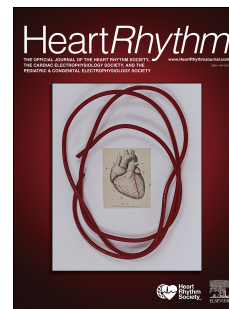


Journal Pre-proof



Prevalence of clinically significant bradyarrhythmias in patients implanted with loop recorders for cryptogenic stroke: a manifestation of atrial cardiomyopathy?

Dr. Gianluigi Bencardino, Dr. Pasquale Alessandro Festa, Dr. Roberto Scacciavillani, Dr. Aldobrando Broccolini, Dr. Serena Abruzzese, Dr. Giovanni Frisullo, Dr. Linda Fulco, Dr. Matteo Vumbaca, Dr. Christian Cardile, Dr. Francesca Augusta Gabrielli, Dr. Maria Lucia Narducci, Dr. Francesco Perna, Dr. Gianluca Commerci, Dr. Gaetano Pinnacchio, Prof. Giovanna Liuzzo, Prof. Francesco Burzotta, Prof. Gemma Pelargonio

PII: S1547-5271(26)00026-3

DOI: <https://doi.org/10.1016/j.hrthm.2026.01.011>

Reference: HRTM 11710

To appear in: *Heart Rhythm*

Received Date: 20 October 2025

Revised Date: 16 December 2025

Accepted Date: 6 January 2026

Please cite this article as: Bencardino G, Festa PA, Scacciavillani R, Broccolini A, Abruzzese S, Frisullo G, Fulco L, Vumbaca M, Cardile C, Augusta Gabrielli F, Narducci ML, Perna F, Commerci G, Pinnacchio G, Liuzzo G, Burzotta F, Pelargonio G, Prevalence of clinically significant bradyarrhythmias in patients implanted with loop recorders for cryptogenic stroke: a manifestation of atrial cardiomyopathy?, *Heart Rhythm* (2026), doi: <https://doi.org/10.1016/j.hrthm.2026.01.011>.

This is a PDF of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability. This version will undergo additional copyediting, typesetting and review before it is published in its final form. As such, this version is no longer the Accepted Manuscript, but it is not yet the definitive Version of Record; we are providing this early version to give early visibility of the article. Please note that Elsevier's sharing policy for the Published Journal Article applies to this version, see: <https://www.elsevier.com/about/policies-and-standards/sharing#4-published-journal-article>. Please also note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 Manuscript Title:

2 Prevalence of clinically significant bradyarrhythmias in patients implanted with loop recorders for
3 cryptogenic stroke: a manifestation of atrial cardiomyopathy?

4 **Short Title:** Bradyarrhythmias in Cryptogenic Stroke

5 Authors:

6 Dr. Gianluigi Bencardino¹, Dr. Pasquale Alessandro Festa¹, Dr. Roberto Scacciavillani¹, Dr. Aldobrando
7 Broccolini², Dr. Serena Abruzzese², Dr. Giovanni Frisullo², Dr. Linda Fulco¹, Dr. Matteo Vumbaca¹, Dr.
8 Christian Cardile¹, Dr. Francesca Augusta Gabrielli¹, Dr. Maria Lucia Narducci¹, Dr. Francesco Perna¹, Dr.
9 Gianluca Comerci¹, Dr. Gaetano Pinnacchio¹, Prof. Giovanna Liuzzo¹, Prof. Francesco Burzotta¹, Prof. Gemma
10 Pelargonio¹

11 Affiliations:

12 ¹ Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
13 ² Department of Neurology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

14 Corresponding Author:

15 Name: Pasquale Alessandro Festa
16 Affiliation: Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS
17 Address: Largo Agostino Gemelli 8, 00168 Rome, Italy
18 Email: alessandrofesta97@gmail.com
19

20 Word Count:

21 Main text: 2747 words

22 Abstract Word Count:

23 247 words

24 Number of Figures:

25 1

26 Number of Tables:

27 3

28 Supplementary Material:

29 Table 1

30 Keywords:

31 Cryptogenic stroke, bradyarrhythmia, sinus node dysfunction, loop recorder, atrial cardiomyopathy

32 Conflicts of Interest:

33 The authors declare no conflicts of interest.

34 Funding:

35 No specific funding was received for this study.

36

37 **Prevalence of clinically significant bradyarrhythmias in patients implanted with loop recorders for**
38 **cryptogenic stroke: a manifestation of atrial cardiomyopathy?**

39

Abstract

40 **Background:**

41 Cryptogenic stroke is often associated with atrial fibrillation (AF), but may also reflect a broader atrial
42 pathology such as atrial cardiomyopathy (AtCM). While implantable loop recorders (ILRs) are used primarily
43 to detect AF in these patients, the burden of bradyarrhythmias is not well established.

44 **Objective:**

45 To evaluate the prevalence and clinical significance of bradyarrhythmias in patients implanted with ILRs
46 after cryptogenic stroke or TIA, compared to a matched control population with ILRs for other indications.

47 **Methods:**

48 We retrospectively analyzed 225 patients receiving ILRs for cryptogenic stroke/TIA (n=139) or other
49 indications excluding syncope (n=86). Bradyarrhythmias were classified according to ESC 2021 guidelines. A
50 1:1 propensity score matching (PSM) was performed based on major covariates. The primary endpoint was
51 the time to first detection of clinically significant SND.

52 **Results:**

53 During a median follow-up of 23 months, SND occurred more frequently in the cryptogenic stroke group
54 than in controls (18.7% vs 4.7%, p=0.003). After PSM (n=114), SND remained significantly more prevalent in
55 stroke patients (22.8% vs 8.8%, p=0.04). Univariate analysis identified cryptogenic stroke/TIA (OR 3.14, 95%
56 CI 1.02–9.64, p=0.045), hypertension, and increased indexed left atrial volume as independent predictors of
57 SND. Kaplan–Meier analysis showed a significantly lower event-free survival for SND in the cryptogenic
58 stroke group (log-rank p=0.034).

59 **Conclusion:**

60 Cryptogenic stroke patients show a significantly higher and earlier incidence of clinically relevant SND
61 compared to matched controls, which may suggest an underlying atrial remodeling process consistent with
62 atrial cardiomyopathy. These findings underscore the importance of comprehensive arrhythmic monitoring
63 beyond AF in this population.

64

65 **Abbreviations:**

66 **AF** - Atrial Fibrillation; **AtCM** - Atrial Cardiomyopathy; **CI** - Confidence Interval; **ESC** - European Society of
67 Cardiology; **ILR** - Implantable Loop Recorder; **OR** - Odds Ratio; **PSM** - Propensity Score Matching; **SND** -
68 Sinus Node Dysfunction; **TIA** - Transient Ischemic Attack

69

70

71 Introduction

72 Sinus node dysfunction (SND) is a significant clinical entity encompassing a range of abnormalities in the formation
73 and conduction of electrical impulses from the sinoatrial node. It represents a major cause of symptomatic
74 bradycardia, and its clinical presentation can vary widely, including persistent sinus bradycardia, sinoatrial block, sinus
75 arrest, chronotropic incompetence or a combination of bradycardia and supraventricular tachyarrhythmias, often
76 referred to as "tachy-brady syndrome". The prevalence and incidence of SND are strongly correlated with age, rising
77 significantly in older populations, which underscores its growing public health importance.¹

78 The clinical impact of SND is considerable, manifesting as symptoms such as syncope, dizziness, fatigue, and dyspnea,
79 all of which can significantly impair quality of life and increase the risk of falls. The pathophysiology of SND is
80 multifactorial, involving a progressive fibrotic and degenerative process within the sinoatrial node and the
81 surrounding atrial myocardium, throughout the right atrium.² This process is frequently associated with aging but can
82 also be linked to ischemic heart disease, inflammatory conditions, and certain medications.³

83 Atrial fibrillation (AF), in contrast, is the most frequent and complex atrial tachyarrhythmia.⁴ Its multifactorial
84 pathophysiology is characterized by atrial remodeling and fibrosis.⁵ Remodeling involves both structural and electrical
85 changes. Structural remodeling includes myocyte hypertrophy and interstitial fibrosis, leading to increased atrial wall
86 stiffness and a loss of myocyte-to-myocyte coupling. This disruption of normal conduction pathways creates multiple,
87 chaotic re-entrant circuits that perpetuate the arrhythmia. Electrical remodeling, driven by chronic rapid firing,
88 includes changes in ion channel expression and function, leading to a shortened atrial refractory period and increased
89 excitability.^{6,7} This shared pathophysiological substrate of remodeling and fibrosis also links AF to SND, where fibrosis
90 within the sinoatrial node impairs its ability to generate and propagate electrical impulses. Therefore, AF and SND are
91 often found coexisting, not merely as comorbidities but as conditions sharing a common underlying pathology of atrial
92 myopathy.^{8,9}

93 Today, AF is frequently diagnosed by implantable loop recorders (ILRs) inserted for monitoring after a cryptogenic
94 stroke.^{10,11,12} Specifically, approximately 10–15% of patients with stroke of unclear origin have documented episodes of
95 AF by ILRs after one year of implantation, and this number rises to 20–25% by the end of the battery life.¹³ Previous
96 studies have investigated the prevalence of incidental findings in stored episodes in patients with cryptogenic stroke,
97 but a high proportion of patients prematurely explanted their devices, which limited the duration of rhythm
98 monitoring.^{14,15} Most patients with cryptogenic stroke are elderly, have a history of vascular disease, diabetes, and
99 hypertension, and are therefore at risk of developing other types of arrhythmias, such as clinically relevant
100 bradyarrhythmias or tachy-brady syndrome.^{16,17} Moreover, brain ischemia can be associated with autonomic
101 dysregulation.¹⁸

102 In this retrospective study, we investigated the prevalence and type of clinically significant bradyarrhythmias in
103 patients implanted with an ILR for acute cryptogenic stroke, comparing them to a control population.

104 Methods

105 The research reported in this paper adhered to Helsinki Declaration as revised in 2013. Consecutive patients with
106 cryptogenic stroke and indication to loop recorder implantation were enrolled. Eligible patients were 40 years of age
107 or older and had received a diagnosis of stroke or transient ischemic attack (TIA), occurring within the previous 90
108 days, that was supported by consistency between symptoms and findings on brain imaging. Stroke was classified as
109 cryptogenic after an extensive diagnostic workup, including 12-lead ECG, 24 hours or more of ECG monitoring, 24-
110 hour ECG Holter, transesophageal echocardiography, screening for thrombophilic condition (in patients <55 years of
111 age), and either magnetic resonance angiography, computed tomography angiography or catheter angiography of the
112 head and neck, had failed to show a clear cause. Ultrasonography of cervical arteries and transcranial Doppler
113 ultrasonography of intracranial vessels, in place of MRA or CTA of the head and neck, were allowed for patients older
114 than 55 years of age. Patients with TIA were enrolled only if symptoms at presentation were speech problems, limb
115 weakness, or hemianopsia. Indications for ILR implantation in the control group included: patients implanted for
116 history of non-sustained ventricular arrhythmias without a formal indication to ICD (61 patients) and patients
117 symptomatic for palpitations of unknown diagnosis (25 patients). After the loop recorder (Medtronic LinQ) was
118 implanted, these patients were then followed over time in remote monitoring (Medtronic Carelink), with automatic
119 transmissions of ECG tracings that were displayed within 24 hours of arrhythmia detection or manual recording
120 performed in case of symptoms. A summary transmission was scheduled every 30 days regardless of arrhythmia
121 detection. All episodes were revised and validated by two electrophysiologists (P.A.F. and R.S.). Sinus node
122 dysfunction was defined, according to the latest 2021 ESC Guidelines on cardiac pacing, as sinus arrests/sinoatrial
123 blocks causing pauses greater than 3 seconds, with indication to pacing in case of pauses lasting more than 3 seconds
124 if symptomatic and more than 6 seconds if asymptomatic.¹⁹ Atrial fibrillation was defined as an episode of irregular
125 heart rhythm, without detectable P waves, lasting more than 6 minutes, automatically detected by loop recorder
126 through a dedicated software. Patients who had implanted loop recorders for indications other than cryptogenic
127 stroke were identified as a control group and followed over time with the same modalities. Patients who had
128 implanted the loop recorder for syncope of unclear origin were excluded due to the high likelihood of finding
129 bradyarrhythmias. If the device detected arrhythmias, the patient was contacted by telephone to verify whether
130 she/he had had symptoms and to plan any outpatient or inpatient check deemed necessary by the referring
131 physicians. All patients provided written informed consent for the implantation of the loop recorder and for the use of
132 their monitoring data for research purposes

133 **Study endpoints**

134 The primary end point was the time to first detection of clinically significant bradyarrhythmia at 6-month follow-up.
135 Secondary end points included the time to first detection of atrial fibrillation at 12-month follow-up.

136 **Statistical Analysis.**

137 Categorical data were summarized as percentages and continuous data as mean \pm Standard Deviation (SD). T-test for
138 independent samples was used to compare the means of continuous variables, Mann-Whitney test in case of a non-
139 normal distribution and χ^2 test for qualitative variables. We used the Kolmogorov–Smirnov test for normality in order
140 to evaluate the assumption of t-test.

141 We used a propensity score matching (PSM) with the “nearest” algorithm to mitigate the imbalance between the two
142 groups (cryptogenic stroke and control in a 1:1 ratio). Covariates included in PSM model were age, gender,
143 hypertension, diabetes, heart failure, obstructive sleep apnea syndrome and beta blockers use. Matching was
144 performed using the nearest neighbor matching protocol and a standardized mean difference (SMD)<0.2. Covariates
145 balance was assessed by examining standardized mean differences (SMD), with values < 0.2 indicating acceptable
146 balance. Cox regression univariate analysis for the occurrence of the primary endpoint was performed. Cumulative
147 event-free survival rates for the population, divided in the two aforementioned groups, were calculated using the
148 Kaplan–Meier method. A p-value<0.05 was considered significant. Statistical analyses were performed using R
149 software (Version 4.3.2) with the *MatchIt package* and SPSS (SPSS version 26, Inc., Chicago, IL, USA).

150

151 **Results.**

152 The study included 225 patients (mean age: 67.71 ± 14.5 years, 53% males) who received an implantable loop
153 recorder for cryptogenic stroke (n = 139) or other indications other than syncope (n = 86; 61 patients for non-
154 sustained ventricular arrhythmias without a formal indication to ICD and 25 for palpitations) at our Institution. Median
155 follow-up duration was 23.63 ± 15.39 months in the control group and 23.25 ±14.25 months in the stroke/TIA group
156 (p=0.73). Before matching, cryptogenic stroke/TIA patients had higher prevalence of hypertension (73% vs 51%;
157 p=0.002) and were more frequently affected by diabetes mellitus (77% vs 23%; p=0.04); concerning the
158 pharmacological therapy, the cryptogenic stroke/TIA cohort was less frequently on beta blockers therapy (35% vs
159 59%; p<0.001), assumed more frequently Renin-Angiotensin-Aldosterone System (RAAS) antagonists (61% vs 36%;
160 p=0.002), and antiplatelet drugs (80% vs 33%; p<0.001) but less anticoagulants (7% vs 16%; p=0.036). Baseline
161 characteristics of the unmatched population are reported in *Table 1*.

162 At the end of follow-up, the most relevant difference was the higher incidence of SND in cryptogenic stroke patients
163 compared with controls during follow-up (18.7% vs 4.7%; p=0.003). Mean time of SND diagnosis from implant was 6 ±
164 3,5 months. New-onset atrial fibrillation was diagnosed in 38 (26.7%) of patients implanted for stroke/TIA and 23
165 (28.7%) of patients implanted for other indications (p=0.84). There were no significant differences in incidence
166 between the two groups for other bradyarrhythmias (such as second-degree, third-degree, or advanced
167 atrioventricular block) or tachyarrhythmias (sustained or non-sustained ventricular tachycardias).

168 Sinus node dysfunction was diagnosed in 26 patients in the cryptogenic stroke group versus 4 patients in the control
169 group. This required pacemaker implantation in 14 cases within the cryptogenic stroke/TIA group (10.1% vs 4.7%;
170 p=0.09). Pacemaker implantation rates, though higher in the cryptogenic stroke/TIA cohort, were lower than the
171 incidence of SND diagnoses, which may suggest that were predominantly driven by clinically non-significant or
172 asymptomatic sinus bradycardia/pauses. Overall, both AF and SND were diagnosed concurrently in 11 patients during
173 follow-up, with 10 of these cases belonging to the cryptogenic stroke/TIA cohort.

174 Propensity score matching based on the variables specified before yielded 57 cryptogenic stroke patients and 57
175 control patients. Baseline characteristics of the matched population are reported in *Table 2*.

176 We found that the association between cryptogenic TIA/stroke and sinus node dysfunction was significant even in
177 matched population analysis (22.8% vs 8.8%; $p=0.04$), furthermore cryptogenic stroke/TIA was significantly associated
178 with grade 2 or higher diastolic dysfunction (14% vs 3.5%, $p=0.047$) and antiplatelet drugs use (78.9% vs 45.6%,
179 $p=0.001$). No significant differences were observed between the two cohorts as for AF diagnosis (48.6% vs 51.4%;
180 $p=0.84$), bradyarrhythmias, tachyarrhythmias and pacemaker implantation. A summary of the results after propensity
181 matching is reported in *Table 3*.

182 At univariate analysis, SND was independently associated with cryptogenic TIA/stroke (OR=3.14, CI 95% 1.02 - 9.64,
183 $p=0.045$). Moreover, SND was significantly associated with indexed left atrial volume (OR= 1.059, CI 95% 1.027 - 1.091,
184 $p=0.02$) and hypertension (OR=4.52, CI 95% 1.030 - 19.895, $p=0.017$)

185 *Figure 1* shows Kaplan-Meier curves of the primary endpoint in patients with and without cryptogenic TIA/stroke (log-
186 rank test $p= 0.034$)

187 Discussion

188 The primary finding of our study is that patients with cryptogenic stroke exhibit a significantly higher incidence of
189 bradyarrhythmias detected by loop recorder compared to patients with other indications for device implantation. This
190 result is consistent with prior research (*actual evidence resumed in Table 1, Supplementary Materials*). For instance, a
191 recent multicenter prospective registry has shown SND without AF is an independent risk marker for ischemic
192 stroke²⁰; an observational study investigating the prevalence of bradyarrhythmias in patients with paroxysmal AF
193 detected by continuous rhythm monitoring found that 18% of patients experienced bradyarrhythmias or a
194 combination of tachy-bradyarrhythmias.^{14,17}

195 We hypothesize that the increased incidence of bradyarrhythmias in patients with a history of cryptogenic stroke,
196 alongside the presence of atrial fibrillation, is part of a complex pathology referred to in the literature as atrial
197 cardiomyopathy (AtCM). AtCM has been defined as "any complex of structural, architectural, contractile, or
198 electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations." It is a
199 term used to describe patients with an abnormal atrial substrate and function, including fibrosis, mechanical and
200 electrical dysfunction, and a hypercoagulable state.²²⁹

201 AtCM is not merely a consequence of aging; it also results from various pathophysiological conditions, including
202 systemic and subclinical inflammatory states such as hypertension, heart failure, and coronary artery disease. These
203 factors interact, leading to the activation of the renin-angiotensin-aldosterone system (RAAS) and the production of
204 angiotensin II (Ang II), which can induce cardiomyocyte hypertrophy, endothelial abnormalities, and myocardial
205 fibrosis.²³ It is important to emphasise that fibrosis and remodelling in these individuals is not merely confined to the
206 anatomic sinus node but has been shown to be present diffusely throughout the right atrium²⁷

207 Growing evidence suggests that AtCM may be a significant and independent predictor of stroke, even in the absence
208 of concurrent atrial fibrillation (AF). The proposed mechanism is a prothrombotic state within the atria, involving
209 abnormal blood flow (stasis) and "thrombogenic endocardial remodeling," which can directly cause clot formation. In
210 this context, AF may be an epiphenomenon, while the true causal pathway between AtCM and stroke is directly

211 attributable to the atria's prothrombotic properties.^{24,25} This correlation may be further supported by the detection of
212 AtCM-related ECG and echocardiographic markers in patients with confirmed cardioembolic ESUS.²⁶

213 Nearly 30% of ischemic strokes are of unknown origin, referred to as cryptogenic strokes (CS). Imaging studies indicate
214 that a large proportion of these cases are consistent with embolism, leading to the term embolic stroke of
215 undetermined source (ESUS).¹¹ This has prompted a series of studies to investigate the presence of asymptomatic
216 atrial fibrillation as a potential pathogenic mechanism for thromboembolism in ESUS patients. These studies have
217 underscored the pivotal role of implantable cardiac monitors (ICMs) in detecting asymptomatic AF in this specific
218 patient group.¹²

219 Recent studies, such as a substudy of the LOOP trial²¹, suggest that in a population of subjects over 70 years of age,
220 with no history of atrial fibrillation but with risk factors, the percentage of bradyarrhythmias detected by loop
221 recorder monitoring may be higher than expected. Many of these arrhythmias were asymptomatic (present in
222 approximately 20% of the population), and subsequent pacemaker implantation was not associated with a reduction
223 in syncope events compared to the control group. Accordingly, in our population (slightly younger on average), most
224 bradyarrhythmias were asymptomatic, and there was no statistically significant difference in the percentage of
225 patients who subsequently underwent pacemaker implantation between the group with previous cryptogenic stroke
226 and the control group.

227 Based on our findings, we can hypothesize that the higher incidence of both symptomatic and asymptomatic
228 bradycardia in our study population, compared to an age-matched group monitored for different indications, could be
229 attributable to a global atrial remodeling and subsequent fibrosis. This process likely causes slowed conduction and
230 leads to both a higher incidence of sinus arrest and an increased propensity for thromboembolic events due to
231 mechanical and electrical dysfunction.

232 Our findings may suggest interesting food for thought both on the complexity of the pathogenesis of cardioembolic
233 strokes and the therapeutic perspectives of these patients. For instance, the presence of SND in combination with
234 echocardiographic features of atrial cardiomyopathy might support the earlier initiation of anticoagulation therapy,
235 even in the absence of documented AF. However, clinical trials evaluating the efficacy of anticoagulation in patients
236 with a history of embolic stroke of undetermined source (ESUS) and subclinical AF detected via implantable loop
237 recorders have shown mixed results, with no clear reduction in overall mortality.²⁷ Furthermore, catheter ablation for
238 atrial fibrillation (AF) might be favored over pharmacological approaches for rate or rhythm control (e.g., beta-
239 blockers, calcium channel blockers), which could unmask or exacerbate underlying SND. Further studies are warranted
240 to validate these hypotheses and clarify the therapeutic implications.

241

242 **Limitations**

243 One of the main limitations of this study is its retrospective design, which inherently carries the risk of bias and limits
244 the ability to establish causality. Although propensity score matching was employed, the sample size remains

245 relatively small, with only 225 patients included in the analysis and just 57 patients per matched group. This limited
 246 cohort as well as the limited number of covariates utilized for matching may reduce the generalizability of the
 247 findings. Additionally, the diagnosis of sinus node dysfunction (SND) was based on the occurrence of sinus pauses
 248 greater than 3 seconds, which may be an overly broad criterion, potentially not being indicative of clinically significant
 249 dysfunction. Neurological events themselves can be accompanied by cardiac events. In particular, bradycardic events
 250 are frequently observed in the acute phase but also afterwards and some of the bradyarrhythmias documented in our
 251 study population could be directly related to stroke. Furthermore, the study did not investigate the time of onset of
 252 atrial fibrillation (AF) in SND patients, an important factor that could have provided valuable insights into the
 253 relationship between SND and AF. These factors suggest that caution is needed when interpreting the results, and
 254 further prospective studies with larger sample sizes are warranted to validate the findings.

255

256 Conclusions

257 In conclusion, our study demonstrates that patients with recent cryptogenic stroke exhibit a higher incidence of
 258 sinoatrial node disease (SND) compared to those who undergo ILR implantation for indications other than syncope. If
 259 confirmed in larger prospective studies, these findings could enhance our understanding of the clinical implications of
 260 atrial cardiomyopathy and potentially lead to changes in the management of these patients.

261

262 **Table 1. Baseline Clinical Characteristics of unmatched population**

263

	Cryptogenic stroke(139)	Controls(86)	P value
Age, years	71.4 ± 11.2	61.5 ± 17.3	0.001
Males % (n)			
Smoke % (n)	30.9 (43)	24.4 (21)	0.43
COPD % (n)	3.6 (5)	2.3 (2)	0.17
Congestive Heart Failure % (n)	8 (11)	6 (5)	0.29
Hypertension % (n)	73 (102)	51 (44)	0.002
Diabetes mellitus % (n)	16.5 (23)	8 (7)	0.043
Coronary Artery Disease % (n)	15.8 (22)	10.5 (9)	0.11
Chronic Kidney Disease % (n)	5 (7)	3.5 (3)	0.17
LVEF %	58.6 ± 6.8	58.6 ± 8.7	0.96
LAVi ml/m²	38 ± 13	33 ± 12	0.058
TAPSE mm	21.8 ± 3.4	21.1 ± 3.6	0.29
PR interval ms	174.8 ± 33	173.3 ± 43	0.814

QRS interval ms	108.8 ± 5.5	105.9 ± 5.9	0.75
Beta blocker % (n)	35.3 (49)	59.3 (51)	0.001
RAAS blocker % (n)	61.2 (85)	36 (31)	0.002
Antiplatelets % (n)	80 (111)	33.7 (29)	0.001
Anticoagulant % (n)	7.2 (10)	16.3 (14)	0.036

264

265

266 **Table 2. Baseline Clinical Characteristics of matched population**

267

	Cryptogenic stroke(57)	Controls(57)	P value
Age, years avg ± ds	67.5 ± 12.7	67.2 ± 13	0.87
Smoke % (n)	36.8 (21)	24.6 (14)	0.15
COPD % (n)	3.5 (2)	1.8 (1)	0.55
Congestive Heart Failure % (n)	7 (4)	5.3 (3)	0.6
Hypertension % (n)	63 (36)	61 (35)	0.84
Diabetes mellitus % (n)	10.5 (6)	8.8 (5)	0.75
Coronary Artery Disease % (n)	14 (8)	7 (4)	0.22
Chronic Kidney Disease % (n)	1.8 (1)	5.3 (3)	0.3
LVEF %	59.4 ± 6.6	59.5 ± 8.2	0.97
LAVi ml/m ²	37 ± 12.7	31.7 ± 10.5	0.017
Diastolic dysfunction >= grade 2 % (n)	14 (8)	3.5 (2)	0.047
TAPSE mm	22.4 3.1	21.8 3.4	0.33
PR interval ms	166.4 25.7	170.9 39.4	0.47
QRS interval ms	103.4 46.3	96.8 15.5	0.97
Beta blocker % (n)	45.6 (26)	52.6 (30)	0.45
RAAS blocker % (n)	56.1 (32)	42.1 (24)	0.13
Antiplatelets % (n)	78.9 (45)	45.6 (26)	0.001
Anticoagulant % (n)	5.3 (3)	15.8 (9)	0.06

268

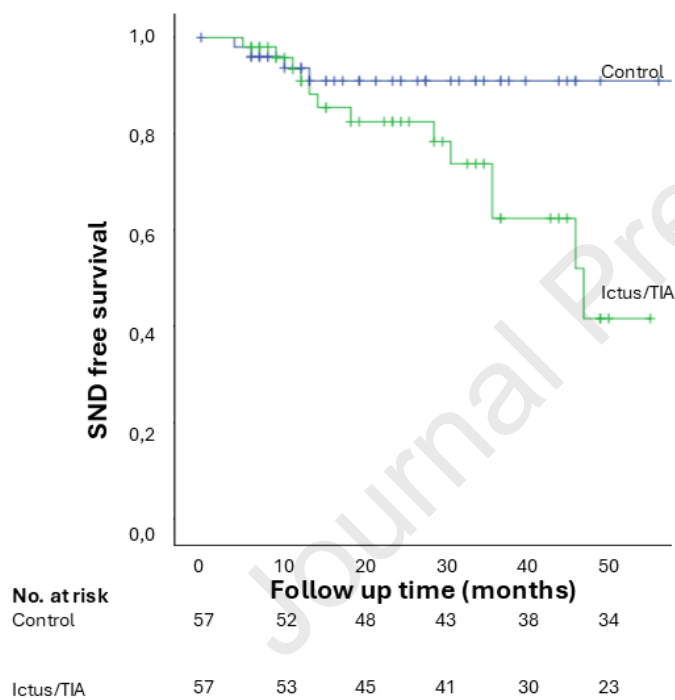
269

270 **Table 3. Main results after propensity matching**

	Cryptogenic stroke/TIA (57)	Controls (57)	P value

Sinus Node Dysfunction % (n)	22.7 (13)	8.8 (5)	0.04
Atrial Fibrillation % (n)	31.6 (18)	33.3 (19)	0.84
AVB II Degree Mobitz 1 % (n)	0 (0)	0 (0)	-
AVB II Degree Mobitz 2 % (n)	0 (0)	1.8 (1)	0.31
AVB III Degree % (n)	1.8 (1)	0 (0)	0.31
Advanced AVB % (n)	0 (0)	3.6 (2)	0.15
S/NS-VT % (n)	3.6 (2)	3.6 (2)	1
Pacemaker implantation % (n)	8.8 (5)	7 (4)	0.72
ICDs implantation % (n)	1.8 (1)	3.6 (2)	0.55

271



272

273

274 **Figure 1 Kaplan Meier curves**

275

276

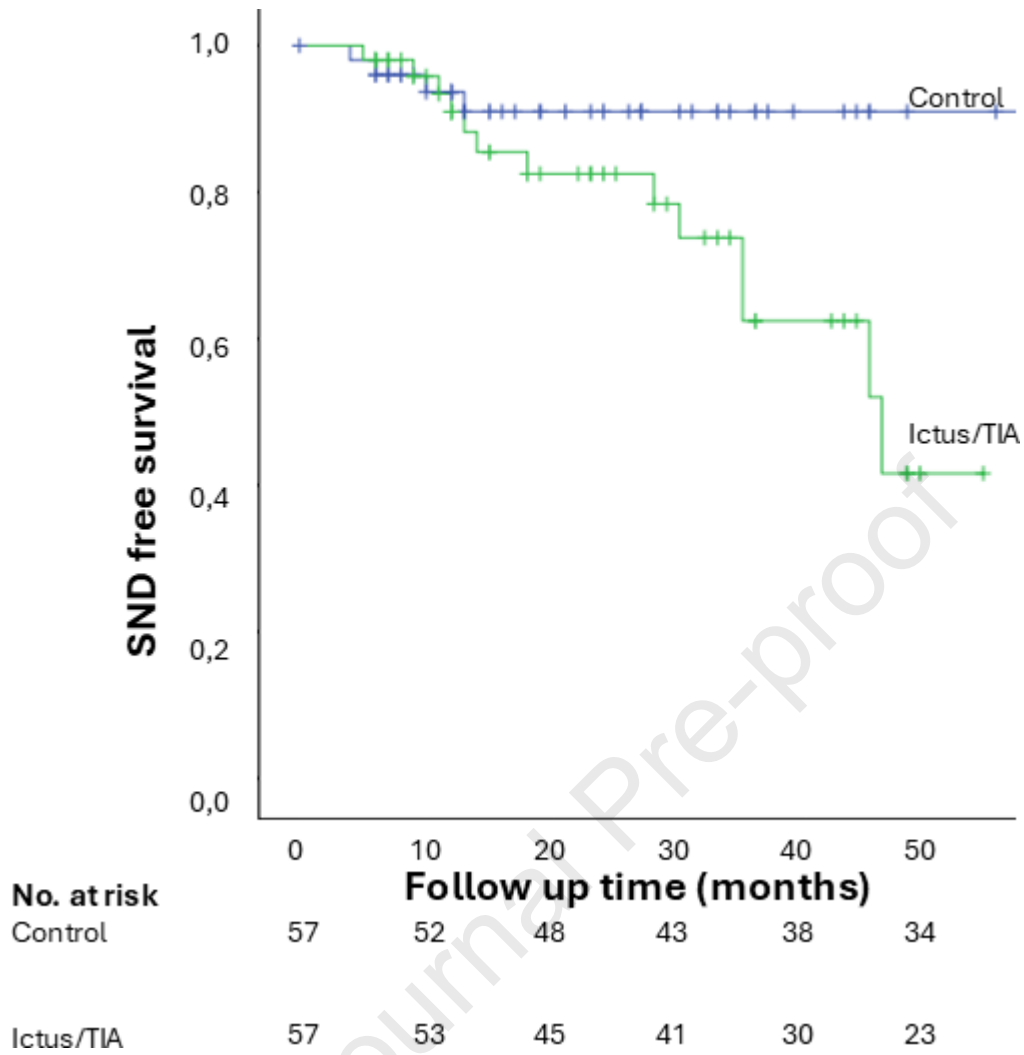
277

278 **References**

- 279 1. John RM, Kumar S: Sinus Node and Atrial Arrhythmias. *Circulation* [Internet] *Circulation*, 2016 [cited
280 2025 Oct 1]; 133:1892–1900. Available from: <https://pubmed.ncbi.nlm.nih.gov/27166347/>
- 281 2. Choudhury M, Boyett MR, Morris GM: Biology of the Sinus Node and its Disease. *Arrhythm
282 Electrophysiol Rev* [Internet] *Arrhythm Electrophysiol Rev*, 2015 [cited 2025 Oct 1]; 4:28–34.
283 Available from: <https://pubmed.ncbi.nlm.nih.gov/26835096/>
- 284 3. Manoj P, Kim JA, Kim S, et al.: Sinus node dysfunction: current understanding and future directions.
285 *Am J Physiol Heart Circ Physiol* [Internet] *Am J Physiol Heart Circ Physiol*, 2023 [cited 2025 Oct 1];
286 324:H259–H278. Available from: <https://pubmed.ncbi.nlm.nih.gov/36563014/>
- 287 4. Van Gelder IC, Kotecha D, Rienstra M, et al.: 2024 ESC Guidelines for the management of atrial
288 fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery
289 (EACTS). *Eur Heart J* [Internet] *Eur Heart J*, 2024 [cited 2025 Oct 1]; 45:3314–3414. Available from:
290 <https://pubmed.ncbi.nlm.nih.gov/39210723/>
- 291 5. Harada M, Van Wagoner DR, Nattel S: Role of inflammation in atrial fibrillation pathophysiology and
292 management. *Circ J* [Internet] *Circ J*, 2015 [cited 2025 Oct 1]; 79:495–502. Available from:
293 <https://pubmed.ncbi.nlm.nih.gov/25746525/>
- 294 6. Andrade J, Khairy P, Dobrev D, Nattel S: The clinical profile and pathophysiology of atrial fibrillation:
295 relationships among clinical features, epidemiology, and mechanisms. *Circ Res* [Internet] *Circ Res*,
296 2014 [cited 2025 Oct 1]; 114:1453–1468. Available from:
297 <https://pubmed.ncbi.nlm.nih.gov/24763464/>
- 298 7. Wakili R, Voigt N, Kääh S, Dobrev D, Nattel S: Recent advances in the molecular pathophysiology of
299 atrial fibrillation. *J Clin Invest* [Internet] *J Clin Invest*, 2011 [cited 2025 Oct 1]; 121:2955–2968.
300 Available from: <https://pubmed.ncbi.nlm.nih.gov/21804195/>
- 301 8. Duan S, Du J: Sinus node dysfunction and atrial fibrillation—Relationships, clinical phenotypes, new
302 mechanisms, and treatment approaches. *Ageing Res Rev* [Internet] Elsevier Ireland Ltd, 2023 [cited
303 2025 Oct 13]; 86. Available from: <https://pubmed.ncbi.nlm.nih.gov/36813137/>
- 304 9. Goette A, Corradi D, Dobrev D, et al.: Atrial cardiomyopathy revisited—evolution of a concept: a
305 clinical consensus statement of the European Heart Rhythm Association (EHRA) of the ESC, the
306 Heart Rhythm Society (HRS), the Asian Pacific Heart Rhythm Society (APHRS), and the Latin
307 American Heart Rhythm Society (LAHRS). *Europace* [Internet] *Europace*, 2024 [cited 2025 Oct 1]; 26.
308 Available from: <https://pubmed.ncbi.nlm.nih.gov/39077825/>
- 309 10. Etgen T, Hochreiter M, Mundel M, Freudenberger T: Insertable cardiac event recorder in detection
310 of atrial fibrillation after cryptogenic stroke: an audit report. *Stroke* [Internet] *Stroke*, 2013 [cited
311 2025 Oct 1]; 44:2007–2009. Available from: <https://pubmed.ncbi.nlm.nih.gov/23674523/>
- 312 11. Hart RG, Diener HC, Coutts SB, et al.: Embolic strokes of undetermined source: The case for a new
313 clinical construct. *Lancet Neurol* [Internet] Lancet Publishing Group, 2014 [cited 2025 Oct 1];
314 13:429–438. Available from: <https://pubmed.ncbi.nlm.nih.gov/24646875/>
- 315 12. Ko D, Dai Q, Flynn DB, et al.: Meta-Analysis of Randomized Clinical Trials Comparing the Impact of
316 Implantable Loop Recorder Versus Usual Care After Ischemic Stroke for Detection of Atrial
317 Fibrillation and Stroke Risk. *American Journal of Cardiology* [Internet] Elsevier Inc., 2022 [cited 2025
318 Oct 1]; 162:100–104. Available from: <https://pubmed.ncbi.nlm.nih.gov/34756594/>

- 319 13. Sanna T, Diener H-C, Passman RS, et al.: Cryptogenic stroke and underlying atrial fibrillation. *N Engl J*
320 *Med* [Internet] *N Engl J Med*, 2014 [cited 2025 Oct 1]; 370:2478–2486. Available from:
321 <https://pubmed.ncbi.nlm.nih.gov/24963567/>
- 322 14. Bettin M, Dechering D, Kochhäuser S, et al.: Extended ECG monitoring with an implantable loop
323 recorder in patients with cryptogenic stroke: time schedule, reasons for explantation and incidental
324 findings (results from the TRACK-AF trial). *Clin Res Cardiol* [Internet] *Clin Res Cardiol*, 2019 [cited
325 2025 Oct 1]; 108:309–314. Available from: <https://pubmed.ncbi.nlm.nih.gov/30167809/>
- 326 15. Gorenek B, Bax J, Boriani G, et al.: Device-detected subclinical atrial tachyarrhythmias: definition,
327 implications and management—an European Heart Rhythm Association (EHRA) consensus document,
328 endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad
329 Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace* [Internet]
330 *Europace*, 2017 [cited 2025 Oct 1]; 19:1556–1578. Available from:
331 <https://pubmed.ncbi.nlm.nih.gov/28934408/>
- 332 16. Svendsen JH, Diederichsen SZ, Højberg S, et al.: Implantable loop recorder detection of atrial
333 fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *The Lancet* [Internet]
334 Elsevier B.V., 2021 [cited 2025 Oct 1]; 398:1507–1516. Available from:
335 <https://pubmed.ncbi.nlm.nih.gov/34469766/>
- 336 17. Frausing MHJP, Van De Lande ME, Maass AH, et al.: Brady- and tachyarrhythmias detected by
337 continuous rhythm monitoring in paroxysmal atrial fibrillation. *Heart* [Internet] *Heart*, 2023 [cited
338 2025 Oct 1]; 109:1286–1293. Available from: <https://pubmed.ncbi.nlm.nih.gov/36948572/>
- 339 18. Jimenez-Ruiz A, Racosta JM, Kimpinski K, Hilz MJ, Sposato LA: Cardiovascular autonomic dysfunction
340 after stroke. *Neurol Sci* [Internet] *Neurol Sci*, 2021 [cited 2025 Oct 1]; 42:1751–1758. Available from:
341 <https://pubmed.ncbi.nlm.nih.gov/33687612/>
- 342 19. Glikson M, Nielsen JC, Leclercq C, et al.: 2021 ESC Guidelines on cardiac pacing and cardiac
343 resynchronization therapy. *Eur Heart J* [Internet] *Eur Heart J*, 2021 [cited 2025 Oct 2]; 42:3427–
344 3520. Available from: <https://pubmed.ncbi.nlm.nih.gov/34455430/>
- 345 20. Virk SA, Ho WWH, Takeuchi F, Morris GM, Kistler PM, Kalman J: Risk of ischemic stroke in sinus node
346 dysfunction with and without atrial fibrillation: Evidence for the presence of a left atrial myopathy in
347 patients with isolated sinus node dysfunction—an analysis of the UK Biobank. *Heart Rhythm*
348 [Internet] Elsevier B.V., 2025 [cited 2025 Nov 10]; 22:e668–e675. Available from:
349 <https://pubmed.ncbi.nlm.nih.gov/40315941/>
- 350 21. Diederichsen SZ, Xing LY, Frodi DM, et al.: Prevalence and Prognostic Significance of
351 Bradyarrhythmias in Patients Screened for Atrial Fibrillation vs Usual Care: Post Hoc Analysis of the
352 LOOP Randomized Clinical Trial. *JAMA Cardiol* [Internet] *JAMA Cardiol*, 2023 [cited 2025 Nov 26];
353 8:326–334. Available from: <https://pubmed.ncbi.nlm.nih.gov/36790817/>
- 354 22. Li M, Ning Y, Tse G, et al.: Atrial cardiomyopathy: from cell to bedside. *ESC Heart Fail* [Internet] *ESC*
355 *Heart Fail*, 2022 [cited 2025 Oct 13]; 9:3768–3784. Available from:
356 <https://pubmed.ncbi.nlm.nih.gov/35920287/>
- 357 23. Goette A, Kalman JM, Aguinaga L, et al.: EHRA/HRS/APHRS/SOLAECE expert consensus on atrial
358 cardiomyopathies: definition, characterization, and clinical implication. *Europace* [Internet]
359 *Europace*, 2016 [cited 2025 Oct 1]; 18:1455–1490. Available from:
360 <https://pubmed.ncbi.nlm.nih.gov/27402624/>

- 361 24. Ning Y, Tse G, Luo G, Li G: Atrial Cardiomyopathy: An Emerging Cause of the Embolic Stroke of
362 Undetermined Source. *Front Cardiovasc Med* [Internet] *Front Cardiovasc Med*, 2021 [cited 2025 Oct
363 1]; 8. Available from: <https://pubmed.ncbi.nlm.nih.gov/34434973/>
- 364 25. Kamel H, Okin PM, Longstreth WT, Elkind MSV, Soliman EZ: Atrial cardiopathy: a broadened concept
365 of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol* [Internet] *Future Cardiol*,
366 2015 [cited 2025 Oct 1]; 11:323–331. Available from: <https://pubmed.ncbi.nlm.nih.gov/26021638/>
- 367 26. Stalikas N, Doundoulakis I, Karagiannidis E, et al.: Prevalence of markers of atrial cardiomyopathy in
368 embolic stroke of undetermined source: A systematic review. *Eur J Intern Med* [Internet] Elsevier
369 B.V., 2022 [cited 2025 Oct 13]; 99:38–44. Available from:
370 <https://pubmed.ncbi.nlm.nih.gov/35065879/>
- 371 27. Geisler T, Keller T, Martus P, et al.: Apixaban versus Aspirin for Embolic Stroke of Undetermined
372 Source. *NEJM evidence* [Internet] *NEJM Evid*, 2024 [cited 2025 Oct 1]; 3. Available from:
373 <https://pubmed.ncbi.nlm.nih.gov/38320511/>
- 374 28. Sanders P, Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A, Vohra JK, Sparks PB, Kalman JM.
375 Electrophysiological and electroanatomic characterization of the atria in sinus node disease:
376 evidence of diffuse atrial remodeling. *Circulation*. 2004 Mar 30;109(12):1514-22
377
378
379
380
381
382
383
384
385
386



Supplementary file: Studies on ILR implantation after cryptogenic stroke and the incidence of sinoatrial node dysfunction and atrial fibrillation in the respective populations

Study name	Year	Study design	Study population	SND incidence during follow-up	AF incidence during follow up
Sanna T et al, CRYSTAL AF trial, NEJM	2014	RCT; ILR vs usual care in Cryptogenic stroke patients; 12-months follow up	ILR: 221 Control: 220	-	ILR: 29 Control: 4
Bettin M et al; TRACK-AF trial, Clin Res Cardio	2018	Prospective trial; ILR in cryptogenic stroke patients; 25 months median follow up	173 patients	8-12 (4.6-7.5%)	33 (19.1%)
Pecha S; Implantable loop recorder monitoring in patients with cryptogenic stroke - Detection and treatment of different clinically relevant arrhythmias, J Electrocardio	2020	Retrospective study; ILR in cryptogenic stroke; 14 months mean follow up	64 patients	Bradyarrhythmias requiring pacemaker 6 (9.4%)	16 (25%)
Bernstein et al. STROKE-AF, JAMA Neurol	2021	RCT, ILR vs usual care in ischemic stroke patients; 3 year follow up	ILR: 242 Control: 250	-	ILR: 46 (21.7%) Control: 5 (2.4%)
Buck et al, PER DIEM, JAMA	2021	RCT; ILR vs external loop recorder in ischemic stroke patients; 12 months follow up	ILR: 150 Control: 150	-	ILR: 23 (15.3%) Control: 7 (4.7%)
Diederichsen SZ et al, Post Hoc analysis LOOP RCT study, JAMA Cardio	2023	Post Hoc analysis RCT; ILR vs usual care in patients with risk factors for AF; 65 months median follow up	ILR: 1501 Control 4503	ILR: 204 (13.6%) Control: 66 (1.5%)	(from original analysis) ILR: 477 (31.8%) Control: 550 (12.2%)
Frausing MHJP et al; Brady- and tachyarrhythmias detected by continuous rhythm monitoring in paroxysmal atrial fibrillation, Heart	2023	Observational trial, ILR in paroxysmal AF patients; 3.4 years median follow up	392 patients	Bradyarrhythmias 69 (18%)	AF/A Flutter 128 (33%)