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**European Academy of Neurology – European Stroke Organisation
consensus statement and practical guidance for pre-hospital
management of stroke**

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ABSTRACT

Reduction of delay between onset and hospital arrival and adequate pre-hospital care of persons with acute stroke are important for improving chances of a favorable outcome. The objective is to recommend evidence-based practices for the management of patients with suspected stroke in the pre-hospital setting.

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to define the key clinical questions. An expert panel then reviewed the literature, established the quality of the evidence, and made recommendations.

Despite very low quality of evidence we strongly recommend educational campaigns to increase awareness of immediately calling emergency medical services. We found moderate quality evidence to support strong recommendations for the training of emergency medical personnel in recognizing the symptoms of a stroke, and implementation of a pre-hospital 'code stroke' including highest priority dispatch, pre-hospital notification, and rapid transfer to the closest 'stroke-ready' center. We found insufficient evidence to recommend a pre-hospital stroke scale to predict large vessel occlusion. Despite very low quality of evidence we recommend restoring normoxia in patients with hypoxia, and refrain from blood pressure lowering drugs and treating hyperglycemia with insulin. There is insufficient evidence to recommend the routine use of mobile stroke units delivering intravenous thrombolysis at the scene. Because only feasibility studies have been reported, no recommendations can be provided for pre-hospital telemedicine during ambulance transport.

These guidelines inform on the contemporary approach to patients with suspected stroke in the pre-hospital settings. Further studies, preferably randomized controlled trials, are required to examine the impact of particular interventions on quality parameters and outcome.

Introduction

Stroke is a leading cause of disability in adults and a major cause of death and disability. Specific therapies for acute stroke are most effective when initiated the sooner after symptom onset. This requires rapid clinical assessment and brain imaging.

Intravenous thrombolysis with recombinant tissue plasminogen activator is effective in acute ischemic stroke up to 4.5 hours of symptom onset, and recent trials have shown significant additional benefits of thrombectomy in patients with large vessel occlusion [1, 2]. As time is critical for improving outcome, appropriate pre-hospital assessment and management of persons suspected with acute stroke are important for reducing delays for revascularization therapies, and in the meantime limiting secondary brain damage during transport.

The purpose of this clinical guideline is to develop recommendations for the management of persons with suspected acute stroke from the scene to the hospital.

Methodology

A working group consisting of experts in acute stroke medicine and neurology, an expert on guideline methodology, and a representative of the European patient organization Stroke Alliance for Europe was proposed by the Stroke Scientist Panel of the former European Federation of Neurological Sciences (EFNS), the European Stroke Organisation (ESO) Guidelines Committee, and the Subcommittee for Cerebrovascular Diseases of the former European Neurological Society (ENS).

The Guideline was developed in concordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [3]. The work of this task force was set up during a stage when the recent standard operating procedures for writing Guideline Documents of the ESO and European Academy of Neurology (EAN) were not yet effective [4, 5].

During a first meeting, the members of the working group established a consensus on 14 specific PICO (patient, intervention, comparator, outcome) questions. For each PICO question two members were assigned to perform a literature search using relevant MeSH terms. A search of MEDLINE, EMBASE and the Cochrane Library was performed up to March 2016. Language restrictions were not applied. Conference reports and case reports were excluded.

All selected articles were cross-referenced to make certain that no relevant studies were excluded. References cited in the selected articles were checked for further relevant articles not identified by the electronic searches. Two reviewers read all identified papers and disagreements were resolved through discussion. When a recent systematic review was available to answer a PICO question, only the literature after publication of the systematic review was further assessed. During a second meeting of the working group, the quality of evidence was derived, and strength of recommendation was decided by consensus. Quality of evidence was graded as high, moderate, low or very low [3]. A summary of findings table to obtain an overall effect estimate is only presented when homogenous RCTs were available. For a number of PICO question, we add an "additional information" box just after the recommendation box.

Results

The recommendations for each PICO question are summarized in table 1.

Rapid recognition of stroke

PICO 1. In people with suspected acute stroke, do educational interventions aimed at the general public increase the likelihood of immediately calling emergency medical services (EMS)?

We did not find RCTs investigating the effect of educational interventions on the interval between onset of symptoms and EMS call. A related but indirect outcome, reduction in pre-hospital delay, was recently assessed in a systematic review [6], including 13 studies. Only one, the Berlin Acute Stroke Study, was a cluster RCT [7]. The educational intervention consisted of a letter indicating stroke symptoms and emphasizing the need to call EMS immediately, accompanied by a sticker with main stroke symptoms and the telephone number of the EMS. A total of 75,720 households received the intervention. The intervention was found to be effective in reducing pre-hospital delays in women but not in men. However, the study had several limitations, including a limited precision of time assessments. The other studies were before and after studies, or observational studies. Ten studies reported a statistically significant reduction in pre-hospital delay following the educational intervention. Heterogeneity and methodological weaknesses limit a proper meta-analysis and generalizability of the observed effects. The working group decided to give a strong recommendation despite the very low quality of evidence, because the possible benefit of early recognizing stroke symptoms by the general population and of immediate EMS call clearly outweighs any possible

harm. Sustained campaigns should remain the cornerstone to educate the general population in recognizing stroke symptoms and the need to call EMS immediately.

Recommendation

We recommend educational campaigns to increase the awareness of immediately calling EMS for people with suspected stroke.

(strong; very low quality of evidence)

PICO 2. For EMS technicians and paramedics, are simple pre-hospital stroke scales useful to identify potential stroke patients?

We identified a recent systematic review, examining the accuracy of recognizing pre-hospital stroke patients using the QUADAS-2 tool. The following simple stroke scales were included: the Face Arm Speech Test (FAST), Cincinnati Pre-Hospital Stroke Scale (CPSS), Los Angeles Pre-Hospital Stroke Screen (LAPSS), Melbourne Ambulance Stroke Screen (MASS), Medic Prehospital Assessment for Code Stroke (Med PACS), Ontario Prehospital Stroke Screening Tool (OPSS), and Recognition of Stroke in the Emergency Room (ROSIER) [6]. All of the above were observational studies and excluded studies in which physicians were involved in pre-hospital application of the stroke scale. Pre-hospital stroke scales varied in their accuracy and globally missed up to 30% of acute strokes in the field. All stroke scales had a high sensitivity, ranging from 74 to 97%. Specificity of the comparable FAST (13%) and CPSS (24-79%) was lower than scales including more items, such as LAPSS (85-97%), MASS (74-86%), and OPSS (86%), with exception of Med PACS (33%) and ROSIER (18%). Despite the low quality of evidence we issued a strong recommendation because the possible benefit of identifying potential stroke victims clearly outweighs any possible harm and the associated resource use is minimal.

Recommendation

We recommend that all EMS technicians and paramedics are familiar with a simple pre-hospital stroke scale to identify potential stroke patients. No specific scale can be recommended.

(strong; low quality of evidence)

Additional information

Current simple pre-hospital stroke scales are not sensitive for detecting posterior circulation stroke.

PICO 3. For EMS technicians and paramedics, are pre-hospital stroke scales useful for predicting large vessel occlusion?

A retrospective analysis of 2 databases including 119 patients reported that a hospital score ≥ 4 on the Los Angeles Motor Scale predicted presence of large artery anterior circulation occlusion with high sensitivity (81%) and specificity (89%) [7]. However this has not been prospectively validated. The Rapid Arterial Occlusion Evaluation (RACE) scale was validated prospectively in the pre-hospital setting by trained EMS technicians in 357 consecutive patients in a single comprehensive stroke center study. Large vessel occlusion was diagnosed by transcranial duplex, CT angiography, or MR angiography. A RACE scale score ≥ 5 had a sensitivity of 85%, specificity of 68%, positive predictive value of 42%, and negative predictive value of 94% for detecting large artery anterior circulation occlusion [8]. There is insufficient evidence that these stroke scales could be useful instruments for selecting stroke patients for direct transport to comprehensive stroke centers.

Recommendation

There is insufficient evidence to recommend a pre-hospital stroke scale to predict large vessel occlusion.
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Rapid stabilization of vital parameters

PICO 4. In people with suspected acute stroke who are hypoxic, does pre-hospital O₂ administration compared to no O₂ administration improve outcome?

Studies investigating in-hospital routine O₂ therapy started < 24 hours after stroke onset (2 or 3 L/min for 24 - 72 h), although showing slight improvement in neurological status 7 days after stroke onset, failed to show a benefit in terms of long-term survival and independence [9-11]. No RCT has compared O₂ administration versus no O₂ administration in persons suspected with acute stroke in the pre-hospital setting. Hypoxia should be avoided because it may amplify ischemic brain damage and worsen outcome [12]. Although there are no supportive RCTs, the working group decided to follow the guidelines published by the British Thoracic Society (BTS) advocating titrated oxygen therapy [13].

Recommendation

In patients with SaO₂ levels < 95% we suggest the administration of O₂ titrated to maintain normoxia. Routine use of O₂ is not recommended.

(weak; very low quality of evidence)

PICO 5. In people with suspected acute stroke, does pre-hospital high blood pressure reduction compared to no intervention on blood pressure improve outcome?

Both hypertension and marked hypotension are associated with poor outcome after stroke [14], and there is considerable clinical uncertainty as to the optimal management of blood pressure acutely after stroke. There are 2 small single center feasibility RCTs in pre-hospital acute stroke patients who were hypertensive (systolic blood pressure ≥ 140 mm Hg or > 160 mmHg) assessing safety and outcome of antihypertensive therapy. The Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial and the Paramedic Initiated Lisinopril for Acute stroke Treatment Trial showed that it was feasible of performing an ambulance-based paramedic-delivered trial of BP lowering in patients with acute stroke (< 4 hours of stroke onset) [15, 16]. Both of the trials selected immediate blood pressure lowering effect as primary outcome. Due to the small size of the studies (55 patients recruited in total) no conclusions on safety, efficacy and outcome could be drawn from this study. Even for systolic blood pressures ≥ 185 mm Hg, which may prolong door to needle time, urgent pre-hospital antihypertensive treatment by paramedics holds a risk for sudden drops of the blood pressure, therefore treatment of high blood pressure in the pre-hospital phase should be avoided.

Recommendation

We do not recommend pre-hospital treatment of high blood pressure in people suspected with acute stroke.

(weak; very low quality of evidence)

PICO 6. In people with suspected acute stroke, does pre-hospital treatment of hyperglycemia with insulin compared to no treatment improve outcome?

Blood glucose should be measured in every patient with suspected stroke because symptoms of hypoglycemia can mimic those of a stroke. Hypoglycemia (< 60 mg/dl or < 3.3 mmol/l) needs to be treated with glucose 20%-40% in 25-50 ml infusion [17].

People with hyperglycemia concomitant with large vessel acute ischemic stroke have greater mortality, stroke severity, and functional impairment when compared with those with normoglycemia. However, this has not been found in patients with a lacunar stroke [18, 19]. We identified only one small feasibility study dealing with lowering glucose in acute stroke patients in the pre-hospital setting [20]. In this study, patients with stroke symptoms and plasma glucose > 108 mg/dl or 6.0 mmol/l were randomized during the pre-hospital phase to receive either a single subcutaneous dose of short-acting insulin (n = 11) or a continuous intravenous insulin infusion (n = 12) at a rate adjusted by glucose levels measured every 10 minutes and targeted to plasma glucose 4.5-6.0 mmol/l. Plasma glucose levels were significantly decreased with no serious adverse events in the intravenously treated group in comparison to a nonrandomized control group (n = 38). The subcutaneous insulin administration did not achieve significant lowering of plasma glucose.

A systematic review showed that the in-hospital administration of intravenous insulin with the objective of maintaining serum glucose within a specific range in the first hours of acute ischemic stroke does not provide benefit in terms of functional outcome, death, or improvement in final neurological deficit, and significantly increased the number of hypoglycemic episodes [21]. Specifically, those people whose glucose levels were maintained within a tighter range with intravenous insulin experienced a greater risk of symptomatic and asymptomatic hypoglycemia than those people in the control group. The situation may, therefore, be even more risky in the pre-hospital phase.

Recommendation

<p>Because of safety concerns we do not recommend pre-hospital administration of insulin in persons with suspected stroke and hyperglycemia. <i>(weak; very low quality of evidence)</i></p>
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PICO 7. In people with suspected acute stroke, does pre-hospital lowering of elevated body temperature compared to no intervention on body temperature improve outcome?

Data of 5305 patients from the Virtual International Stroke Trials Archive data set showed that delayed hyperthermia was more strongly associated with poor outcome than elevated body temperature seen in the hours after stroke [22]. A prospective study in 725 patients also found that initial elevated body temperature in hyperacute ischemic stroke was not associated with worse outcome, but a rise in body temperature in severe strokes was related to poor outcome. It was concluded that elevated body temperature within 6 hours of stroke onset had no prognostic influence on stroke outcome at 3 months [23].

Antipyretic drugs and cooling methods can lower body temperature in stroke patients. However, no clinical studies have investigated pre-hospital treatment of elevated body temperature in acute stroke patients.

Recommendation

In the absence of clinical studies no recommendations can be made on pre-hospital interventions for lowering elevated body temperature
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Rapid care by a dedicated stroke-team

PICO 8. In patients with suspected acute stroke, does implementation of pre-hospital 'code stroke' protocols compared to no implementation of such protocols reduce onset to admission time, door to needle time, and frequency of thrombolysis?

The search revealed 43 citations, of which 9 studies, including 1 RCT, were considered relevant. The RCT, performed in the Stockholm area, compared the effect of upgrading the priority level at the Emergency Medical Communication Center (EMCC) from the standard level 2 (ambulance arrival at scene within 30 minutes unless no priority 1 alarms required that ambulance) to level 1 (immediate ambulance response) [24]. In the group randomized to level 1 there was a significant shorter delay (13 minutes) from EMCC call to arrival at the hospital ($P < 0.001$) and a significant increase in thrombolysis frequency (24% versus 10%; $P < 0.001$). The door to needle time was not significantly different as eligible patients from the control group were also prioritized at the emergency department.

Several observational studies have reported that pre-hospital notification of the receiving hospital without or with prioritized transport to designated hospitals with stroke expertise (bypassing the nearest hospitals) led to significantly shorter door to needle time or door to brain imaging time [25-32] and higher rates of intravenous thrombolysis [25, 26, 28-31]. Most studies compared findings either with findings from a historical control group (6) or with findings from a parallel observation of patients for whom no pre-notification intervention was used (2). In most studies improved pre-hospital management was also associated with improved in-hospital reorganization, indicating that pre-hospital 'code stroke' and in-hospital 'code stroke' are a continuum aimed at shortening onset to treatment time. A meta-analysis of these observational studies is not feasible because of different study designs and methodological approaches, and qualitative differences in regional EMS organization where the studies were performed. However, all studies consistently show that implementing a pre-hospital 'code stroke' protocol including priority EMS dispatch, rapid transport to the closest 'stroke ready' center (bypassing nearest hospitals that are not 'stroke ready'), and pre-arrival notification to the receiving hospital, leads to faster times to treatment and higher treatment rates.

Recommendation

We recommend that all EMS implement a 'code stroke' protocol, including highest priority dispatch, pre-hospital notification, and rapid transfer to the closest 'stroke-ready' center.

(strong; moderate quality of evidence)

PICO 9. In people with suspected stroke does pre-hospital telemedicine, compared to no telemedicine, improve outcome?

Telemedicine with real-time bidirectional audio-video communication between the ambulance and a stroke physician may enable early assessment of a patient with suspected stroke and might thereby reduce in-hospital delays to receive relevant treatment. 36 papers were identified. Pilot studies indicate that this approach is feasible [33, 34]. We did not find RCTs on whether pre-hospital telemedicine in acute stroke patients speeds up door to treatment time and improves outcome. Only one observational study compared door to imaging time in patients that received pre-hospital telemedicine (n=16) versus controls (n=42). No statistically significant difference was found between door to imaging time in patients that

received pre-hospital telemedicine: median [IQR] – 59.5 [67.5] minutes versus controls 57.5 [80] minutes, $p=0.65$ [33].

Recommendation

No recommendation on the additional value of pre-hospital telemedicine can be made.

PICO 10. In patients with acute stroke, does the use of mobile emergency stroke units, compared to no use of such means, improve outcome?

Studies with mobile emergency stroke units, which are specialized ambulances staffed by a neurologist/physician or nurse, paramedic/emergency medical technician, and radiology technician, and equipped with a CT scanner, point-of-care laboratory, and telemedicine connection. Thrombolysis was administered at the scene. The search revealed 3 relevant studies: 2 RCTs [35, 36], and 1 small observational study [37]. Studies were unblinded and specific to the local setting

Grading of the quality of evidence was based on the 2 RCTs comparing mobile emergency stroke unit intervention with hospital intervention (GRADE table in appendix). In the mobile emergency stroke unit group, rate of thrombolysis was increased (OR 1.79; 95% CI: 1.44 to 2.33), with a median reduction in call to needle time of 24 to 34 minutes and a median reduction in onset to needle time of 24 to 81 minutes. No safety concerns have been raised. There was no increase in symptomatic intracranial hemorrhage (OR 0.59; 95%CI: 0.25 to 1.38) in the mobile emergency stroke unit group. However, there were insufficient data about functional outcome to determine effectiveness. Only one study investigated 7 day outcome [35]. There was no significant difference between the mobile emergency stroke unit group and control group in the number of patients who were independent defined as a mRS score < 3 . In the large PHANTOM-S trial [36], mean door to needle time in the control group receiving usual hospital care was 42 minutes, which could be further improved by reducing in-hospital delays. Two studies provided arguments in support of cost-effectiveness of mobile emergency stroke units [38, 39].

Recommendation

We do not recommend the routine use of mobile emergency stroke units because there is insufficient evidence that they lead to better functional outcome.
(weak; low quality of evidence)

Additional comments

Although the influence of mobile emergency stroke units on outcome of patients with stroke is uncertain, they can reduce onset to needle times for intravenous thrombolysis in patients with ischemic stroke, and can be an option for certain regions where traditional ambulance transport would result in significant delays.

PICO 11. In persons with suspected acute stroke, does the use of pre-hospital point-of-care (POC) laboratory analysis of blood count and International Normalized Ratio (INR), compared to no use of such means, speed up door to needle time in ischemic stroke or interventions to prevent worsening of hemorrhagic stroke?

Determination of the platelet count and INR is important in patients taking vitamin K antagonists, with liver dysfunction, hemorrhagic diathesis, or with an unclear medication history. Observational studies reported that measuring these parameters by POC testing in the Emergency Department, instead of awaiting central laboratory results, reduced door to needle time [40, 41]. No clinical trial has assessed whether pre-hospital POC analyses of INR and blood count have an additional effect in reducing door to needle time or improving management of hemorrhagic stroke.

Recommendation

No recommendation on the use of pre-hospital POC laboratory analysis of blood count and INR can be made.
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PICO 12. In persons with suspected acute stroke, can biomarkers accurately differentiate between ischemic stroke, hemorrhagic stroke, or a stroke mimic?

A comprehensive systematic review using QUADAS criteria for assessing the quality of studies found that no individual biomarker has adequate sensitivity and specificity for a clinical useful diagnostic test [42]. A number of studies have attempted a multi-marker panel approach in order to improve sensitivity and specificity. However, thus far none has been successful in a clinical setting. None of these studies were performed in a pre-hospital setting [42].

Recommendation

No recommendation can be made on the use of currently available biomarkers in persons with a suspected stroke.

PICO 13. In persons suspected with acute stroke, does air medical transport compared to ground transport improve outcome?

The search revealed 88 citations, of which only 1 observational study made an acceptable comparison to ground transport. This retrospective examination of the Austrian Stroke Unit Registry found that air transport was associated with greater thrombolysis activity compared to standard ambulance (OR 3.36; 95%CI 2.8-4.0) and physician ambulance (OR 1.45; 95%CI 1.2-1.7), and a mean 30 (95%CI 41 to 18) minutes less onset to hospital arrival time compared to standard ambulance, but not physician ambulance (5 minutes longer; 95%CI 1 to 9) [43]. However there was no information regarding air transport availability or the criteria used to trigger its dispatch in preference to ground transport when it was available.

Recommendation

We do not suggest air medical transport outside of settings where a pragmatic decision has been taken that geographical conditions favor air transport.
(*weak; very low quality of evidence*).

PICO 14. In acute stroke patients do pre-hospital neuroprotective therapies improve outcome?

We identified 3 RCTs of neuroprotective therapies initiated before hospital admission.

The first study was a randomized, controlled, double blind, placebo controlled study of oral nimodipine 30mg every 6 hours for 10 days in patients in whom treatment could be initiated within 6 hours of stroke onset [44]. There was no significant difference between the nimodipine group and the placebo group on the primary outcome, which was defined as death or dependency at 3 months.

The second study was a randomized, placebo controlled double blind study of intravenous infusion of magnesium sulphate started in the ambulance in both ischemic and hemorrhagic stroke [45]. The study included all stroke patients in

whom treatment could be initiated up to 2 hours after symptom onset. Active treatment did not decrease the risk of being dead or dependent 90 days after the stroke.

The third study was a placebo-controlled, open label study of remote ischemic preconditioning for ischemic stroke [46]. The primary endpoint was penumbral salvage, defined as the volume of the perfusion–diffusion mismatch not progressing to infarction after 1 month. The trial failed to show a difference between patients receiving remote ischemic preconditioning and not.

Recommendation

We do not recommend the use of any neuroprotective intervention in persons with suspected acute stroke in the pre-hospital setting.
(strong; high quality of evidence).

Discussion

A serious limitation of this guideline is the paucity of RCTs available on pre-hospital management of stroke. The GRADE system only allows grading of the strength of recommendation as strong or weak. This on one hand allows a clear statement on a specific PICO question, but on the other hand does not allow an intermediate recommendation in cases assumed to have insufficient data. For a number of PICO questions no recommendation could be given because of insufficient data. Based on consensus we did give a strong recommendation for some PICO questions for which no RCTs were available, for example when observational studies consistently showed a similar effect, or if the panel found that desirable consequences outweigh undesirable consequences, or if most or all patients would be best served by a particular management strategy.

Despite low quality of evidence we strongly support public educational campaigns to increase public awareness of immediately calling EMS for persons with suspected acute stroke. Studies were very heterogeneous, and the potential clinical benefit of public campaigns may be difficult to identify in a short-term follow-up. Further studies are required to find out which methods are most effective in successfully educating the general public about the urgency of stroke.

We found moderate quality of evidence to strongly support the training of EMS personnel in recognizing the symptoms of stroke using simple stroke scales, such as the FAST or LAPSS. No recommendation can be given for a specific stroke scale.

We found moderate quality of evidence to strongly support implementing a pre-hospital 'code stroke' system by the EMS, which includes highest priority ambulance dispatch, prioritized transport to the closest 'stroke-ready' center, and pre-notification of the receiving hospital. When possible, EMS should bypass hospitals that are not ready to immediately deliver appropriate acute stroke treatment. Pre-notification allows the stroke team to get ready before the patient actually arrives at the hospital.

Further studies are required to investigate whether pre-hospital stroke scales predicting large vessel occlusion might be used as a triaging tool to select stroke patients for direct transport to comprehensive stroke centers capable of endovascular interventions.

Very low quality of evidence is available for pre-hospital management of physiological parameters, such as treatment of hypoxia, management of blood pressure and hyperthermia. Nevertheless, we strongly recommend maintaining normoxia, and do not recommend the use of blood pressure lowering medication and the use of insulin in persons with suspected stroke and hyperglycemia, unless in cases of extreme urgency.

Preliminary studies using bi-directional audiovisual telemedicine during ambulance transport show that this method is feasible and may provide valuable information to the hospital stroke team. However, such intervention should not cause any delay in the pre-hospital stroke care pathways, and its additional value on top of existing pre-hospital 'code stroke' systems, including systematic pre-notification of the receiving hospital, will have to be supported by RCTs. In spite of recent studies reporting the feasibility of mobile emergency stroke units in delivering intravenous thrombolysis at the scene, there is currently no evidence that this costly intervention improves outcome. Mobile stroke units allowing CT angiography could be useful for the early identification of patients with large artery occlusion.

We found no evidence for the pre-hospital use of laboratory biomarkers in diagnosing stroke, POC laboratory analysis for blood count and INR, and neuroprotective therapies.

Disclosure of conflicts of Interest

GAF developed the FAST and ROSIER scales and was chief Investigator of the PILFAST study. JDK is involved in pre-hospital telemedicine studies.

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