

# Indications for the use of diagnostic implantable and external ECG loop recorders

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## Preamble

ECG loop recorders have a retrospective (loop) memory which continuously records and deletes the patient's ECG. They include a patient-activation function that allows the patient to activate ECG storage as a result of symptoms and an auto-activation feature that allows the capture of arrhythmic events without relying on patient compliance or perception of symptoms. Loop recorder devices can be both implantable (ILR) and external (ELR). *Table 1* summarizes the characteristics of the most common diagnostic loop recorders. The retrospective memory differentiates loop recorders from prospective-only event recorders. While event recorders have some usefulness in patients with intermittent palpitations, they have no indication to detect syncope.

Knowledge of what occurs during a spontaneous event is the ideal gold standard for evaluation. Patients with infrequent short-duration transient symptoms, recurring over weeks or months,

are unlikely to be diagnosed by conventional Holter monitoring, since the likelihood of symptom-ECG correlation is very low. Consideration should be given to patient-activated event recording in such patients, but this technique has important limitations that might prevent a successful ECG recording of the event, especially for those with syncope, as it implies the activation of recording by the patients once the patient has already recovered consciousness. In such circumstances, consideration should be given to implantable and external ECG loop recorders. It is likely that loop recorders will become increasingly important, and their use will increasingly be appropriate instead of, or before, many current conventional investigations. This early loop recorder approach implies, on the one hand, the need for careful initial risk stratification in order to exclude from such a strategy patients with potential life-threatening conditions that require immediate hospitalization or intensive evaluation and treatment. On the other hand, as a general rule ECG loop recorders are indicated only when there is a high pre-test probability of identifying a heart rhythm abnormality responsible of symptoms. These conditions will be discussed in the document.

Ultimately, technology may allow recording of multiple signals in addition to the ECG (e.g. blood flow or pressure, EEG, etc.) and the automatic immediate wireless transmission of pertinent data to a central monitoring station. Such advances will permit greater emphasis on the documenting and characterizing of spontaneous episodes. Conversely, they will result in less reliance for current diagnostic testing techniques that are largely designed to assess susceptibility to the provocation of syncope or palpitations in the laboratory.

**Table 1** Most common implantable and external loop recorders

Device/ company	Mode	Expected monitoring duration*	Total memory	Loop memory (patient activated)	Brady algorithms (auto-activated)	Tachy algorithms (auto-activated)	AF detection algorithms	Remote data transmission	Additional features
Reveal DX/ Medtronic	Implantable	3 years	42 min	5' pre + 1' post each (×3 episodes)	Asystole and bradycardia, (physician-defined)	16 consecutive intervals and probabilistic fast tachycardia (12/16 intervals), programmable rate boundary	No	Data stored in the device are sent on demand through an analogical telephone transmission to a web server. Physician accesses data via Internet with a secure log-in	Sensing and Detection Algorithm
Reveal XT/ Medtronic	Implantable	3 years	42 min	5 + 1min each (×3 episodes)	Asystole and bradycardia, (physician-defined)	16 consecutive intervals and probabilistic fast tachycardia (12/16 intervals), programmable rate boundary	Yes	Data stored in the device are sent on demand through an analogical telephone transmission to a web server. Physician accesses data via Internet with a secure log-in	Sensing and Detection Algorithm HR variability
Sleuth/Transoma	Implantable	28 months	630 min	3 + 2 min	When one R–R interval is less than the low heart rate setting	When 6 of 8 consecutive R-R intervals are greater than the high heart rate setting	No	Wireless (real-time) to personal data manager and then trans-telephonic to service centre. Daily + urgent reports from service centre to physician	HR trending data every four hours
Confirm DM2100/ St Jude	Implantable	3 years	48 min (147 episodes)	1'–4' pre + 0.5'–1' post	Asystole and bradycardia, (physician-defined)	Tachycardia (physician-defined)	No	Data stored in the device are sent on demand through an analogical telephone transmission to physician. Local software for analysis	HR trending data
Confirm DM 2102(a)/St Jude	Implantable	3 years	48 min (147 episodes)	1'–4' pre + 0.5'–1' post	Asystole and bradycardia, (physician-defined)	SVT and VT discrimination algorithm programmable rate boundary	Yes	Data stored in the device are sent on demand through an analogical telephone transmission to physician. Local software for analysis	AF burden
MCOT (b)/ Cardionet	External	Few weeks	21-days continuous monitoring	Patient's notes	Asystole and bradycardia, programmable duration	Rhythm changes and morphology	Yes (if applicable)	<i>Continuous</i> or 24 h loop memory, wireless (real-time) to personal data manager and then trans-telephonic to service centre. Daily + urgent reports from service centre to physician	HR trending data
LifeStar ACT/ LifeWatch	External	Few weeks	21-days retrievable monitoring	1' pre +0.5' post (total 20')	Asystole and bradycardia, programmable duration	No	Yes	Automatic ECG transmission of predefined events via Bluetooth wireless link to service centre. Daily + urgent reports from service centre to physician	Remotely programmable. Daily summary reports

LifeStar/LifeWatch	External	Few weeks	10 min	1' pre +0.5' post (total 9')	Asystole and bradycardia, programmable duration	No	Yes (when enabled)	Dial-in trans-telephonic (delayed on demand) or via Service Centre (fax, e-mail) or when the device is returned. Local software for analysis	
eVolution/eCardio	External	Few weeks	30 min	6 events (total 9')	Asystole and bradycardia, programmable duration	No	Yes	Automatic ECG transmission of predefined events via Bluetooth wireless link or over telephone line. Physician accesses data via Internet with a secure log-in	
3300 BT/Vitaphone	External	Few weeks	20 min	5 pre-/post-time settings, max 15 events	Asystole and bradycardia	Tachycardia	Yes	Automatic ECG transmission of predefined events via Bluetooth wireless link. Physician accesses data via Internet with a secure log-in	Display and acoustic feedback
V-PATCH/Medical System	External	Few weeks	30 h	30 s pre/30 s post	Asystole and bradycardia	Tachycardia	No	Automatic ECG transmission of predefined events via Bluetooth wireless link. Physician accesses data via Internet with a secure log-in	
King of the Heart/Instromedics	External	Few weeks	6 min	1–60 events	Bradycardia (physician-defined)	Tachycardia (physician-defined)	Yes	Dial-in trans-telephonic (delayed on demand) or via Service Centre (fax, e-mail) or when the device is returned. Local software for analysis	
SpiderFlash/Sorin	External	Few weeks	Several hours (c)	7.5'–15' pre + 7.5'–15' post (×1–2 episodes)	No	No	No	Dial-in trans-telephonic (delayed on demand) or when the device is returned. Local software for analysis	Daily auto-trigger Ecg (max 15 min)
Cardiocal/Reynolds Esaote	External	Few weeks	18 min	3'–16 pre + 1'–2' post	No	No	No	Dial-in trans-telephonic (delayed on demand) or when the device is returned	
Super/I-Cardia	External	Depends on patient compliance	2 recordings	40 s + 40 s each (×2 episodes)	No	No	No	Trans-telephonic (delayed on demand) or via Service Centre (fax, e-mail)	Disposable
Cardio PAL/Medicomp	External	Depends on patient compliance	Na	No	No	No	Yes	via Service Centre (fax, e-mail)	AF burden detection (real time analysis)

a, coming soon (not yet available); b, mobile cardiac outpatient telemetry; c, depends on Memory Card capacity.

\*Monitoring duration is determined by the battery longevity for implantable devices and by average maximum patients' compliance for external devices.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatments and the level of evidence as indicated in the tables below:

## Classes of recommendations

Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness /efficacy of the treatment;
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb	Usefulness/efficacy is less well established by evidence/opinion;
Class III	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

## Levels of evidence

Level of Evidence A	Data derived from multiple, randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single, randomized clinical trial or non-randomized study
Level of Evidence C	Consensus of opinion of the experts and/or small studies, re-prospective studies, registries

The Task force was unable to give formal recommendations for non-established indications, i.e. atrial fibrillation and risk stratification, due to the lack of sufficient trial-based evidence. In these fields, loop recorders remain very interesting research tools.

## Part I: Established indications

### 1. Management (diagnosis and treatment) of transient loss of consciousness (T-LOC)

#### Key points for use of ILR and ELR

- Clinical evaluation is enough to establish a likely mechanism of syncope in the majority of patients
- Exclude high-risk patients, i.e. those with a clear indication for ICD, pacemaker, or other treatments independent of a definite diagnosis of the cause of syncope
- Be aware that the pre-test selection of the patients influences the subsequent findings. Include patients with a high likelihood of arrhythmic events
- Include patients with a high probability of recurrence of syncope in a reasonable time period
- Due to the unpredictability of syncope recurrence, be prepared to wait for a substantial time before obtaining such a correlation
- Your ideal goal should be to obtain a correlation between ECG findings and syncopal relapse. Weaker end-points are non-syncopal arrhythmias.

### Epidemiology and natural history of syncope (probability of recurrence of syncope)

Syncope is extremely frequent in the general population and probably more than 50% of the general population complains of an episode of T-LOC of suspected syncopal nature during life. Approximately 30–40% of young adults experience at least one episode of T-LOC with a peak between the age of 10 and 30 years. T-LOC becomes also increasingly frequent after the age of 60. In the Framingham Heart Study, for example, the incidence of syncope shows a sharp rise from 5.7 events per 1000 person-years in men aged 60–69 years to 11.1 in men aged 70–79 years.<sup>1</sup> However, only one-third of these subjects present in a clinical setting and an even smaller proportion deserve some specialized evaluation. An exhaustive review of this issue can be found in the recent 2009 ESC guidelines.<sup>2</sup>

For the purpose of this document, the knowledge of the probabilities of syncope recurrence within the operational duration of the loop device (in general, 4 weeks for external and up to 3 years for implantable devices) becomes crucial for an appropriate selection of the candidates for these diagnostic evaluations. Number of episodes of T-LOC and their frequency are the strongest predictors of recurrence. Table 2 provides T-LOC recurrence rates in young patients (<40 years) without structural heart disease,<sup>3</sup> and Tables 3 and 4 provide the same probability observed in the pooled population of patients aged >40 years, at low-risk according ESC classification (see below), who participated in the ISSUE 1 and 2 studies because affected by unexplained syncope or suspected neurally mediated syncope.<sup>4–7</sup> Conversely, age, sex, tilt-test response, severity of presentation,<sup>3</sup> and presence or absence of structural heart disease<sup>8</sup> have minimal or absent predictive value on probability of syncope recurrence and therefore are not useful for the selection of the patients. However, the presence of structural heart disease increases the likelihood of documentation of an arrhythmia, which will have therapeutical consequences.

#### Implantable loop recorders

##### Value of implantable loop recorder in diagnosis of syncope

In the initial clinical experience, the ILR was used for diagnosis in patients with unexplained syncope at the end of unsuccessful full conventional work-up. In a small series of highly selected patients, symptom–ECG correlation was achieved in 88% of patients within a mean of 5 months of implantation.<sup>8</sup> Pooled data from nine studies<sup>4–6,9–14</sup> for a total of 506 patients with unexplained syncope at the end of a complete conventional investigation show that a correlation between syncope and ECG was found in 176 patients (35%); of these 56% had asystole (or bradycardia in few cases) at the time of the recorded event, 11% had tachycardia, and 33% had no arrhythmia (Figure 1). In pooled data from seven studies,<sup>4–6,10–13</sup> pre-syncope was much less likely to be associated with an arrhythmia than syncope raising some concern to be an accurate surrogate for syncope in establishing a diagnosis (Figure 2). Asystole is only rarely observed during pre-syncope, suggesting that asystole is quite specific for syncope. The diagnostic yield of ILR was hampered by the failure to document a syncopal relapse in further 5 to 9% of the patients (16% of the events) despite the manual and automatic features of the device<sup>4,6,10</sup> and by false-positive arrhythmia detection even in the most recent devices.

**Table 2** Prognosis of patients <40 years with T-LOC of suspected syncopal nature (modified from Sheldon and Rose<sup>3</sup>)

Number of syncopes during life	Risk of recurrence of syncope after the index episode	
	Actuarial risk 1 year (%)	Actuarial risk 2 years (%)
1	10	10
2	19	29
≥3	40	54
≥6	43	60

**Table 3** Prognosis of patients with uncertain diagnosis and low risk >40 years according the number of syncopes during life

Number of syncopes during life	Risk of recurrence of syncope after the index episode		
	Actuarial risk 1 year (%)	Actuarial risk 2 years (%)	Estimated risk 4 years <sup>a</sup> (%)
1–2	15.4	19.7	28.2
3	36.5	41.7	52.2
4–6	37.0	43.8	57.4
7–10	37.5	43.7	56.2
>10	44.3	56.4	80.7

<sup>a</sup>Assuming a linear increase.**Table 4** Prognosis of patients with uncertain diagnosis and low risk >40 years according the number of syncopes during the previous 2 years

Number of syncopes during last 2 years	Risk of recurrence of syncope after the index episode		
	Actuarial risk 1 year (%)	Actuarial risk 2 years (%)	Estimated risk 4 years <sup>a</sup> (%)
1–2	22.8	27.5	37.1
3	29.1	35.7	48.9
4–6	43.0	50.8	66.3
7–10	43.2	48.8	59.9
>10	85.6	98.1	100

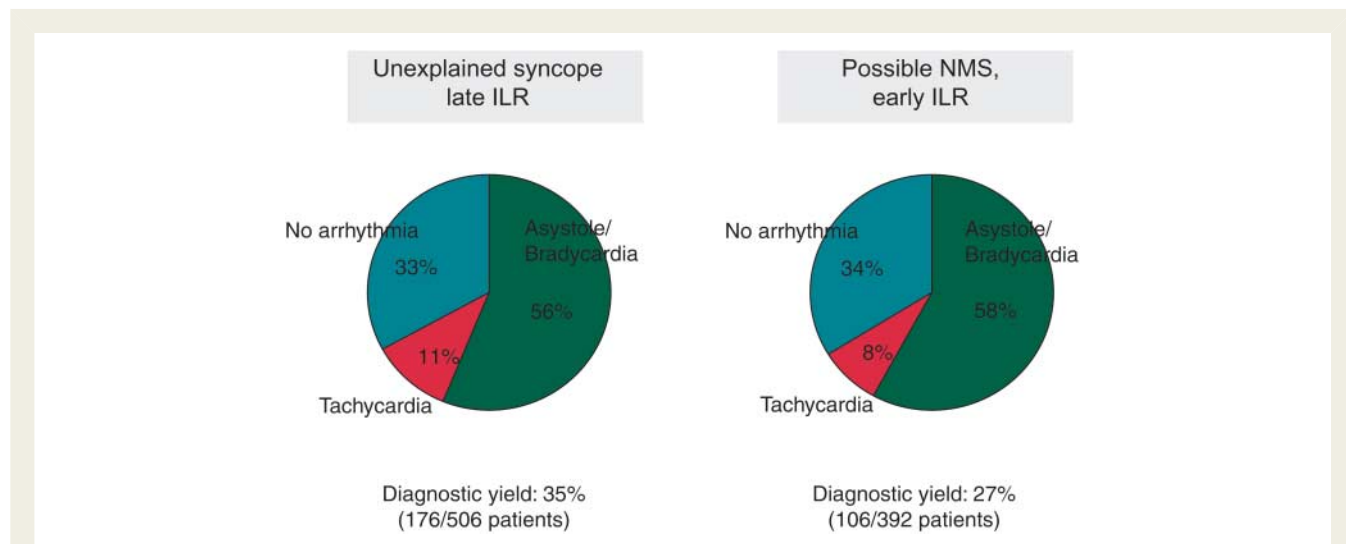
<sup>a</sup>Assuming a linear increase.

The correlation of a specific ECG finding with a spontaneous syncope can be considered as the gold standard, provided that this finding is reproducible in different episodes. There are few data on reproducibility of ILR findings in the literature, mainly

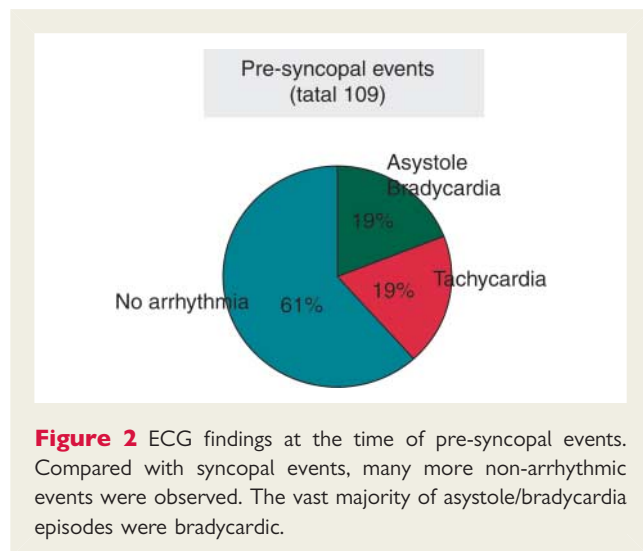
case reports. Pooling data from ISSUE-1<sup>4,5</sup> and ISSUE-2<sup>7</sup> studies, 26 patients had at least two syncopal episodes documented by ILR, 9 of whom due to an arrhythmia: in 25 of these the finding during the second syncopal episode was the same than that observed during the first syncope. These data suggest that, in the vast majority of patients, the presence or absence of an arrhythmia during the first documented syncope can be considered a diagnostic finding and a therapeutic decision can be taken. However, the number of observations still remains small and the ISSUE data cannot be regarded as conclusive.

From the initial experience in patients with unexplained syncope, it appears that the ILR might become the reference standard to be adopted when an arrhythmic cause of syncope is suspected but not sufficiently proved to allow an aetiological treatment. There are several situations in which ILRs were proved to be useful. These are:

- Unexplained syncope in the presence of detectable cardiac abnormalities:
  - (a) Patients with bundle branch block in whom a paroxysmal AV block is likely despite a negative electrophysiological evaluation;<sup>6,15</sup> in these patients, despite a negative invasive evaluation, including electrophysiological study, the most frequent finding is an intermittent AV block, which was discovered by ILR in 63% of the documented events within a median of 48 days;<sup>6</sup> these results were recently confirmed in the B4 study<sup>15</sup> in which an intermittent AV block that was discovered by ILR was found in 71% of the documented events. Admittedly, however, these patients represented only 33 and 34%, respectively, of the patients undergoing ILR implantation, leaving unresolved the issue of the mechanism of syncope in those patients who did not have syncopal recurrence during the ILR follow-up period;
  - (b) Patients with definite structural heart disease in whom an arrhythmia is likely despite a negative cardiological work-up;<sup>5,8,16</sup>
  - (c) Patients with cardioinhibitory carotid sinus hypersensitivity when the understanding of the exact mechanism of spontaneous syncope is needed to guide a specific therapy<sup>17</sup>
  - (d) In paediatric patients in whom a cardiac cause of syncope is suspected due to structural heart disease or electrocardiographical abnormalities;<sup>18</sup> in pooled data on 89 patients from six small series,<sup>18</sup> a diagnosis was achieved in 67% of patients: 33% of these had a bradycardia or asystole at the time of the recorded event, 23% had tachycardia and 43% had no arrhythmia
- Mechanism likely, but justification of therapy needed: patients who have a likely diagnosis of neurally mediated syncope after the initial evaluation, either positive or negative response during tilt testing, in order to capture an asystolic event when cardiac pacing would be justified by the severity and unpredictability of symptoms and lack of alternative therapies.<sup>7</sup>
- Diagnosis of syncope not established, just suspected:
  - (a) Patients in whom epilepsy was suspected but the treatment has proved ineffective<sup>19</sup> and in patients with established epilepsy in order to detect peri-ictal cardiac arrhythmias that require treatment;<sup>20</sup>



**Figure 1** Diagnostic yield in patients with unexplained syncope and implantable loop recorder inserted at the end of conventional work-up and in patients with suspected neurally mediated syncope and implantable loop recorder inserted early after initial evaluation. The vast majority of asystole/bradycardia episodes were asystole.



**Figure 2** ECG findings at the time of pre-syncope events. Compared with syncopal events, many more non-arrhythmic events were observed. The vast majority of asystole/bradycardia episodes were bradycardic.

- (b) Patients with major depressive diseases and frequent recurrent unexplained episodes of LOC in order to exclude an arrhythmic cause of syncope;<sup>16</sup>
- (c) In older patients with non-accidental falls to establish the syncopal nature of the event<sup>21</sup>

Similar findings were observed when ILR was inserted in patients with unexplained syncope at the end of the conventional work-up<sup>4,9–12,14</sup> and when ILR was inserted in patients with suspected neurally mediated syncope in an early phase after the initial evaluation<sup>7</sup> (Figure 1). In both cases, a prolonged asystole (either due to sinus arrest or due to AV block) on average 10–15 s in duration was the most frequently observed event.

The diagnostic yield was similar in patients with and without structural heart diseases (including abnormal ECG): 58 vs. 51% in the study of Solano et al.,<sup>10</sup> 45 vs. 51% in the study of Pezawas

et al.<sup>16</sup> and 39 vs. 50% in the study of Pierre.<sup>14</sup> While patients with and without structural heart disease had similar incidence of syncope recurrence, its mechanism was different: patients with structural heart disease more frequently had paroxysmal AV block and tachyarrhythmias and patients without structural heart disease more frequently had sinus bradycardia/sinus arrest or no arrhythmia; on the other extreme, the patients with major depressive diseases only seldom showed arrhythmic events.<sup>16</sup> More patients with structural heart disease finally received an ILR-guided therapy.

The diagnostic yield was higher in the older patients. In one study,<sup>22</sup> the patients aged >65 years had a 2.7 higher syncope recurrence rate (56 vs. 32%) than those aged <65 years, and were 3.1 more times likely to have an arrhythmia at time of syncope (44 vs. 20%). An increased incidence of bradycardia with advancing age was also noted by Krahn et al.<sup>23</sup>

Solano et al.<sup>8</sup> estimated that about 28% of patients with unexplained syncope at the end of a conventional work-up (which corresponds to 5% of all patients referred for evaluation to a tertiary syncope facility) ultimately have an indication for ILR implantation; the corresponding need for ILR implantation in the general population was estimated to be 34 per million inhabitants/year. If we add this estimate to the new ILR indication for ISSUE-like patients (i.e. those affected by suspected neurally-mediated syncope, history of recurrent syncope beginning in middle or older ages and frequent injuries),<sup>7</sup> the need for ILR implantation could probably increase to about 135 per million inhabitants/year.

#### *The diagnostic value of non-syncopal episodes documented by implantable loop recorder*

This issue is of practical importance, since a good correlation with the index syncope would allow the use of non-syncopal documented events, either pre-syncope or asymptomatic, as surrogate endpoints predictive of the mechanism of syncope, to increase the

diagnostic yield, and/or to anticipate treatment without waiting for documentation of a syncopal episode.

Few studies correlate syncopal with non-syncopal episodes within the same patient in order to evaluate the positive predictive value of the finding of a non-syncopal episode. In the study of Krahn *et al.*,<sup>24</sup> the six patients with an arrhythmia during pre-syncope (bradycardia in four patients and tachycardia in two) also had the same arrhythmia during syncope; on the contrary, discordant findings were found in three patients without arrhythmia during pre-syncope who had an arrhythmia when they experienced a syncopal attack. Similarly, in the ISSUE 2 study,<sup>25</sup> of the 32 patients with non-syncopal episodes, 9 patients had an arrhythmia (defined as asystole >3 s or tachyarrhythmia  $\geq 160$  bpm lasting  $\geq 32$  bpm) and all of them had the same arrhythmia during the index syncope; on the contrary, discordant findings were found in 7 (30%) of 23 patients without arrhythmia during non-syncopal episodes who had a significant arrhythmia during the index syncope.

A low predictive value was also observed with non-syncopal sinus bradycardia (that classified as type 2 in the ISSUE classification). In the Krahn study,<sup>26</sup> among four patients with bradycardic asymptomatic events, two had prolonged asystole at the time of symptomatic events and the other two had absence of any arrhythmia. In the ISSUE-2 study,<sup>25</sup> among 11 patients with bradycardic non-syncopal events, only 5 (45%) had a bradycardic syncope (2 bradycardic and 3 asystolic syncope) whereas the remaining had no bradycardia at the time of the index syncope.

To summarize, the absence of a significant arrhythmia (including sinus bradycardia) during non-syncopal episodes (either symptomatic or asymptomatic) has a low predictive value for the diagnosis of the mechanism of syncope. In contrast, the presence of an asystole or a primary tachyarrhythmia, either patient-activated or asymptomatic (automatically activated), usually predicts the mechanism of syncope, reinforcing the strategy of considering these non-syncopal arrhythmias as diagnostic findings. The meaning of these findings is in accordance and reinforced by similar conclusions made with other forms of prolonged ECG monitoring and reported in current guidelines.<sup>2,27</sup> Using the criteria of an asystole >3 s or a primary tachyarrhythmia  $\geq 180$  bpm lasting  $\geq 32$  beats, in the ISSUE 2 study the diagnostic yield would have increased by 9% (from 26 to 35%) (M. Brignole, personal communication) and diagnosis would have been anticipated on average by 137 days in respect of diagnosis made by documentation of syncope.<sup>25</sup> Admittedly, this task force underlines that these cut-off for asystole and tachycardia are both largely arbitrary.

#### Technical aspects

Although auto-activation feature increases the diagnostic yield, this feature can be compromised by the detection of false arrhythmias<sup>28,29</sup> and the missed detection of true arrhythmias.<sup>30,31</sup> Documented causes of false arrhythmia storage in ILRs include undersensing related to sudden reductions in R-wave signal amplitude during both normal sinus rhythm<sup>32</sup> and arrhythmias,<sup>31</sup> undersensing by transient loss of ECG signal related to device amplifier saturation,<sup>29</sup> T-wave<sup>28</sup> and myopotential.<sup>28</sup> A systematic analysis of a large series of 2613 previously recorded, automatically detected episodes from 533 patients with the Reveal Plus model showed that a total of 71.9% of episodes were inappropriately detected

by the original ILR, and at least 88.6% of patients had one or more inappropriate episodes.<sup>33</sup> Even if most of these misdetections can easily be recognized, they can potentially determine misdiagnosis with consequent administration of useless therapies. The prevalence of misdiagnosis is unknown. Corresponding data concerning the new generations of ILR are still missing. However, avoidance of misdetection is clearly a priority of research.

Finally, like all implanted devices, ILRs also carry the risk of pocket infections that resolve with device explantation. This complication, which can occur either in the periprocedural phase or late during the follow-up, was reported in a percentage of 1 to 5% of the patients.<sup>7,10</sup>

#### Classification of responses

Because of the heterogeneity of findings and the wide variety of rhythm disturbances recorded with the ILR at the time of syncope, the ISSUE investigators have proposed a classification that groups the observations into homogeneous patterns in order to define an acceptable standard, useful for future studies and clinical practice (Table 5).<sup>34</sup> Type 1 (asystole) was the most frequent finding that was observed in 63% of patients; type 2 (bradycardia) was observed in 5% of patients; type 3 (no or slight rhythm variations) was observed in 18% of patients; and type 4 (tachycardia) was observed in 14% of patients. This classification has become widely used and validated by others.<sup>16,35,36</sup> The ISSUE classification has some pathophysiological implications, which are helpful to distinguish different types of arrhythmic syncope and have potentially different diagnostic, therapeutic, and prognostic implications. In types 1A, 1B, and 2, the findings of progressive sinus bradycardia, most often followed by ventricular asystole due to sinus arrest, or progressive tachycardia followed by progressive bradycardia and, eventually, ventricular asystole due to sinus arrest, suggest that the syncope is probably neurally mediated. In type 1C, the finding of prolonged asystolic pauses due to sudden-onset paroxysmal AV block with concomitant increase in sinus rate suggests another mechanism, namely intrinsic disease of the His–Purkinje system as observed in Stokes–Adam attacks. In types 4B, 4C, and 4D, a primary cardiac arrhythmia is typically responsible for syncope. In the other types, in which no arrhythmia is detected, the exact nature of syncope remains uncertain because of the lack of contemporary recording of blood pressure; however, the finding of progressive heart rate increase and/or decrease at the time of syncope suggests a (primary or secondary) activation of the cardiovascular system and a possible hypotensive mechanism.

#### ILR in syncope: where in the workup?

In the initial experience, the ILR was used as last resort in the evaluation of syncope after all investigations were negative. However, several studies have shown a poor correlation between the responses of tilt testing,<sup>4,37,38</sup> ATP test<sup>36–38</sup> and electrophysiological study,<sup>6,15</sup> and the ECG observation at the time of spontaneous syncope (the reference standard). In other words, the poor sensitivity and specificity of some of the most important tests for diagnosis raise concern on their real utility in the diagnostic work-up. Given the limited diagnostic value of short-term ECG monitoring (Holter, external loop recorder),<sup>27</sup> several investigators have proposed an early usage of the ILR soon in an initial phase of the diagnostic work-up.

**Table 5** The ISSUE classification of ECG-documented spontaneous syncope

- **Type 1, Asystole.** RR pause  $\geq 3$  s.
  - (a) *Type 1A, Sinus arrest:*
    - Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest.
  - (b) *Type 1B, Sinus bradycardia plus AV block*
    - Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate
    - Sudden onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate
  - (c) *Type 1C, AV block*
    - Sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate
- **Type 2, Bradycardia.** Decrease of heart rate  $>30\%$  or  $<40$  bpm for  $>10$  s.
  - (a) *Type 2A.* Decrease of heart rate  $>30\%$
  - (b) *Type 2B.* Heart rate  $<40$  bpm for  $>10$  s.
- **Type 3, No or slight rhythm variations.** Variations of heart rate  $<30\%$  and heart rate  $>40$  bpm.
  - (a) *Type 3A.* No variation or  $<10\%$  variation in heart rate
  - (b) *Type 3B.* Increase in heart rate  $>10\%$  but  $<30\%$  and  $<120$  bpm; or, decrease  $>10\%$  but  $<30\%$  and  $>40$  bpm
- **Type 4, Tachycardia.** Increase of heart rate  $>30\%$  and heart rate  $>120$  bpm.
  - (a) *Type 4 A.* Progressive sinus tachycardia
  - (b) *Type 4 B.* Atrial fibrillation
  - (c) *Type 4 C.* Supraventricular tachycardia (except sinus)
  - (d) *Type 4 D.* Ventricular tachycardia.

One study<sup>39</sup> randomized 60 patients with unexplained syncope to 'conventional' testing with external loop recorder and tilt and electrophysiological testing or to prolonged monitoring with the ILR. The results were that a strategy of implantation of the loop recorder in an initial phase of the work-up is more likely to provide a diagnosis than conventional testing (52 vs. 20%) during a 12-month follow-up period. However, patients at high risk of life-threatening arrhythmias, as were those with an ejection fraction of  $<35\%$ , were excluded. These results were confirmed in the Eastbourne Syncope Assessment Study<sup>40</sup> in 201 patients who, following a basic clinical work-up, were randomized to receive the ILR or conventional investigation and management. The ILR group patients had a 6.5 higher probability of achieving a diagnosis when compared with the conventional group (43 vs. 6%) during a follow-up of 17 months. There were eight deaths in the ILR and nine in the conventional group. An early ILR implantation immediately after the initial evaluation was also performed in the ISSUE 2 study in 392 patients with suspected neurally mediated syncope.<sup>7</sup> Patients with severe structural heart disease were excluded. A diagnosis was achieved in 26% of the patients during a median follow-up of 9 months. During the study period, seven patients died, none of these due to arrhythmic causes (two due to strokes and five due to non-cardiovascular). Severe trauma secondary to syncope relapse occurred in 2% and mild trauma in 4%.

In conclusion, all the above studies showed that early ILR implantation can be safely performed in the initial phase of the diagnostic evaluation, provided that patients at risk of life-threatening events are carefully excluded. According to the guidelines of syncope of the European Society of Cardiology,<sup>2,27</sup> the patients at risk who require immediate hospitalization and intensive evaluation can be identified after the initial evaluation (Table 6). In particular:

- the patients with an established indication for implantable cardioverter-defibrillator (ICD) implantation according to guidelines (6) should receive this therapy upfront. The monitoring function of the defibrillator can subsequently be used to study the mechanism of syncope.
- the patients with previous myocardial infarction and non-sustained ventricular tachycardia should undergo an electrophysiological study, which includes premature ventricular stimulation; ILR should be considered only at the end of a negative complete work-up;
- the patients with clinical or electrocardiographic features that suggest an intermittent bradycardia should undergo in-hospital prolonged telemetric monitoring and eventually an electrophysiological evaluation; ILR should be considered at the end of a negative complete work-up.

When these risk features are absent, an ILR strategy can safely be undertaken in the patients at risk for arrhythmic syncope who have a severe presentation of syncope (because of high risk of trauma or high frequency of episodes) which can benefit of a mechanism-specific therapy. In the less severe forms, clinical evaluation is sufficient to establish a likely mechanism of syncope in the majority of

**Table 6** Short-term high-risk criteria that require immediate hospitalization or early intensive evaluation as appropriate (according ESC guidelines on syncope<sup>2</sup>)

- Situations in which there is a clear indication for ICD or pacemaker treatment independently of a definite diagnosis of the cause of syncope according to recent ICD/CRT guidelines
- Severe structural cardiovascular or coronary artery disease (heart failure or low ejection fraction or previous myocardial infarction)
- Clinical or ECG features suggesting an arrhythmic syncope:
  - Syncope during exertion or supine
  - Palpitations at the time of syncope
  - Family history of sudden death
  - Non-sustained ventricular tachycardia
  - Bundle branch block (QRS duration  $\geq 0.12$  s)
  - Inadequate sinus bradycardia ( $<50$  bpm) or sinoatrial block in the absence of negatively chronotropic medications except physically-trained person
  - Pre-excited QRS complexes
  - Prolonged or short QT interval
  - Right bundle branch block pattern with ST-elevation in leads V1–V3 (Brugada syndrome)
  - Negative T waves in right precordial leads, epsilon waves, and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia
- Important comorbidities (severe anaemia, electrolytic disturbance, etc)



patients and no further investigation is usually necessary. Patients at low risk for arrhythmic syncope are not candidates for ILR monitoring. Although the estimation of the usefulness of ILR implantation is largely individual, as a general rule, ILR is not indicated when the probability of syncope recurrence during the longevity of the battery is low (see Tables 2–4) and when the knowledge of a precise ECG–symptom correlation is not required for therapeutic decisions.

A schematic flow chart is provided in Figure 3. The recommended indications and diagnostic criteria are summarized in the proper section.

*Therapy guided by implantable loop recorder*

Little is known about the outcomes after ILR-guided specific therapy.

In the Eastbourne Syncope Assessment Study,<sup>40</sup> performed on a typical unselected population, the patients randomized to ILR management demonstrated an increased diagnostic rate and ECG-directed treatments than conventional investigation group. Despite a specific ECG-directed therapy could only be used to a minority of patients, the long-term follow-up demonstrated a significant reduction in syncopal events with improved quality of life.

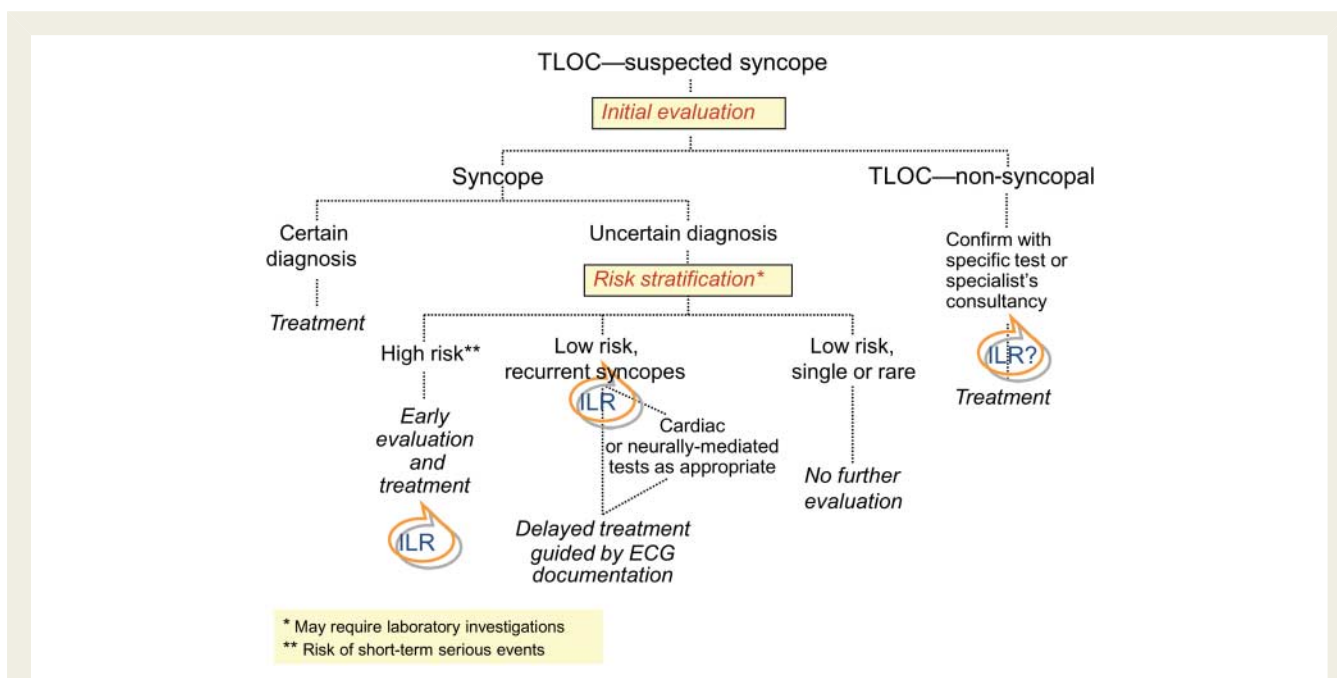
Since prolonged asystole is the most frequent finding at the time of syncope recurrence, cardiac pacing is the specific therapy most used in ILR population. In the initial ILR experience, bradycardia leading to pacemaker implantation was detected in 17% of 206 patients undergoing ILR insertion.<sup>10</sup> In pooled data of 1011 ILR patients from eight studies,<sup>4–6,14,17,23,35,40</sup> a pacemaker was implanted in 184 (18%) of patients (50% of those who had had an ILR documented syncope). This rate ranged from 12% in patients with suspected neurally mediated syncope<sup>7</sup> to 44% in the patients with a baseline bundle branch

block.<sup>6</sup> Few data are available on the subsequent outcome. In general, ILR-guided cardiac pacing reduces syncope burden in patients with asystole, but does not prevent all syncopes. ILR does not alter the course of non-arrhythmic syncope. In the ISSUE 2 study,<sup>7</sup> the 1-year burden of syncope decreased from  $0.83 \pm 1.57$  episodes per patient/year in the control group of patients without any ILR-guided specific therapy to  $0.05 \pm 0.15$  episodes per patient/year in the patients treated with a pacemaker (87% relative risk reduction,  $P = 0.001$ ). In the study of Sud *et al.*,<sup>35</sup> after the insertion of a cardiac pacemaker, syncope burden decreased from 2.17 per year to 0.45 per year in patients with 1A or 1B ECG pattern of the ISSUE classification ( $P = 0.02$ ) and from 4.57 per year to 0 per year in the type 1C syncope ( $P = 0.001$ ) patients.

In pooled data of 799 ILR patients from seven studies,<sup>4–6,8,14,17,40</sup> an ICD and radiofrequency catheter ablation were also consistently used in 1 and 1% of the patients who had had ILR-documented ventricular and atrial tachyarrhythmias, respectively. Antiarrhythmic drugs were finally used in rare cases in patients with paroxysmal atrial fibrillation and flutter.

**External loop recorders**

The major limitation of ELRs for diagnosis of unpredictable and infrequent symptoms such as syncope is that the patients must wear continuously external electrodes in order to activate loop memory. The ELR appears to have its greatest role in motivated patients with frequent (pre)-syncopes where spontaneous symptoms are likely to recur within 4–6 weeks. This time frame is usually the maximum that a patient can comply; shorter duration yield lower diagnostic yield.<sup>41</sup> ELR can also be used if the clinical presentation suggests that documenting an ECG during pre-syncope will elucidate the mechanism of syncope. Indications are



**Figure 3** Implantable loop recorder in the work-up of transient loss of consciousness (T-LOC).

similar to those for ILRs but the patient selection depends on the knowledge of the probability of recurrence (see Epidemiology and natural history). Also diagnostic criteria are the same as for ILRs.

In randomized comparison studies, ELRs proved to yield a higher diagnostic value than conventional evaluation or Holter monitoring<sup>42,43</sup> but lower than ILRs.<sup>39</sup>

Since true syncope usually recurs unpredictably over months or years, the indications for ELR are limited to few selected patients with high probability of recurrence in a very short time. The diagnostic yield in such patients is even quite low. In one study,<sup>44</sup> among 24 patients with a mean of three episodes during the previous 6 months and no structural heart disease, only 1 syncopal episode could be recorded by ELR which showed sinus tachycardia. In another study,<sup>45</sup> among 57 patients with a median of 10 syncopes during last year, a diagnosis was made in 25%, a significant arrhythmia being diagnosed in 5 (9%).

External loop recorders proved to be more useful when frequent pre-syncopal symptoms were considered in addition to true syncopal episodes and less specific positivity criteria are used, mainly in order to exclude an arrhythmic cause of symptoms. For example, in COLAPS trial,<sup>43</sup> an ECG–symptom correlation was found in 44 of 78 patients (56%), but an arrhythmia was identified in only 1 patient whereas it could be excluded in the other 43. In a multicenter study,<sup>45</sup> a symptom–arrhythmia correlation was found in 15% and symptom–absence of arrhythmia correlation was found in another 25% of 51 patients; these rates were 27 and 14%, respectively, when an auto-trigger MCOE device was used in another 62 patients.

With the new auto-triggered devices, a lot of asymptomatic tachy-arrhythmias are usually recorded.<sup>46</sup> It should be stressed that, in absence of study of correlation with syncopal events, their positive predictive value is unknown, and monitoring should be continued until diagnosis is confirmed by symptom documentation whenever possible.

## Recommendations

### Indications for ILRs and ELRs in patients with syncope

#### ILRs

*Class I.* ILR is indicated:

- In an early phase of evaluation of patients with recurrent syncope of uncertain origin who have:
  - absence of high-risk criteria that require immediate hospitalization or intensive evaluation, i.e. those listed in the *Table 5*; and
  - a likely recurrence within battery longevity of the device (*Level of evidence A*)
- In high-risk patients in whom a comprehensive evaluation (that listed in *Table 5*) did not demonstrate a cause of syncope or lead to specific treatment (*Level of evidence B*)

*Class II A.* ILR may be indicated:

- To assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain neurally mediated syncope presenting with frequent or traumatic syncopal episodes (*Level of evidence B*)

*Class II B.* ILR may be indicated:

- In patients with T-LOC of uncertain syncopal origin in order to definitely exclude an arrhythmic mechanism (*Level of evidence C*)

#### ELRs

*Class II A.* ELRs may be indicated in patients with recurrent (pre)syncope who have:

- inter-symptom interval of  $\leq 4$  weeks, and
- suspicion of arrhythmic origin and
- absence of high-risk criteria that require immediate hospitalization or intensive evaluation, i.e. those listed in *Table 5* (*Level of evidence B*)

### Interpretation of ILR and ELR findings in patients with syncope

*Class I*

- ILR and ELR findings are diagnostic when:
  - a correlation between syncope and an arrhythmia (brady- or tachyarrhythmia) is detected (*Level of evidence B*)
  - in the absence of such correlation, periods of Mobitz II or III degree AV block or a ventricular pause  $> 3$  s (with possible exceptions for young trained persons, during sleep, medicated patients or rate-controlled atrial fibrillation), or rapid prolonged (i.e.  $\geq 160$  bpm for  $> 32$  bpm) paroxysmal atrial or ventricular tachyarrhythmias are detected (*Level of evidence C*)
- ILR and ELR findings exclude an arrhythmic cause when there is no correlation between syncope and rhythm variation (*Level of evidence B*).

*Class III.* ILR and ELR findings are not diagnostic and monitoring should be continued in case of:

- Pre-syncope without any relevant arrhythmias as those listed above (*Level of evidence C*).
- Asymptomatic arrhythmias (other than those listed above) (*Level of evidence C*).
- Sinus bradycardia (in absence of syncope) (*Level of evidence C*)

*Note:* This task force recognizes that, in real world practice, there is occasionally the need to make a therapeutic decision with weaker diagnostic criteria. Physicians should be aware that effectiveness of therapy is not well documented in such cases.

## 2. Diagnosis of undocumented palpitations

### Key points for use of ILR and ELR

- ELRs are much more useful for palpitations than for syncope evaluation
- ILRs consequently are less frequently indicated
- Event records may be useful only when symptoms last enough to allow the patient to activate the recorder
- The diagnostic value of loop recorders is higher than Holter.

### The rationale for loop monitoring in patients with undocumented palpitations

Palpitations represent a very common symptom for which people search medical attention.<sup>47–49</sup> They may be due either to cardiac arrhythmias (ranging from single premature atrial and ventricular beats to sustained atrial and ventricular tachyarrhythmias) or to sinus tachycardia related to non-cardiac reasons, such as anxiety, psychiatric disorders, fever, anaemia, drug effects, hyperthyroidism, and so on. In several cases, especially in patients with infrequent symptoms, a diagnosis is difficult to establish in spite of careful clinical evaluation that includes standard ECG and Holter monitoring.<sup>50</sup> The

usefulness of *event recorders*, which are positioned or activated by the patient immediately after symptom onset, is hampered by the fact that they are unable to detect the mechanism of onset of episodes, the short-lasting episodes and by the lack of automatic detection.

Although the nature of palpitations remains unexplained ('unexplained palpitations'), a correlation between symptoms and ECG findings can still be warranted by the usage of ELR and ILR.

Many patients with palpitations can be managed on out-patient basis. However, high-risk patients may need aggressive interventions, including hospitalization and invasive tests to rule out life-threatening arrhythmias. High-risk criteria are summarized in *Table 6* (see section on syncope). On the other hand, some patients with rare and well tolerated symptoms and no underlying cardiac disease can be reassured and followed without further tests even if a final diagnosis cannot be reached. Therefore, the patients at low risk with frequent and / or severe symptoms are the best candidates for loop recorders.

#### The diagnostic value of external loop recorder

They are superior to Event Recorders, since they are capable of recording retrospective and prospective ECG activated by the patient. Furthermore, they allow automatic recording of asymptomatic arrhythmias. Since continuous maintenance is required, continuous monitoring cannot be carried out for more than 4 weeks. Accordingly, patients with weekly recurrence of short-lasting palpitations represent the ideal candidates.<sup>51–56</sup> Of course, ELR can be used intermittently for a longer time, as well as event recorders, when the duration of palpitation is long enough to allow the application of the device by the patient immediately after symptom onset. In clinical studies in which patients with at least weekly recurrence of palpitations, ELRs as well as event recorders showed a consistent diagnostic power of 66–75%, superior to that of conventional Holter monitoring.<sup>52,57–62</sup> Owing to the nature of short-lasting palpitations in low-risk patients, the most frequent findings are atrial and ventricular premature beats and atrial tachyarrhythmias; ventricular tachycardia and pauses are less frequently encountered.

Since palpitations recur more frequently than syncope, ELRs are much more useful for palpitation than for syncope evaluation. In a consecutive series of 125 patients affected by recurrent palpitations, pre-syncope, or syncope, all with an inter-symptom interval of  $\leq 4$  weeks, ELRs were applied in 86, 8, and 6% of cases, respectively.<sup>62</sup> However, the ECG–symptom correlation rate was similar in those with palpitations, pre-syncope, and syncope.

#### The diagnostic value of implantable loop recorder

Implantable loop recorders, due to their invasive nature and costs, play a minor role in patients with recurrent unexplained palpitations when compared with those with syncope. They may be implanted in patients with infrequent palpitations (less than monthly) associated with haemodynamic impairment when all other tests result inconclusive. Few studies are available on the use of ILR in patients with unexplained palpitations.<sup>63</sup> In the RUP (Recurrent Unexplained Palpitations) study, 50 patients were enrolled with infrequent ( $\leq 1$  episode/month) and sustained ( $> 1$  min) palpitations. 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), or to ILR implantation with 1-year monitoring. 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.<sup>63</sup> After a diagnosis was reached, patients were followed up for at least 12 months. Palpitations were completely eliminated in 22 patients with arrhythmic diagnosis treated with ablation, pacemaker, or drugs.

The main advantages, drawbacks, and indications for Event Recorders, ELR, and ILR are summarized in *Table 7*.<sup>64</sup>

#### Interpretations of external loop recorder and implantable loop recorder findings

As for syncope, the gold standard for loop recorder use is the correlation between ECG recordings and symptoms. The specificity of the technique is high when an arrhythmia is documented during symptoms. Normal sinus rhythm during palpitations excludes an

**Table 7** Comparative advantages, drawbacks and indications for event recorders, ELR and ILR (modified from Giada et al.<sup>63</sup>)

	Event recorders	ELR	ILR
Advantages	Low cost; easy to use	Retrospective and prospective ECG records; possibility to record asymptomatic arrhythmias automatically	Retrospective and prospective ECG records; quite good ECG records; monitoring capability up to 36 months; possibility to record asymptomatic arrhythmias automatically
Drawbacks	Short-lasting arrhythmias are not recorded; arrhythmic triggers are not revealed; poor ECG records	Monitoring cannot be carried out for more than 3–4 weeks; continual maintenance is required; devices are uncomfortable; quite poor ECG recordings	Invasiveness; risk of local complications at the implantation site; higher cost
Indications	Compliant patients; infrequent and fairly long-lasting palpitations unaccompanied by haemodynamic impairment that is likely to hinder use of the device.	Weekly short-lasting palpitations associated to haemodynamic impairment, in very compliant patients	Monthly palpitations associated with haemodynamic impairment; when all other investigations result inconclusive

arrhythmic cause. The sensitivity of loop recorders is extremely variable and strongly depends on several factors that include monitoring technique and duration, frequency of symptoms, and patient compliance.

## Recommendations

### Indications for ILRs and ELRs in patients with undocumented palpitations

**Class I:** ELRs are indicated in patients with recurrent palpitations, undocumented by conventional ECG techniques, who have: inter-symptom interval <4 weeks and absence of high-risk criteria (Table 6), which require immediate hospitalization or intensive evaluation (Level of evidence B)

**Class IIa:** ILRs may be indicated in selected cases with severe infrequent symptoms when ELRs and other ECG monitoring systems fail to document the underlying cause (Level of evidence B).

### Interpretation of ILRs and ELRs findings in patients with undocumented palpitations

**Class I**

- ILR and ELR findings are diagnostic when a correlation between palpitation and an arrhythmia is detected (level of evidence B)
- ILR and ELR findings exclude an arrhythmic cause when there is no correlation between palpitation and rhythm variation (level of evidence B)

**Class II**

The outcome of asymptomatic arrhythmias remains uncertain.

**Note:** This task force recognizes that, in real world practice, there is occasionally the need to make a therapeutic decision with weaker diagnostic criteria. Physicians should be aware that effectiveness of therapy is not well documented in such cases.

## Part II: Non-established indications

### 3. Atrial fibrillation: therapy guided by loop recorder observations

#### Key points

- There is a poor correlation of symptoms with atrial fibrillation (AF), especially after rhythm control therapy is started, which makes subjective evaluation of the effect of any therapy unreliable
- There are two main potential reasons for accurate arrhythmia monitoring: in clinical practice to determine the efficacy of rhythm control therapy; in rhythm control trials when freedom from AF is the outcome parameter
- Owing to the unpredictable nature of recurrences, AF is significantly underdetected by intermittent monitoring systems
- Continuous monitoring by implantable devices further increases the detection of AF, but it is hampered by misdetections and artefacts.
- Technological improvements are required for significant reduction of maldetection. Manual analysis can improve diagnostic yield if stored electrograms are provided. The results of some on-going studies with new generation devices are awaited
- The clinical relevance of Loop Recorders to guide medical and device therapy has yet to be demonstrated

### The rationale for ECG monitoring in atrial fibrillation patients

While sophisticated techniques are usually not required for rate control therapy of AF, ECG monitoring plays the key role in assessing the efficacy of rhythm control therapies. Indeed, in contrast to rate control, the efficacy of rhythm control therapy is more challenging to evaluate. We have learned that the distribution and duration of AF recurrences are often clustered and do not show a random pattern.<sup>65,66</sup> Furthermore, there is a poor correlation of symptoms with arrhythmia<sup>67-71</sup> (Figure 4). AF often recurs without clinical signs or symptoms, even in previously symptomatic patients. In some patients, palpitations due to extra beats or sinus tachycardia may lead to misinterpretation and overestimation of AF recurrence. Rhythm control therapy itself may modify the perception of the arrhythmia. In antiarrhythmic drug therapy as well as in catheter ablation, the number of asymptomatic AF episodes was found to increase during follow-up and previously symptomatic patients became asymptomatic despite further AF recurrences.<sup>71</sup>

There are two main potential reasons for a close arrhythmia monitoring:

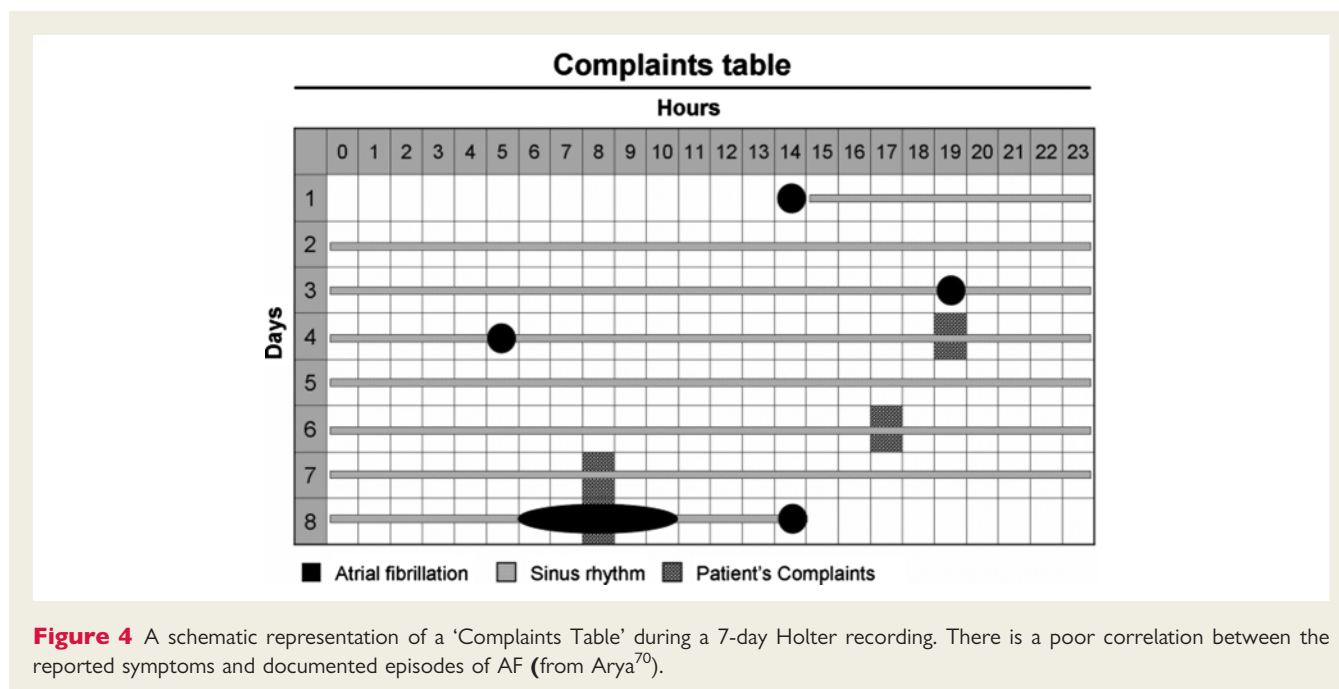
- In rhythm control trials, the precise determination of freedom from AF is a crucial outcome parameter and a prerequisite for establishing new therapeutic strategies.<sup>66</sup>
- From a clinical point of view, it is desirable to correlate symptoms with corresponding ECG findings especially when the nature of symptoms is multifactorial. Other potential indications are the screening for asymptomatic AF in patients prone to AF-related complications and the evaluation of the efficacy of the rhythm control therapy; however, the clinical relevance of these therapeutic indication (for example, continuation of anticoagulation therapy after AF ablation) has yet to be demonstrated. Some recent studies<sup>72,73</sup> suggest that the thrombo-embolic risk is influenced by the presence of AF and duration. In one study,<sup>72</sup> AF lasting >24 h, but not AF <24 h, was independently associated with embolic risk. Another study<sup>73</sup> suggests that the thrombo-embolic risk estimated by CHADS 2 score can be further tuned by combining AF presence/duration. Two subpopulations with markedly different risks of events (0.8 vs. 5%) were identified, the former corresponding to AF duration of <5 min with CHADS 2 score ≤2, or AF duration from 5 min to 24 h with CHADS 2 score ≤1, or AF duration >24 h with CHADS 2 score = 0.

Assessment of rhythm can be conducted with continuous (implanted devices) or intermittent monitoring. Intermittent monitoring includes resting ECG, Holter (24 h to 7 days), and event recorders with or without loop memory.

#### Intermittent atrial fibrillation monitoring

It is well established that the likelihood of detecting symptomatic as well as asymptomatic AF increases with the duration of the monitoring period. Extending the duration of *Holter recordings* from 24 h to 7 days clearly enhanced the sensitivity of diagnosing recurrent AF.<sup>74</sup>

Another approach is the use of the *event-recorder* for routine daily ECG recording plus additional recording during times of perceived symptoms. Thus, both asymptomatic and symptomatic



**Figure 4** A schematic representation of a 'Complaints Table' during a 7-day Holter recording. There is a poor correlation between the reported symptoms and documented episodes of AF (from Arya<sup>70</sup>).

AF episodes may be detected. Most systems transmit the ECG via telephone or internet while some others store the data on a memory card. The device is not attached to the body at all times and is held only against the chest for the ECG recording time of 30–60 s. The easy handling of the device makes it feasible for long follow-up periods that are required to assess AF. A disadvantage of the event recorder is its inability to provide information on the duration of single AF episodes. However, for detection of AF recurrences, 1 min daily transtelephonic monitoring yields similar detection rates as regular 24 h/month Holter ECG monitoring.<sup>69,71,75</sup> Therefore, the current consensus statements on rhythm control therapy in AF<sup>66,76,77</sup> recommend to detect asymptomatic AF by regular 1–7 day Holter monitoring or daily event-recorder-based ECG recording. In addition, symptomatic patients should be evaluated with an event recorder. However, using this technique, one has to accept that with the above-mentioned monitoring intensity, no more than about 70% of all AF recurrences will be detected.<sup>74,78</sup>

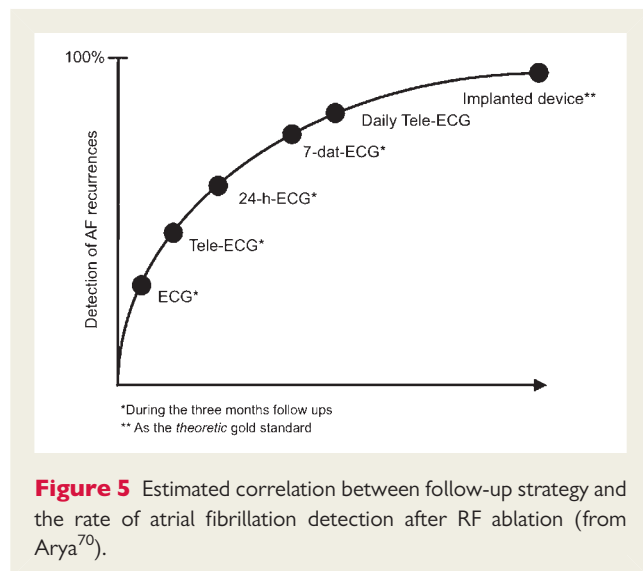
*External loop recorder* is ideal for capturing brief episodes of arrhythmias when it takes too long to apply an event recorder or for capturing ECG recordings of episodes that are associated with incapacitating symptoms such as syncope. ECG recording is triggered automatically according to the implemented arrhythmia detection algorithm or triggered manually by the patient. ELRs require permanent attachment of adhesive electrodes on the skin for activation of the loop memory. This appears to be tolerated only by highly motivated patients for a limited period of time, usually 1 week with a maximum of 4 weeks.<sup>79</sup> Previous studies have indicated that reporting compliance is poor when patients are asked to use ELRs for too long.<sup>80</sup> Such a limited recording period, however, is not adequate for long-term follow-up of rhythm control therapy in patients with AF. Thus, the ELR plays no major role for

this purpose. However, in single patients, the ELR may help to correlate symptoms with recurrences of AF over a short period of time.

#### Continuous atrial fibrillation monitoring

Previous experience with continuous AF monitoring is derived from analysis of data stored in implantable devices such as pacemakers and ICDs equipped with an atrial lead. They allow assessment of AF burden by tracking the number and duration of AF episodes. AF episodes irrespective of their duration or associated symptoms can be detected. Analysis of pacemaker stored data has shown that intermittent Holter recording compared with continuous pacemaker AF monitoring significantly underestimates AF recurrence rate after AF ablation procedure. However, the reliability of the counter data depends on the correct detection of AF. Atrial oversensing due to far-field sensing and atrial undersensing may complicate interpretation of AF onsets, number and duration of AF episodes. In an analysis of AF onset scenarios, 37% of AF onset recordings had to be excluded from analysis due to false-positive or -negative AF detection.<sup>81</sup> Therefore, technical improvements are required for significant reduction of AF misdetection. Nevertheless, only continuous monitoring is able to elucidate the full amount of symptomatic and asymptomatic AF episodes. An estimation of the correlation between follow-up strategy and the rate of AF detection has been proposed by Arya<sup>70</sup> (Figure 5). A recent study<sup>73</sup> comparing intermittent with continuous monitoring by implanted pacemakers showed that one-third of AF episodes would have been lost with 1 month Holter monitoring. Certainly, this most accurate way of evaluating AF recurrence is available only in the limited number of pacemaker or ICD patients.

*Implantable loop recorders* play a major role in patients with infrequent symptoms and suspected arrhythmias. The device opens an emerging field of broader monitoring of heart rhythm



**Figure 5** Estimated correlation between follow-up strategy and the rate of atrial fibrillation detection after RF ablation (from Arya<sup>70</sup>).

and physiological changes. Its first use in AF patients intended to analyse initiating mechanisms of AF.<sup>82,83</sup> In an investigational study of 29 paroxysmal AF patients, 105 of 318 (33%) patient-activated AF episodes were suitable for analysis, showing a broad variability of onset patterns in most patients. As in pacemaker studies, a significant incongruity between symptoms and electrocardiographic AF episodes was found.<sup>83</sup> A number of ECG recordings had to be excluded from analysis due to electromyographic artefacts. The main limitation of the first device models is a lack of automatic AF detection algorithms that makes determination of asymptomatic AF and total AF burden impracticable. Therefore, the ILR played so far no role in guiding AF therapy. The latest model of the ILRs (see Table 1) provides automatic AF detection software based on rhythm (ir-)regularity. Further investigations like the ongoing XPECT study have to evaluate the capability of this surface-ECG-based device to reliably detect AF. This multicenter prospective trial compares AF detection of the Reveal XT ILR with 48 h Holter monitoring. In cryptogenic stroke patients, the CRYSTAL-AF study is designed to determine the incidence of AF detected by the ILR compared with standard of care.

#### 4. Implantable loop recorder in risk stratification

##### Key points:

- Asymptomatic arrhythmias and especially high-degree AV block are relatively frequent among post-MI patients with depressed LV function and patients with AV-block have a high risk of death.
- ILRs are useful tools for clinical research and epidemiology of cardiac arrhythmias
- The clinical usefulness of ILR to guide medical and device therapy in patients surviving myocardial infarction has yet to be demonstrated
- ILRs have a potential role in identifying the correlation between symptoms and suspected ventricular tachyarrhythmia in selected high-risk patients affected by Brugada ECG pattern, long or short QT, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia.

##### Previous myocardial infarction

Current clinical usage and research using ECG loop recorders has mostly been focused on symptomatic patients, especially patients with syncope, aimed at documenting the arrhythmic origin of infrequently occurring symptoms. The ILR also offers a research tool for diagnosing arrhythmias in certain asymptomatic pre-specified patient groups. Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study<sup>84</sup> was designed to document the incidence and prognostic significance of cardiac arrhythmias after acute myocardial infarction in patients with left ventricular ejection fraction (LVEF)  $\leq 40\%$ .<sup>65</sup> In this study, significant brady- and/or tachyarrhythmias were recorded in 137 patients (46%) during a 2 year follow-up, 86% of these being asymptomatic. The ILR documented a 27% incidence of new onset AF ( $\geq 125$  bpm), 13% non-sustained VT ( $\geq 16$  bpm), 10% high-degree AV-block ( $\leq 30$  bpm, duration  $\geq 8$  s), 7% sinus bradycardia ( $\leq 30$  bpm,  $\geq 8$  s), 5% sinus arrest ( $\geq 4.5$  s), 3% had sustained ventricular tachycardia, and 3% experienced ventricular fibrillation. Monitoring was hampered by misdetections and artefacts. Intermittent high-degree AV-block was also associated with an increased risk of cardiac mortality during the follow-up. ILRs were also used in documenting ventricular tachyarrhythmia events as a primary endpoint of risk stratification tests performed 6 weeks post-AMI. The experience of CARISMA study showed that ILRs are well suited for clinical research of cardiac arrhythmias in various clinical settings.

##### Inherited cardiomyopathies

In addition to documented clinical indications, ILRs have a potential to be used as a diagnostic tool in specific inherited cardiomyopathies, although there is no scientific evidence for this indication (opinion-based approach). For example, ILR can well be used in documenting the arrhythmic origin of pre-syncope and syncope among patients with phenotypic or genotypic evidence of inherited cardiomyopathies, such as Brugada syndrome, long or short QT syndromes, hypertrophic cardiomyopathy, or arrhythmogenic right ventricular dysplasia.

In these settings, syncope is usually regarded as an ominous finding predicting sudden cardiac death and an ICD implantation should be considered. Nevertheless, the mechanism of syncope may be heterogeneous being caused by life-threatening arrhythmias in some, but being of a more benign origin, i.e. vasovagal, in many others. In a multicenter study,<sup>85</sup> 40% of 220 patients with Brugada syndrome implanted with an ICD had a history of syncope, but the patients with syncope were not at a higher risk of appropriate ICD discharge than those who had been asymptomatic. Similarly, in a single centre study,<sup>86</sup> a history of syncope was present in 55% of 47 patients who received an ICD, but was unrelated to appropriate ICD discharge; one might reasonably infer from these observations that the likely diagnosis in those who had syncope relapse after the ICD implantation was vasovagal and not a potentially life-threatening arrhythmia. Finally, in a large metaanalysis<sup>87</sup> encompassing 1217 patients (275 of them [23%] with a history of syncope), the patients with syncope had an intermediate risk of ventricular tachyarrhythmias that was significantly lower than those presenting with documented cardiac arrest.

In a large multicentre, prospective, observational trial<sup>88</sup> performed on 812 adult patients affected by long-QT syndrome (LQTS), the outcome parameters included syncope (transient abrupt onset and offset of loss of consciousness), cardiac arrest (requiring defibrillation), and LQTS-related sudden death. These outcome parameters occurred in 192 (23%) patients. When syncope was removed from the outcome parameters, cardiac arrest and sudden death occurred in only 50 (6%) patients showing that syncope is three times more frequent than the other endpoints. Therefore, in this setting, it seems that syncope does not necessarily carry a higher risk of major life-threatening cardiac events. On the other hand, syncope was associated with a significant 5-fold increased risk of cardiac arrest or sudden death, which occurred in a minority of patients. In other words, as a marker for life-threatening events, syncope has low sensitivity.

Differentiation between benign and malignant forms is usually very difficult in the setting of an inherited disease based on conventional investigations. Consequently, in many patients, there is a rationale for more precise diagnosis (i.e. ILR documentation) of the mechanism of syncope before embarking in ICD therapy. This hypothesis requires to be formally validated by trials.

Finally, ECG loop recorders may give useful information on making the definitive clinical decision regarding implantation of a cardioverter-defibrillator in young patients with characteristics of inherited arrhythmia syndromes but without documented life-threatening arrhythmia. Again, this hypothesis requires to be validated.

## Perspectives

### 5. Future clinical and technological needs

It is likely that prolonged monitoring will become increasingly important, and its use will increasingly be appropriate instead of, or before, many current conventional investigations.

The ultimate goal of therapy guided by ILR should be to *improve the clinical outcome* of the patients, i.e. prevention of syncopal recurrences, severe injuries, and death. How much ILR-guided strategy is superior to conventional evaluation strategy remains largely to be demonstrated. This task force recognizes the importance of planning future outcome studies.

*Continuous long-term ECG home monitoring* is going to become a widely accepted diagnostic methodology. Data are transmitted through a standard telephone line to a secure network, such as in the current technology for remote monitoring of pacemakers and defibrillators. New generation monitors may identify AF episodes, as previously discussed in this document. For this purpose, RR cycle analysis algorithms and advanced discrimination criteria similar to those implemented in implantable defibrillators have been introduced. Remote monitoring through advanced telecommunications technology will potentially be useful for the management of patients with chronic disease. Thanks to this technology, continuous monitoring of patient's ECG and other physiological signals are possible (e.g. blood flow or pressure and electroencephalography), and patients will be able to self-transmit diagnostic information stored in the device memory for scheduled routine follow-up, or post-event follow-up or in case of unexplained

symptoms. *Blood pressure recording* is crucial for the majority of clinical situations and will add important information for therapy. Physicians may check their patients directly via the website. This will allow prompt reaction to clinical events as well as time saving with potential cost reduction to healthcare system. *New sensors* for monitoring vital and haemodynamic parameters, like intra-thoracic fluid status through thoracic impedance in heart failure patients and blood pressure in hypertensive patients, are awaited. They will be extremely useful for tailoring drug therapy and preventing serious adverse events such as heart failure hospitalizations. Acoustic alarms incorporated into the implanted devices and a network providing telemetric data to specialists would be helpful and would dramatically improve the efficiency of patient management. Thus, new monitoring strategies may switch the use of implantable monitors from arrhythmia detection to a heart disease management strategy.

Programmers for monitoring devices would be simplified and based on *standard PC or PDA*, making possible interrogation and programming of the device anywhere. Access to device information would be possible not only for electrophysiologists, but also for cardiologists, neurologists, and general practitioners. This will simplify communication and will allow integrated management of patients with cardiac disease.

A further step could be the use of implantable monitors for *detection of ischaemia* and to improve management of patients with chronic ischaemic heart disease. Future improvements in electrogram sensing, signal filtering, and sampling rate (at least 256 Hz as in standard surface electrocardiogram) would allow morphological analysis with fast and appropriate detection of ST changes in case of ischaemic episodes.

Finally, *reduction in device size and weight* would simplify the implant procedure and would increase patient and physician's acceptance. Device miniaturization could increase the use of cardiac monitors, which could become the new standard of care for serious adverse event prevention and long-term monitoring of patients with chronic cardiac diseases.

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