out-of-hours services? A cross-sectional study

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ABSTRACT

Objectives Telephone triage of patients suspected of transient ischaemic attack (TIA) or stroke is challenging. Both TIA and stroke more likely occur during daytime, with a peak in the morning hours. Thus, the time of calling might be a helpful determinant during telephone triage. We assessed the time of calling in patients with stroke-like symptoms who called the out-of-hours services in primary care (OHS-PC), and evaluated whether the time of calling differed between patients with TIA or stroke compared with those with mimics.

Design Cross-sectional study.

Setting Six OHS-PC locations in the Netherlands.

Participants 1269 telephone triage recordings of patients calling the OHS-PC because of stroke-like symptoms. We collected information on patient characteristics, symptoms, time of calling and urgency allocation. The final diagnosis related to each triage call was based on letters from the neurologist (retrieved from the patient's general practitioner).

Primary and secondary outcome measures The primary outcome measures were the time of calling hourly and 4 hourly, and the risk of TIA or stroke/hour. The secondary outcome measure was the risk ratio of TIA or stroke in the morning (08:00—12:00h) versus other hours.

Results Mean age was 68.6 (SD±18.5) years, 56.9% were women and 50.0% had a TIA or stroke. The risk ratio of TIA or stroke among people calling with stroke-like symptoms between 08:00—12:00h versus other hours was 1.13 (95% CI 1.00 to 1.28, p=0.070). After correction for age and sex, the adjusted risk ratio was 0.94 (95% CI 0.80 to 1.10, p=0.434).

Conclusion In patients who called the OHS-PC because of stroke-like symptoms, the time of calling did not differ between patients with TIA or stroke and patients with mimics.

Trial registration number The Netherlands National Trial Registry (NTR7331).

Strengths and limitations of this study

- ► This is the first study that examined the time of calling as a possible predictor of transient ischaemic attack (TIA) or stroke at out-of-hours services in primary care.
- ► All people with stroke-like symptoms were included, and not only patients with established TIA or stroke.
- ► The researchers were blinded to the final diagnosis at the time of data collection, which limited the influence of hindsight bias.
- ► As the exact time of onset was often unknown, we used the time of calling.

BACKGROUND

Early recognition and timely diagnosis of patients with a transient ischaemic attack (TIA) or stroke is of vital importance in order to initiate interventions that can reduce the risk of (permanent) brain injury and recurrent stroke.[1–4] The risk of subsequent ischaemic stroke after TIA is highest in the first few days and gradually decreases in the following weeks.[5 6] Previous studies on the early risk of subsequent ischaemic stroke after TIA reported reduction rates of such stroke ranging from 60% within 6 weeks to 80% within 3 months after early start of antiplatelet therapy and oral anticoagulation in those with atrial fibrillation.[1 6–8] In order to achieve early treatment, neurological symptoms must be interpreted adequately, which can be rather challenging.[9–11] Other diseases can mimic the signs and symptoms of TIA (eg, migraine aura, seizure and syncope) or stroke (eg, seizure, brain tumour and syncope).[12 13] Moreover, symptoms can be non-specific, and in the case of TIA symptoms can be short-lasting and thus resolved by the time a patient calls for medical help.[12–14]

In the Netherlands, as in other European countries, a large number of suspected TIA or stroke patients first contact the general

practitioner (GP). During out-of-office hours (ie, evenings, nights, weekends and holidays), patients can contact the out-of-hours services in primary care (OHS-PC).[15] At the OHS-PC, trained nurses perform telephone triage, and they are supported by a semi-automatic decision support tool called the Netherlands Triage Standard (NTS).[16] The NTS is based on the hospital-based Manchester Triage System.[16 17] The aim of the NTS is to allocate adequate urgencies based on an algorithm that helps the triage nurse to assess patient's problems. These automatically generated urgencies are linked to a certain time period within which a GP or ambulance should examine the patient. Since the implementation of the NTS at Dutch OHS-PCs in 2011, an increase in higher urgency allocations was seen,[18] without an increase in clinically critical disorders, suggesting the NTS results in a more defensive triage process than a less structured history-taking applied by triage nurses.[19] Also, the care demand and workload at Dutch OHS-PC increased over time,[20 21] underlining the urgent need for determinants that could optimise telephone triage.

Previous studies already showed that, compared with other acute cardiovascular diseases, stroke more often occurs during daytime than at night, with a peak incidence in the morning hours between 06:00—12:00h,[22–26] and a less prominent peak in the (early) evening.[27–32] This circadian rhythm applies to both ischaemic and haemorrhagic stroke,[24–27 33] and also to TIA.[25] A similar circadian pattern was found in telephone calls for acute neurological events at the emergency department.[34] Whether the time of calling helps to triage calls for neurological events in OHS-PC settings is unknown. This would be the case, if during certain time periods, the incidence of TIA or stroke is higher than that of mimics compared with other time periods (ie, a higher risk ratio of TIA or stroke).

To date, studies concerning the time of calling and the circadian rhythm in TIA or stroke have been executed in secondary care settings, and only evaluated those with established TIA or stroke.[24] We aimed to assess whether urgency allocation in telephone triage at the OHS-PC could be improved if the time of calling was considered in patients with stroke-like symptoms, that is, whether the incidence of TIA or stroke was different from that of mimics (ie, a difference in risk ratio) over 24 hours.

METHODS

Study design and data collection

This cross-sectional study is part of a larger research project called Safety First.[35]

Telephone triage recordings of patients with stroke-like symptoms who called the OHS-PC between 2014 and 2016 were evaluated. Data was collected from six OHS-PC locations in the vicinity of Utrecht, the Netherlands, covering rural and urban areas.[36]

The triage recordings were selected based on (1) keywords in the OHS-PC electronic health records suggesting stroke-like symptoms (online supplemental table 1) and on (2) International Classification of Primary Care (ICPC) codes linked to the calls, which reflected our study domain (ie, K89 TIA, K90 stroke, N17 vertigo/dizziness, N18 paralysis/weakness, N19 speech problems, N29 other symptoms related to the nervous system, N89 migraine and N91 facial palsy/Bell's palsy).[37]

Both patients with ongoing and already faded symptoms were included. After the aforementioned selection, we re-listened a random sample of >1000 recordings and collected information about symptom presentation, and in addition, other patient characteristics and urgency allocation. The time of calling was considered as the time of first medical contact. The final diagnosis of each patient who has contacted the OHS-PC was retrieved from the electronic health record of the patient's own GP. Thus, for all patients referred to the hospital, the final diagnosis of TIA or stroke was based on discharge letters from the neurologist (or the emergency department). We defined a final diagnosis of TIA or stroke as (1) a TIA, (2) a minor ischaemic stroke or (3) major ischaemic stroke. TIA or stroke mimics were defined as stroke-like symptoms, but with a diagnosis other than TIA or stroke. For patients who were not referred to the hospital, we used follow-up data up to 1 month on possible recurrence of TIA or stroke from the GP's electronic health record.

Data analyses

The occurrence of TIA or stroke was first analysed hourly. We calculated, based on time period, the absolute number of patients with a final diagnosis of TIA or stroke and the whole population of those calling with stroke-like symptoms. By dividing the absolute number of TIA or stroke patients by the total number of callers with stroke-like symptoms, the risk ratio of TIA or stroke/hour was calculated. Furthermore, we calculated the risk ratios of TIA or stroke for several time periods in order to identify time period(s) in which the risk ratio of TIA or stroke was the highest. Also, we calculated the adjusted risk ratios for TIA or stroke after correction for age and gender. We reported the risk ratios with corresponding 95% CI. Patient characteristics, symptoms, medical history and urgency allocation were compared between the time period in which the risk of TIA or stroke was highest and other time periods. We used the χ^2 test or Fisher's exact test for categorical variables and the independent samples t-test for continuous variables in order to compare callers with and without established TIA or stroke. The duration of symptoms was dichotomised to <4.5 hours and >4.5 hours, in line with the recommendation of the prevailing Dutch GP national guidelines from 2014.[38] At that time, ischaemic stroke patients were considered eligible for thrombolysis if symptoms lasted <4.5 hours.[39–41] Urgency levels were dichotomised to high (U1–U2) and low (U3–U5) according to the NTS hierarchy of urgencies (U1: medical help within 15 min (by ambulance); U2: patient must be seen by a GP in <1 hour; U3: patient must be seen in <3 hours; U4: patient must be seen in <24 hours; U5: telephone advice is considered

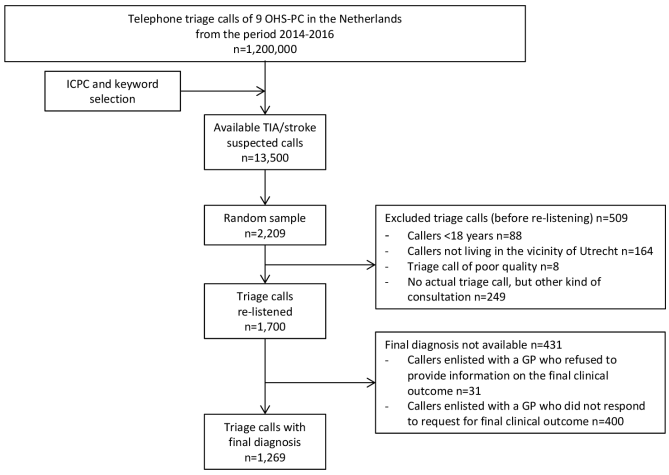

Figure 1 Flowchart. GP, general practitioner; ICPC, International classification of primary care; OHS-PC, out-of-hours services in primary care; TIA, transient ischaemic attack.

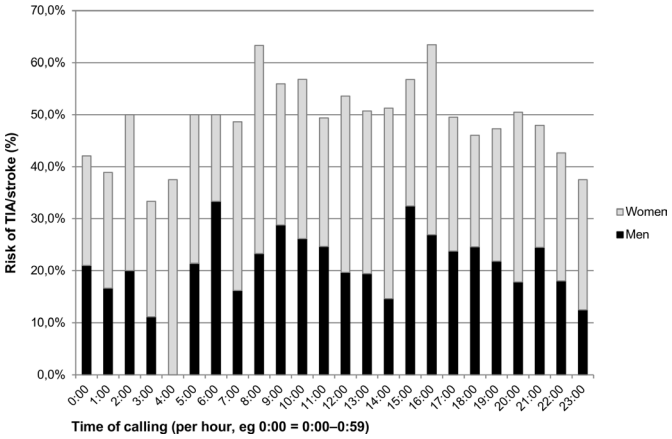

Figure 3 Risk of TIA or stroke/hour of 1269 patients with neurological symptoms suggestive of TIA or stroke calling the OHS-PC, divided into men and women. OHS-PC, out-of-hours services in primary care; TIA, transient ischaemic attack.

adequate).[35] Data analyses were performed using SPSS V.25.0 (IBM, Armonk, New York, USA).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, or in developing plans for design; however, they were involved in the implementation of the study. In addition, they were asked to advise on interpretation and writing up of results. Results will be shared and discussed with the national patient community of cardiovascular diseases.

RESULTS

Our study population consisted of 1269 patients of whom we could obtain a final diagnosis. A flowchart of the inclusion and exclusion criteria, and the number of eligible patients and final included study population is displayed in figure 1.

The mean age was 68.6 (SD±18.5) years and 722 (56.9%) were women. In total, 291 (22.9%) patients were diagnosed with TIA, 143 (11.3%) with minor ischaemic stroke, 201 (15.8%) with major ischaemic stroke and 61 (4.8%) with other (neurological) life-threatening events (LTE), including haemorrhagic stroke. The remaining 573 (45.2%) patients were diagnosed with non-urgent disease (eg, migraine with aura, syncope or peripheral vestibular disorder). Men had somewhat more often a TIA or minor stroke than women (37.3% vs 31.9%, p=0.043) and women tended—non-significantly—to more often have a major ischaemic stroke than men (14.4%% vs 16.9%, p=0.236). Of all 1269 patients, 67.8% were referred to the hospital (ie, 58.7% to the neurologist and 9.1% to the emergency department), while the remaining 32.2% remained under the care of the GP. Importantly, 90.9% of the patients still had problems while calling and 70.2% were seen within 3 hours by a physician (29.5% by the GP on duty for the OHS-PC, and 70.5% by the neurologist or emergency department physician after referral to the hospital).

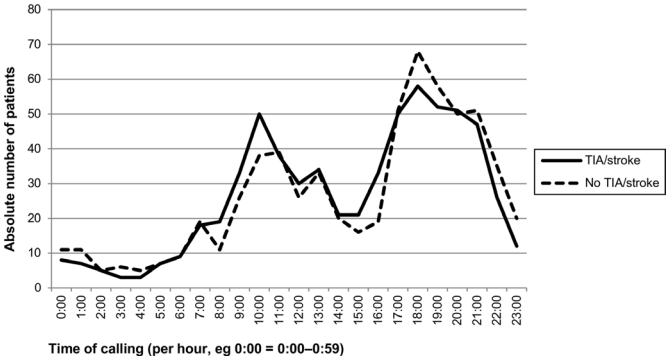

Figure 2 Time of calling of 1269 patients with neurological symptoms suggestive of TIA or stroke calling the OHS-PC, divided into patients with and without TIA or stroke. OHS-PC: out-of-hours services in primary care; TIA, transient ischaemic attack.

In figure 2, the absolute numbers/hour are shown of patients with and without TIA or stroke. Most patients with TIA or stroke called during daytime, with a peak incidence between 08:00—12:00h; 140 (22.0%) and a peak between 14:00—18:00h; 125 (19.7%). The lowest incidence of TIA or stroke was between 01:00—05:00h; 18 (2.8%). The distribution in time of patients calling with mimics of TIA or stroke was similar to those with TIA or stroke.

The overall risk of TIA or stroke was 50.0% (51.7% in men and 48.9% in women). In figure 3, the distribution of the risk of TIA or stroke/hour divided into men and women is plotted. The risk distribution of TIA or stroke/hour was comparable for men and women. A sensitivity analysis for TIA or minor stroke and major stroke separately showed similar results as for the combination of TIA or stroke.

Based on the 4-hourly analysis (figure 4), most patients with stroke-like symptoms called between 16:00—20:00h

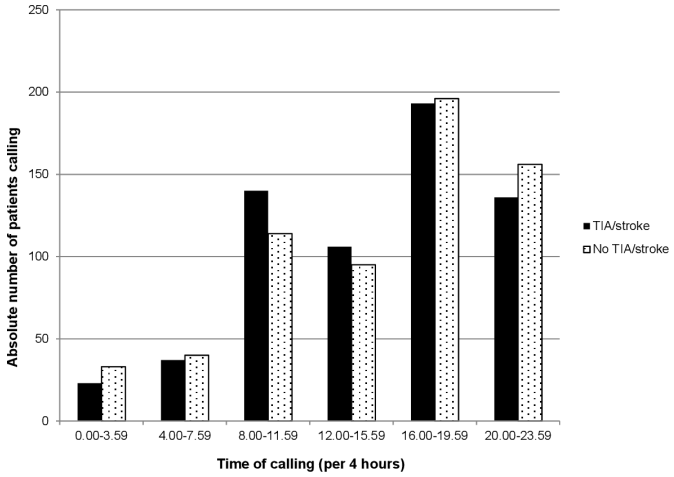

Figure 4 Time of calling (every 4 hours) of 1269 patients with neurological symptoms suggestive of TIA or stroke calling the OHS-PC, divided into patients with and without TIA or stroke. OHS-PC, out-of-hours services in primary care; TIA, transient ischaemic attack.

(30.7%). Only 4.4% called at night between 24:00—04:00h, and 6.1% between 04:00—08:00h . Of those who received a final diagnosis of TIA or stroke, 30.4% called between 16:00—20:00h, and 3.6% called during the night between 24:00—04:00h. The risk of TIA or stroke during the day ranged from 46.6% (20:00—24:00h) to 55.1% (08:00—12:00h) while this was 41.1% at night from 24:00—04:00h.

The risk ratio of TIA or stroke from 08:00—12:00h compared with other hours was 1.13 (95% CI 1.00 to 1.28, p=0.070); 1.25 (95% CI 1.05 to 1.49, p=0.022) for men and 1.04 (95% CI 0.87 to 1.25, p=0.666) for women. After correction for age and gender, the adjusted risk ratio for TIA or stroke from 08:00—12:00h compared with other hours was 0.94 (95% CI 0.80 to 1.10, p=0.434).

The baseline characteristics of patients calling during the time period with the highest risk of TIA or stroke (ie, between 08:00—12:00h) and those who called during other hours are shown in table 1. Patients calling between 08:00—12:00h were significantly older (76.0 years vs 71.0 years, p=0.003), more often experienced arm weakness (51.3% vs 40.8%, p=0.19), and more often had patient delay (ie, more often called ≥4.5 hours after the start of symptoms, 54.0% vs 37.4%, p<0.001) than those calling during other hours (50.0% vs 35.6%, p=0.005). Also, patients calling in the morning had less speech problems (71.7% vs 79.5%, p=0.042) and (near) fainting (5.4% vs 9.8%, p=0.041). Both groups were comparable with respect to medical history, cardiovascular medication use, cardiovascular risk factors and call characteristics. The majority of patients calling for stroke-like symptoms received a high urgency allocation: 65.4% in the 08:00—12:00h group and 59.5% in the group calling other hours (p=0.088). Patients calling between 08:00—12:00h were significantly more often diagnosed with TIA or minor stroke than those calling during other hours (39.8% vs 32.8%, p=0.037), whereas the proportion of major ischaemic stroke and other LTEs (eg, haemorrhagic stroke, subarachnoid haemorrhage, sepsis or meningitis) as final diagnoses were comparable in both groups.

DISCUSSION

Patients with stroke-like symptoms most often called during daytime, with a peak in the morning between 8 am and noon and a peak between 2 pm and 6 pm. There was no time period in which the relative risk of TIA or stroke among callers with stroke-like symptoms was substantially higher than in other time blocks.

This is the first study in which the time of calling among patients with stroke-like symptoms is assessed in the OHS-PC setting and in which data on the ratio between TIA or stroke and all people calling for stroke-like symptoms are presented. Previous studies included patients with established TIA or stroke only, were performed in emergency department settings, and showed that TIA or stroke occurred more frequently during daytime than nighttime, and, in particular, more frequently during the morning (06:00—12:00h) than the afternoon.[24–27 33] Pathophysiological mechanisms like an increase of heart rate, blood pressure and peaks in clotting factors, cortisol and epinephrine levels start in the early morning, and have been shown to be underlying mechanisms of the occurrence of cardiovascular events (eg, acute coronary syndrome or rupture of aortic aneurysms).[24 27 42] TIA and stroke probably share, at least in part, these pathophysiological mechanisms with cardiovascular events.[32 34] Nevertheless, some studies also reported a second peak in the early evening between 4 pm and 8 pm.[29 30]

Analysed hourly and 4 hourly, we could reproduce the morning peak as well as a peak in the afternoon among TIA or stroke patients, and the lowest number of TIA or stroke during the night, similar to previous literature.[25] In a meta-analysis of 31 publications including more than 11 000 strokes, based on the time of onset of symptoms, a crude OR for stroke of 1.79 (95% CI 1.72 to 1.87) between 06:00—12:00h was found compared with other hours.[25] In our study, based on the time of contacting the OHS-PC, the crude risk ratio was 1.13 (95% CI 1.00 to 1.28, p=0.070) for 08:00—12:00h compared with other hours. The results of the meta-analyses and our study may also be affected by difference in settings (emergency department vs OHS-PC), and thus, case-mix with differences in prevalence of TIA or stroke.

While other studies suggested to organise care processes (eg, quality and quantity of staff in the emergency department) based on the demand during the TIA or stroke peak hours,[34] our study shows that this seems not to be worthwhile in the OHS-PC setting because the risk ratio of TIA or stroke did not substantially differ over time.

An important strength of our study is that we considered all people with stroke-like symptoms, and not only patients with established TIA or stroke. Also, there was a low susceptibility to hindsight or recall bias, because the

Table 1 Baseline characteristics of 1269 patients who called the OHS-PC for symptoms suggestive of TIA or stroke, divided into those calling from 08:00—12:00h and other hours

	08:0012:00h n=254 (20.0%)	Other hours n=1015 (80.0%)	P value*
Patient characteristics:			
Mean age in years (SD)	71.9 (16.7)	67.7 (18.9)	0.001
Female sex	147 (57.9)	575 (56.7)	0.725
Medical history and cardiovascular medication:			
Cardiovascular disease (n=882)	126 (74.6)	554 (77.7)	0.382
TIA (n=637)	36 (29.0)	140 (27.3)	0.697
Stroke (n=637)	26 (21.0)	147 (28.7)	0.084
Coronary artery disease (n=303)	15 (23.8)	39 (16.3)	0.163
Arrhythmia (n=292)	9 (16.4)	48 (20.3)	0.512
Antithrombotics use (n=939)	78 (41.3)	361 (48.1)	0.091
Cardiovascular risk factors:			
Hypertension (n=421)	38 (45.2)	168 (49.9)	0.449
Hypercholesterolaemia (n=395)	32 (40.5)	138 (43.7)	0.611
Diabetes mellitus (n=417)	23 (29.1)	127 (37.6)	0.158
Call characteristics:			
Mean call duration in min:s (SD)	07:26 (03:31)	07:49 (03:47)	0.154
Initial call by someone else than the patient	194 (76.4)	769 (75.8)	0.838
Triage nurse consulted the GP	142 (55.9)	612 (60.3)	0.203
Symptoms mentioned during the call:			
Face drooping (n=713)	75 (52.4)	276 (48.4)	0.389
Arm weakness (n=772)	78 (51.3)	253 (40.8)	0.019
Leg weakness (n=653)	68 (51.1)	218 (41.9)	0.056
Sensory disturbances (n=375)	72 (90.0)	270 (91.5)	0.669
Speech problems general (n=769)	104 (71.7)	496 (79.5)	0.042
Vision disorder (n=184)	23 (85.2)	127 (80.9)	0.595
Headache (n=497)	56 (55.4)	231 (58.3)	0.600
Ataxia (n=236)	52 (91.2)	144 (80.4)	0.059
Dizziness (n=312)	60 (82.2)	203 (84.9)	0.573
ANS-associated symptoms:			
Sweating (n=208)	17 (45.9)	75 (43.9)	0.817
Nausea or vomiting (n=311)	39 (59.1)	139 (56.7)	0.731
Pallor (n=255)	15 (30.0)	66 (32.2)	0.765
Ashen skin (n=198)	5 (12.8)	25 (15.7)	0.651
(Feeling of nearly) fainting (n=1103)	12 (5.4)	86 (9.8)	0.041
Course of symptoms:			
Per acute onset (within seconds) (n=211)	15 (53.6)	93 (50.8)	0.786
Duration of symptoms ≤4.5 hours (n=986)	92 (46.0)	492 (62.6)	<0.001
Symptoms still present at time of calling (n=1254)	237 (94.4)	917 (91.4)	0.117
NTS urgency:			
High (U1 or U2)	166 (65.4)	604 (59.5)	0.088†
Low (U3, U4 or U5)	88 (34.6)	411 (40.5)	
Referred to:			
Neurologist	148 (58.3)	597 (58.8)	0.873

Continued

Table 1 Continued

	08:0012:00h n=254 (20.0%)	Other hours n=1015 (80.0%)	P value*
Emergency department	21 (8.3)	94 (9.3)	0.622
Not referred (remained under GP care)	85 (33.5)	324 (31.9)	0.638
Final diagnosis:			
TIA/minor stroke	101 (39.8)	333 (32.8)	0.037
Major stroke‡	39 (15.4)	162 (16.0)	0.813
Life threatening events§	9 (3.5)	52 (5.1)	0.292
Intracerebral haemorrhage	3 (33.3)	19 (36.5)	0.585
Other non-urgent diseases¶	105 (41.3)	468 (46.1)	0.172

*Pearson χ^2 test for categorical variables, Fisher's exact test for categorical variables if cell counts <5, and Mann-Whitney U test for not-normally distributed continuous variables.
†P value for high versus low NTS urgency.
‡Including lacunar infarction and stroke not otherwise specified.
§Among others sepsis, acute coronary syndrome, meningitis and herpes encephalitis.
¶Among others migraine (with aura), syncope, peripheral vestibular disorder and Bell's palsy.
ANS, autonomic nervous system; GP, general practitioner; NTS, Netherlands triage standard; TIA, transient ischaemic attack.

researchers were blinded to the final diagnosis at the time of data collection.

A limitation is that we could not use the time of symptom onset, because in the vast majority of patients, the exact time of onset was unknown and patients could only indicate whether symptoms existed less than or more than 4.5 hours. There could have occurred some diagnostic misclassification because in 67.8%, the diagnosis was based on the findings (including brain imaging) of the neurologist or emergency department physician, while the remaining 32.2% was based on a GP diagnosis only. However, it is unlikely this has affected our conclusions regarding the time of calling. Furthermore, we had missing values on several symptoms, a phenomenon inextricably linked to research with routine care data. However, these missing values did not affect our primary outcome (the final diagnosis of TIA or stroke), making multiple imputation unnecessary in order to perform multivariable analysis. We had also missing outcome data, but fortunately, we could compare rather detailed patient characteristics of those in whom the GP delivered the final diagnosis and those in whom the GP did not (online supplemental table 2). This comparison showed no substantial differences, and, therefore, missing outcome data unlikely resulted in selection bias by only using the data of patients in whom the final diagnosis was known. Finally, patient delay could have created 'a shift to later hours' in our study, because we used the time of contacting the OHS-PC, while previous studies used the time of onset of symptoms for evaluating the incidence over 24 hours.

CONCLUSION

In patients who called the OHS-PC because of stroke-like symptoms, the time of calling did not differ between patients with TIA or stroke and patients with mimics.

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Contributors DLZ and FHR conceived the idea for the study and gained funding. All authors designed the study. DCE and GHvdM collected and analysed the data. DCE prepared the manuscript and wrote the first draft, supervised by FHR. LTCMW, EDG, RAMJD and AWH provided intellectual input and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Medical Ethics Review Committee Utrecht, the Netherlands, approved this study (National Trial Register identification number: NTR7331, reference number WAG/mb/16/003208). In addition, a waiver of informed consent was granted as our study involved minimal risk to participants and this study would not have been practicable without the waiver. All personal and research data were handled and stored according to the European General Data Protection Regulation.

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