Early use of an implantable loop recorder in syncope evaluation: A randomized study in the context of the French healthcare system (FRESH study)

Utilisation précoce d’un enregistreur implantable d’événements dans l’évaluation des syncopes inexpliquées : une étude randomisée dans le contexte du système de santé français

Cristian Podoleanu a, Antoine DaCosta b, Pascal Defaye c, Jérôme Taieb d, Daniel Galley e, Paul Bru f, Philippe Maury g, Philippe Mabo h, Serge Boveda i, Gilles Cellarier j, Frédéric Anselme k, Claude Kouakam l, Nicolas Delarche m, Jean-Claude Deharo n,∗, for the FRESH investigators

a University of Medicine and Pharmacy, Târgu Mures, Romania
b CHU Nord, Saint-Étienne, France
c CHU La Tronche, Grenoble, France
d Centre hospitalier Aix-en-Provence, Aix-en-Provence, France
e Centre hospitalier Albi, Albi, France
f Centre hospitalier La Rochelle, La Rochelle, France
g CHU Rangueil, Toulouse, France
h CHU Pontchaillou, Rennes, France
i Clinique Pasteur, Toulouse, France
j HIA Sainte-Anne, Toulon, France
k CHU Charles-Nicolle, Rouen, France
l CHRU de Lille, Lille, France
m Centre hospitalier Pau, Pau, France
n Cardiologie 9e étage, CHU La Timone, 263, rue Saint-Pierre, 13385 Marseille cedex 5, France

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Abbreviations: CER, cost-effectiveness ratio; CONV, conventional evaluation; ECG, electrocardiogram; GP, general practitioner; ILR, implantable loop recorder; SF-36, Medical Outcomes Study 36-item short form; QoL, quality of life.

∗ Corresponding author. Cardiologie 9e étage, CHU La Timone, 263, rue Saint-Pierre, 13385 Marseille cedex 5, France.
E-mail address: jean-claude.deharo@ap-hm.fr (J.-C. Deharo).

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**KEYWORDS**
Syncope; Implantable loop recorder; Cost

**MOTS CLÉS**
Syncope ; Enregistreur électrocardiographique implantable ; Coût

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**Summary**

**Background.** — The role of implantable loop recorders (ILRs) in the evaluation strategy for recurrent syncope in France is limited by lack of knowledge of the cost.

**Aim.** — To compare a conventional evaluation strategy for syncope with the early use of an ILR in low-risk patients, in terms of diagnostic yield, cost and impact on quality of life (QoL).

**Methods.** — National prospective randomized open-label multicenter study of patients with a single syncope (if severe and recent) or at least two synapses in the past year.

**Results.** — Seventy-eight patients (32 men) were randomized to the ILR strategy (ILR group, n = 39) or the conventional evaluation strategy (CONV group, n = 39): mean age 66.2 ± 14.8 years; 4.3 ± 6.4 previous synapses. After 14 months of follow-up, a certain cause of syncope was established in 18 (46.2%) patients in the ILR group and two (5%) patients in the CONV group (P < 0.001). Advanced cardiological tests were performed less frequently in the ILR group than in the CONV group (0.03 ± 0.2 vs. 0.2 ± 0.5 tests per patient; P = 0.05). Patients in the ILR group were hospitalized for a non-significantly shorter period than patients in the CONV group (5.7 ± 3.2 vs. 8.0 ± 1.4 days). There was no difference between the two groups in terms of QoL main composite score.

**Conclusion.** — In patients with unexplained syncope, the early use of an ILR has a superior diagnostic yield compared with the conventional evaluation strategy, with lower healthcare-related costs.

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**Background**

Syncope is a common condition, affecting 3.5% of the population, and is recurrent in 30% of cases. Identification of the cause leads to the most effective treatment. However, after an often-complex and non-standardized diagnostic process, no cause is identified in 13–42% of cases [1].

The implantable loop recorder (ILR) is now part of our practice and its use is recommended very early in the diagnostic process in low-risk patients [1]. However, the precise determination of its role in the evaluation strategy for recurrent syncope in France is limited by lack of knowledge of the cost.

The aims of this French Study on implantable Holter recorders in syncope (FRESH) were to compare the diagnostic yield and costs of a common evaluation strategy for syncope with the early use of an ILR in low-risk patients, and to analyse the quality of life (QoL) associated with the two strategies.

**Methods**

**Study population**

We included all consecutive patients from the hospitalization ward or outpatient department who presented with one
of the following criteria: a single syncope, if severe (i.e., not preceded by prodrome, which resulted in an injury) and recent (i.e., occurring within the previous six months); or at least two syncopes in the past 12 months. The syncope had to remain unexplained at the end of the clinical examination, and after performing a 12-lead electrocardiogram (ECG), echocardiography and head-up tilt-test, meaning that a further diagnostic workup was mandatory. The exclusion criteria were as follows: significant heart disease (i.e., left ventricular ejection fraction < 40%); a history of myocardial infarction or unstable coronary artery disease; a history of arrhythmia; potentially arrhythmogenic drug use; a family history of sudden death; presence of bifascicular intraventricular conduction disturbance on the ECG; hypertrophic cardiomyopathy with or without obstruction; and aortic stenosis. Patients provided written informed consent to participate in the study. Institutional review board approval was obtained at all study sites.

Study design

This national prospective randomized open-label multicenter study included a representative sample of French academic and non-academic hospitals.

Included patients were randomized either to receive an ILR (Reveal® or Reveal® Plus, Medtronic Inc., Minneapolis, MN, USA) immediately (ILR group) or to be investigated according to the conventional evaluation strategy commonly used by the attending physician, with exclusion of the use of an ILR (CONV group). By protocol, the final diagnosis, whether ECG-documented or not, was left to the investigator.

Patients were randomly allocated into the CONV and ILR groups using a computer-generated randomization list. The patients were followed for a period of 14 months, with outpatient consultations scheduled at two, six, 10 and 14 months in the ILR group and at six and 14 months in the CONV group. As these visits were performed only for the purpose of the study, they were not entered into the cost analysis. In both arms, non-scheduled consultations were performed if necessary and were entered into the cost analysis.

Cost analysis

To evaluate the economic burden on healthcare providers, we assessed the duration of the hospitalizations and the number of different consultations and medical tests performed. The costs were assessed based on the number of hospitalization days and the number of consultations or tests, to put the analysis in the context of society. Of note, the cost of the ILR was not included in the cost analysis as it was not reimbursed at that time in France.

Consultations were defined as physician visits according to the French care system, done by the general practitioner (GP) or a specialist (cardiologist, neurologist or other specialist). We identified four categories of tests, as follows: standard cardiological tests (12-lead ECG, transthoracic echocardiography, 24-hour Holter monitoring, head-up tilt test); advanced cardiological tests (transoesophageal echocardiography, electrophysiological study, carotid ultrasound, ambulatory blood pressure monitoring, treadmill test, coronary angiography); neurological tests (electroencephalogram, brain computed tomography scan); and any other tests (blood sampling, chest X-ray, any other non-detailed tests).

For the tests listed above, the cost unit was the total number of examinations performed. This arbitrary listing provides a plausible order of magnitude.

Quality-of-life analysis

An analysis of QoL using the 36-Item Short Form Health Survey (SF-36) questionnaire was performed at baseline, six months and the end of the study. The SF-36 questionnaire is a self-administered questionnaire that measures health in eight multi-item dimensions, covering functional status, well-being and overall evaluation of health [2].

Statistical analysis

Analysis was by intention-to-treat. Variables are expressed as mean ± standard deviations. Comparisons were made, where appropriate, by Fisher’s exact test or the Mann–Whitney U test.

Diagnosis efficacy was compared between the two methods. An analysis based on the comparison, by volume, of the various tests for each of the different diagnostic methods was performed.

Regarding the number of patients to include, a preliminary study (not published) showed that the cost-effectiveness ratio (CER) using the conventional strategy for a patient referred for syncope to our department was €9336/percentages of diagnosis, and that the relative CER was €12,195/percentages of diagnosis. We considered that the variance of the costs and effectiveness would be identical with both methods, with a magnitude effect of 1. Assuming a bilateral situation, with a power of 80% and a type I error risk of 5%, a sample of 35 patients was necessary in each group to detect an effect size of 30%. In view of losses to follow-up and dropouts, the sample size was increased by 10%, resulting in a requirement for 77 patients to be included in the study.

Results

Between April 2004 and August 2008, 79 patients met the inclusion criteria in 13 centres in France and were screened for randomization; one patient withdrew his consent immediately after being screened and was therefore excluded from the study.

Of the 78 patients, 39 were randomized to receive an ILR and 39 were randomized to the conventional evaluation strategy. According to local practice in each centre, patients allocated to the ILR group were implanted 6.6 ± 9.5 days after randomization.

The demographic and clinical characteristics of patients are presented in Table 1. All of the patients were in sinus rhythm, except for two patients who were in atrial fibrillation. The PR interval duration was 168.1 ± 22.9 ms (range 120–230 ms) and the QRS complex was normal in 73 patients; four patients presented with isolated right bundle branch block and one had isolated left anterior haemiblock. The patients had no heart disease that could explain
Early use of an implantable loop recorder in syncope evaluation

Table 1  Patient characteristics.

<table>
<thead>
<tr>
<th>Cause of syncope</th>
<th>ILR (n = 39)</th>
<th>CONV (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.6 ± 13.7</td>
<td>64.8 ± 15.8</td>
<td>0.40</td>
</tr>
<tr>
<td>Age ≥ 70 years</td>
<td>22 (56)</td>
<td>15 (38)</td>
<td>0.17</td>
</tr>
<tr>
<td>History of syncope (years)</td>
<td>2.5 ± 4.6</td>
<td>4.4 ± 8.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Inclusion after one severe recent syncope</td>
<td>7 (18)</td>
<td>14 (36)</td>
<td>0.12</td>
</tr>
<tr>
<td>Total number of synapses (n)</td>
<td>4.6 ± 8.2</td>
<td>4.1 ± 3.9</td>
<td>0.71</td>
</tr>
<tr>
<td>Number of synapses in the last 6 months (n)</td>
<td>2.2 ± 2.5</td>
<td>1.8 ± 2.0</td>
<td>0.24</td>
</tr>
<tr>
<td>Traumatic syncope</td>
<td>20 (51)</td>
<td>20 (51)</td>
<td>1.0</td>
</tr>
<tr>
<td>Syncope with jerking movements</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous admission for syncope</td>
<td>17 (44)</td>
<td>8 (20)</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart disease</td>
<td>17 (44)</td>
<td>12 (31)</td>
<td>0.34</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>5 (13)</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (13)</td>
<td>6 (15)</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%) or mean ± standard deviation. CONV: conventional evaluation; ILR: implantable loop recorder.

Follow-up

After 14 months of follow-up, a certain cause of syncope was established in 18 (46.2%) patients in the ILR group and two (5%) patients in the CONV group (P < 0.001), demonstrating a highly improved diagnostic performance in the ILR group. The causes of syncope in both groups are presented in Table 2. In the CONV group, at the end of the workup, the supposed aetiology was reflex syncope in eight patients. Six patients in the ILR group and two in the conventional group received a pacemaker; all other patients received drugs or counselling. One patient died during follow-up; this death was due to acute respiratory failure and was not related to syncope.

The number of hospitalization days, visits and tests are listed in Table 3. Patients in the ILR group were hospitalized for a non-significantly shorter period than patients in the CONV group: 5.7 ± 3.2 vs. 8.0 ± 1.4 days (P = 0.55). The numbers of GP and specialist visits indexed by patients were similar in both groups, but the numbers of tests done during these visits were lower in the ILR group than in the CONV group: 0.1 ± 0.4 standard cardiological tests per patient in the ILR group compared with 0.3 ± 0.9 in the CONV group (P = 0.8); 0.03 ± 0.2 advanced cardiological tests per patient compared with 0.2 ± 0.5 in the CONV group (P = 0.05).

QoL, as shown by the results of the SF-36 questionnaire after 14 months of follow-up, was not different in the ILR group in terms of the physical and psychological components (Table 4). There were no differences between the main composite scores suggestive of general physical and psychological wellbeing. While there were no differences in physical functioning (i.e. intensity of exercise or walking distance), social functioning and mental health between the two groups, we observed a significantly better score in ‘role limitations due to physical problems’ (i.e. unspecified limitation of any kind and feeling of less accomplishment) in the ILR group. The scores for ‘role limitations due to emotional problems’ were not statistically different between the two groups.

Discussion

The main results of the study are that the early use of an ILR after syncope, in the context of the French healthcare system, allows for a higher number of certain diagnoses compared with the conventional strategy. This higher diagnostic yield is obtained along with a reduction in the number of advanced cardiological tests performed. The
Table 3  Clinical events, hospitalization days, visits and tests that occurred during the 14 months of follow-up.

<table>
<thead>
<tr>
<th></th>
<th>ILR (n = 39)</th>
<th>CONV (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization days (n)</td>
<td>5.7 ± 3.2</td>
<td>8.0 ± 1.4</td>
<td>0.55</td>
</tr>
<tr>
<td>GP visits (n per patient)</td>
<td>1.3 ± 2.2</td>
<td>1.1 ± 3.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardiologist visits (n per patient)</td>
<td>0.46 ± 1.5</td>
<td>0.47 ± 0.95</td>
<td>0.8</td>
</tr>
<tr>
<td>Neurologist visits (n per patient)</td>
<td>0.31 ± 0.9</td>
<td>0.06 ± 0.25</td>
<td>0.3</td>
</tr>
<tr>
<td>Other specialist visits (n per patient)</td>
<td>0.15 ± 0.43</td>
<td>0.09 ± 0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Standard cardiological tests (n per patient)</td>
<td>0.1 ± 0.4</td>
<td>0.3 ± 0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Advanced cardiological tests (n per patient)</td>
<td>0.03 ± 0.2</td>
<td>0.2 ± 0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Neurological tests (n per patient)</td>
<td>0.05 ± 0.2</td>
<td>0.06 ± 0.3</td>
<td>0.85</td>
</tr>
<tr>
<td>Any other tests (n per patient)</td>
<td>0.18 ± 0.8</td>
<td>0.09 ± 0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Syncope recurrence (n per patient)</td>
<td>0.46 ± 1.2</td>
<td>0.47 ± 1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Presyncope recurrence (n per patient)</td>
<td>1.2 ± 4.8</td>
<td>0.8 ± 2.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. CONV: conventional evaluation; GP: general practitioner; ILR: implantable loop recorder.

ILR was well tolerated in terms of quality of life, as it did not impair the physical and social functioning of the patients.

In this study, we followed patients with severe syncope of unknown aetiology after initial evaluation and/or atypical clinical presentation (absence of premonitory signs and of prodromal symptoms). In these patients, the underlying mechanism of the syncope needs to be clarified, either by prolonged monitoring or by further cardiological examinations, including provocative tests [1]. These two approaches may either delay therapy until an ECG symptom correlation can be established or increase the number of tests done to unmask the supposed aetiology. The latter approach has also the disadvantage of leading to a supposed and uncertain aetiology [3].

In our study, delayed therapy in the ILR group did not impact patient outcome. Only one patient died during follow-up and his death was not related to the study protocol. The number of syncope recurrences did not differ between groups. Similarly, in a study by Farwell et al., there were no increases in the numbers of subsequent syncopal episodes and mortality rates in patients who received an ILR [4].

The diagnostic yield of the ILR in our study was 46.2% over a period of 14 months, which is in accordance with published data: during a period of 18 months, the diagnostic yield was, on average, 32% and increased to approximately 50% when the monitoring period was extended to two years [5].

The higher diagnostic yield of the early use of an ILR is in line with previous studies. A single-centre study that aimed to investigate the impact of ILRS on an unselected population of 421 patients presenting acutely for syncope showed that ILR significantly increased the rate of diagnosis in patients with recurrent syncope: an ECG diagnosis was identified in 33% of ILR patients compared with 4% of patients evaluated conventionally [4].

A study that included 60 consecutive patients with unexplained syncope randomized to conventional testing or to prolonged monitoring with an ILR, showed that prolonged monitoring was more likely to result in a diagnosis than conventional testing. A diagnosis was obtained in 14 of 27 patients randomized to prolonged monitoring compared with in six of 30 patients undergoing conventional testing (52% vs. 20%; P = 0.012) [6].

In the present study, even if the necessary tests were decided upon by the treating physician, there were fewer

Table 4  SF-36 questionnaire at the 14-month evaluation.

<table>
<thead>
<tr>
<th></th>
<th>ILR (n = 39)</th>
<th>CONV (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>69.2 ± 31.6</td>
<td>63.1 ± 31.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Social functioning</td>
<td>75.5 ± 24.6</td>
<td>78.2 ± 26.2</td>
<td>0.57</td>
</tr>
<tr>
<td>Role limitation (physical problems)</td>
<td>61.3 ± 43.2</td>
<td>79.3 ± 33.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Role limitation (emotional problems)</td>
<td>73.1 ± 42.5</td>
<td>82.8 ± 31.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Mental health</td>
<td>60.6 ± 18.7</td>
<td>62.2 ± 17.6</td>
<td>0.79</td>
</tr>
<tr>
<td>Vitality</td>
<td>46.4 ± 18.6</td>
<td>52.9 ± 22.9</td>
<td>0.39</td>
</tr>
<tr>
<td>Pain</td>
<td>62.3 ± 23.7</td>
<td>58.7 ± 27.9</td>
<td>0.61</td>
</tr>
<tr>
<td>General health perception</td>
<td>56.1 ± 16.0</td>
<td>63.0 ± 22.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Physical composite score</td>
<td>43.6 ± 12.8</td>
<td>43.7 ± 8.7</td>
<td>0.82</td>
</tr>
<tr>
<td>Psychological composite score</td>
<td>46.7 ± 11.3</td>
<td>46.6 ± 11.7</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. CONV: conventional evaluation; ILR: implantable loop recorder.
advanced cardiological tests done in the ILR group compared with the CONV group. As these tests are at a higher cost, our study suggests that the ILR strategy decreases the cost of investigations after syncope. Accordingly, in a study by Farwell et al., ILR patients had fewer investigations after randomization and fewer hospital days, resulting in a cost saving. In the PICTURE registry, which enrolled 570 patients, the median number of tests performed per patient in the total study population was 13; the tests performed most frequently were echocardiography, ECG, ambulatory ECG monitoring, in-hospital ECG monitoring, exercise testing and orthostatic blood pressure measurements [7]. This study reported a high diagnostic yield with ILRs, which guided the diagnosis in 78% of patients with recurrent syncope and provided useful information in another 6%.

We did not observe a difference in duration of hospitalization between groups. This unexpected result probably reflects the fact that, at the time of the study, the evaluation of syncope was not performed on an outpatient basis in most cases. We hypothesize that the length of hospital stay in the ILR group will be shorter nowadays, especially as very small insertable devices have become available.

A recent study assessed the efficacy of a standardized care pathway approach with early ILR implantation, based on European Society of Cardiology guidelines [1], compared with a conventional approach in a high-volume hospital in the USA. The authors found that by using a standardized approach only 4% of patients were hospitalized, compared with 20% in the conventional group, and the rate of diagnosis at 45 days was greater in the standardized group (57% vs. 45% in the total population) [1]. The number of tests or consultations associated with additional charges was significantly lower in the standardized group than in the conventional group [8]. We observed a similar number of GP and non-cardiological specialist visits, including neurological consultations, in both groups, which reflects the variable clinical presentation of syncopal episodes that can be frequently misdiagnosed as neurological disorders [9]. Our study shows that, parallel to the cardiological assessment, physicians look for other causes of loss of consciousness. Obviously, the early ILR strategy could not affect the number of non-cardiological investigations and visits.

QoL was assessed using the SF-36 questionnaire and showed that ILR had no significant negative impact. Earlier studies estimated a reduction in QoL in syncope patients, caused mainly by the fear of syncope recurrence. Given that the incidence of recurrent episodes was similar in the both groups, it is not surprising that there were no differences between the groups. In a study of 201 patients who received an ILR, the authors reported that there was improved QoL in the ILR group for general wellbeing using the SF-12 questionnaire [10]. A recently published trial using quality-adjusted life-years to assess the cost-effectiveness of ILRs in people with transient loss of consciousness found that this strategy resulted in an increased gain for ILR [11].

**Study limitations**

The limitations of our study result from the small number of patients included; this was due to the relative low rate of ILR implantations and poor knowledge of this diagnostic tool in France during the study period, mainly because the device and implantation were not reimbursed. We hope that such a study may help to increase the rate of implantation of ILRs in France. Another limitation was related to the cost of the device, which was not taken into account in the cost analysis because it was heterogeneous at that time in France. A current evaluation would have to incorporate this cost into the economic analysis.

**Conclusion**

In patients with unexplained syncope, the early use of an ILR has a superior diagnostic yield compared with the conventional strategy, with lower healthcare-related costs. Our results, in the context of the French healthcare system, may encourage better reimbursement of the device, implantation procedure and follow-up visits, which, in turn, may increase the use of the ILR, as recommended by the guidelines [1].

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**Acknowledgements**

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