

Synopsis of the National Institute for Health and Clinical Excellence Guideline for Management of Transient Loss of Consciousness

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Description: Transient loss of consciousness (TLoC) is common and often leads to incorrect diagnosis, unnecessary investigation, or inappropriate choice of specialist referral. In August 2010, the National Institute for Health and Clinical Excellence published a guideline that addressed the initial assessment of and most appropriate specialist referral for persons who have experienced TLoC. The guideline focused on correct diagnosis and relevant specialist referral and did not make treatment recommendations. This synopsis describes the principal recommendations concerning assessment and referral of a patient with TLoC.

Methods: The National Clinical Guideline Centre developed the guidelines by using the standard methodology of the National Institute for Health and Clinical Excellence. A multidisciplinary guideline panel generated review questions, discussed evidence, and formulated recommendations. The panel included a technical team from the National Clinical Guideline Centre, who reviewed and graded all relevant evidence identified from literature searches published in English up to November 2009 and performed health-economic modeling. Both guideline development and final modifi-

cations were informed by comments from stakeholders and the public.

Recommendations: The panel made clear recommendations regarding the assessment of a person after TLoC, which emphasized the importance of clinical reasoning in diagnosis. Persons with uncomplicated faint, situational syncope, or orthostatic hypotension should receive electrocardiography but do not otherwise require immediate further investigation or specialist referral. Persons with features that suggest epilepsy should be referred for specialist neurologic assessment; brief seizure-like activity was recognized as a common occurrence during syncope that should not be regarded as indicating epilepsy. Persons with a suspected cardiac cause for TLoC or in whom TLoC is unexplained after initial assessment should receive specialist cardiovascular assessment. Guidance was provided on the appropriate choices of cardiovascular investigation, according to the presenting clinical circumstances.

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Transient loss of consciousness (TLoC) is very common and affects one quarter to one half of the population in the United Kingdom at some point in their lives. A TLoC event, often described as a “blackout,” may be defined as a spontaneous, transient, loss of consciousness with complete recovery. The causes of TLoC include cardiovascular disorders (the most common causes); neurologic conditions, such as epilepsy; and psychological factors. The diagnosis of the underlying cause of TLoC is variable, with wrong diagnoses often leading to inaccurate, inefficient, and delayed care. The true burden of misdiagnosis is difficult to estimate, but Fitzpatrick and Cooper (1) report that 20% to 30% of persons thought to have epilepsy actually have an underlying cardiac cause of TLoC. A wrong diagnosis leads many persons to have inappropriate and excessive tests and can substantially affect quality of life (2). To address this issue and others, the National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom to review both clinical and cost-effectiveness evidence and produce guidance to improve the patient care pathway (3).

GUIDELINE FOCUS

The recommendations in the guideline focus on the initial assessment of persons who have experienced TLoC and present to any health care setting in the United Kingdom, including ambulance paramedics, emergency departments, and primary care. The guideline was commissioned

for use in the United Kingdom National Health Service, but NICE guidelines are commonly used by other providers, including volunteers and those in the private sector. The guideline also focuses on diagnosis and appropriate referral for specialist assessment and recommends appropriate choices for further assessment and investigation in secondary care. The full version of the guideline is available on the NICE Web site at <http://guidance.nice.org.uk/CG109/guidance/pdf>.

TARGET POPULATION

The guideline addresses TLoC in persons aged 16 years or older. It does not address those who have experienced TLoC as a result of physical injury (such as a head injury), collapse without loss of consciousness, or prolonged loss of consciousness without spontaneous recovery. The duration of loss of consciousness was not specified; however, by definition, spontaneous recovery of consciousness had occurred.

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GUIDELINE DEVELOPMENT PROCESS

The topic of TLoC was selected by using the process developed by NICE for topic selection and described in the methods paper in this series (4). The guideline was developed in accordance with the NICE guidelines manual (5).

An open process was used to recruit guideline panel members to bring together a range of health care professionals who are involved in caring for persons who present with TLoC across relevant settings. Patient representatives were also recruited. All applicants were asked to declare any potential conflicts of interests, and these were reviewed throughout development. Appendix B of the guideline, on the NICE Web site (3), contains full details of the declarations of each guideline panel member.

The guideline panel developed clinical questions at its first meeting, which led to the formulation of systematic review protocols. The clinical questions focused on the following:

1. Initial stage aspects of clinical history (including eyewitness accounts) before, during, and after TLoC; physical examination; and 12-lead electrocardiography (ECG) and other tests that are useful for discriminating among different causes of TLoC;

2. Initial stage symptoms and signs that are associated with an increased risk for adverse events (poor prognosis);

3. Risk stratification tools that may be used to discriminate between persons with TLoC who should be hospitalized or urgently referred for specialist assessment and those who can be discharged safely; and

4. Further diagnostic tests, including ambulatory ECG, carotid sinus massage, tilt-table tests, and exercise tests, for persons who did not receive a firm diagnosis in the initial assessment stage.

The guideline panel met regularly to review the evidence obtained from searches and health economic analyses. This evidence was presented by members of the technical team and used to formulate the recommendations. When evidence was not available or strong enough to guide decisions, recommendations were made on the basis of clinical consensus.

EVIDENCE REVIEW AND GRADING

Review protocols prespecified the population (including the suspected cause of TLoC and previous tests that study participants may have had); the index tests, prognostic factors, or risk stratification tools; the reference standard (or adverse outcome); and the target condition. The technical team produced search strategies for MEDLINE, EMBASE, CINAHL, PsycInfo, and the Cochrane Library; searched these databases up to 2 November 2009 with no date restrictions; and identified articles published in English that met the criteria in the protocols (3, 4). The search filters used for diagnostic reviews in evidence-based medicine are currently under development

and can be inefficient; they generated numerous abstracts sifted by reviewer and checked by another.

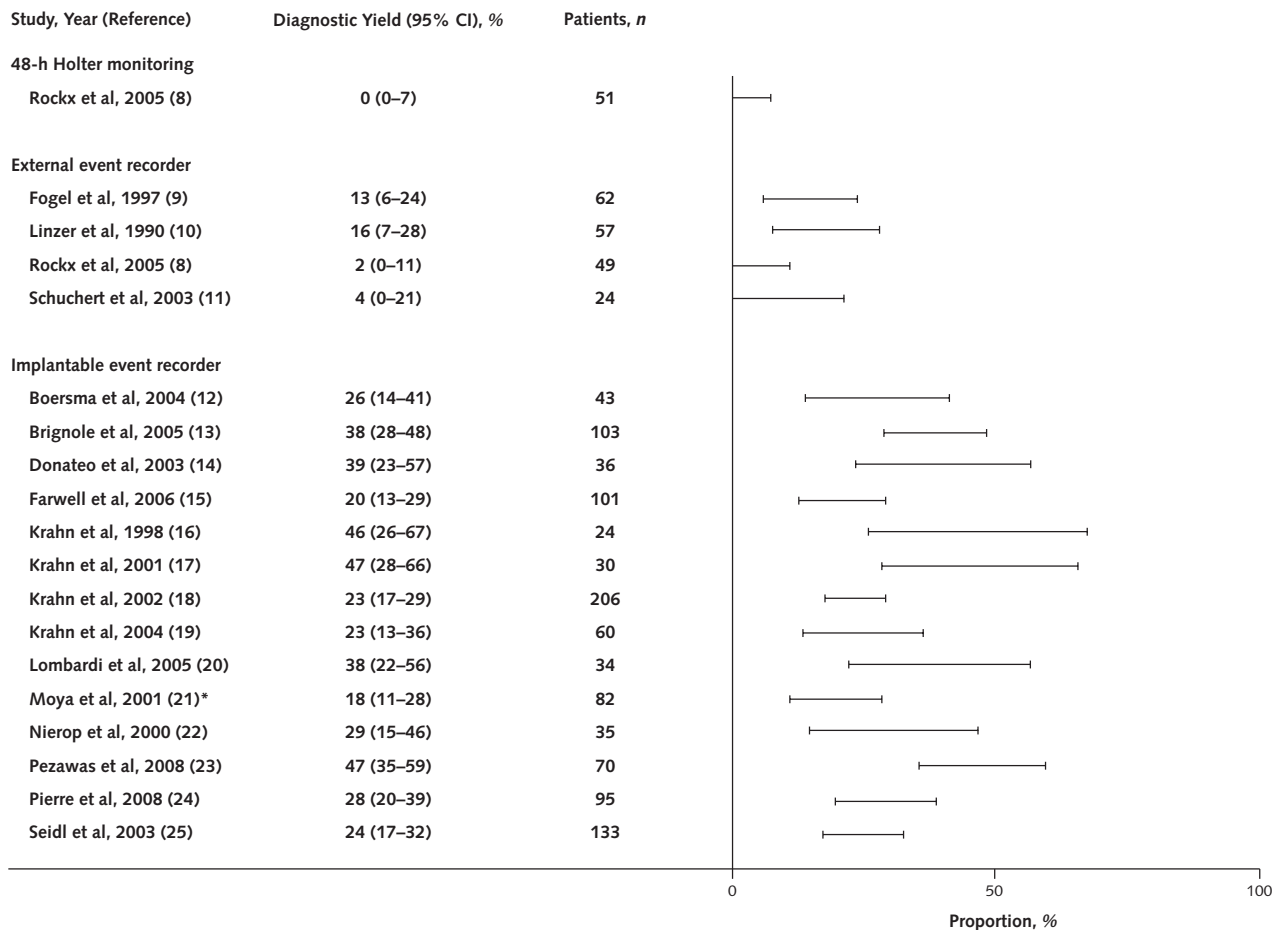
The technical team conducted 3 main types of systematic review. First, prognostic factor reviews for investigating signs and symptoms focused on prospective cohort studies with univariate or multivariate analyses, using the likelihood ratio (for prognosis) or the risk ratio (for adverse events). Second, reviews of the predictive accuracy of risk stratification tools and the accuracy of further diagnostic tests focused on sensitivity and specificity; studies were either cohort or case-control studies. Finally, diagnostic yield of ambulatory ECG tests was reviewed. Diagnostic test accuracy methods could not be used for these reviews because the reference standard was the same as the index test; study designs were mainly case series.

The technical team extracted data and assessed the quality of each study by using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool (6) or a prognostic quality assessment, as appropriate for the study design. The technical team also graded the overall quality of the evidence, on the basis of assessment of risk of bias; indirectness of the population, index test, and reference standard; imprecision around the estimates; and inconsistency among studies. This approach was based on that of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group (7), adapted for prognostic and diagnostic studies. Evidence quality was generally low. Results were presented in forest plots (Figure 1) (8–25) and, where appropriate, as summary receiver-operating characteristic curves (Figure 2).

Two priority areas were identified for health economic analysis: the role of ambulatory ECG in patients referred for specialist cardiovascular assessment after their initial assessment, including those in whom syncope is suspected to be due to cardiac arrhythmia and those with unexplained TLoC, and appropriate testing strategies (for example, tilt-table testing, ambulatory ECG, or sequences of these tests) for patients with suspected vasovagal syncope in whom pacemaker therapy is being considered.

The technical team reviewed the health economic literature and identified 3 studies, each of which had potentially serious limitations as a source of cost-effectiveness evidence (3). They therefore developed a *de novo* cost-effectiveness model to evaluate the costs and benefits of alternative recommendations in each of these priority areas. Modeling was carried out according to the NICE reference case for economic evaluations (26) by using the best available evidence. Benefits were measured in terms of quality-adjusted life-years gained, and cost was assessed from National Health Service and personal social services perspectives. The net present value of future costs and benefits was discounted at 3.5%. The importance of key model assumptions and data limitations was explored by using sensitivity analysis.

The guideline panel took the quality of the evidence into consideration when making recommendations. They

Figure 1. Diagnostic yield and 95% asymmetric CI for arrhythmia during transient loss of consciousness, by type of device.

Cause of loss of consciousness was unexplained after secondary testing.

* Unexplained; negative result on tilt-table testing.

were guided by the apparent size of any effect and by their clinical expertise and experience, including that of the patient representatives. The strength of the recommendation was reflected in their wording.

COMMENT AND MODIFICATIONS

As a standard part of the guideline development process, NICE called for organizations with an interest in the topic to register as stakeholders. Stakeholders are national or regional organizations that have an interest in TLoC and represent patients and carers, health care professionals, companies that manufacture medicines or devices, researchers in the topic, health care providers, or statutory bodies. The 114 organizations that registered were invited to submit comments on the initial scope of the planned guideline and on a draft version of the guideline that was posted on the NICE Web site in January 2010. Stakeholder names, comments, and responses are available on the NICE Web site (27). The guideline was modified in

light of comments received, and the final version was published in August 2010.

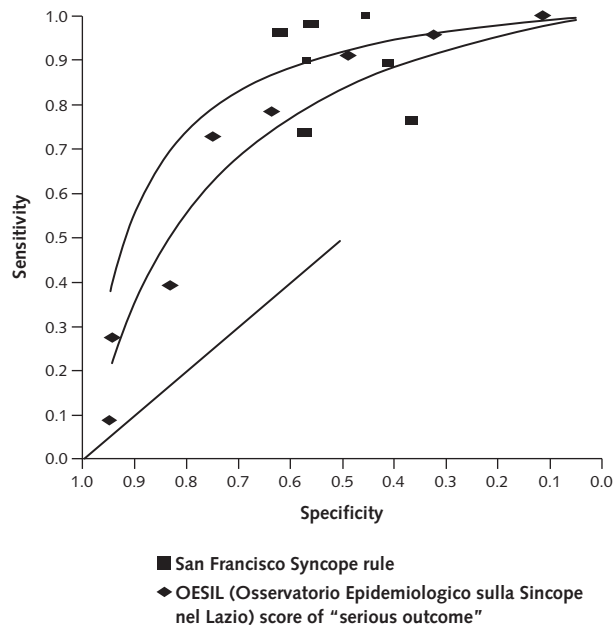
CLINICAL RECOMMENDATIONS

Evidence

Twenty-seven studies investigated prognostic factors or risk stratification tools for the initial stage assessment, identifying signs and symptoms that predicted causes of TLoC or serious adverse events. The guideline panel decided against recommending particular risk stratification tools. Fifteen studies reported on the use of 12-lead ECG findings in the initial stage assessment.

One hundred two studies investigated tests for further cardiovascular assessment, including 52 studies for ambulatory ECG and 41 for tilt-table tests. Seven studies investigated tests to direct pacing therapy and 3 studies compared the tilt-table test directly with ambulatory ECG for the diagnosis of cardioinhibitory syncope. The health economic model showed that ambulatory ECG is cost-

Figure 2. Receiver-operating characteristic curves for risk stratification tools for adverse events.



effective in patients with unexplained TLoC or suspected cardiac arrhythmic syncope who have been referred for specialist cardiovascular assessment, although patients who require an implantable event recorder incur a high initial cost. Tilt-table testing is probably the most cost-effective testing strategy for patients with suspected vasovagal syncope in whom pacemaker therapy is being considered.

Recommendations

The Table outlines the panel’s recommendations.

Initial Assessment

The guideline emphasizes the importance of a clear account that includes symptoms before, during, and after the TLoC event, as reported by both patients and witnesses, and addresses the specific aspects of the history that can help determine the cause of the event. In addition, a clinical examination should be done at the initial assessment of a person with TLoC, and 12-lead ECG is an essential, integral part of this assessment. The guideline panel reviewed the issue of ECG reporting and recommended an initial automated report, with subsequent expert review if the automated report identified a possible abnormality. The patient should receive a copy of the ECG and the report.

Diagnosing Uncomplicated Faints

An uncomplicated faint due to vasovagal syncope (sometimes previously referred to as “neurocardiogenic syncope”) is very common and can be diagnosed in many persons on the basis of a typical clinical history, in the

absence of any suspicion of heart disease from physical examination or ECG findings. Suggestive features include any of the “3 Ps”: posture, that is, occurrence during prolonged standing, or similar previous episodes that have been aborted by lying down; provoking factors, such as pain or a medical procedure; or prodromal symptoms, such as sweating or feeling warm or hot before TLoC.

Other relevant factors in the clinical history include the patient’s age and the period over which recurrent episodes have occurred. Persons who have an uncomplicated faint should not be subjected to unnecessary investigations, which may involve some risk (such as irradiation from computed tomography), cause anxiety and inconvenience, and result in unnecessary health care costs. Tilt-table testing is not necessary when the initial assessment indicates an uncomplicated faint.

Specialist Assessment for Epilepsy

Most episodes of TLoC have a cardiovascular cause. The guideline describes features that should raise a strong suspicion of epilepsy, and patients with these features should be referred for early assessment by a specialist in epilepsy. The diagnosis and management of epilepsy is addressed in a separate guideline (28). In the absence of clear pointers to epilepsy (or if the cause of TLoC is unclear), patients should initially undergo cardiovascular assessment and electroencephalography should not be requested. Brief seizure activity can occur during syncope (including vasovagal syncope); when the history is clearly one of syncope, this type of seizure activity does not require neurologic investigation or referral. The inappropriate use of electroencephalography in such patients may lead to misdiagnosis.

Urgent Specialist Referral

Some episodes of TLoC may be due to a serious condition that requires immediate treatment. For example, persons with TLoC in whom initial assessment reveals severe bradycardia due to atrioventricular block require urgent cardiac pacing, and persons in whom TLoC is the presenting symptom of severe internal bleeding require treatment for the underlying cause. Such persons need prompt treatment and no further assessment to find the cause of their TLoC.

Urgent specialist assessment and treatment must also be arranged for patients who have TLoC due to a cardiac condition that may place them at risk for severe adverse events, including sudden death. The guideline therefore recommends prompt cardiovascular assessment by a specialist for those in whom the history, physical signs, or ECG findings raise any suspicion of an inherited cardiac condition (such as the long QT syndrome), any other propensity for cardiac arrhythmia (such as TLoC during exercise, history or physical signs of heart failure, or ECG abnormality), or structural heart disease.

Further Cardiovascular Assessment

The guideline recommends further appropriate clinical assessments to identify cardiovascular disorders that may result in TLoC, including orthostatic hypotension, the carotid sinus syndrome, structural heart disease, and cardiac arrhythmia.

If structural heart disease is suspected, further assessment should include cardiac imaging, usually by echocardiography first. However, the guideline emphasizes that persons with structural heart disease may also have vasovagal syncope or TLoC due to orthostatic hypotension (usually because of drug therapy) or cardiac arrhythmia, in addition to the mechanical effects of the structural abnormality (such as severe aortic stenosis).

If cardiac arrhythmia is the suspected cause of TLoC or if the cause is unclear, ambulatory ECG recording is recommended as the next investigation. The choice of recording device should be dictated by the frequency of recurrent TLoC and by the 12-lead ECG findings. If the ECG shows a conduction abnormality, a 24- to 48-hour Holter recording may be used to look for asymptomatic severe atrioventricular block, which may require pacing on prognostic grounds and, when present, increases the probability that TLoC was due to atrioventricular block. In all other patients, the aim should be to obtain an ECG recording of cardiac rhythm at the time of another TLoC event. A device that requires operation by the patient to make a recording is inappropriate for assessment of TLoC. A brief period of Holter recording is unlikely to be helpful

unless episodes occur on almost a daily basis, but a longer period of continuous event recording is appropriate for patients with relatively frequent symptoms. An implantable event recorder is recommended if episodes occur only every few weeks or less frequently.

Tilt-table testing is not recommended as a first-line investigation for a person with unexplained TLoC. It should be reserved for patients with suspected vasovagal syncope who have recurrent episodes that adversely affect their quality of life or represent a high risk for injury, to assess whether the syncope is accompanied by a severe cardio-inhibitory response (usually asystole).

For suspected carotid sinus syncope or for unexplained syncope in persons older than 60 years, carotid sinus massage is the most appropriate initial investigation. This should be conducted in a controlled environment, with ECG recording, and resuscitation equipment should be available. Published risk data (29) suggest odds of slightly less than 1 in 1000 for adverse neurologic events, including transient ischemic attacks and stroke; however, because of the severity of the potential adverse event, informed consent should be obtained from the patient.

RECOMMENDATIONS FOR FUTURE RESEARCH

On the basis of its review of the evidence, the guideline panel made several recommendations for research to improve NICE guidance and patient care in the future. The full set of research recommendations can be reviewed

Table. Summary of Clinical Recommendations for TLoC

Topic	Recommendations
Initial assessment	Take a detailed history, especially from witnesses. Carry out a clinical examination. Record and interpret 12-lead ECG.
Uncomplicated faints	These can often be diagnosed from the history. Suggestive features are the 3 Ps: Posture: occurrence during prolonged standing or similar previous episodes avoided by lying down; Provoking factors, such as pain or a medical procedure; and Prodromal symptoms, such as sweating or feeling warm or hot before TLoC. Further investigation and specialist referral are not needed.
Epilepsy	Suggestive features are a bitten tongue; head turning to 1 side during TLoC; no memory of abnormal behavior that occurred before, during, or after TLoC; unusual posturing; prolonged limb-jerking (brief seizure-like activity often occurs during syncope, including uncomplicated faints); confusion after the event; or prodromal déjà vu or jamais vu. If features of epilepsy are present, arrange for early review by an epilepsy specialist and refer to NICE clinical guideline 20. Do not arrange for electroencephalography before neurologic assessment. Note that brief seizure-like activity often occurs during syncope, including uncomplicated faints. Do not suspect epilepsy unless suggestive features are present. Arrange for cardiovascular assessment if the cause of TLoC is unclear.
Urgent specialist referral	Give immediate treatment for clinically urgent problems (such as complete atrioventricular block or severe bleeding). Arrange for urgent specialist cardiovascular assessment for patients at risk for a severe adverse event (such as those with long QT interval, cardiac arrhythmia, or structural heart disease).
Further cardiovascular assessment	Focus on specific disorders that may cause TLoC, such as orthostatic hypotension, the carotid sinus syndrome, structural heart disease, or cardiac arrhythmia. Assessment should include repeated history, clinical examination, and 12-lead ECG. For suspected cardiac arrhythmia or unexplained TLoC, use ambulatory ECG for further assessment: Very frequent episodes: Use 24- to 48-hour Holter monitoring. Moderately frequent episodes: Use external event monitoring. Infrequent episodes: Use an implantable event recorder.

ECG = electrocardiography; TLoC = transient loss of consciousness.

in the full guideline; several key issues were highlighted as particular priorities.

Investigation of the Accuracy of Automated ECG Interpretation

Most ECGs recorded today are acquired digitally and interpreted automatically. Studies have been done to compare the accuracy of automatic interpretation with expert interpretation in the general population. However, no published studies are available in a population selected for TLoC, and studies are therefore needed to assess the accuracy of automatically interpreted ECGs in this population.

Diagnostic Yield of Repeated ECG Recordings

Current practice often relies on a single ECG to provide the same diagnostic yield as serial recordings for high-risk features in patients with TLoC, despite little evidence to support this approach. Because high-risk abnormalities (such as QT prolongation and conduction abnormalities) may be intermittent, serial ECG may be more sensitive for identifying patients at high risk for important cardiac arrhythmia.

Investigation of the Benefit and Cost-Effectiveness of 12-Lead ECG in Uncomplicated Faints

Uncomplicated fainting is a very common cause of TLoC; has a good prognosis; and can usually be diagnosed from the history and a witness without the need for testing. Much less commonly, rare heart conditions cause TLoC in otherwise healthy young persons who are at risk for dying suddenly unless the condition is recognized and treated. To minimize the risk of missing any such high-risk condition, the guideline panel recommended that 12-lead ECG should be part of the initial assessment in all persons who have TLoC. Although most persons who faint have normal ECG findings, ECG features of no importance may generate unnecessary concern and further tests in a few persons. It would be useful to establish whether diagnosing an uncomplicated faint from typical clinical features, without ECG, would miss dangerous heart conditions that could otherwise have been identified, and to assess the cost-effectiveness of performing ECG in large numbers of persons with uncomplicated faints to avoid missing a more dangerous condition in a smaller number of persons.

Cost-Effectiveness of Implantable Event Recorders

The guideline recommends that persons with TLoC from a suspected cardiac cause who have infrequent episodes (<1 every 2 weeks) should be offered an implantable cardiac event recorder. It is unclear whether this is more cost-effective than an alternative strategy, such as external event recording.

CONCLUSION

The guideline was developed to address inadequacies in the assessment and diagnosis of TLoC in persons who present to health care professionals. It does not make rec-

ommendations about when persons who have had TLoC should contact a health care provider, but this information may be extrapolated from the guideline. When the guideline is implemented, patients who have experienced an uncomplicated faint should be identified promptly, with no need for further investigations, whereas those at risk for serious cardiac disorders should receive urgent specialist review. Appropriate identification of uncomplicated faints should reduce inappropriate neurology referrals and avoid the misdiagnosis of epilepsy, and any increased activity that results from cardiology outpatient referrals may be offset by reduced emergency hospitalizations.

The guideline panel identified certain investigations that may have a low yield and can be misleading. However, all patients must receive 12-lead ECG. This is of low cost, and although serious abnormalities may be rare, ECG can reveal potentially life-threatening but treatable disorders. Unless episodes of TLoC are very frequent, short periods of external ambulatory ECG recording are of low yield; implantable event recorders are more costly but may be more cost-effective. The guideline gives indications for the appropriate use of such recorders and recommends less reliance on Holter monitoring, echocardiography (unless structural heart disease is suspected), tilt-table testing, or electroencephalography.

Ensuring that patients follow appropriate pathways that reflect the most likely cause of their TLoC should reduce inappropriate and potentially costly investigations and ensure correct and timely management, thus reducing inappropriate referrals and the risk for misdiagnosis.

The challenges of implementing these guidelines include the need to increase awareness of the clinical manifestations of syncope. They also include the need to educate clinicians that some readily available investigations may have limited clinical utility, whereas others that seem invasive and costly, such as an implantable event recorder, have specific cost-effective roles.

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Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1329.

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