International Study on Syncope of Uncertain Etiology 2: the management of patients with suspected or certain neurally mediated syncope after the initial evaluation

Rationale and study design

The Steering Committee of the ISSUE 2 study

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Study design

Multi-centre, prospective observational study.

Objectives

Main objective is to verify the value of implantable loop recorder (ILR) in assessing the mechanism of syncope and the efficacy of the ILR-guided therapy after syncope recurrence.

Inclusion criteria

Patients who met the following criteria are included: suspected or definite neurally mediated syncope based on initial evaluation; ≥3 syncope episodes in the last 2 years; severe clinical presentation of syncope requiring treatment initiation in the judgement of the investigator and age ≥30 years.

Exclusion criteria

Patients with one or more of the following are excluded: carotid sinus syndrome; suspected or definite heart disease and high likelihood of cardiac syncope; symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; loss of consciousness different from syncope (e.g. epilepsy, psychiatric, metabolic, drop-attack, TIA, intoxication, cataplexy) and subclavian steal syndrome.

End-points

The primary end-points are the ECG-documented syncopal events and the syncope recurrences after application of ILR-guided therapy.

Sample size and duration

A minimum of 400 patients will be enrolled during an anticipated period of 3 years. (Europace 2003; 5: 317–321)

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Key Words:

Syncope, neurally mediated syncope, electrocardiographic monitoring, implantable loop recorder.

Background

The recently published International Study on Syncope of Uncertain Etiology (ISSUE) focussed on the mechanism of spontaneous syncope in patients with tilt-positive syncope and tilt-negative probable neurally mediated syncope, the so-called ‘isolated syncope’, which is defined as a negative work-up and absence of structural heart disease. Patients were implanted with a continuous loop recorder that disclosed asystole/bradycardia in about three quarters of the patients who experienced a syncope recurrence. This finding was largely unexpected since both the experience derived from tilt testing and pathophysiological data suggest that the vasodepressor component is dominant in the genesis of neurally mediated syncope. Therefore, the correlation between the cardiovascular response observed during tilt testing and the mechanism of the


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spontaneous syncope appears to be weak. The ISSUE results provided an explanation of the more favourable than expected results of pacing therapy in patients with tilt-positive syncope in three recent controlled clinical trials, i.e. the VPS\(^{[2]}\), the VASIS\(^{[3]}\) and the SYDIT\(^{[4]}\) trials.

As the clinical characteristics and outcome of the patients with tilt-negative probable neurally mediated syncope have been reported as very similar to that of the patients with positive tilt testing, it could be hypothesized that the sensitivity and specificity of tilt testing are questionable. It might even be hypothesized that patients with neurally mediated syncope and patients with unexplained syncope share similar syncope aetiologies.

It is generally agreed that a simple initial evaluation, based on patient history, physical examination, standard electrocardiogram, carotid sinus massage and the measurement of supine/upright blood pressure, is able to risk stratify patients with syncope and to identify the patients likely to have cardiac syncope and who would need immediate further cardiological investigations.

Therefore, based only on this initial evaluation, a group of patients who are not identified as of high risk of cardiac syncope will be observed and followed through the implantation of a loop recorder (ILR). Eventual subsequent treatment will be guided by the ILR results.

Although this strategy can be considered as complying with the recent Guidelines on Management of Syncope of the ESC\(^{[5]}\), and has been positively evaluated in a recently published small trial\(^{[6]}\), it remains to be prospectively validated through a large prospective observational study.

ISSUE 2 will assess the effectiveness of a strategy based on simple initial evaluation, early application of an ILR and ILR-guided therapy after documentation of syncope recurrence in patients with neurally mediated syncope. The electrocardiographic data collected by the ILR will contribute to the definition of the exact syncope mechanisms in patients with suspected or certain neurally mediated syncope. Furthermore, due to its automatic ECG storage option, the ILR will eventually disclose a correlation between possible asymptomatic arrhythmia and documented arrhythmia-related syncope. The predictive accuracy of the results provided by tilt testing, adenosine triphosphate (ATP) testing and non-diagnostic carotid sinus massage will be determined through a prospective assessment of the rhythmologic and clinical outcome of the patients. ISSUE 2 will therefore provide further data on the diagnostic and prognostic yield of these three tests.

**Significance of the ISSUE 2**

The ISSUE 2 study is based on recommendations issued from the Guidelines on Syncope of the European Society of Cardiology\(^{[5]}\) and is therefore expected to provide further support to the current guidelines. Furthermore, the present study also validates the unexpected findings from the ISSUE trial. Inclusion and exclusion criteria as well as patients’ diagnostic flow chart (Table 1) are derived from the recommendations included in the Guidelines on Syncope of the ESC\(^{[5]}\).

**Study objectives**

**Main objective**

The main objective of this study is to verify the value of ILR in assessing the mechanism of syncope and the efficacy of ILR-guided therapy after documentation of syncope recurrence in patients with suspected or definite neurally mediated syncope.

**Secondary objectives**

The study has four secondary objectives:

1. To define the exact mechanism of syncope in patients with suspected or definite neurally mediated syncope based on the initial evaluation.
2. To evaluate prospectively the correlation between tilt-induced syncope, ATP-induced asystolic response and/or carotid sinus hypersensitivity and ILR-documented spontaneous syncope associated with bradycardia and/or asystole.
3. To assess the relationship between asymptomatic and symptomatic asystoles.
4. To assess the effectiveness of pacing therapy for preventing syncope recurrence in patients implanted with a pacemaker after an ILR-documented syncope associated with asystole/bradycardia.

The ILR will be used to document, quantify and classify the syncope-related ECG episodes.

**Study design**

ISSUE 2 is a multi-centre, prospective and observational study evaluating the diagnostic contribution of the implantation of an ILR in patients with suspected or definite neurally mediated syncope after an initial evaluation consisting of patient history, physical examination, standard ECG, supine and upright blood pressure measurements, carotid sinus massage, tilt test and ATP test.

The patients’ clinical status and the loop recorder memory content will be quarterly assessed until first syncope recurrence. Syncope-related ECG will be stored by manual ILR activations.

The patients’ outcome after administration of ILR-guided therapy will be assessed during the second observational phase of the study. As the decision to implant an ILR is left to the investigator’s discretion, it
is expected that some eligible patients will not receive the ILR. It is expected that some patients may refuse ILR implantation. All the patients, who for any reason, does not receive ILR implantation will be followed as in Phase 1 (ILR not-implanted group).

**Inclusion criteria**

Patients must fulfil all the following inclusion criteria:

1. Suspected or definite neurally mediated syncope, based on the Guidelines recently published by the Task Force on Syncope of the European Society of Cardiology.

2. Syncope episodes (≥3) in the last 2 years.

3. Severe clinical presentation of syncope (because of high number or high risk) requiring treatment initiation. The final assessment whether the severity of the clinical presentation warrants treatment is left to the discretion of the physician but the following definitions are provided as guidelines. High-risk settings is defined as syncope associated with the occurrence of, or potential risk for, physical injury or as syncope that may result in occupational

### Table 1 Patient stratification during the initial evaluation (according the Guidelines on Syncope of the European Society of Cardiology)\(^5\)

<table>
<thead>
<tr>
<th>Age ≥30 years</th>
<th>If yes, continue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope (≥3) during last 2 years</td>
<td>If yes, continue</td>
</tr>
<tr>
<td>So severe presentation to require treatment, if any</td>
<td>If yes, continue</td>
</tr>
<tr>
<td>Non-syncopal loss of consciousness:</td>
<td>If no, continue</td>
</tr>
<tr>
<td>● Epilepsy likely</td>
<td></td>
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<tr>
<td>● Psychiatric disorder likely, e.g. somatization, hysteria and conversion reaction</td>
<td></td>
</tr>
<tr>
<td>● Metabolic disorder likely, e.g. hypoglycemia, hypoxia and hyperventilation</td>
<td></td>
</tr>
<tr>
<td>● Drop attacks likely</td>
<td></td>
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<tr>
<td>● Intoxication likely</td>
<td></td>
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<tr>
<td>● Transient ischaemic attack likely</td>
<td></td>
</tr>
<tr>
<td>● Cataplexy likely</td>
<td></td>
</tr>
<tr>
<td>Symptomatic orthostatic hypotension</td>
<td>If no, continue</td>
</tr>
<tr>
<td>Suspected or definite heart disease and high likelihood of cardiac syncope*:</td>
<td>If no, continue</td>
</tr>
<tr>
<td>● Syncope during exercise</td>
<td></td>
</tr>
<tr>
<td>● Overt heart failure</td>
<td></td>
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<tr>
<td>● Ejection fraction ≤ 40%</td>
<td></td>
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<tr>
<td>● Old or recent myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>● Hypertrophic cardiomyopathy</td>
<td></td>
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<tr>
<td>● Dilated cardiomyopathy</td>
<td></td>
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<tr>
<td>● Significant valvular disease</td>
<td></td>
</tr>
<tr>
<td>● Sinus bradycardia &lt; 50 bpm or sino-atrial block</td>
<td></td>
</tr>
<tr>
<td>● Mobitz I second degree atrioventricular block</td>
<td></td>
</tr>
<tr>
<td>● Mobitz II second or third degree atrioventricular block</td>
<td></td>
</tr>
<tr>
<td>● Bundle branch block</td>
<td></td>
</tr>
<tr>
<td>● Rapid paroxysmal supraventricular tachycardia or ventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>● Pre-excited QRS complexes</td>
<td></td>
</tr>
<tr>
<td>● Prolonged QT interval</td>
<td></td>
</tr>
<tr>
<td>● Right bundle branch block pattern with ST elevation in leads V1–V3 (Brugada syndrome)</td>
<td></td>
</tr>
<tr>
<td>● Negative T waves in right pre-cordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia</td>
<td></td>
</tr>
<tr>
<td>Subclavian steal syndrome</td>
<td>If no, continue</td>
</tr>
<tr>
<td>Induction of syncope by carotid sinus massage (carotid sinus syndrome)**</td>
<td>If no, continue</td>
</tr>
<tr>
<td>Tilt test performed(^1)</td>
<td>Recommended</td>
</tr>
<tr>
<td>ATP test performed(^3)</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

*In the case of suspected structural heart disease, an echocardiogram may be required to confirm or rule out the diagnosis of structural heart disease.

**Carotid sinus syndrome must be ruled out by a carotid sinus massage of 10-s duration, supine and upright, according to the ‘method of symptoms’. Carotid sinus syndrome is defined if syncope is reproduced during or immediately after the massage in the presence of asystole ≥ 3 s and/or a fall in systolic blood pressure ≥ 50 mmHg. An asymptomatic ventricular pause lasting ≥ 3 s and a fall in systolic blood pressure ≥ 50 mmHg is defined as carotid sinus hypersensitivity. Similarly, a ventricular pause lasting ≥ 3 s and a fall in systolic blood pressure ≥ 50 mmHg that causes symptoms different from syncope (i.e. pre-syncope, lightheadedness, etc) is defined as carotid sinus hypersensitivity. Patients with carotid sinus hypersensitivity or negative sinus massage are eligible for enrollment.

\(^1\)The recommended tilt test protocol comprises a 60° passive tilting (20 min) followed by a 0.4 mg nitroglycerine challenge (15 min) when the passive phase fails to induce syncope. Isoproterenol challenge is permitted as alternative, though discouraged.

\(^3\)The ATP test consists of a rapid (<3 s) intravenous injection of 20 mg ATP dissolved in 10 ml of saline solution into a suitable ante-cubital vein in the patient in supine position. ATP can be replaced by adenosine at the same dosage according to local practice.
implications. High-number settings corresponds to an occurrence rate of events likely to affect patient’s quality of life.

4. Age > 30 years.

Exclusion criteria

The patients with one or more of the following are excluded:

1. Induction of syncope by carotid sinus massage (carotid sinus syndrome).
2. Suspected or definite heart disease and high likelihood of cardiac syncope, i.e. syncope during exercise; overt heart failure; ejection fraction ≤40%; old or recent myocardial infarction; hypertrophic cardiomyopathy; dilated cardiomyopathy; significant valvular disease; sinus bradycardia < 50 bpm or sino-atrial block; Mobitz I second degree atrioventricular block; Mobitz II second or third degree atrioventricular block; bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; right bundle branch block pattern with ST elevation in leads V1–V3 (Brugada syndrome) and negative T waves in right pre-cordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia.
3. Symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement.
4. Loss of consciousness different from syncope (e.g. epilepsy, psychiatric, metabolic, drop-attack, TIA, intoxication and cataplexy).
5. Subclavian steal syndrome.

Study protocol

ISSUE 2 consists of a pre-study screening phase, an enrollment phase and two follow-up phases. All syncope patients are consecutively included in the pre-study screening phase, which will determine each patient’s eligibility for enrolment in the ISSUE 2 study. A screening flow chart is shown in Table 1.

All eligible patients, after giving informed consent, will be enrolled in the study if they undergo ILR implantation or in the ILR not-implanted group if they do not receive an ILR. The results of the carotid sinus massage, tilt test and ATP test performed during the screening phase will be collected. Tilt test and ATP test are recommended but they are not mandatory for the inclusion of the patients in the study group. It is expected that some patients will receive ILR implant even if they have not undergone tilt test or ATP test.

After ILR implantation, all patients will be followed-up quarterly during the first 18 months with an additional follow-up at month 24 (Phase 1). The patient should keep a logbook for registration of symptoms such as palpitations, dizziness, pre-syncpe and syncope. It will also contain a date for the next study appointment and telephone numbers of the investigator/implanting centre. Through the whole study, the patient is instructed to activate the ILR and to contact a doctor in case of any syncope in order to interrogate the device as soon as possible. Phase 1 follow-up scheme will be continued until first documented syncope recurrence or end of the study whichever comes first. Phase 1 follow-up ends at the time of the first ECG-documented syncope recurrence.

The second follow-up phase will document the patient outcome after administration of ILR-guided therapy. Due to the observational character of the study, the decisions and type of treatments of the patients in Phase 2 are left to the discretion of the physicians. The recommended therapies are cardiac pacing in asystolic and bradycardiac patients, counselling, no specific therapy in patients with normal sinus rhythm, including those with mild sinus tachycardia, and antiarrhythmic therapy in tachyarrhythmic patients. Phase 2 consists of follow-up visits (clinical status) until the study ends. All patients will be followed-up quarterly during the first 18 months with an additional follow-up at month 24.

All patients belonging to the ILR not-implanted group will be followed-up quarterly during the first 18 months with an additional follow-up at month 24 with the same scheme as in Table 3 starting from the enrolment date. The end-point for these patients is the first syncopal recurrence, total number of pre-syncopes and clinical status. The follow-up ends at the time of the first syncopal recurrence.

End-points

The primary end-point of Phase 1 is the first ECG-documented syncopal event. The primary end-point of Phase 2 is the first syncope recurrence after application of ILR-guided therapy.

The secondary end-points of Phase 1 are the asymptomatic ILR-documented arrhythmic episodes and the ILR-documented pre-syncpe/s. The secondary end-point of Phase 2 is the total number of syncopal and pre-syncopal recurrences.

Statistics

The study’s sample size should be sufficiently large in order to derive an accurate assessment of positive and negative predictive accuracy of tilt test, ATP test and carotid sinus hypersensitivity for predicting bradycardiac/asystolic syncope. The confidence interval should each be maximally 25% wide. To achieve this, independently of the true predictive accuracies, each test outcome must be observed at least 67 times.

The expected occurrence rates are: ATP test negative in 80% and positive in 20%, and tilt test negative in 50% and positive in 50% of the patients. To observe at
least 67 ATP tests positive with some certainty, 350 patients must be included in the analysis. This is also adequate for the other outcomes. To account for 15% patients, who are not evaluated, the sample size of the study is set at 400 patients. Moreover, it is expected that eligible ILR not implanted patients should be less than 10% of the enrolled patients.

As it is anticipated that between 5 and 10% of all syncope patients can be enrolled in this study, between 4000 and 8000 patients with syncope need to be screened. Patient enrolment time is anticipated to last 3 years. As the study will continue for a period of 6 months after the enrolment of the last patient, total study duration will be approximately 4 years.

Appendix A

A.1 Regulatory procedures of the ISSUE 2

ISSUE 2 study is officially endorsed by the Working Group of Pacing of the European Society of Cardiology with the organizational support of Medtronic Inc. The Steering Committee has the intellectual property of the protocol. The Steering Committee is the proprietor of the database. The analysis of data including statistical analysis will be performed personally by the members of the End-point Committee. Data management is made electronically by an external company (RDES SL, Barcelona, Spain). Data are collected from each investigator who is responsible for them and who keeps a printed copy of his file. During the study the access to the database is only permitted to the members of the End-point Committee who are responsible for it. The investigators have on-line access to the database regarding their own cases. The Steering Committee has the faculty for reviewing all data and all the events if necessary. The Steering Committee has the responsibility for the final reports and for the defined end-points.

A.2 Steering Committee

Michele Brignole, Richard Sutton, Carlo Menozzi, Angel Moya, Roberto Garcia-Civera, David Benditt, Panos Vardas, Wouter Wieling, Dietrich Andresen, Roberta Migliorini and David Hollinworth.

A.3 End-point Committee

Michele Brignole, Richard Sutton, Carlo Menozzi and Angel Moya.

A.4 Study monitor

Nicoletta Grovale.

References