

GIMSI E SYNCOPÉ UNIT

Studi GIMSI: Italian CNA I e II

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Right atrial cardioneuroablation of asystolic reflex syncope ^e

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ABSTRACT

BACKGROUND Cardioneuroablation (CNA) should focus on the vagal ganglia located in the right atrium close to the sinoatrial and the atrioventricular nodes.

OBJECTIVE The study aimed to evaluate the efficacy and safety of right atrial CNA.

METHODS Patients with severe, asystolic reflex syncope identified by implantable loop recorder (ILR) or tilt testing underwent right atrial CNA and were subsequently monitored using ILR.

RESULTS The population included 28 patients with a mean age of 40.5 ± 13.4 years, of whom 71% were men. Over a median follow-up period of 12.5 months, 8 patients experienced 44 episodes of asystole lasting longer than 3 seconds, as recorded by an ILR. The burden of asystolic episodes significantly reduced from 0.89 episodes per month before CNA (145 over 163 patient-months) to 0.11 episodes per month after CNA (44 over 397 patient-months), with a relative risk reduction of 0.12, $P = .0001$. Similarly, the burden of syncopal episodes decreased from 0.23 episodes per month before CNA to 0.06 episodes per month after CNA, resulting in an relative risk reduction of 0.24, $P = .0001$. Median heart rate increased from 75 bpm (interquartile range: 72–79) before ablation to 83 bpm (interquartile range: 78–85) after ablation, lasting up to 9 months post-procedure. No patients experienced complications during the procedure. During follow-up, 2 patients received pacemakers, 1 underwent a redo procedure, and 4 experienced mild transient symptoms: 3 had palpitations and 1 had dyspnea, none requiring therapy.

CONCLUSION Right atrial CNA reduced asystolic episodes by 88% and syncopal episodes by 76% during the mid-term follow-up. Adverse events were infrequent and mild.

KEYWORDS Asystole; AV node; Catheter ablation; Implantable loop recorder; Neurally-mediated syncope; Reflex syncope; Sinoatrial node; Syncope; Tilt testing



❖ Studio clinico **multicentrico** (7 Ospedali Italiani) con il patrocinio di GIMSI

❖ **Obiettivo** → Valutare efficacia e sicurezza della CNA destra in pazienti con sincope asistolica riflessa

CRITERI DI INCLUSIONE

Età: 18-60 anni

Anamnesi di sincope ricorrente grave (≥ 2 nell'ultimo anno o ≥ 3 negli ultimi 2 anni)

Presenza di almeno 2 pause asistoliche ≥ 3 sec (al LRI con o senza sincope o una sincope asistolica indotta durante tilt test)

Diagnosi clinica di sincope riflessa in base ai criteri di classe I delle linee guida ESC

CRITERI DI ESCLUSIONE

Malattia del nodo del seno (MSA)

Blocco atrio-ventricolare (BAV)

Cardiopatía strutturale

Diagnosi alternativa di sincope

Tabella 1. Criteri diagnostici di sincope riflessa in base alle linee guida ESC (1,2)

Recommendations	Class	Level
Reflex syncope		
1. VVS is highly probable if syncope is precipitated by pain or fear or standing, <i>and</i> is associated with typical progressive prodrome (pallor, sweating, nausea).	I	C
2. Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers.	I	C

ENDPOINTS



Primario

Episodi asistolici al mese (monitoraggio LRI pre- e post- CNA)

Secondari

- 1) *Episodi sincopali pre- e post-CNA*
- 2) *Assenza di complicanze post CNA*
- 3) *Andamento dell'HR rivelato al LRI pre- e post- CNA*
- 4) *Andamento dell'HRV rilevato al LRI pre- e post- CNA*

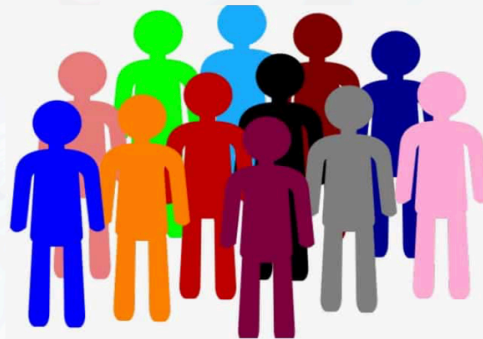


Table 1 Clinical characteristics of the study population at enrolment

Clinical characteristic	Population (n = 28)
Mean age, yrs	40.5 ± 13.4
Mean age at first syncope, yrs	30.5 ± 13.3
Men	20 (71)
Syncope, median number during life (IQR)	6 (5–10)
Syncope, median number last 2 years (IQR)	4 (3–5)
Syncope, median number last year (IQR)	3 (2–3)
History of pre-syncope	16 (57)
Hospitalization for syncope	18 (64)
Syncope, severe trauma	7 (25)
Syncope, mild trauma	20 (71)
Antihypertensive medications	5 (18%)
ECG abnormalities	4 (14)
Mild structural heart disease	1 (4)
Orthostatic hypotension	4 (14)
Tilt testing:	
- performed	21 (75)
- positive response	17/21 (81)
- asystolic response	15/21 (71)
- mean asystole duration, s	21.1 ± 19.9
Implantable loop recorder before CNA:	
- performed	22 (79)
- median duration of ILR monitoring, IQR	5.3 (2.8–11.2)
- asystolic episodes	21/22 (95)
- total number of asystole episodes	145
- type 1A	84 (58)
- type 1B	56 (39)
- type 1C	5 (3)
- mean number of asystolic episodes per patient	6.6 ± 6.1
- mean longest asystole duration, s	11.5 ± 7.4

Values are n (%) and continuous variables are given as mean ± standard deviation.

CNA = cardioneuroablation; ECG = electrocardiogram; ILR = implantable loop recorder; IQR = interquartile range.



❖ 28 Pazienti

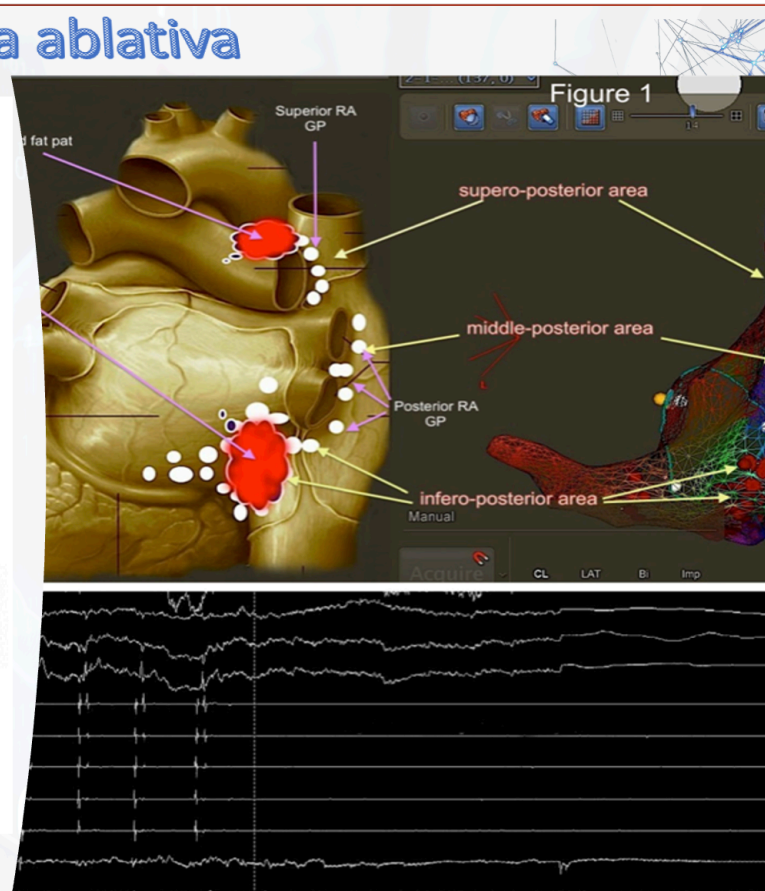
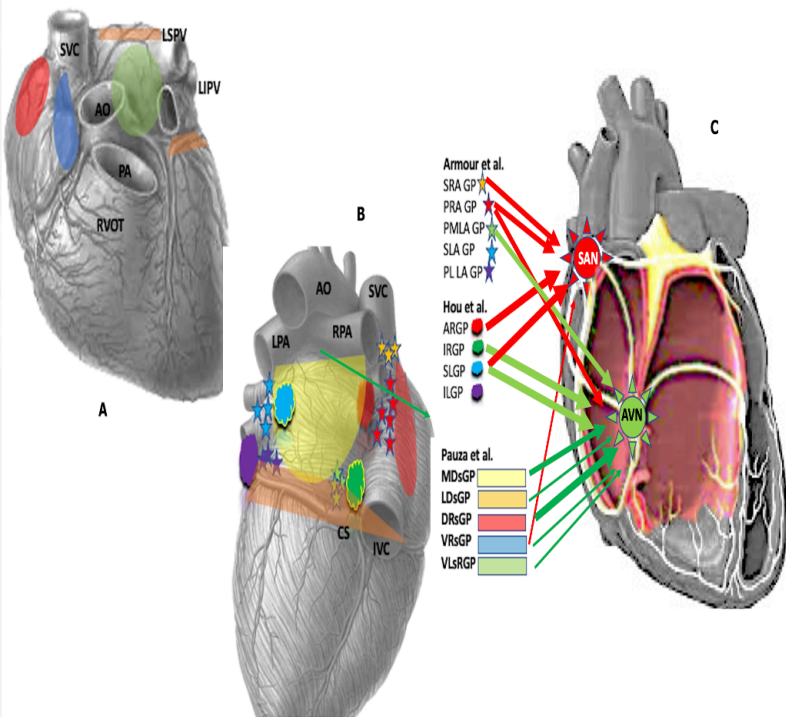
❖ 22 → LRI pre-CNA

❖ 6 → LRI durante CNA

❖ 21 → Tilt test → 15 con asistolia

❖ 12.5 mesi → Durata mediana FU post-CNA

Procedura ablativa



Procedura ablativa

Successo in acuto definito come:



1) $\uparrow$ FC > 20-25% dopo 10 min

2) $\downarrow$ Intervallo AH > 25% rispetto al basale e/o punto di Wenckebach < 500 ms

3) Intervallo P-P < 70% rispetto al basale, oppure < 600 ms (calcolati come media di 10 cicli consecutivi), dopo 10 min dall'ultima erogazione



RISULTATI DELL'ITALIAN-CNA

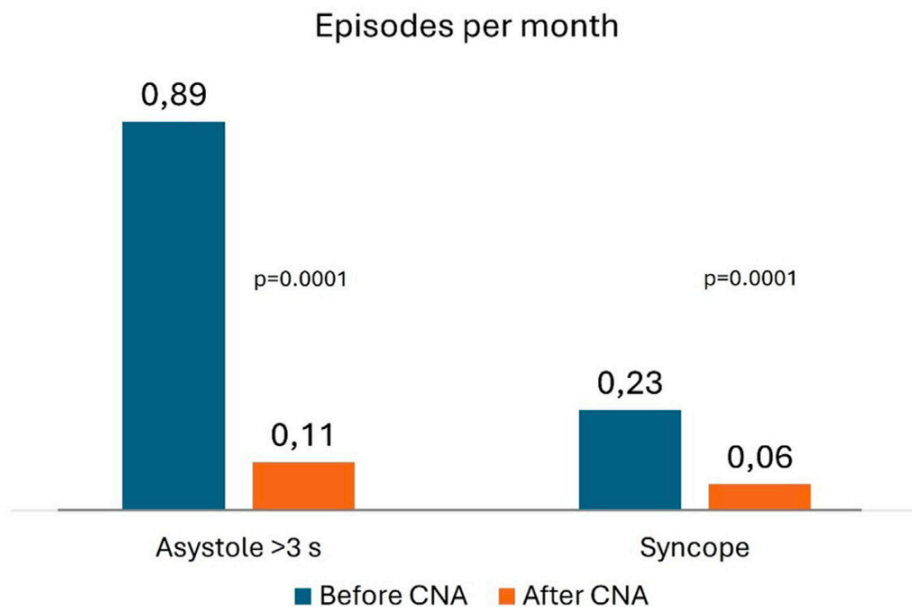


Figure 1

Monthly burden of asystolic and syncopal episodes before and after CNA procedure. CNA = cardioneuroablation.



RISULTATI DELL'ITALIAN-CNA

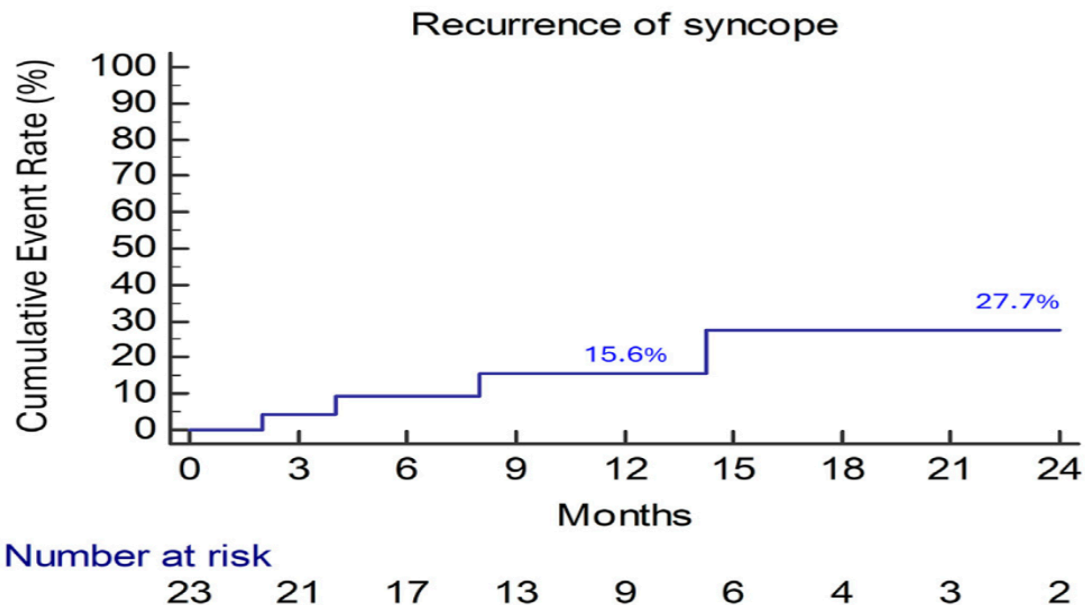


Figure 2

Kaplan-Meier estimated recurrence rate of syncope after CNA. CNA = cardio-neuroablation.



RISULTATI DELL'ITALIAN-CNA

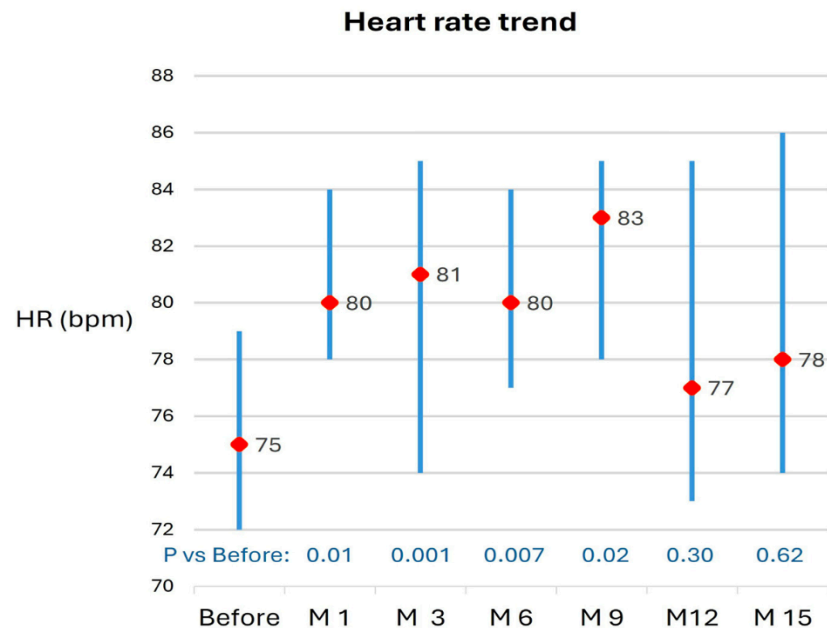


Figure 3

Heart rate (HR) trend. HR is reported as the median (red bullets) and interquartile range (blue vertical lines) over 30-day periods: the month before ablation, the month immediately after ablation (M1), and months 3 (M3), 6 (M6), 9 (M9), and 12 (M12). Monthly HR is the median HR (with its interquartile range) of each patient over 30 days. The Wilcoxon matched-pair test compared intra-individual values.



RISULTATI DELL'ITALIAN-CNA

Table 2 Adverse events during the follow-up (according to the Kulakowski classification^{1,4})

Adverse event	Population (n = 28)
Redo CNA	1
Pacemaker implantation	2
Transient dyspnea	1
Chronic chest pain	0
Decreased exercise capacity	0
Transient palpitations (< 3 months)	3
Persistent palpitations	0

CNA = cardioneuroablation.

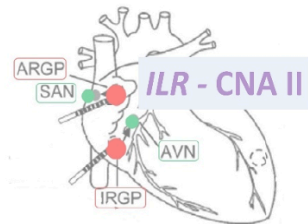
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TAKE HOME MESSAGE ITALIAN CNA I

- Ablazione mirata alle aree vicine ai NSA e NAV → efficace nel trattamento della sincope asistolica riflessa (riduzione dell'88% di episodi asistolici e del 76% delle recidive sincopali durante il FU)
- La maggior parte dei pazienti è risultata asintomatica o con pochi eventi avversi lievi → CNA procedura semplice e sicura!
- L'aumento della FC post-CNA (secondaria alla riduzione dell'attività vagale) è stato immediato ed è durato fino a 9 mesi, per poi diminuire
- Limiti dello studio Italian-CNA:
 - 1) mancata correlazione tra variazione dell'HR e dell'HRV con le recidive sincopali → estrema variabilità interindividuale
 - 2) mancanza di un gruppo di controllo
 - 3) campione ristretto
 - 4) breve durata del FU, tale da mostrare risultati sul lungo termine circa l'efficacia e la sicurezza della CNA
- CNA destra vs CNA bi-atriale: maggiore beneficio nella riduzione delle recidive sincopali ma un tasso più elevato di eventi avversi e complicanze (approccio più aggressivo)



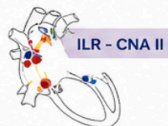


STUDIO ITALIAN CNA II



Gruppo Italiano Multidisciplinare per lo Studio della Sincope





Why a new study?

GAP IN KNOWLEDGE



The best method of CNA is debated, with **no studies comparing right atrial versus bi-atrial** ablation.



Meta-analyses suggest a **signal favoring bi-atrial CNA** for efficacy, but with higher risk of complications.

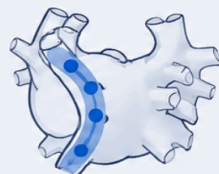


Right atrial CNA is associated with a **lower risk** of complications.



No head-to-head comparison is currently available.

RIGHT ATRIAL CNA



- ✓ Simpler technique
- ✓ Shorter procedure time
- ✓ Lower risk of complications
- ✓ Preservation of left atrial neural structures

VS

BI-ATRIAL CNA



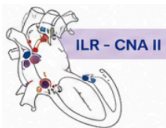
- ✓ More extensive denervation
- ✓ Potentially greater efficacy
- ✓ Possibly lower recurrence rate
- ✓ Higher procedural complexity and complication risk



No head-to-head ILR-based comparison currently exists

CNA, cardioneuroablation; ILR, implantable loop recorder.





STUDY RATIONALE

The ILR revolution in CNA follow-up

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per lo Studio della Sincope

IMPLANTABLE LOOP RECORDER (ILR – Lux-Dx™)



CONTINUOUS • AUTOMATIC • REMOTE
LONG-TERM ECG MONITORING



OBJECTIVE MONITORING

Continuous detection of asystolic events, independent of symptoms and patient recall.



CONTINUOUS ECG SURVEILLANCE

Accurate quantification of asystolic burden, heart rate, and heart rate variability over time.



REDUCTION OF EXPECTATION BIAS

Minimizes the influence of patient and physician expectations on outcome assessment.

“

*More objective monitoring
can be achieved with ILR.*

”

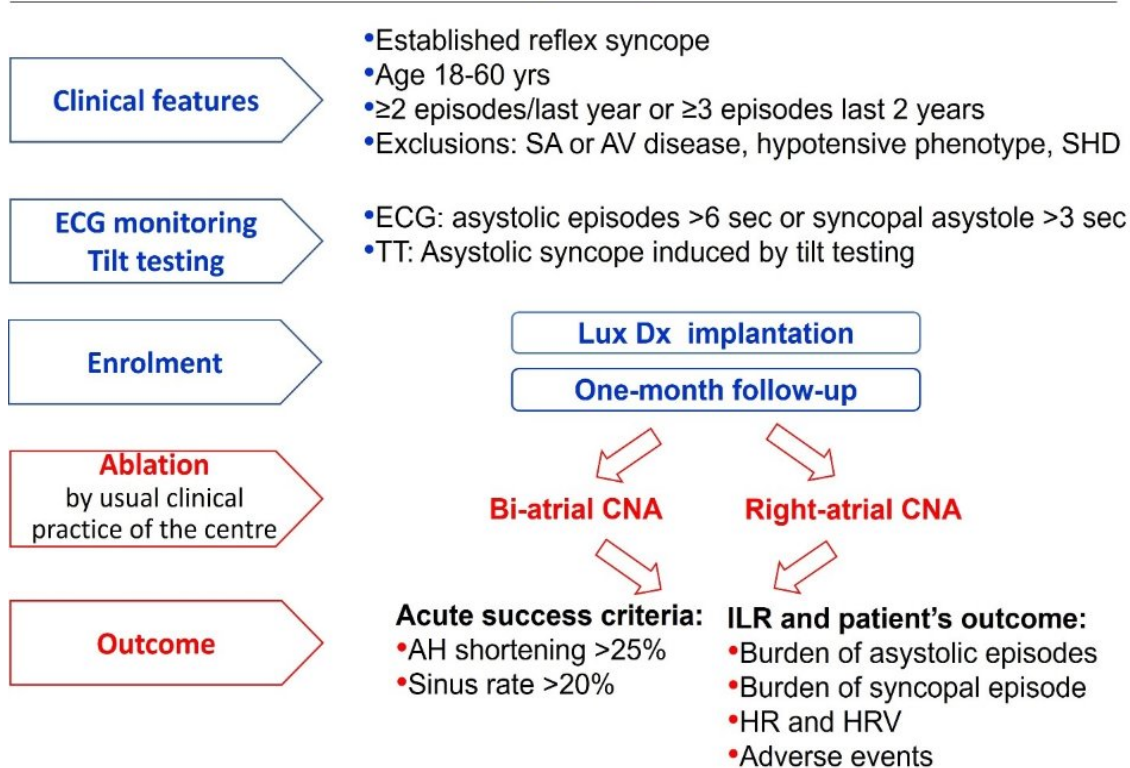


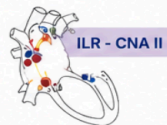
ILR-based follow-up provides a robust and unbiased assessment of CNA efficacy.

CNA, cardioneuroablation; ILR, implantable loop recorder.



Study design



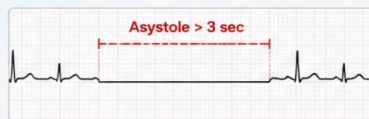


Patient selection

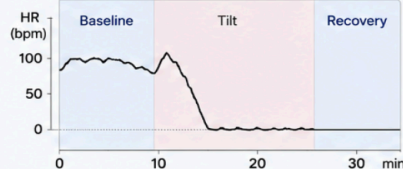
Who will be included in Italian CNA II?

DOCUMENTED CARDIOINHIBITORY SYNCOPE

ILR-documented asystole



Tilt-induced cardioinhibitory response



Severe, recurrent syncope with documented asystolic mechanism

INCLUSION CRITERIA

1

Age 18–60 years
(at enrolment)



2

Severe recurrent reflex (vasovagal) syncope with a high impact on quality of life



3

ILR-documented asystolic episodes (pause > 3 seconds)



4

Tilt-induced asystolic response (mainly asystole > 3 seconds)



Selection of patients with a clearly documented cardioinhibitory mechanism ensures a homogeneous population for the comparative analysis.

ILR, implantable loop recorder; CNA, cardioneuroablation.





ILR - CNA II

PRIMARY AND SECONDARY ENDPOINTS

Italian CNA II (ILR-CNA Study)

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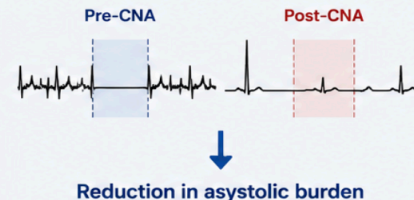
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PRIMARY ENDPOINT



BURDEN OF ASYSTOLIC PAUSES > 3 SECONDS / MONTH

Assessed by continuous ILR monitoring
over 12 months after CNA.



SECONDARY ENDPOINTS



SYNCOPE RECURRENCE

Time to first syncope
recurrence during
12-month follow-up.



PROCEDURAL SAFETY

Rate of procedure-related
complications within
30 days.



HEART RATE AND HRV

Changes in heart rate
and heart rate variability
over time.



PACEMAKER IMPLANTATION

Need for permanent
pacemaker implantation
during follow-up.



ADVERSE EVENTS

All serious adverse events
related to the procedure
or during follow-up.



All endpoints will be assessed through continuous ILR monitoring and clinical follow-up.

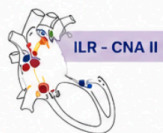
ILR, implantable loop recorder; CNA, cardioneuroablation; HRV, heart rate variability.



Continuous ILR follow-up

ILR monitoring	Enrolment	Before CNA (M-1)	M 3	M 6	M 9	M 12
Structured history	X					
Active standing test	X					
Prolonged ECG monitoring	X					
24-hour ambulatory BP monitoring	X					
Tilt testing	X					
Carotid sinus massage	X					
Data from ILR monitoring		Continuous				
Asystolic syncopes		X	X	X	X	X
Non-asystolic syncopes		X	X	X	X	X
Adverse events			X	X	X	X





WHY THIS STUDY MATTERS

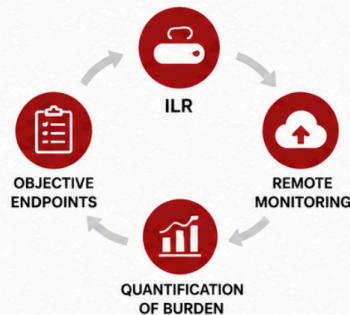
Italian CNA II (ILR-CNA Study)

1 FIRST ILR-DRIVEN COMPARATIVE CNA REGISTRY



- ✓ Head-to-head comparison between right atrial and bi-atrial CNA.
- ✓ Objective assessment of efficacy through continuous ILR monitoring.
- ✓ Addresses a major gap in current evidence.

2 OBJECTIVE CONTINUOUS ECG FOLLOW-UP



- ✓ Minimizes recall and expectation bias.
- ✓ Captures asymptomatic asystolic events.
- ✓ Provides robust and reproducible data.

3 POTENTIAL IMPACT ON CLINICAL PRACTICE AND FUTURE GUIDELINES

- Results may help define the **optimal CNA strategy** for asystolic reflex syncope.
- Improve patient selection and personalize therapy.
- Generate evidence to inform **future EHRA/ESC recommendations**.
- Ultimately improve outcomes and quality of life of patients.



*The future of cardioneuroablation requires objective evidence.
Italian CNA II is designed to provide it.*

