**Recurrence Unexplained Palpitations (RUP) Study**

Comparison of Implantable Loop Recorder Versus Conventional Diagnostic Strategy

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**Objectives**

The aim of the study was to compare the diagnostic yield and the costs of implantable loop recorder (ILR) with those of the conventional strategy in patients with unexplained palpitations.

**Background**

In patients with unexplained palpitations, especially in those with infrequent symptoms, the conventional strategy, including short-term ambulatory electrocardiogram (ECG) monitoring and electrophysiological study, sometimes fails to establish a diagnosis.

**Methods**

We studied 50 patients with infrequent (≤1 episode/month), sustained (>1 min) palpitations. Before enrollment, patients had a negative initial evaluation, including history, physical examination, and ECG. Patients were randomized either to conventional strategy (24-h Holter recording, a 4-week period of ambulatory ECG monitoring with an external recorder, and electrophysiological study) (n = 24) or to ILR implantation with 1-year monitoring (n = 26). Hospital costs of the 2 strategies were calculated.

**Results**

A diagnosis was obtained in 5 patients in the conventional strategy group, and in 19 subjects in the ILR group (21% vs. 73%, p < 0.001). Despite the higher initial cost, the cost per diagnosis in the ILR group was lower than in the conventional strategy group (€3,056 ± €363 vs. €6,768 ± €6,672, p = 0.012).

**Conclusions**

In subjects without severe heart disease and with infrequent palpitations, ILR is a safe and more cost-effective diagnostic approach than conventional strategy. (J Am Coll Cardiol 2007;49:1951–6) © 2007 by the American College of Cardiology Foundation

Implantable loop recorders (ILRs) could prove useful in the study of palpitations (1), but no data are currently available regarding their diagnostic yield in this setting.

The aim of this trial was to compare the diagnostic yield and costs of ILR with those of the conventional strategy, in patients with infrequent unexplained palpitations.

**Methods**

**Study design.** This trial was a multicenter, prospective, randomized study. The primary end point was to establish the cause of the palpitations. Patients were randomized either to conventional strategy or to ILR implantation. Crossover was not mandated by the study protocol, but if conventional strategy did not provide a diagnosis, patients were invited to cross over to ILR. The study was approved by the ethics committee of each center, and all patients gave written, informed consent.

**Patient eligibility.** Consecutive patients referred for palpitations (defined as an unpleasant sensation of the awareness of the heart beat) as their chief complaint underwent an
initial evaluation including history, physical examination, and ECG. Patients also underwent echocardiography in order to exclude severe structural heart disease (SHD), and blood chemistry examinations in order to exclude palpitations of noncardiac origin, according to the criteria of Weber and Kapoor (4).

Subjects with evident extrasystolic or anxiety-based palpitations were not enrolled. We excluded patients with severe SHD or hereditary arrhythmogenic syndrome, because of concerns of the potential risk of sudden death during recurrence of palpitations.

Patients were enrolled if they had a negative initial evaluation, no apparent or only mild heart disease (ejection fraction >35%), and sustained (>1 min), infrequent (=1 episode/month), and clinically significant (associated to presyncope, diaphoresis, chest pain, and asthenia) palpitations.

**Conventional strategy.** The conventional strategy comprised 24-h Holter recording, a 4-week period of ambulatory ECG monitoring with an ER, and EPS, when the 2 previous examinations yielded negative results, on a day case basis. Monitoring was regarded as diagnostic only when a symptom–rhythm correlation was established during spontaneous palpitations resembling the symptoms during recurrence of palpitations.

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**ILR.** Patients underwent ILR implantation (Reveal Plus, Medtronic Inc., Minneapolis, Minnesota) on a day case basis. Implantable loop recorder monitoring was regarded as diagnostic only when a symptom–rhythm correlation was established during spontaneous palpitations resembling the symptoms before enrollment (1,5). Implantable loop recorder monitoring was regarded as nondiagnostic when arrhythmias were not associated to any symptoms.

**Cost assessment.** The perspective was that of the hospital. The third payer, patients, and societal costs were not evaluated. For each investigation, the items that were considered are presented in Table 1. The incremental cost-effectiveness ratio (ICER) was calculated as the difference between the total cost of ILR and conventional strategy, divided by the difference in the percentage of diagnoses made between ILR and conventional strategy. To evaluate the economic impact of the various investigations, a sensitivity analysis was performed.

**Statistical analysis.** Differences between strategies were tested by means of Student t test for unpaired data, Wilcoxon rank sum test, and Fisher exact test, as requested. A value of p < 0.05 was considered significant.

**Sample size.** In patients with infrequent palpitations, we hypothesised that ILR was superior to conventional strategy, and we estimated a diagnostic yield of 75% and 45%, respectively. The resulting sample size was 25 patients for each group.

### Results

**Patient characteristics.** Fifty patients with unexplained palpitations were randomized: 24 to the conventional strategy group and 26 to the ILR group. There were no differences in baseline clinical characteristics between groups (Table 2). A diagnosis was obtained in 30 of the 50 patients (60%) (Fig. 1); in 22 of these 30 (73%), a significant arrhythmia was diagnosed (Table 3). No adverse events were observed, and there were no facility visits other than those planned in the study protocol.

**Primary end point.** In the conventional strategy group, a diagnosis was obtained in 5 (21%) patients (mean time to diagnosis 36 ± 26 days). Holter monitoring proved negative

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*Including hospital overheads; †Implantation and removal procedure.
EPS = electrophysiological study; ILR = implantable loop recorder; € = 2005 Euro.
in all patients. During monitoring with ER (mean duration 40 ± 25 days), atrial fibrillation (AF) was recorded in 1 case and supraventricular tachycardia (SVT) in 1 case, palpitations did not recur in 16 patients, 5 patients failed to activate the device during an episode of palpitations, and there was 1 case of device malfunction. Electrophysiological study induced SVT in 3 cases. Three of the 4 patients with SVT underwent successful ablation of their arrhythmias, while the other 1, together with the patient with AF, received antiarrhythmic drugs.

In the ILR group, a diagnosis was obtained in 19 (73%) subjects (mean time to diagnosis 279 ± 228 days). Thus, the diagnostic yield of ILR was significantly higher with respect to conventional strategy (73% vs. 21%, p < 0.001). During monitoring (mean duration 321 ± 235 days), ILR recorded SVT in 6 cases (Fig. 2), AF in 4 cases, atrial flutter in 2
cases, sinus tachycardia (ST) (>100 beats/min) in 4 cases, sinus bradycardia (SB) (<40 beats/min) in 2 cases, and paroxysmal atrioventricular block (AVB) in 1 case. Palpitations did not recur in 6 patients; 1 patient failed to activate the device during an episode of palpitations. The automatic detection mode was activated, but no significant arrhythmias were recorded because the memory of the devices was always saturated by inappropriate activations.

Of the 6 patients with SVT, 4 underwent successful ablation of their arrhythmias, while the other 2 received antiarrhythmic drugs. Patients with AF or flutter were treated with antiarrhythmic drugs, those with ST received anxiolytic therapy, and those with SB and AVB underwent pacemaker implantation.

**Costs.** The mean cost per patient was significantly higher, while the mean cost per diagnosis was significantly lower in the ILR group than in the conventional strategy group. The ICER for the ILR strategy was €1,576. Sensitivity analysis confirms the results, except for EPS 50% (Table 4).

**Crossover.** Nine of the 19 patients in whom conventional strategy proved negative consented to crossover ILR. A diagnosis was obtained in 6 (67%) (mean time to diagnosis 316 ± 226 days). During monitoring (mean duration 326 ± 236 days), ILR recorded SVT in 1 case, ST in 4 cases, and paroxysmal AVB in 1 case, while symptoms did not recur in 3 patients. The patient with SVT underwent ablation, the 4 subjects with ST received anxiolytic therapy, and the patient with AVB underwent pacemaker implantation.

**Follow-up.** After a diagnosis was reached, patients were followed up for at least 12 months (mean duration 334 ± 210 days). Palpitations were completely eliminated in 22 patients with arrhythmic diagnosis treated with ablation, pacemaker, or drugs, while they were considerably reduced (from a median number of 9 episodes/year before enroll-
ment, to 1.4 episodes/year) in 8 patients with nonarrhythmic diagnosis who received anxiolytic therapy.

**Discussion**

**Main findings.** This study shows that, in patients with infrequent symptoms and without severe SHD, the diagnostic yield of conventional strategy is low, and that ILR is more likely to provide a diagnosis. Moreover, ILR explained the likely nature of palpitations in most of the patients with negative conventional strategy who consented to crossover to prolonged monitoring strategy. Similar observations have been made by Krahn et al. (7,8) on evaluating patients with syncope. In patients with arrhythmic diagnosis, the prescribed treatment completely eliminated symptoms, thus confirming that the assigned diagnoses really represented the cause of palpitations.

The ILR yielded more diagnoses than conventional strategy, resulting in greater cost-effectiveness. Moreover, the ICER for the ILR strategy was low in relation to the costs of further investigations, which are necessary when the diagnoses are fewer. However, if only 50% of patients had undergone EPS, a proportion close to common clinical practice, the cost per diagnosis of conventional strategy would no longer have proved significantly higher than that of ILR. These data confirm that EPS constituted the main driver of cost, and that it is not cost-effective in patients without SHD (2).

The low diagnostic value of conventional strategy found in our study, however, does not negate the role of conventional diagnostic testing. Indeed, both ILR and conventional strategy have advantages and disadvantages, and may be considered complementary.

Our results may be influenced by the infrequency of symptoms, the absence of severe SHD, and the relatively young age of our patients. Indeed, the diagnostic values of ER and EPS mainly depend on the frequency of palpitations and the presence of SHD, respectively (1–3,5,6). Moreover, older patients are frequently unable to use ER properly (3,5,6). Thus, the baseline characteristics of the population are critical to predicting the diagnostic value of the investigations.

**Minor findings.** Most patients with palpitations are found to have premature beats, ST, SVT, and AF, while ventricular tachycardia is much less common, and is typical of patients with severe SHD (3). Our results are in line with the aforementioned observations. Indeed, as patients with extra-systolic palpitations and severe SHD were not enrolled, we found a high prevalence of SVT and AF, but no premature beats or ventricular tachyarrhythmias. However, the fairly high percentage of ST during symptoms in our patients suggests that initial evaluation often fails to individualize patients with anxiety-based palpitations.

Many subjects are not able to use ER properly (3,5). Indeed, in this study, 6 of 24 patients (25%) proved unable to use ER correctly, while only 1 of 25 patients (4%) was unable to activate ILR. The inclusion of prescriptive diagnostic categories based on the auto-activation feature of the new generation ambulatory ECG recorders could offer the advantage of overcoming the inability of some patients to activate the devices appropriately, further increasing the diagnostic yield of monitoring (9). However, the auto-activation mode did not prove to be useful in the present study.

**Study limitations.** As our study population included a group of highly selected patients, these results cannot be generalized to the entire population with palpitations, particularly those with frequent symptoms, who may benefit from ER, and those with severe SHD, in which EPS plays a much greater diagnostic role. Moreover, in the majority of patients, palpitations are a well-tolerated and benign condition, and initial evaluation is sufficient to yield a diagnosis or to exclude major arrhythmic disorders. Therefore, further investigations should be considered only in patients with SHD and in those with associated symptoms in which palpitations can be due to important arrhythmias, and prove very troublesome (1–4).

Given the possible placebo effect of invasive procedures, the open-label structure of the study may be considered a limitation. Indeed, probably as a consequence of a placebo effect of the surgical procedure, the mean time interval to the first palpitation recurrence during monitoring with ILR was higher than expected, taking into account the mean
time interval between each episode of palpitation in the year before ILR implantation (279 vs. 52 days).

Conclusions
This study demonstrates that, in subjects with infrequent unexplained palpitations and without severe SHD, ILR is a safe and cost-effective diagnostic approach. Thus, ILR may be a useful primary strategy in these patients, and in those who are poorly compliant with other recording devices. In particular, ILR should be offered to patients with persistent symptoms that suggest an arrhythmic cause, when conventional testing fails to yield a diagnosis.

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REFERENCES