European Stroke Organisation (ESO) guidelines on management of transient ischaemic attack

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Guideline

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Abstract

The aim of the present European Stroke Organisation Transient Ischaemic Attack (TIA) management guideline document is to provide clinically useful evidence-based recommendations on approaches to triage, investigation and secondary prevention, particularly in the acute phase following TIA. The guidelines were prepared following the Standard Operational Procedure for a European Stroke Organisation guideline document and according to GRADE methodology. As a basic principle, we defined TIA clinically and pragmatically for generalisability as transient neurological symptoms, likely to be due to focal cerebral or ocular ischaemia, which last less than 24 hours. High risk TIA was defined based on clinical features in patients seen early after their event or having other features suggesting a high early risk of stroke (e.g. ABCD2 score of 4 or greater, or weakness or speech disturbance for greater than five minutes, or recurrent events, or significant ipsilateral large artery disease e.g. carotid stenosis, intracranial stenosis). Overall, we strongly recommend using dual antiplatelet treatment with clopidogrel and aspirin short term, in high-risk non-cardioembolic TIA patients, with an ABCD2 score of 4 or greater, as defined in randomised controlled trials (RCTs). We further recommend specialist review within 24 hours after the onset of TIA symptoms. We suggest review in a specialist TIA clinic rather than conventional outpatients, if managed in an outpatient setting. We make a recommendation to use either MRA or CTA in TIA patients for additional confirmation of large artery stenosis of 50% or greater, in order to guide further management, such as clarifying degree of carotid stenosis detected with carotid duplex ultrasound. We make a recommendation against using prediction tools (eg ABCD2 score) alone to identify high risk patients or to make triage and treatment decisions in suspected TIA patients as due to limited sensitivity of the scores, those with score value of 3 or less may include significant numbers of individual patients at risk of recurrent stroke, who require early assessment and treatment. These recommendations aim to emphasise the importance of prompt acute assessment and relevant secondary prevention. There are no data from randomised controlled trials on prediction tool use and optimal imaging strategies in suspected TIA.

Keywords

Transient ischaemic attack (TIA), TIA clinic, dual anti-platelet treatment (DAPT), clopidogrel, ticagrelor, aspirin, secondary prevention, large vessel stenosis, clinical prediction tools, ABCD2

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Introduction

Transient ischaemic attack (TIA) and suspected TIA are a common presentation to acute stroke services. An increased risk of stroke following TIA is recognised, especially in the acute phase. In about a quarter of stroke patients, a TIA has preceded the stroke.[1] A TIA may provide a short window of opportunity to reduce the risk of long-term morbidity and mortality.[2]

Diagnosis of TIA can be challenging, with significant inter-rater variability.[3,4] TIA definition for the purpose of these guidelines, and for generalisability across settings, is clinically diagnosed and based on symptom duration of less than 24 hours.

Early stroke specialist input can influence TIA diagnosis and subsequent management. To reduce the risk of stroke and other vascular outcomes, different treatment strategies and choice of assessment settings have been developed including TIA clinics and urgent assessment in stroke units.[4–7] The structures and resources to investigate and manage TIA varies across different settings, and thus may need to reflect differences in health systems including telemedicine, or challenges such as infrastructural crisis/pandemic or limited capacity.[8,9]

Major advances have been made in TIA management, including improved treatments (eg. antiplatelet and lipid-lowering medications), advanced neuroimaging techniques and enhanced models of care/triage in recent years.[1,10–13] In routine practice, suspected TIA, confirmed TIA and minor stroke are often initially managed in similar healthcare settings. Neurovascular imaging of the brain and extracranial or intracranial vessels may identify potential high-risk mechanisms and patterns of ischaemia, but have limitations.[12,14]

The aim of this guideline is to provide recommendations to guide stroke care providers to reach clinical decisions in practice when assessing patients with suspected TIA, along with investigation and management strategies to reduce the risk of long-term disability. Accurately identifying high risk patients may be helpful in triage decisions for assessment and treatment decisions.[15]

These guidelines focus on issues specific to early TIA management. Therefore, aspects such as carotid stenosis, investigation of a cardioembolic a etiology after a TIA or late secondary prevention measures are to be found in other ESO guidelines.

Due to space constraints, the print version of this guideline incorporates the abstract and the synoptic table summarizing the evidence-based recommendations and the expert opinions (Table 1). The full guideline document is available online.

Methods

The guidelines for management of transient ischaemic attacks (TIA) follow the standard operations procedure (SOP) defined by the European Stroke Organization (ESO),[16] that is based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.[17]

Two chairpersons (ÁM and ACF) were selected by the ESO guidelines committee to assemble and coordinate a working group. Nine European experts from different countries and backgrounds were invited to participate. The ESO guidelines board and ESO Executive committee approved the composition of the working group. All participants were asked to disclose any conflict of interest that could influence their participation. The group communicated using in-person meetings, e-mail and teleconferences.

For these guidelines, we used a time-based definition of TIA. A TIA was defined as an acute loss of focal cerebral or ocular function with symptoms lasting less than 24 hours and which after adequate investigation was presumed to be due to embolic or thrombotic vascular disease.[18] A time-based definition was chosen to maximise generalisability of the guidelines, and to allow the existing evidence regarding TIA as it manifests initially to be used. These guidelines only refer to adults.

High risk TIA was defined based on clinical features in patients seen early after their event and having other features suggsting a high early risk of stroke (e.g. ABCD2 score of 4 or greater, significant large artery disease eg carotid stenosis, intracranial stenosis, weakness or speech disturbance for greater than five minutes, recurrent events).[10,11,13,14,19,20]

Presence of infarction on imaging is also considered as a marker of high stroke recurrence risk.[13,14,20]

Low risk TIA was defined by absence of high risk features (i.e. those in whom brain-tissue damage has not been detected on diffusion-weighted imaging, with no documented stenosis in the ipsilateral cerebral artery, no major cardiac source of embolism, no small vessel disease, and an ABCD2 score of less than 4).[20]

The working group selected eight Population, Intervention, Comparator, Outcome (PICO) questions that were considered relevant for TIA management and treatment. These PICO questions cover issues ranging from services organization to secondary prevention of TIA. Relevance of possible outcomes was voted on by all members of the working group according to the GRADE methodology using a scale from 1 to 9 (limited to critical importance) using Delphi methods. The final score, based on the mean votes from all participants, was the following: Ischaemic stroke recurrence 9; Functional outcome 8; Long term disability 7; Quality of life 7; symptomatic intracranial bleeding 7;

Table 1. Synoptic table of all recommendations and expert consensus statements.

Topic / PICO Question	Recommendations	Expert consensus statement
Services Organization 1.1: In patients suspected of TIA does stroke specialist review of the patient within 24 hours compared to more than 24 hours reduce TIA/stroke recurrence?	In patients with a TIA, we recommend specialist review of the patient within 24 hours after the onset of symptoms compared to assessment more than 24 hours after symptoms onset. Quality of evidence: Low ⊕⊕ Strength of recommendation: Strong for intervention ↑↑	
2.1: In patients suspected of TIA does stroke specialist review of the patient in a TIA clinic within 24 hours compared to conventional outpatient appointment more than 24 hours?	In patients with a TIA, we suggest specialist review in a TIA clinic within 24 hours over a conventional outpatient appointment more than 24 hours after the TIA. Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak for intervention ↑?	
3.1: In patients suspected of high-risk TIA does stroke specialist review of the patient in a TIA clinic within 24 hours compared to hospitalization in a stroke unit reduce stroke recurrence risk?	There is insufficient evidence to provide a recommendation.	In patients suspected of high-risk TIA, 9/9 experts suggest that prompt review in a TIA clinic or hospitalization in a stroke unit are reasonable options as settings for evaluation by a stroke specialist, depending on local available resources and the patients´ preferences, in the absence of evidence comparing each approach.
Risk prediction tools 4.1 In patients suspected of TIA does the use of risk prediction tools by primary care physicians compared to not using risk prediction tools reduce the risk of stroke recurrence, accurately identify high-risk patients, and improve diagnostic accuracy of TIA?	For patients with suspected TIA, we suggest not to use prediction tools alone to identify high risk patients/ make triage and treatment decisions. Quality of evidence: Very low ⊕ Strength of recommendation: Weak against intervention ↓	
Imaging 5.1: For patients with suspected TIA does the use of MRI (DWI/PWI) or CT Perfusion vs standard CT alone decrease stroke recurrence by accurately identifying an ischaemic mechanism and therefore patients at high stroke risk?	There is insufficient evidence to provide a recommendation.	In suspected TIA patients, to confirm ischaemic pathophysiology of transient neurological symptoms, where it will influence treatment and /or there is diagnostic uncertainty, 8/9 experts suggest to use MR (multimodal) or CT perfusion, if feasible, instead of non-contrast CT.
6.1: In suspected TIA patients is the use of MR angiogram (MRA) compared to CT angiography (CTA) superior for identifying patients with large artery stenosis of 50% or greater and therefore patients with high risk of stroke recurrence?	In TIA patients, we suggest using either MRA or CTA for additional confirmation after ultrasound of large artery stenosis of 50% or greater, to guide further management. Quality of evidence: Very low ⊕ Strength of recommendation: Weak for intervention ↑?	
Secondary prevention 7.1: In patients with suspected acute TIA does "de	In patients suspected of TIA, if a wait of more than 24 hours to planned imaging is foreseen and a delay is	

(continued)

Table 1. Continued.

Topic / PICO Question	Recommendations	Expert consensus statement
novo" antiplatelet usage (prior to imaging) compared to delayed antiplatelet usage reduce stroke recurrence?	judged to increase the risk of further ischaemic events, above the risk of starting antiplatelet medication, we suggest "de novo" antiplatelet monotherapy usage compared to not starting antiplatelet monotherapy. Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak for intervention ↑?	
8.1: In patients with non-cardioembolic acute TIA does dual antiplatelet therapy (DAPT) compared to monotherapy reduce the risk of stroke recurrence?	In patients with acute non-cardioembolic high risk TIA (ABCD2 score of 4 or more), we recommend short term dual antiplatelet therapy with aspirin and clopidogrel over monotherapy, subsequently followed by monotherapy. Quality of evidence: High ⊕⊕⊕⊕ Strength of recommendation: Strong for intervention ↑↑	For patients with acute non-cardioembolic low risk TIA or uncertain TIA diagnosis, 9/9 experts voted against using dual antiplatelet therapy over monotherapy.

All bleeding 7. Following the voting process, ischaemic stroke recurrence was considered the main outcome by the group for the analysis of the PICO questions.

The PICO questions were reviewed and approved by the ESO guidelines committee.

A systematic review of literature was done to collect evidence to answer the PICO questions. This search was performed by a professional methodologist (AL). The following databases were searched: MEDLINE, EMBASE, CINAHL, SCOPUS, COCHRANE controlled trials registers. Searches were done from inception to 6 of June of 2018. Articles relevant to the topic were additionally included as they were published and identified by the group members. The specific search terms and search strategies that were followed are outlined in Supplemental material. We included observational studies, clinical trials, meta-analysis and systematic reviews. Studies had to include at least 10 patients. Studies were excluded if they used a tissue based definition of TIA exclusively instead of a clinical definition or if they were written in a language other than English, French, German, Spanish, Portuguese or Italian.

For each PICO question, a PICO group consisting of two Working Group (WG) members was formed. The members of each PICO group confirmed that, to the best of their knowledge, no randomised trial (RCT) or systematic review had been omitted in the systematic literature search. If no RCT or systematic review relevant to a PICO question was identified, the PICO group confirmed that no important observational study was omitted in the literature search. The software CONVIDENCE (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) was used to screen the titles and abstracts retrieved from the search for each PICO questions. This task was independently performed by two group members per each PICO question. Discrepancies were solved after discussion to reach a consensus or after analysis by a third party. Selected full texts were assessed. Whenever, possible a random effects meta-analysis was conducted using Review Manager (RevMan) 5.3 COCHRANE Collaboration software. Results were presented as relative risks (RRs) with 95% confidence intervals (CIs). Meta-analysis of area under the curve (AUC) for receiver operating characteristic curve (ROC) was performed using MEDCALC software, MedCalc Software Ltd, Belgium. The I^2 statistic, an expression of inconsistency of studies' results and describing the percentage of variation across studies due to heterogeneity rather than by chance, was calculated. A high value of I^2 (>50%) and p value <0.05 indicate statistically significant heterogeneity among the studies for an outcome. The reasons for high heterogeneity were explored. A random effects model was used for all outcomes.

Recommendations were made according to the available evidence. The characterization of the quality of evidence and strength of recommendation was done according to the GRADE methodology. The analysis of evidence was completed using the software programme GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.).

In this manuscript, the analysis of each PICO question was addressed in distinct sections. Each section, includes an initial description of the available evidence followed by the ensuing recommendation. Whenever a recommendation was not possible due to the unavailability of data, an expert suggestion was made if deemed relevant. Expert suggestions were voted by all members of the guideline group using the Delphi method and are not evidence based. An additional information section was added if considered relevant for clinical practice or research purposes.

A representative of SAFE reviewed the phrasing of the recommendations and expert suggestions to ensure their accessibility to a broad readership.

The Guidelines document was reviewed several times by all MWG members, and modified using a Delphi approach until consensus was reached. The document was subsequently reviewed and approved by two external reviewers, the ESO Guidelines Board and Executive Committee, and the Editor of the *European Stroke Journal*.

Results

Services organization

1. In patients suspected of TIA does stroke specialist review of the patient within 24 hours compared to more than 24 hours reduce TIA/stroke recurrence?

Analysis of current evidence. The pooled risk of stroke following a TIA at 7 days is estimated to be 2.06% (95% CI, 1.83 – 2.33%) with half of the events occurring in the first 48 hours (1.36% (95% CI, 1.15–1.59) 95% CI 1.15–1.59).[21] Therefore, timely assessment and treatment of TIA patients could help to prevent subsequent stroke and impact prognosis.

A stroke specialist with specific training and experience in TIA care can optimize the yield from clinical history, neurological examination, complementary exams and management of TIA patients.

In a systematic literature review, no RCTs that analysed this PICO question were identified. Three observational studies were identified that evaluated the effect of rapid assessment by a specialist of patients with TIA on subsequent stroke rates. One such study was a prospective, single centre study in which assessment was done in a rapid access TIA clinic in Paris, France (SOS-TIA) that included neurological, arterial and cardiac imaging within 4 hours of admission.[6] In all patients, anti-thrombotic treatment was started immediately. A total of 1085 suspected TIA patients (definitive and possible TIAs, minor ischaemic strokes and patients with "other diagnosis") were included and 97% were followed up to determine stroke recurrence risk. The median time from symptoms onset to examination by a vascular neurologist in SOS-TIA was 1 day (IQR 0–8). Five hundred and seventy-four patients (53%) were seen within 24 hours. A total of 13 strokes occurred at 90-days after the TIA which corresponds to a 90-day stroke rate of 1.24% (95%CI 0.72–2.12). Out of the thirteen events, seven occurred in TIA patients with no acute imaging lesion, five in TIA patients with new lesions and 1 in a possible TIA patient. Restricting the analysis to definitive TIA patients without new imaging lesions, the 90-day stroke rate was 1.34% (0.64–2.78). When the sample was restricted to the 552 suspected TIA patients seen within 24 hours of symptoms onset, the 90-day stroke rate was 1.63% (95% CI 0.85–3.12). This stroke rate was lower than the risk predicted (6.49%) from the SOS TIA study participants ABCD2 scores. The 90-day stroke rate was 2.08% (1.09–3.96) for 434 patients with definite or possible TIA or minor stroke who had been seen within 24 h of symptom onset.

The TIAregistry project was an international, prospective, observational study that aimed to describe the demographic factors, a etiologic factors, and outcomes in patients with a TIA or minor ischaemic stroke (30% of the patients included) who received care in health systems that offered urgent evaluation by stroke specialists.[2] In this study, a total of 4013 patients (87.6%) sought medical attention within 24 hours after symptom onset, and 89.5% of these patients were examined by stroke specialists within 24 hours.[2] In an unadjusted risk analysis of stroke according to the time from symptom onset to evaluation by a stroke specialist dichotomized into within 24 hours versus more than 24 hours, there was not a statistically significant difference ($p = 0.32$ by log-rank test), although there was a higher rate of stroke recurrence in the group that was evaluated less than 24 hours after symptoms onset. The increased risk, although not significant, that was observed in patients seen within 24 hours was partially explained by the authors by confounding factors (namely higher presenting ABCD2 scores). Patients evaluated by a stroke specialist within 24 hours after symptom onset had a higher ABCD2 score than patients seen after 24 hours; the mean (±SD) ABCD2 score was 4.7 ± 1.5 in patients seen within 24 hours, as compared with 3.8 ± 1.6 in patients seen after 24 hours ($P < 0.001$).[2]

The EXPRESS study was an observational study that prospectively compared the 90-day risk of recurrent stroke in TIA or minor stroke patients that were either seen in a study clinic by a specialist with a median time of 3 days (IQR 2–5) in phase 1 or within a median time of 1 day (IQR 0–3) in phase 2.[5] Median delay to first prescription of preventive medications was 20 days (IQR 8–53) in phase 1 and 1 day (IQR 0–3) in phase 2. The 90-day risk of recurrent stroke was 10.3% (32/310 patients) in phase 1 and 2.1% (6/281 patients) in phase 2 (adjusted hazard ratio 0.20, 95% CI 0.08–0.49; p = 0.0001). In the EXPRESS study, there was no specific division of patients into those assessed more or less than 24 hours.

Recommendation

In patients with a TIA, we recommend specialist review of the patient within 24 hours after the onset of symptoms compared to assessment more than 24 hours after symptoms onset

Quality of evidence: Low ⊕⊕

Strength of recommendation: Strong for intervention ↑↑

Additional information. It is frequently difficult to distinguish TIA from other transient neurological attacks.[22] Up to 60% of patients with suspected TIA may have a mimic syndrome.[23] The differential diagnosis of transient ischaemic attack with transient focal neurological episodes includes cerebral amyloid angiopathy with cortical superficial siderosis . Persistent neurological deficits like neglect and visual field defect can be better detected by a stroke specialist and should be evaluated as stroke, not as a TIA.[24] Specialist evaluation of TIA patients can be performed in different settings, depending on local practices, including: a TIA clinic with round-the-clock access, same day open access clinics available during standard office hours, emergency departments or stroke-unit based.

Patients with minor, improving or fluctuating deficits may have large vessel arterial occlusions that should be evaluated immediately by stroke specialists.

Given the predicted benefits of early assessment and treatment of TIA patients, any further study of randomization to early versus delayed assessment could be considered unethical and unfeasible.

2. In patients suspected of TIA does stroke specialist review of the patient in a TIA clinic within 24 hours compared to conventional outpatient appointment more than 24 hours reduce TIA/stroke recurrence risk?

Analysis of current evidence. TIA clinics usually comprise specialist assessment, rapid completion of investigations and urgent initiation of secondary stroke prevention strategies.[24] TIA clinics may allow for dedicated protected resources when there are finite clinical resources available such as protected time slots for neuro-imaging or guaranteed access to same day cardiac rhythm assessment.

TIA clinics are often designed to ensure that there is a clear pathway for patients initially seen in the emergency department for whom acute inpatient hospital admission may be avoided.

Our literature review did not identify RCTs to answer this PICO question.

In the TIAregistry.org study, at 1 year follow up, the Kaplan–Meier estimate of the risk of the composite outcome of major fatal or nonfatal cardiovascular events was 6.2%, and the Kaplan-Meyer estimate of the risk of stroke was 5.1%. The risk of recurrent stroke at 2 days, 7 days, 30 days, 90 days, and 1 year was less than half that expected from historical cohorts. The lower event rates in this large, observational, prospective and international study were attributed to the contemporary care provided by TIA clinics.[2]

The SOS-TIA study compared the incident rate of ischaemic stroke in patients seen within 24 hours versus the incidence rate that could be expected by their ABCD2 scores. The 90-day stroke rate was 1.63% (95%CI 0.85–3.12). This rate was lower than the risk expected from the ABCD2 scores, that was calculated to be 6.49%.[6]

Recommendation

In patients with a TIA, we suggest specialist review in a TIA clinic within 24 hours over a conventional outpatient appointment more than 24 hours after the TIA.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Weak for intervention ↑?

3. In patients suspected of high-risk TIA does stroke specialist review of the patient in a TIA clinic within 24 hours compared to hospitalization in a stroke unit reduce stroke recurrence risk?

Analysis of current evidence. No RCTs were identified on the systematic literature search to address this PICO question.

A meta-analysis that aimed to establish the risk of early stroke recurrence, using data from studies that offered urgent care to TIA patients in different settings, did not find heterogeneity in the risk of subsequent stroke.[21] From the fifteen studies that were included in this meta-analysis, 4 managed patients in the emergency department, 7 in a TIA clinic, 2 in a stroke unit, 2 simultaneously integrated care in and outpatient setting and stroke unit facilities. The ratio of hospitalization in

the meta-regression model was also not related to stroke recurrence.[21]

TIA clinics may facilitate the early discharge and outpatient assessment of patients seen in emergency departments. Hospital admission of TIA patients has been used mainly in hospitals that do not have a structured TIA pathway with access to rapid investigations for clinic patients. In high risk TIA patients, hospitalization could theoretically include surveillance for early stroke recurrence and early stroke treatment with thrombolysis or thrombectomy. Hospital admission compared to TIA clinics assessment was previously shown to be associated with higher costs and admission of patients with TIA mimic syndromes.[20,25]

In the SOS-TIA study, some TIA patients initially seen in a TIA clinic were admitted to a stroke unit if they fulfilled predefined criteria: a) TIAs that increase in frequency, duration or severity (crescendo TIA), b) 24 hour cardiac monitoring warranted (paroxysmal atrial fibrillation strongly suspected), c) A suspected or identified cause of TIA such as high-grade stenosis of intracranial or extracranial arteries, low blood flow in the middle cerebral artery, potential cardiac sources of high-risk of recurrent embolism.[6]

An observational study, investigated differences in outcomes for patients admitted to the hospital with TIA according to care on a stroke unit (SU) or alternate ward setting up to 180 days post event.[26] This study, included data from 3007 patients with TIA admitted to 40 hospitals participating in the Australian Stroke Clinical Registry during 2010–2013. There is no quantification in this study of how many of the patients included were high risk TIAs. Treatment in an SU, compared to alternative wards, was associated with improved cumulative survival at 180 days post event (hazard ratio 0.57, 95% confidence interval 0.35–0.94; $p = 0.029$), despite not being statistically significant at 90 days (hazard ratio 0.66, 95% confidence interval 0.33–1.31; $p = 0.237$). These results were comparable to studies of the benefits of rapid-access TIA clinics as the 90-day survival rates fell within their 95% confidence limits.[26]

Recommendation
There is insufficient evidence to provide a recommendation.

Additional information. Ideally evidence to answer this PICO question should be derived from a RCT. A RCT could compare the stroke recurrence rate in patients assessed in a TIA clinic versus hospitalization within 24 hours. Such a clinical trial is feasible and desirable. However, randomized clinical trials of complex interventions such as stroke services offer unique challenges, even if conducted with a cluster/place-randomised design.[27] It is often difficult to develop and describe the intervention adequately, to blind the trial participants to their treatment and to rule out confounding from other aspects of care. Even if a service is shown to work well in one setting, specific local factors may have influenced the results.[27]

Expert consensus statement
In patients suspected of high-risk TIA, 9/9 experts suggest that prompt review in a TIA clinic or hospitalization in a stroke unit are reasonable options as settings for evaluation by a stroke specialist, depending on local available resources and the patients´ preferences, in the absence of evidence comparing each approach.

Risk prediction tools

4. In patients suspected of TIA does the use of risk prediction tools by primary care physicians compared to not using risk prediction tools reduce the risk of stroke recurrence, accurately identify high-risk patients, and improve diagnostic accuracy of TIA?

Analysis of current evidence. No RCTs were identified where a prediction tool use was compared to non-use for the outcome of prevention of stroke recurrence. No observational studies were found which compared use of a prediction score to make clinical decisions, to without use of a score.

To examine if prediction tools/clinical scores could accurately identify high risk patient suspected of TIA in primary care settings, studies of prediction scores using clinical parameters were identified. Scores which included information from brain or vascular imaging were not included as they were not designed for use in primary care. Scores that could be used in primary care (components did not need to be acquired in secondary care) were included. Studies in a primary care setting, or partially primary care setting (eg where the data for calculating the score was acquired/may be collected in primary care) were included. The ABCD2 ABCD, ABCD3, California and Essen scores were analysed. The ABCD2 score ranges from 0–7 points and consists of Age, Blood pressure, Clinical symptoms, Duration, Diabetes mellitus. The score can be calculated by physician/healthcare worker at the first point of contact using the following scoring parameters (age $\geq$60 years [1 point]; initial blood pressure $\geq$140/90 mm Hg [1 point]; clinical features of weakness [2 points] or speech impairment[1 point]; duration of symptoms $\geq$60 min [2 points] or 10–59 min [1 point];

diabetes mellitus [1 point]. ABCD2 score has a range of 0–7, however patients are typically grouped according to trichotomised ABCD2 score (0–3, 4–5, 6–7).[1] The ABCD score predated the ABCD2 score and did not include diabetes mellitus and has a range of 0–6.[28] The ABCD3 score adds recurrent preceding TIA within 7 days ('Dual TIA') to the component of ABCD2 with a 2-point weighting to give an ABCD3 score range of 0–9.[13] The ABCD3 score was validated in a population-based setting including primary care data. The California score demonstrated that simple clinical variables (Age, presence of diabetes mellitus, duration of episode greater than 10 minutes, weakness and speech impairment during episode) were associated with the risk of stroke at 90 days in patients with a diagnosis of TIA who were initially admitted to an Emergency Department.[29] The Essen Stroke Risk Score (ESRS) was retrospectively derived from the data subset of a clinical trial population of cerebrovascular disease patients.[5] The Essen score takes into account risk factors including age, hypertension, diabetes, previous myocardial infarction, other cardiovascular disease, smoking and previous TIA/stroke in a 9-point scale.[30]

Studies of prediction scores in primary care or those applicable to non-stroke specialist assessments, with clinical stroke outcomes available and where external validation studies had been performed, were included in a pooled analysis.

An ABCD2 score threshold greater than or equal to 4 ($\geq$4) and a threshold of greater than or equal to 6 ($\geq$6) were examined for identifying patients at high risk of stroke recurrence. A pooled analysis of the results of observational studies of ABCD2 showed recurrent ischaemic stroke at 7 days was increased in patients with an ABCD 2 score $\geq$4 (n = 34 studies, N = 35,867). In this study, an ABCD2 score ($\geq$4) was associated with almost 3-fold increased risk of stroke (Odds ratio 2.97 95% CI 2.23, 3.96), $p < 0.00001$. The cumulative 7 day stroke in patients with ABCD2 score of 3 or less was 1.8%, but in the high risk category (ABCD2 $\geq$4) the 7 day stroke risk was 5.3%. This pooled analysis showed similar findings at 3 days (OR 3.52, 95% CI 2.62, 4.72) and at 30 days (OR 2.28 95% CI 1.54, 3.39) (Tables 2 and 3).

Discrimination was measured with Receiver Operator characteristic (ROC) analysis for clinically useful time points, focused on early time points where triage and management decisions are typically made. A pooled analysis (random effects) of the results of observational studies of ABCD2, where ROC data was available, showed a c-statistic of 0.69 (0.65–0.72) for discrimination of patients with recurrent ischaemic stroke at 7 days (n = 23 studies, N = 48,588) (Figure 1, Table 4). Between-study heterogeneity and moderately wide CIs were seen. Heterogeneity was substantial and statistically significant across the studies.

Analysis of predictive sensitivity and specificity of ABCD2 < 4 compared to greater than 4 was only possible in a limited proportion of studies that reported clinical outcomes - for stroke outcome by 7 days average sensitivity: 87.2%; (n = 4692; Studies = 5), specificity: 28.4%; (n = 4692; Studies = 5)

Using an ABCD2 threshold/cut-point greater than or equal to 6 ($\geq$6) for identifying highest risk patients showed a 7.7% stroke risk by 7 days in patients with an ABCD2 score of 6 or 7, compared to 3.6% in patients with an ABCD 2 score of between 0 and 5, (OR 2.88 [2.28, 3.64], $P < 0.00001$, with heterogeneity $I^2 = 59\%$).

ABCD3, California and Essen score evaluation showed statistically significant heterogeneity (eg ABCD3 (c-statistic of 0.69 (CI 0.59–0.78, $p < 0.001$) for discrimination of patients with recurrent ischaemic stroke at 7 days (n = 2 studies, N = 4579 I^2, p 90%, <0.0001), wide confidence intervals (eg California score (c-statistic of 0.68 (CI 0.21–1.0, $p < 0.004$) , or only had outcome data reported for 3 months and beyond (Essen Stroke risk score).

No RCT was identified which looked at prediction tool use compared to non-use for improving TIA diagnostic accuracy. Although not the initial intended use, some risk prediction tools may have diagnostic properties, and thus help identify 'True TIA' compared to mimics. 5 studies were identified which investigated the

Table 2. $ABCD^2$ ($\geq$ 4 vs < 4)-risk prediction tool and occurrence of stroke in patients with TIA

	Recurrent stroke (%)					
Outcome	$ABCD^2$, $\geq$4	$ABCD^2$, <4	*n* (N)	OR [95% CI]	I^2, *p*	*p* value
Stroke						
• $\leq$3 days	2.3% (470/20692)	0.7% (57/8313)	13 (29,005)	3.52 [2.62, 4.72]	4%, 0.40	<0.00001
• 7 days	5.3% (1257/23942)	1.8% (212/11925)	34 (35,867)	2.97 [2.23, 3.96]	57%, <0.0001	<0.00001
• 1 month	9.8% (198/2083)	4.1% (38/935)	8 (3018)	2.28 [1.54, 3.39]	6%, 0.38	<0.0001

OR: odds ratio, I^2; *p*: heterogeneity analysis.

Table 3. GRADE evidence profile for 7 day stroke risk using an ABCD2 threshold of 4 or more (≥4).

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABCD2 ≥ 4	< 4	Relative (95% CI)*	Absolute (95% CI)	Certainty	Importance
34	Observational studies	Serious[a]	Serious[b]	Not serious	Not serious	Strong association	1257/23942 (5.3%)	212/11925 (1.8%)	OR 2.97 (2.23 to 3.96)	33 more per 1000 (from 21 more to 49 more)	⊕◯◯◯ Very low	Critical

*Relative effect reflects comparison of ABCD2 score category 4–7 with ABCD2 score category 0–3.
[a]Possible risk of bias.
[b]Heterogeneities detected, $I^2 = 57\%$, $p < 0.001$.

ABCD2 score for identification of a cerebrovascular event (stroke or TIA) in patients presenting with transient neurological symptoms, identified by the 'gold standard' experienced stroke specialist clinical diagnosis following history, clinical examination and access to relevant investigations.[4,31–33] An ABCD2 score of 4 or greater was associated with greater likelihood of a final diagnosis of a true cerebrovascular event (odds ratio 4.84 (CI 1.92–12.19) (Table 5). However, the included studies had small study numbers overall with wide confidence intervals.

Recommendation

For patients with suspected TIA, we suggest not to use prediction tools alone to identify high risk patients/make triage and treatment decisions

Quality of evidence: Very low ⊕

Strength of recommendation: Weak against intervention ↓

Additional information. A previous meta-analysis has highlighted the low specificity of prediction tools for identifying 7 day stroke risk following TIA.[34] Patients with an ABCD2 of 4 or more are categorised as high risk based on the ABCD2 prediction tool. Due to limited sensitivity of the scores, those with 3 or less may include significant numbers of individual patients at high risk of recurrent stroke who require early assessment and treatment.

Concern exists that use of prediction tools may unnecessarily delay timely assessment of people at risk of stroke, particularly those who may benefit from a specific intervention (such as endarterectomy or anti-coagulation) if identified early. The data required for calculation of positive and negative predictive values of predictions tools, as well as discrimination properties, was only available for a small proportion of studies examined for these guidelines. Prospective studies of score sensitivity and specificity, as well as negative and positive predictive value data for clinical prediction tools are needed for both confirmed TIAs and mimics/possible TIA.

Application of prediction tools in routine clinical practice to make secondary prevention decisions has not been studied extensively. Additional studies of long-term vascular risk prediction, especially where therapeutic strategies vary depending on risk category, have been limited. Studies of prediction tools in secondary or tertiary care (after or prior to specialist assessment) with relevant clinical outcomes may be helpful for clarifying if different secondary prevention strategies have a significant impact on long term outcomes (eg event free survival). Imaging based tools

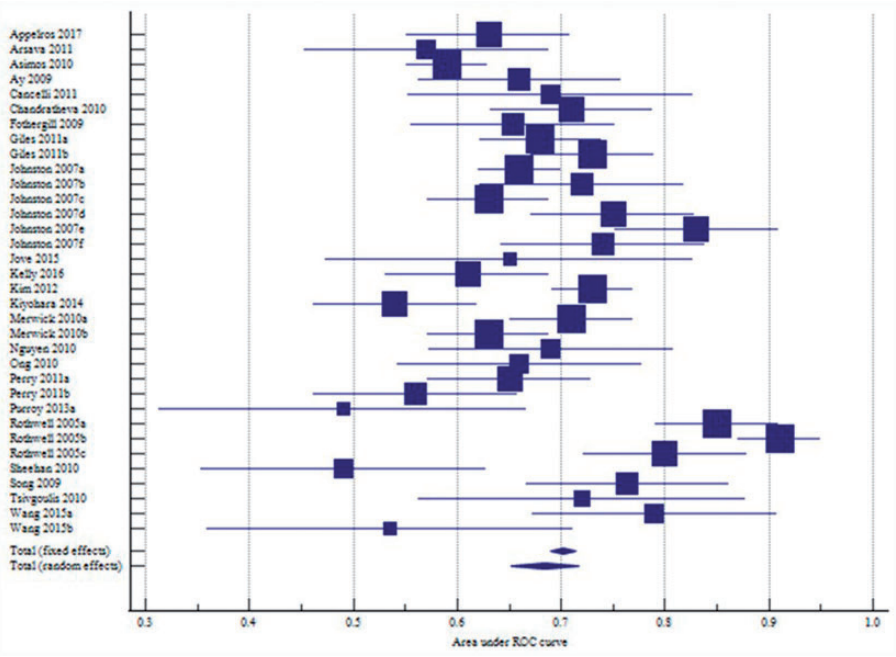

Figure 1. Pooled analysis of areas under the curve of ROC curves for ABCD2 and occurrence of stroke at 7 days.

Table 4. Pooled analysis of areas under the curve of ROC curves with ABCD2-risk prediction tools and occurrence of stroke in patients with TIA.

ABCD2	ROC (95% CI)	*n* (N)	I^2, *p*	*p**
≤3 days	0.69 (0.65–0.73)	11 (25,895)	66%, 0.0001	<0.001
7 days	0.68 (0.65–0.72)	24 (48,728)	88%, <0.0001	<0.001

*p for discrimination analysis level of significance

were not included as they were not designed for use in primary care, but may have utility in other settings where neuroimaging is accessible, especially for identifying high risk patients.[13] Imaging based scores which incorporate brain parenchyma and carotid imaging eg ABCD2-I, ABCD3-I may be useful for identifying subgroups of TIA patients with high early stroke risk[7,13,20,35]

We suggest cluster RCTs to examine utility, safety, cost effectiveness and patient preferences regarding use of prediction tools in clinical decision making, including imaging-based tools for secondary care/specialist use or patient selection in clinical trials.

The diagnosis of TIA is clinically based and significant variation in inter-rater reliability for diagnosis has been reported, even amongst stroke specialists.[4] Assessing diagnostic accuracy of the ABCD2 score has to allow for the variability in the 'Gold standard' of a clinical TIA diagnosis.

The Dawson care score and DOT TIA are tools specifically designed to aid diagnosis of TIA, and thus are not risk prediction tools, and beyond the scope of this PICO question.[36,37] If robustly externally validated across different settings dedicated diagnostic tools such as DOT TIA, DAWSON score may be helpful as part of a clinical assessment. Additional research into diagnostic scores or biomarkers (including neuroimaging) may lead to improved accuracy of TIA diagnosis.

Imaging

5. For patients with suspected TIA does the use of MRI (DWI/PWI) or CT Perfusion vs standard CT alone decrease stroke recurrence by accurately identifying an ischaemic mechanism and therefore patients at high stroke risk?

Analysis of current evidence. The fundamental standard for TIA diagnosis is clinically based and therefore the lack of an ischaemic neurological feature on neuroimaging does not exclude a TIA. However, agreement on clinical diagnosis and the ischaemic pathophysiology of transient neurological symptoms, even among stroke specialists, is low.[3] Advanced imaging can identify footprints of acute hypoperfusion changes after transient neurological symptoms. Infarction can be identified by Magnetic resonance Diffusion weighted imaging (MR DWI) and focal hypoperfusion on CT Perfusion (CTP) or Magnetic resonance Perfusion weighted imaging (MR PWI).

The literature search did not identify any completed RCTs comparing the different modalities. Observational data and clinical series were identified,

Table 5. GRADE evidence profile for ABCD2 $\geq$ 4 compared to <4 for diagnosis of stroke or TIA.

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABCD2 $\geq$ 4	<4	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
5	Observational studies	Seriousa	Seriousb	Not serious	Not serious	Publication bias strongly suspected very strong association[c]	283/803 (35.2%)	161/935 (17.2%)	OR 4.84 (1.92 to 12.19)	329 more per 1000 (from 113 more to 545 more)	⊕◯◯◯ Very low	Critical

CI: confidence interval; OR: odds ratio.
[a]Possible risk of bias.
[b]Heterogeneity among the studies, I^2: 86%, $p = 0.0001$.
[c]Five studies reported this outcome.

however none directly evaluated if a strategy of using advanced imaging versus non contrast brain CT was associated with a lower risk of stroke recurrence.

Diagnostic yield for identifying ischaemic changes on standard non contrast CT imaging in TIA patients is low (1.8–6%).[38–40]

MR DWI imaging detected a positive DWI lesion in 34.3% (95% CI 30.5% to 38.4%) of probable TIA patients, in a univariate random-effects meta-analysis based on studies of 9078 patients, with heterogeneity between studies demonstrated by both forest plot and a high I^2-statistic of 89.3%.[41]

Amongst patients with atypical or non-focal neurological transient symptoms a positive DWI lesion rate of 23% has been reported.[42]

Observational studies have demonstrated that the presence of an acute positive DWI lesion is independently associated with an increased rate of early and late stroke recurrence. In the OXVASC population-based study, a positive DWI was associated with an increased 10 year risk of recurrent ischaemic stroke after an index TIA (hazard ratio [HR] 2.66, 95%CI 1.28–5.54, $p < 0.01$).[2,43,44]

Several cohort studies demonstrated that MR-PWI and/or arterial spin labelling (ASL) detect an acute focal ischaemic lesion in between 32 and 47% of TIA patients (7/22 (31.8%);[45] 21/62 (33.9%),[46] 14/43 (33%),[47] 29/90 (32.2%),[48] 30/64 (46.9%).[49] Up to half of the patients with an MRI PWI lesion had no ischaemic lesion on DWI. The rate of no DWI abnormality detection in patients with PWI lesion ranged from 10–50% (2/20 (10%),[46] 7/14 (50%),[47] 14/29 (48.3%),[48] 14/30 (46.7%)[49])

In an observational study of TIA and minor stroke, 37.3% of patients (156/418; 95%CI, 32.8–42%) had a perfusion deficit (Tmax _ 2 seconds delay) on MRI imaging, DWI abnormality was seen in 55.5% (232/418; 95% CI, 50.6–60.3) of patients, and a total of 143/418 (34.2%; 95% CI, 29.7–39%) patients had concurrent perfusion and diffusion deficits.[50] One third of the acute PWI lesion progressed to infarction on follow up imaging.[49]

Additional MR sequences such as T2*-weighted gradient-recalled echo (GRE), FLAIR, T1 may help in the differential diagnosis of other cause of transient neurological symptoms that may alter patient management such as cerebral amyloid angiopathy with transient focal neurological episodes (TFNE); haemorrhage, tumour; inflammatory disorders; etc.[51]

CTP detects an acute focal ischaemic lesion in 35–42% of TIA patients, and thus shows comparable rates of abnormalities to perfusion MRI. (12/34 (35.3%).[40,52,53] In a series of consecutive supratentorial TIA patients 110/265 (42%) had focal perfusion abnormalities on CTP.[40] Acute standard non-contrast

computed tomography showed early ischaemic lesions in 6%, and acute/subacute magnetic resonance imaging was abnormal in 52 of the 109 cases (47.7%) where it was performed.[40]

In an observational series of 34 acute consecutive patients with a discharge diagnosis of possible or definite TIA, who received no revascularization therapy, standard non-contrast CT was negative in all cases, while CTP identified an ischaemic lesion in 12/34 patients (35%). In a subgroup of 17 patients with multimodal MRI, an ischaemic lesion was found in six (35%) patients using CTP versus nine (53%) on MRI (five DWI, nine PWI).[53] A stroke-unit based series of 122 consecutively admitted TIA patients found a lesion corresponding to the transient neurological deficits in 21/110 on DWI MRI and 2/109 on standard non-contrast CT brain.[38]

Recommendation
There is insufficient evidence to provide a recommendation.

Additional information. The presence of an acute positive DWI lesion is an independent predictor of the risk of recurrent ischaemic stroke.

MRI has recognized limitations in both transient symptoms as well as clinical stroke where focal neurological symptoms persist but MRI is DWI negative (or initially negative). Delayed time from symptoms to MRI scan, type of symptoms (eg posterior circulation territory symptoms) and technical factors relating to MR sequences, slice thickness and magnetic strength that may influence DWI abnormality rates.[54,55]

PWI may add on the diagnostic yield of DWI when it is negative and may be considered in patients with negative DWI or when other MRI sequences (FLAIR/GRE/MRA) disclose no alternative diagnosis.

Expert consensus statement
In suspected TIA patients, to confirm ischaemic pathophysiology of transient neurological symptoms, where it will influence treatment and/or there is diagnostic uncertainty, 8/9 experts suggest to use MR (multimodal) or CT perfusion, if feasible, instead of non-contrast CT.

6. In suspected TIA patients is the use of MR angiogram (MRA) compared to CT angiography (CTA) superior for identifying patients with large artery stenosis of 50% or greater and therefore patients with high risk of stroke recurrence?

Analysis of current evidence. No RCTs have been identified that directly addressed this question. No comparison studies were identified in adults with suspected TIA. Observational data, clinical series, systematic reviews and meta-analysis were identified in asymptomatic and TIA cases.

An increased risk of early recurrent stroke is recognized in patients with suspected TIA and significant symptomatic large artery disease.[56,57] Prompt access to neurovascular imaging techniques to evaluate large artery stenosis reduces stroke recurrence in TIA patients.[58,59]

In many centres, duplex ultrasonography (DUS) is the first step in the evaluation of carotid arteries. It has a high sensitivity and specificity to detect proximal internal carotid stenosis and it is a good cost effective screening tool.[60,61] MRA or CTA may increase effectiveness slightly at disproportionately higher costs.[61]

In routine practice,[62] Duplex ultrasonography (as first-line), computed tomographic angiography and/or magnetic resonance angiography are recommended for evaluating the extent and severity of extracranial carotid stenoses by the European Society for Vascular Surgery.[62]

It has been reported that the use of two complementary non-invasive techniques improves the accuracy of the measurement of arterial stenosis. In patients with TIA and carotid disease either MRA or CTA are cost-effective strategies.[60,63]

Major RCTs, published in the 1990s, examining carotid stenosis in stroke and TIA patients were based on digital subtraction angiography (DSA), as the gold standard for detecting the degree of arterial stenosis. However, due to the need for sensitive, prompt neurovascular imaging and to reduce the risk of diagnostic procedural complications, non-invasive techniques have replaced DSA as an investigative tool. With continuous development of non-invasive medical imaging techniques such time-of-flight MR angiography (TOF-MRA), contrast-enhanced MR angiography (CE-MRA), multi-section computed tomography angiography (CTA), and multi-slice CT angiography (MS-CTA) the diagnostic accuracy has improved. The reported values for detection of arterial disease are variable because stenosis grading is dependent on the examination methods, post-processing techniques[64–66] and the assessment method (e.g. NASCET, ECST, CCA). Meta-analysis comparing DSA with both MRA and CTA imaging techniques showed that these techniques have a sensitivity and specificity higher than 90% for the detection of carotid stenosis $\geq$70% (Table 6).[66–69]

However, when a large vessel has a moderate stenosis between 50–69% these non-invasive techniques have a lower sensitivity and specificity for the accurate detection of the degree of stenosis.[66–71] In recent years, there are no comparative studies of the two modalities with DSA in any large series of patients.

Table 6. Non-invasive evaluation in high-grade degree of carotid artery stenosis.

Exam	Stenosis	Sensitivity % (95% IC)	Specificity % (95% IC)	Assessment method	Study
DUS	70–99%	89 (85–92)	84 (77–89)	NASCET	Wardlaw[67]
CTA		77 (68–84)	95 (91–97)		
MRA		88 (82–92)	84 (76–97)		
CE MRA		94 (85–97)	93 (89–96)		
TOF MRA	≥70–99%	92.5 (90.0–94.5)	87.8 (86.0–89.4)	NASCET	Debrey[69]
CE MRA		94.5 (92.2–96.3)	91.5 (89.7–93.0)		
DUS	>70%	89 (81–96)	91 (85–97)	NASCET	Al Shuhaimy[66]
CTA		89 (85–92)	93 (89–96)		
MRA		94 (91–96)	87 (82–91)		
CTA	>70%	96*	93*	NASCET	Forjoe[68]
DUS		92.3*	89*		

A recent review that included previous and more contemporary studies of reported sensitivity and specificity for CTA of 81.7% and 85.6%, that may be lower than those reported for contrast-enhanced MRA.[68,69] A comparative study between DUS, MRA, CTA and DSA[70] and another study that compared imaging techniques with endarterectomy histological specimens, showed a better correlation with CTA than with MRA, to detect moderate carotid stenosis.[71]

Recommendation:
In TIA patients, we suggest to use either MRA or CTA for additional confirmation after ultrasound of large artery stenosis of 50% or greater, in order to guide further management.
Quality of evidence: Very low ⊕
Strength of recommendation: Weak for intervention ↑

Additional information. Each imaging modality has advantages and disadvantages and availability varies across centres. Therefore, other factors may determine the selection of the optimum testing modality for an individual patient. MRA evaluation of arterial disease includes overestimation of stenosis (more so with non-contrast examinations)[69] and inability to discriminate between subtotal and complete arterial occlusion. Patients who have claustrophobia, extreme obesity, or incompatible implanted devices such as pacemakers or defibrillators cannot undergo MRA. In patients with renal failure or nephrogenic systemic fibrosis, the use of gadolinium contrast-enhanced MRA is contraindicated.

A notable strength of MRA compared to carotid ultrasound and CTA is its relative insensitivity to arterial calcification.[72]

To select the imaging modality technique of choice at an individual centre, the speed of access, diagnostic sensitivity/specificity, cost/benefit ratio, and facility for post-processing of images needs to be considered.

In many institutions, CTA is more readily available than MRA. CTA is undergoing rapid technological evolution. Dual-source systems and increased number of detector rows (16-, 32-, 64-, 256-, and 320-) facilitate faster, higher-resolution imaging and larger fields of view with less radiation and ionized contrast. Renal failure, intolerance to ionized contrast are limitations of CTA.

The reference standard for the diagnosis of intracranial stenosis and occlusion is DSA and, recently, CTA, MRA, or contrast-enhanced MRA.[73] A Cochrane review that assessed the diagnostic accuracy of Trancranial Doppler (TCD) and transcranial colour Doppler (TCCD) for detecting stenosis and occlusion of intracranial large arteries in people with acute ischaemic stroke showed that TCD or TCCD, administered by professionals with adequate experience and skills, can provide useful diagnostic information for detecting stenosis or occlusion of intracranial vessels or guide the request for more invasive vascular neuroimaging, especially where CT or MR-based vascular imaging are not immediately available.[73]

Secondary prevention

7. In patients with suspected acute TIA does "de novo" antiplatelet usage (prior to imaging) compared to delayed antiplatelet usage reduce stroke recurrence?

Analysis of current evidence and evidence-based recommendation. Literature searches identified no RCTs comparing the outcome of patients with TIA who had been treated with antiplatelet medication only following

Table 7. GRADE evidence profile for PICO 7.

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Ischaemic stroke												
2	Randomised trials	Not serious	Not serious	Serious	Not serious	None	51/4472 (1.1%)	74/4417 (1.7%)	RR 0.68 (0.48 to 0.97)	5 fewer per 1000 (from 9 fewer to 1 fewer)	⊕⊕◯◯ Low	Critical
Haemorrhagic stroke and non-cerebral haemorrhage												
2	Randomised trials	Not serious	Not serious	Serious	Serious[a]	None	43/4472 (1.0%)	40/4417 (0.9%)	RR 1.06 (0.69 to 1.63)	1 more per 1000 (from 3 fewer to 6 more)	⊕◯◯◯ Very low	Critical
Death												
2	Randomised trials	Not serious	Not serious	Serious	Not serious	None	246/4472 (5.5%)	266/4417 (6.0%)	RR 0.91 (0.77 to 1.08)	5 fewer per 1000 (from 14 fewer to 5 more)	⊕⊕◯◯ Low	Critical
Death or stroke												
2	Randomised trials	Not serious	Not serious	Serious	Not serious	None	385/4472 (8.6%)	421/4417 (9.5%)	RR 0.90 (0.79 to 1.03)	10 fewer per 1000 (from 20 fewer to 3 more)	⊕⊕◯◯ Low	Critical

CI: confidence interval; RR: risk ratio.

[a]Events are few and confidence intervals crosses the line of no effect.

Table 8. GRADE evidence profile for PICO 8 (clopidogrel and aspirin compared to aspirin for stroke).

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Double antiplatelets	Single antiplatelet be used acutely	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Ischaemic stroke												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	316/5016 (6.30%)	450/5035 (8.94%)	RR 0.70 (0.61 to 0.81)	25 fewer per 1000 (from 34 fewer to 15 fewer)	⊕⊕⊕⊕ High	Critical
Death												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	28/5016 (0.57%)	22/5035 (0.44%)	RR 1.28 (0.73 to 2.23)	0 fewer per 1000 (from 4 fewer to 9 more)	⊕⊕⊕◯ Moderate	Critical
Quality of life, low												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	none	142/2562 (5.54%)	175/2569 (6.81%)	RR 0.81 (0.66 to 1.01)	13 fewer per 1000 (from 23 fewer to 1 more)	⊕⊕⊕⊕ High	Critical
Haemorrhage, all												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	121/2782 (4.35%)	68/2780 (2.45%)	RR 1.79 (1.20 to 2.69)	19 more per 1000 (from 3 more to 46 more)	⊕⊕⊕⊕ High	Critical

CI: confidence interval; RR: risk ratio explanations.

[a]Low events and or wide confidence interval.

brain imaging and those treated prior to brain imaging. No observational studies were identified that examined specifically antiplatelet usage prior to imaging compared to a delayed usage strategy in adults with suspected acute TIA. Therefore, there was no evidence based on RCTs to directly answer this question. Due to absence of any direct RCT evidence, the working group has based suggestions on RCTs in presumed ischaemic stroke, clinical experience and knowledge of the topic.

A meta-analysis of the data from 40,000 individual patients from two RCTs (the Chinese Acute Stroke Trial (CAST)[74] and the International Stroke Trial (IST)),[75] found among 8889 stroke patients (22%) randomized within 48 hours without a prior CT scan, aspirin appeared to be of net benefit with no unusual excess of haemorrhagic stroke.[76]

A CT scan was not performed before randomisation in 12% of those in CAST and 33% of those in IST. Seven hundred seventy-three patients (2%) were subsequently found to have been randomised, inadvertently after an intracerebral haemorrhage, rather than an ischaemic stroke. However; aspirin had no significant effect on the incidence of another symptomatic cerebral haemorrhage (29 [7.3%] versus 26 [6.9%], not significant), and appeared to reduce the incidence of other strokes (1 [0.3%] versus 8 [1.1%], $p = 0.04$). All stroke recurrence was 1.1% in the aspirin group compared to 1.7% in the control group (Risk ratio [RR] 0.68 [0.48, 0.97], $p = 0.03$) (Table 7). Mortality was 5.5% in the aspirin group compared to 6.0% in the control group (RR 0.91 [0.77, 1.08], $p = 0.29$).These data relate to stroke patients and the haemorrhage risk is likely to be even smaller in patients with transient symptoms.[76]

The number of patients with suspected TIA who have alternative diagnoses (subdural haematoma, intracerebral haemorrhage, vascular malformations, convexity SAH and superficial siderosis and microbleeds) which would be perceived as increasing the risks of starting antiplatelet therapy are probably very small. For example, the incidence of convexity SAH has been estimated at about 5–10/per million/per year compared with a TIA incidence of at least 500/million/yr.[77,78]

The risk of ischaemic recurrent events is highest within the period immediately after the TIA,[2,79] with 2% risk by 2 days in a large international TIA registry study, and may be higher in population-based studies.[80] The benefits of antiplatelet therapy are greatest (in both relative and absolute terms) within the first 24 hours following a TIA. Pooled analysis of the individual patient data from RCTs of aspirin versus control in secondary prevention after TIA or ischaemic stroke, showed the risk of recurrent ischaemic stroke was reduced by day 2 after randomisation (HR 0.44, 95% CI 0.25–0.76, $p = 0.0034$) in patients with mild and moderately severe initial deficits.[81]

Early trials of aspirin in TIA and presumed minor ischaemic stroke, which did not employ brain imaging, demonstrated reductions in poor outcomes, although most patients had not been enrolled in the acute phase.[82]

In a systematic review of published trials comparing any antiplatelet agent with control, among patients with any acute intracranial haemorrhage (1997 patients), the OR for death among patients allocated to antiplatelet treatment compared with control was 0.85 (95% confidence interval, CI, 0.63–1.15)[83] and for recurrent intracranial haemorrhage was 1.00 (95% CI 0.73–1.37). The corresponding ORs for patients with intraparenchymal cerebral haemorrhage were 0.96 (0.62–1.5) and 1.02 (0.5–1.8), respectively, but 65% of these patients received only a few doses of antithrombotic treatment. Additionally, RESTART, a prospective, randomised, open-label, blinded endpoint, parallel-group trial of patients with intracerebral haemorrhage showed a benefit from anti-antiplatelet usage, without any signal of major bleeding risk. Twelve (4%) of 268 participants allocated to antiplatelet therapy had recurrence of intracerebral haemorrhage compared with 23 (9%) of 268 participants allocated to avoid antiplatelet therapy (adjusted hazard ratio 0·51 [95% CI 0·25–1·03]; $p = 0·060$). Eighteen (7%) participants allocated antiplatelet therapy experienced major haemorrhagic events compared with 25 (9%) participants allocated to avoid antiplatelet therapy (0·71 [0·39–1·30]; $p = 0·27$), and 39 [15%] participants allocated to antiplatelet therapy had major occlusive vascular events compared with 38 [14%] allocated to avoid antiplatelet therapy (1·02 [0·65–1·60]; $p = 0·92$).[84]

Notably in the RESTART study less than 5% of patients were treated in the first week after ICH and over 45% had moderate to severe disability at randomisation (ie a different profile and timeline to treatment to most suspected TIA cases).

The Keir et al. meta analysis examined safety of anti-thrombotic therapy including antiplatelet treatment for a range of durations and not exclusively in the hyperacute (within24 hour) time frame that would be most relevant to this PICO question.

Recommendation

In patients suspected of TIA, if a wait of more than 24 hours to planned imaging is foreseen and a delay is judged to increase the risk of further ischaemic events, above the risk of starting antiplatelet medication, we suggest "de novo" antiplatelet monotherapy usage compared to not starting antiplatelet monotherapy.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Weak for intervention ↑

Additional information. In patients with suspected TIA, brain imaging should be done urgently and antiplatelet treatment started without delay. If brain imaging is delayed, the available evidence suggests that the benefit of beginning antiplatelet treatment prior to brain imaging exceeds risks associated with intracranial haemorrhage. However, access to very early specialist assessment and to immediate brain imaging, for patients with suspected TIA varies greatly between healthcare systems. In some, it is routine for patients to be sent to an emergency department where they can access both 24/7. However, in other health systems with limited access to imaging a delay in initiation of antiplatelet treatment while awaiting imaging risks worsening patient outcomes.[9]

Specific national and regional resources and their limitations need to be considered in choosing optimal imaging strategies.

MRI has diagnostic and prognostic utility in suspected TIA however obtaining a timely MRI in all patients may not be feasible due to technical or infrastructural reasons. Witholding an anti-platelet in the acute phase following TIA while awaiting a MRI may not be justified based on available evidence, even in the presence of microbleeds as increasingly it is reported that microbleeds are not only markers of bleeding propensity but also markers of future ischemic events.

8. In patients with non-cardioembolic acute TIA does dual antiplatelet therapy (DAPT) compared to monotherapy reduce the risk of stroke recurrence?

Analysis of current evidence. Our literature search identified four RCTs[10,11,19,85] which tested DAPT in patients with TIA in the acute phase and a prespecified subgroup analysis from a RCT.[86] Three RCTs tested the combination of aspirin and clopidogrel versus aspirin alone and one RCT tested aspirin and ticagrelor versus aspirin in patients within 24 hours of a high-risk TIA, or minor ischaemic stroke. The subgroup analysis of the RCT tested aspirin and ticagrelor versus aspirin.[86]

The RCTs that tested DAPT with aspirin and clopidogrel have been included in a recent meta-analysis of both published and unpublished data.[87]

The three trials included a total of 10,447 patients. Compared with aspirin alone, dual antiplatelet therapy with clopidogrel and aspirin given within 24 hours after high risk TIA or minor ischaemic stroke, reduces all non-fatal recurrent stroke by about 19 in 1000 population, with a possible increase in moderate to severe extracranial bleeding of 2 per 1000 population.[87]

- reduced the risk of non-fatal ischaemic stroke (RR 0.69, 95% CI 0.60 to 0.79, I2 = 0%, absolute reduction 2.0%, high quality evidence).
- Trend to increased risk of symptomatic non-fatal intracranial haemorrhage (RR 1.27, 95% CI 0.55 to 2.89, I2 = 0%, moderate quality evidence).
- reduced the net combined outcome of non-fatal recurrent ischaemic or haemorrhagic stroke (RR 0.70, 95% CI 0.61 to 0.80, I2 = 0%, absolute risk reduction of 1.9% (high quality evidence).
- Trend to increased risk of non-fatal moderate or severe extracranial bleeding (RR 1.71, 95% CI 0.92 to 3.20, I2 = 0%, an absolute risk increase of 0.2% (moderate quality evidence).
- Trend to increased risk of all-cause mortality (RR 1.27 95% CI (0.73 to 2.23) (moderate quality evidence) (Table 8).

Ischaemic stroke dominated all stroke events and was more common than haemorrhagic stroke (total of 786 ischaemic strokes, 23 haemorrhagic strokes). The CHANCE and POINT trial investigators provided previously unpublished data, including the time from randomisation to events in the two treatment arms. This allowed incidence curves for stroke to be constructed, and further analyses to determine the balance of risk and benefit for different durations of DAPT.[87] Most stroke events, and the separation in stroke incidence (including both ischaemic and haemorrhagic strokes) curves between aspirin and clopidogrel arm and aspirin alone arm, occurred within 10 days of randomisation; conversely the separation in incidence of bleeding continued to increase throughout the treatment period. There was no net benefit from continuing treatment beyond three weeks. Moreover, large RCTs of aspirin and clopidogrel vs antiplatelet monotherapy in the chronic phase, including the CHARISMA,[88] SPS2[89] and MATCH[90] trials have not shown any net benefit, because any reduction in ischaemic events has been largely offset by bleeding.[91]

The subgroup analysis that was found was derived from the SOCRATES (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) RCT.[86] SOCRATES compared ticagrelor with aspirin in patients with acute ischemic stroke (NIHSS $\leq$5) or transient ischemic attack ($ABCD^2$ $\geq$4) (n = 13,199). Primary end point was time to stroke, myocardial infarction, or death.

In a prespecified subgroup analysis it was hypothesized that aspirin intake before randomization could enhance the effect of ticagrelor by conferring dual antiplatelet effect during a high-risk period for subsequent stroke. Therefore, the efficacy and safety of ticagrelor versus aspirin in the patients who received any aspirin the week before randomization was analysed.

In this secondary analysis from SOCRATES, fewer primary end points occurred on ticagrelor treatment than on aspirin in patients receiving aspirin before

randomization (HR, 0.76; 95% CI, 0.61–0.95; P = 0.02), but there was no significant treatment-by-prior-aspirin interaction.

This hypothesis was further explored in the THALES study.[85]

In the THALES study[85] patients with TIA or minor stroke were randomised to receive either ticagrelor plus aspirin or matching placebo plus aspirin. The risk of the composite outcome of stroke or death within 30 days was lower with ticagrelor and aspirin than with aspirin alone, but the incidence of disability did not differ significantly between the two groups. Effects are similar to those seen with clopidogrel and aspirin, but have been demonstrated in only one RCT to date. In a subgroup analysis including only TIA patients, no significant difference was found between the two treatment arms of the THALES study for the composite outcome, HR 0.80 (95%CI 0.42–1.52). Severe bleeding was more frequent with ticagrelor and aspirin than in the aspirin group (P = 0.001).

Patients with lower risk TIAs, or where the diagnosis of TIA is uncertain, were not included in the acute phase RCTs testing dual antiplatelet therapy with aspirin and clopidogrel, or aspirin and ticagrelor.

Recommendation

In patients with acute non-cardioembolic high risk TIA (ABCD2 score of 4 or more), we recommend short term dual antiplatelet therapy with aspirin and clopidogrel over monotherapy, subsequently followed by monotherapy.

Quality of evidence: High ⊕⊕⊕⊕

Strength of recommendation: Strong for intervention ↑↑

Additional information. About fifty patients need to be treated with aspirin and clopidogrel for three weeks instead of monotherapy, to avoid one stroke.

Five hundred patients treated with aspirin and clopidogrel for three weeks compared with monotherapy will cause one to have a moderate to severe extracranial bleed.

Which patients this applies to:

These results apply to patients that have high risk TIAs according to the definition that was used in the CHANCE and POINT trials (ABCD2 score of ≥4).

More studies are needed to establish if the results of these RCTs also apply to acute TIA patients with other features suggesting a high early risk of stroke (eg significant ipsilateral large artery disease eg carotid stenosis, intracranial stenosis, weakness or speech disturbance for greater than five minutes, recurrent events or with infarction on neuro-imaging).

Patients should have brain imaging to exclude acute intracranial bleeding, or other causes of symptoms, prior to starting DAPT.

Dual antiplatelet therapy with aspirin and clopidogrel should be started as soon as possible, and ideally within the first twenty-four hours.

When starting either aspirin or clopidogrel we suggest giving a single loading dose (at least 150 mg of aspirin, and 300 mg of clopidogrel) before switching to a daily maintenance dose.

The CHANCE study used clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days in comparison to placebo plus aspirin (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. In the POINT study, patients in the clopidogrel plus aspirin group were given a 600-mg loading dose of clopidogrel, followed by 75 mg per day from day 2 to day 90, and a dose of open-label aspirin that ranged from 50 mg to 325 mg per day. Patients in the aspirin-only group received placebo that matched the appearance and taste of the clopidogrel tablets and the same range of aspirin doses. In the two groups, the dose of aspirin was selected by the treating physician. A dose of 162 mg daily for 5 days followed by 81 mg daily was recommended in the POINT study to investigators. The first dose of trial medication was to be given as soon after randomization as possible.

Patients with high grade carotid stenosis and planned revascularisation were excluded from POINT, CHANCE and THALES.

In the FASTER study, all patients were given 81 mg aspirin daily for the study duration, with a loading dose of 162 mg if they were naïve to aspirin before study enrolment. In addition, patients were randomly assigned in a 2 × 2 factorial design to either placebo or 300 mg clopidogrel loading dose immediately followed by 75 mg clopidogrel daily.

In patients already taking either aspirin or clopidogrel alone, we suggest continuing with the maintenance dose of that medication, and loading with the other, before continuing both medications at their maintenance dose.

Between 10 days and three weeks after starting dual antiplatelet therapy (DAPT) we suggest stopping one of the antiplatelet medications, and thereafter continuing the other antiplatelet as monotherapy based on local protocols and patient preference.

In the THALES study patients with TIA or minor stroke were given either ticagrelor (180 mg loading dose followed by 90 mg twice daily) plus aspirin (300 to 325 on the first day followed by 75 to 100 mg daily) or matching placebo plus aspirin.

Patients in the THALES trials were considered to have a high-risk TIA if they had an ABCD2 $\geq$ 6 or a symptomatic intracranial or extracranial arterial stenosis ($\geq$50% narrowing in the diameter of the lumen of an artery that could account for the TIA).

Patients with high grade carotid stenosis and planned revascularisation were excluded from POINT, CHANCE and THALES.

DAPT with ticagrelor and aspirin could be considered as an alternative DAPT regime in patients for whom clopidogrel and aspirin is not an option and with an ABCD2 score of $\geq$6 or symptomatic intracranial or extracranial arterial stenosis ($\geq$50% narrowing in the diameter of the lumen of an artery that could account for the TIA) according to the criteria used in the THALES trial to define high risk TIA.

An actively recruiting RCT (CHANCE-2) is seeking to assess the effects of ticagrelor plus aspirin versus clopidogrel plus aspirin on reducing the 3-month risk of any stroke (both ischemic and haemorrhagic, primary outcome) when initiated within 24 hours of symptom onset in patients with TIA or minor stroke and a specific genetic variation related to drug metabolism via cytochrome P450 (CYP2Y19 loss of function alleles carriers).[92]

Expert consensus statement

For patients with acute non-cardioembolic low risk TIA or uncertain TIA diagnosis, 9/9 experts voted against using dual antiplatelet therapy over monotherapy.

Discussion

The highest level of evidence was found for recommendations associated with secondary prevention treatment with dual antiplatelets. Overall, we obtained low evidence levels for recommendations regarding clinical care service organization and patient evaluation.

Most studies identified in the literature (including the RCTs) used a clinical definition of TIA. This shows that a clinical definition is still the most widely used definition in research and clinical practice, which is important for generalising the findings of these studies.

The available data show the importance of timely recognition of symptoms, assessment and commencement of secondary prevention following a TIA. Prompt assessment of patients with early initiation of secondary prevention was associated with a lower risk of stroke recurrence.

We did not find RCTs directly comparing early evaluation of TIA patients in different medical care setting (emergency department, TIA clinic, and hospital admission). The EXPRESS study TIA clinic model was associated with cost effectiveness compared to appointment-based clinic reviews.[5] However, the overall cost of interventions and long-term safety of different secondary prevention regimens and models of investigation in a variety of settings remains unclear.

Accurately identifying high risk TIA patients may be helpful in decisions relating to initial triage for assessment and treatment. The ABCD2 score, with a threshold of 4 or more, has been used in RCTs of DAPT to identify high risk patients and has good discrimination properties when used in primary care to identify patients at highest risk of stroke within 7 days of TIA. However, in view of the limited sensitivity of prediction scores or robust data to support their diagnostic properties, triage and treatment decisions should not be based on the use of prediction scores alone.

Early access to imaging and cost of CT and MRI varies across different health systems. Non-contrast brain CT shows ischaemic changes in less than 10% of patients. Advanced imaging such as MR (multimodal) or CT perfusion can identify acute ischaemic lesions after transient neurological symptoms and thus may accurately confirm ischaemic pathophysiology and help identify ischaemic mechanism. The overall benefit and cost-effectiveness of different imaging approaches in suspected TIA requires further research.

Our analyses of the currently available evidence show that early initiation of DAPT with aspirin and clopidogrel in high risk non-cardioembolic TIA patients for up to 21 days reduces the risk of stroke recurrence over single antiplatelet treatment. These results apply to patients that have high risk TIAs according to the definition that was used in the CHANCE and POINT trials (ABCD2 score of $\geq$4). More studies are needed to establish if the results of these RCTs also apply to TIA patients with other features suggesting a high early risk of stroke (e.g. significant ipsilateral large artery disease e.g. carotid stenosis, intracranial stenosis, weakness or speech disturbance for greater than five minutes, recurrent events or with infarction on neuro-imaging).

In clinical trials DAPT was started within 24 hours from symptoms onset in high-risk non-cardioembolic TIA (ABCD2 score of $\geq$4). The evidence base for maximal benefit-risk balance is with early and time limited (10 to 21 days) use of DAPT. An actively recruiting RCT (CHANCE-2) seeks to answer remaining questions regarding different DAPT regimens.[92] This current guideline only addressed selected issues related to TIA management. However, it is important to highlight that TIA secondary prevention also includes medium and longer-term pharmacological and non-pharmacological measures that aim to control risk

factors for late vascular events. Although prompt and targeted evaluation for symptomatic carotid stenosis is a key aspect of TIA evaluation, other investigations to determine TIA aetiology and risk factor are required, such as assessment for atrial fibrillation to guide optimal secondary prevention.

For the current recommendations, our working group defined stroke recurrence as the outcome with the highest importance. However, this may not be the outcome that patients may consider as the most relevant. Outcome measures for future studies will need to reflect patients' priorities and patient engagement in agreeing such outcomes is required.

Future challenges and areas that merit further research include treatment of recurrent TIA, utility of telemedicine in TIA management and TIA assessment in resource-limited settings.

Additional comparative-effectiveness studies and RCTs investigating the effect of different imaging techniques, models of care, and triage strategies, prediction tools (clinical and imaging-based tools) and diagnostic scores on clinical outcomes are required. RCTs investigating, optimal secondary-prevention approaches in very old adults (>80 years) and management of low-risk TIA are also needed.

Public health strategies to improve early recognition of TIA in members of the general public are also needed to optimise stroke prevention after TIA.

Plain language summary

A transient ischaemic attack or TIA (also known as a mini-stroke) is similar to a stroke except that the symptoms last for a short amount of time. A TIA may act as a warning for a more serious and disabling stroke and it is a frequent reason that people seek medical care. Recognition of the significance of TIAs allows for prompt specialist treatment, which may include medications to reduce the risk of subsequent stroke.

For some people with a high risk of a stroke, and whose TIA is not due to a heart problem' taking two medicines together as tablets (Aspirin and clopidogrel), within the first day after a TIA and for up to 3 weeks afterwards, can reduce the risk of stroke.

For every 50 'at-risk' patients treated in this way, one patient will avoid having a recurrent stroke.

For someone who has had a TIA, it is recommended that they have a specialist review in a TIA clinic within the first day of the TIA, rather than waiting for more than a day to attend a regular outpatient appointment.

Healthcare professionals will sometimes use simple equations, known as risk prediction tools, to help them assess who is most at risk of a subsequent stroke. However, these prediction tools should not be the only way in which the risk is assessed. TIA is a clinically based diagnosis and calculated prediction scores should not replace a clinical assessment where a diagnosis is made by an experienced stroke-specialist healthcare professional.

Brain scans using a specialist CT or an MRI scanner may help to confirm that temporary neurological symptoms are indeed due to a TIA. These specialist scans are considered more useful than a standard CT brain scan, however these advanced scans may not always be possible to perform in every location.

When diagnosing a TIA, it is important to try to see if there is any narrowing of certain large blood vessels in the brain. Blood tests that are done in conjunction with a brain scanner e.g. MRA (an MRI based blood vessel test) or CTA (a CT based blood vessel test also known as an angiogram) should be available to help detect any narrowing and to decide the best course of treatment.

It is still not known which is the best healthcare setting to treat TIA. Large research studies are needed to compare TIA treatment, in for example, a TIA clinic, or on a stroke unit, or in an emergency department etc., to see which of them is the most useful and cost effective in preventing stroke.

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