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Short title: Ultra-early ICM to detect AF in cryptogenic stroke

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Disclosures

Biotronik, Inc gently provided 35 of the implantable cardiac monitors (Biomonitor®) required for this study. No other conflicts of interest regarding the present work.

Abstract

Background and aims: Subclinical atrial fibrillation (AF) is known to underlie a number of cases of cryptogenic stroke (CrS). However there is need to define the most effective strategy for AF detection. We analyzed the diagnostic usefulness of a strategy based on ultra-early continuous monitoring in patients with CrS in terms of AF detection, oral anticoagulation treatment and stroke recurrence, in comparison to a standard outpatient strategy.

Methods: Patients with ischemic stroke of undetermined origin and confirmed to be cryptogenic after extensive work-up were searched for AF with: a) a conventional strategy (historical cohort, n=101) with serial ECGs and 24h-Holter monitoring; or b) an ultra-early monitoring strategy with insertable cardiac monitor (ICM) implanted before discharge (prospective cohort, n=90). AF episodes lasting > 1 minute, anticoagulant treatment and stroke recurrence were recorded.

Results: During admission, AF was similarly detected in both cohorts (24% of patients). After discharge (mean follow-up 30 ±10 months), AF detection rates were 17/80 (21.3%) and 38/65 (58.5%) for patients in the conventional versus the ultra-early ICM group (p<0.001). Up to 41% of AF cases in the ICM cohort were detected within the first month. Oral anticoagulation was initiated in 37.6% versus 65.5% (p<0.001), and stroke recurrence recorded in 10.9% versus 3.3% (p 0.04) in the conventional versus the ICM cohort.

Conclusions: Pre-discharge ICM implant allows detection of AF during follow-up in up to 58% of selected patients with CrS. Compared to a conventional strategy, ultra-early ICM implant results in higher anticoagulation rates and a decrease stroke recurrence.

Introduction

About 25-30% of patients admitted to Stroke Units have a cryptogenic stroke (CrS), where an underlying etiology cannot be determined after a comprehensive evaluation.(1,2) In these cases single antiplatelet therapy at discharge is recommended.(3) However, paroxysmal atrial fibrillation (AF) is believed to be the underlying cause of a significant proportion of CrS.(1) The presence of AF in the setting of a stroke requires initiating oral anticoagulation (OAC), the most effective treatment for secondary prevention of cardio-embolic strokes.(4)

Although active search of AF should be pursued in all patients with CrS, the best strategy in this regard is poorly established.(3,5) Subcutaneous insertable cardiac monitors (ICM), with the capability of continuous 24/7 monitoring, seem optimal for AF detection.(5) Nevertheless, ICMs are expensive and invasive, and have demonstrated variable diagnostic yield in the setting of CrS, with apparently less AF detection rates in series with late ICM implant.(6,7) Thus, the benefit of the systematic use of ICMs and the best timing for implant in patients with CrS remain unresolved issues.

Recent data from patients with cardiac electronic devices and patients monitored at the Stroke Units point to a high incidence of AF early prior and after the stroke.(8,9) We hypothesized that a strategy based on prompt and continuous cardiac monitoring would favor AF detection, and potentially provide a clinical benefit in patients with CrS. We therefore analyzed the diagnostic usefulness of an ultra-early ICM implant in patients with CrS in terms of AF detection, and secondarily, OAC treatment and stroke recurrence, in comparison to a standard non-invasive outpatient strategy.

Methods

Study population and standard of care

All patients admitted to our Stroke Unit from October 2010 to September 2016 were recruited. Patients included between 2010-2013 constitute the historical/conventional cohort, whereas those between 2013-2016 constitute the prospective/ultra-early ICM-monitored cohort. All patients were required to meet the following criteria: 1) ischemic stroke or transient ischemic attack (TIA); 2) age between 50-89 years; 3) undetermined origin at hospital admission according to the SSS-TOAST criteria.(2) Patients with history of hemorrhagic stroke, prior AF or atrial flutter, permanent contraindication or indication for OAC for other reasons, recent (<1 month) major surgery or cardiac events, severe cardiac abnormalities, and those with life expectancy <1 year or severe stroke (modified Rankin Scale >4) were excluded. The diagnosis of CrS was revisited in all patients 3 months after the index episode, and those found to have any potential cause other than AF were additionally excluded. The study followed the national and international principles (Declaration of Helsinki) and was approved by the local Ethics Committee. All patients or next-of-kin were required to sign the specific informed consent.

Demographic, vascular risk factors and comorbidities were retrieved from the past medical history. Work-up during admission included, at least: complete neurological exam, 12-lead ECG, brain CT, blood test and neurovascular imaging (angioMRI, angioCT and/or 2D-ultrasound of supra-aortic trunks and intracranial territory). Patients were immediately treated with antiplatelet treatment. OAC was started if AF was detected during admission. While in the Stroke Unit, all patients were continuously ECG-monitored for at least 48 hours, and underwent a cardiac transthoracic echocardiogram.

Strategies for AF detection

After discharge from the Stroke Unit, patients in the conventional group were studied with daily ECGs while admitted at the hospital (Figure 1). Outpatient serial ECGs were performed at the time

of each visit at the Neurology clinic at 3, 6, and 12 months after the stroke, and every 6 months thereafter. Additional ECGs were performed if patients had symptoms potentially related to AF. In those thought to be at high risk of cardio-embolic stroke, a 24h-Holter monitoring was scheduled 1 month after discharge, followed by a 7-day Holter monitoring if AF was not found.

Patients in the ultra-early ICM group underwent ICM implant 3-5 days after the stroke and prior to discharge (Figure 1). All devices (Biomonitor® and Biomonitor-2®, Biotronik) were implanted subcutaneously under local anesthesia in the left chest region, and programmed with the specific algorithm for AF detection, defined by an R-R interval variability >12.5% for >1 minute. Cycle lengths below 200 ms were considered noise. All patients were included in remote monitoring (Biotronik Home Monitoring®). All ICM recordings were reviewed by a specialized cardiologist. Patients were seen at the Arrhythmia and the Neurology outpatient clinics at 3, 6 and 12 months after the stroke, and every 6 months thereafter.

End-points and follow-up

AF was defined by the presence of a confirmatory ECG, Holter or ICM recording. OAC was initiated if AF was detected. Stroke recurrence was defined as a new neurological event recorded after hospital discharge and validated by a vascular neurologist.

Statistical analysis

Results are reported as mean (SD), median (p25-p75) or frequency (%). Comparisons between groups were performed with the Student t-test or chi-square analysis. The association between clinical variables and the study end-points was evaluated using survival analysis methodology (Cox regression models). The Kaplan–Meier method was used to estimate the cumulative probability of AF detection and stroke recurrence in both groups, and comparisons were made by the Log-rank

test. Significance was set at $p<0.05$. Statistical analyses were performed with SPSS Inc (version 20.0 for Windows, Chicago, IL).

Results

Study population

A total of 101 patients met the inclusion criteria during the period 2013-2016, and were investigated with the conventional strategy, whereas from 2013-2016, 90 patients were eligible for the ultra-early ICM strategy. ICMs were implanted at a median date of 5±2 days after the stroke. Details on patient recruitment are summarized in Supplemental Figure S1.

Demographics of the study population are presented in Table 1. Mean age of the series was 75.64 ± 8.8 years. Patients from the historical and the prospective cohorts were similar regarding baseline characteristics, past medical history, and stroke characteristics. Twenty-nine (15.1%) out of the 191 patients had a TIA.

Detection of AF

Overall, the rate of AF detection was remarkably higher in the ICM cohort compared to the conventional cohort (70.0% vs 37.6%, $p<0.001$, Table 2). During hospital admission, AF episodes (65% paroxysmal) were detected in 24% of patients, similarly in both cohorts. Mean follow-up after discharge was 30 ± 10 months for both groups, with all patients being followed during a minimum of 14 months. AF was detected in follow-up in 17/80 (21.3%) patients with the conventional strategy and in 38/65 (58.5%) patients assessed with the ultra-early ICM strategy ($p<0.001$). The rate of AF detection was similar in patients with CrS and in those with TIA. AF was paroxysmal in 74.3% of cases, indicating that, in the search of subclinical AF in CrS patients, most episodes could be underdiagnosed without a continuous-monitoring based approach.

Figure 2 shows the survival curves of AF detection throughout follow-up. After discharge, the ultra-early ICM strategy led to significantly greater AF detection than the conventional strategy (Log rank test p<0.001). Interestingly, most of these cases were detected within the first 4 months (26 cases, 68.4% of all AF cases) and particularly within the first month after discharge (16 cases, 42.1%). This highlights the importance of active AF search immediately and early after the stroke. Time to AF detection was 93 days (63.5-260.5) in the conventional group and 51 days (15.75-191.75) in the ultra-early ICM group.

By Cox-regression methodology, we explored the potential predictors of AF detection. An age >75 years and the use of ultra-early ICM strategy were the only predictors of AF detection in the multivariable analysis. The ultra-early ICM strategy was associated with a 2.45-fold increased risk of AF detection in follow-up (Table 3).

Secondary end-points

A total of 38 (37.6%) patients in the historical cohort versus 59 patients (65.6%) in the ICM cohort initiated treatment with OAC during follow-up (Table 2). OAC was disregarded in 4 patients of the ICM cohort due to important sequelae (n=2) or patient's refusal (n=2). Additionally OAC was withdrawn during follow-up in 3 patients of the conventional cohort and 1 of the ICM cohort due to hemorrhagic complications or clinical worsening. Due to temporal differences in both cohorts, more patients were treated with direct oral anticoagulants (DOAC) in the ICM group.

In the same period, 11 (10.9%) patients in the conventional cohort and 3 (3.3%) in the ultra-early ICM cohort had a new stroke (all ischemic) (p=0.04, Table 2). Interestingly, incidental AF was documented at the time of stroke in all stroke recurrences in the ICM cohort, and also in 4 cases of stroke recurrence of the historical cohort. This reflects a high temporal association between AF and stroke recurrence. Survival plots of stroke recurrence for both cohorts are depicted in Figure 3 (Log rank test p=0.04). The use of the ultra-early ICM strategy was associated with nearly a 70% risk

reduction of stroke recurrence, with marginal statistical significance (Cox regression, HR 0.29 [95% CI 0.08-1.04], p=0.05). Bleeding complications (1.9% vs. 2.2%) and death during follow-up (10.9% vs. 6.7%) were not different between groups in the conventional and prospective cohorts, respectively. Of note, one third of deaths in both groups were attributable to stroke recurrence or stroke-related complications.

Discussion

In this study, we found that, in selected patients with CrS, a strategy based on ultra-early and continuous monitoring by pre-discharge implant of an ICM leads to higher rates of AF detection and OAC treatment, and a significant reduction in stroke recurrence during follow-up compared to a conventional strategy. To our knowledge, ours is the first series that supports the benefit of ultra-early ICM implant, not only in increasing AF detection, but also in reducing a robust clinical end-point such as stroke recurrence in patients with CrS.

In our series AF detection rates were surprisingly high, mostly after discharge, particularly with the ultra-early ICM strategy. Previous series with CrS patients using different approaches of outpatient telemetry recordings have found variable AF detection rates between 2-20%.(10–12) With ICMs, the reported rates of AF are between 9-35% depending on the series.(6,7,13–15) The variability of the results may rely on differences in patient selection, variable AF definitions, and unstandardized monitoring strategies.(16)

Careful selection of patients has been demonstrated to lead to higher AF detection rates.(10) In our series, to ensure the inclusion of pure CrS, all patients were revisited 3 months after discharge, and those found to have other potential etiologies in follow-up were excluded. Therefore, ours was a very selected population with little margin for other etiologies and more likely to harbor an underlying AF. Our strict eligibility criteria resulted in inclusion of relatively elderly patients (mean

age 75 years vs. 61-68 years reported in previous CrS series)(6,7,11). This could also contribute to the high AF incidence in our cohorts since, as shown by our data, age was a determinant factor for AF detection.

Of note, we pre-defined AF by a compatible recording of ≥1 minute duration. Different thresholds of AF burden have been used in the past, from 30 seconds in the CRYSTAL study,(6) to 2 minutes(7,13,14), 5-6 mins in the MOST(17) and the ASSERT(18) studies or even 5.5 hours in the TRENDS study(19), with no established cut-off value.(5,16) Our results support that a 1-minute AF duration might already be clinically relevant, since guided OAC therapy based on this definition led to a reduction in stroke recurrence.

However, we believe that the strikingly high AF incidence (58.5%) in the ultra-early ICM cohort was mostly determined by a very prompt ICM implant. In the CRYSTAL-AF trial, where 441 CrS patients were allocated to ICM vs conventional monitoring, randomization could be performed up to 90 days after the index stroke. This strategy resulted in an AF detection rate of 8.9% at 6 months and 12.4% at 12 months in the ICM group(6). In the larger real-life series published thus far, including more than 1200 patients, Ziegler et al found an incidence of AF of 12.2% at 6 months and 16.3% at 12 months when ICM was implanted at any point in the clinical work-up.(7) Our data show that multiple paroxysmal AF episodes in CrS patients occur early after the stroke, particularly within the first month, which could be potentially dismissed if a continuous monitoring strategy is not promptly undertaken. Current evidence supports a temporal relationship between stroke and prior AF.(8) From our data, it would seem that the AF burden would continue to be high during the first days and even weeks after the stroke.

Very importantly, early AF detection and initiation of OAC treatment in the ultra-early ICM group was associated with a decrease in stroke recurrence during follow-up. In the presence of a small sample size, we only obtained marginal statistical significance supporting a stroke risk reduction of

70% in the ICM group compared to the conventional strategy (p=0.05). This issue has been only previously addressed by the CRYSTAL-AF, where no differences in stroke recurrence at 1 year were found between patients monitored with ICM (7.1%) or a conventional strategy (9.1%), probably due to a much lower AF detection rate in the interventional group.(6) It is worth to mention that, although mortality rates did not reach a significant difference between both groups (10.9% vs 6.7%, conventional versus ICM-strategy), stroke-related deaths accounted for a third of all deaths in our population of CrS patients. Larger series will be needed to confirm the potential clinical benefit in terms of stroke recurrence, and possibly mortality rates, in patients managed with ultra-early ICM monitoring and guided OAC therapy.

Our study has several limitations. Sample size was small. Comparisons were established between a prospective and a historical cohort, with the inherent potential collection and registration bias. No transesophageal echocardiograms or other tests in search of patent foramen ovale were perfomed, although patients with higher risk of paradoxal stroke (<50 years) were excluded. OAC regimens were different in both groups according to temporal trends, which might have had an impact in outcomes. Finally, ultra-early (i.e. before discharge) ICM implant led to unnecessary procedures in a number of patients who later in follow-up were disregarded as CrS (8 patients).

In conclusion, an ultra-early and continuous monitoring strategy for AF with pre-discharge ICM implant allows detection of AF in a majority of patients with CrS, leading to prompt OAC treatment and primary data indicating a decrease in stroke recurrence. Further prospective and ideally randomized studies with larger population of patients are warranted.

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Figure Legends

Figure 1. Study design illustrating the two AF detection strategies used in the historical and prospective cohorts.

Figure 2. Kaplan-Meier plots of overall AF detection (top), AF detection during admission (bottom, left) and AF detection after discharge (bottom, right) in the historical and prospective cohorts.

Figure 3. Kaplan-Meier survival analysis of stroke recurrence in the historical and prospective cohorts.

Tables

Table 1: Characteristics of the study population

	Conventional strategy n=101	ICM strategy n=90	p
Baseline characteristics and past medical history			
Age	75.27 (8.22)	76.06 (9.51)	0.540
Gender, women	57 (56.4)	41 (45.6)	0.133
BMI, Kg/m2	27.34 (4.75)	27.42 (5.34)	0.914
Hypertension	82 (81.2)	74 (82.2)	0.854
Diabetes mellitus	31 (30.7)	15 (16.7)	0.024
Hyperlipidemia	53 (52.5)	47 (52.2)	0.972
Current smoking	18 (17.8)	16 (17.8)	0.994
Peripheral artery disease	3 (3.0)	8 (8.9)	0.080
Coronary artery disease	16 (15.8)	8 (8.9)	0.148
Heart failure*	6 (5.9)	5 (5.6)	0.909
Prior stroke/TIA	12 (11.9)	14 (15.6)	0.460
Prior Rankin score	0 (0-1)	0 (0-1)	0.726
CHA2DS2- VASc	5 (4-5)	4.5 (4-5)	0.133
Stroke characteristics			
TIA	17 (16.8)	12 (13.3)	0.501
Oxford scale, available for n=184			0.182
- TACI	28 (28)	25 (29.8)	
- PACI	42 (42)	43 (51.2)	
- LACI	6 (6)	3 (3.6)	
- POCI	13 (13)	11 (13.1)	
NIHSS, admission	5 (2-13)	5.5 (2-14)	0.414
Fibrinolysis	31 (30.7)	30 (33.3)	0.696
NIHSS, discharge	1 (0-6)	1 (0-4)	0.216
Rankin, discharge	2 (1-3)	2 (0.75-3)	0.600

* Including heart failure with mid-range (40-49%) or reduced (<40%) left ventricular ejection fraction.

BMI: body mass index; TACI/PACI/LACI: total/partial/lacunar anterior circulation infarct; POCI: posterior circulation infarct; NIHSS: National Institutes of Health Stroke Scale. See other abbreviations in the text.

Table 2: Main end-points during follow-up in both cohorts

	Conventional strategy n=101	ICM strategy n=90	p
AF detection	38 (37.6)	63 (70.0)	<0.001
Time of detection:			
• During admission	21 (20.8)	25 (27.8)	0.260
- Stroke Unit	17 (16.8)	19 (21.1)	0.450
- Conventional floor	4 (4.0)	6 (6.7)	0.402
Hospital stay, days, med (p25-75)	5 (3-7)	5.5 (3-8.25)	0.548
• During follow-up:	17/80 (21.3)	38/65 (58.5)	<0.001
- ICM recording	-	38 (58.5)	
- Ambulatory Holter monitoring	9 (12.5)	-	
- ECG	8 (10.0)	-	
Follow-up, months, mean (SD)	30.01 (10.85)	31.43 (10.46)	0.359
AF detection by stroke subtype:			
- CrS	32/84 (38.1)	55/78 (70.5)	<0.001
- TIA of undetermined origin	6/17 (35.3)	8/12 (66.7)	0.096
AF subtype:			0.736
- Paroxysmal	27/38 (71.1)	48/63 (76.2)	
- Persistent/permanent	11/38 (28.9)	15/63 (23.8)	
Initiation of OAC treatment	38 (37.6)	59 (65.5)	<0.001
- Acenocumarol	29 (28.7)	29 (32.2)	
- DOAC	8 (7.9)	30 (33.3)	
Clinical end-points			
Stroke/TIA recurrence	11 (10.9)	3 (3.3)	0.045
All-cause death	11 (10.9)	6 (6.7)	0.222
Hemorrhagic complications	2 (1.9)	2 (2.2)	1.000

See abbreviations in the text.

Table 3: Predictors of AF detection in both cohorts

	Univariable analysis			Multivariable analysis		
	HR	95% CI	p	HR	95% CI	p
Age ≥ 75 years	1.92	1.24-2.97	0.004	1.98	1.28-3.07	0.002
Gender, women	1.18	0.80-1.75	0.404	--	--	--
BMI	1.00	0.96-1.04	0.893	--	--	--
Hypertension	0.69	0.43-1.12	0.131	--	--	--
Diabetes mellitus	0.84	0.53-1.36	0.482	--	--	--
Hyperlipidemia	0.86	0.58-1.27	0.449	--	--	--
Prior stroke/TIA	1.13	0.64-1.99	0.673	--	--	--
CHA2DS2- VASc score	1.12	0.93-1.35	0.219	--	--	--
Oxford scale, TACI	1.57	1.04-2.37	0.033	1.42	0.94-2.16	0.098
NIHSS upon admission	1.03	0.98-1.06	0.081	0.99	0.95-1.04	0.727
Ultra-early ICM strategy	2.40	1.59-3.60	<0.001	2.45	1.63-3.69	<0.001

See abbreviations in the text.

Figures

Figure 1

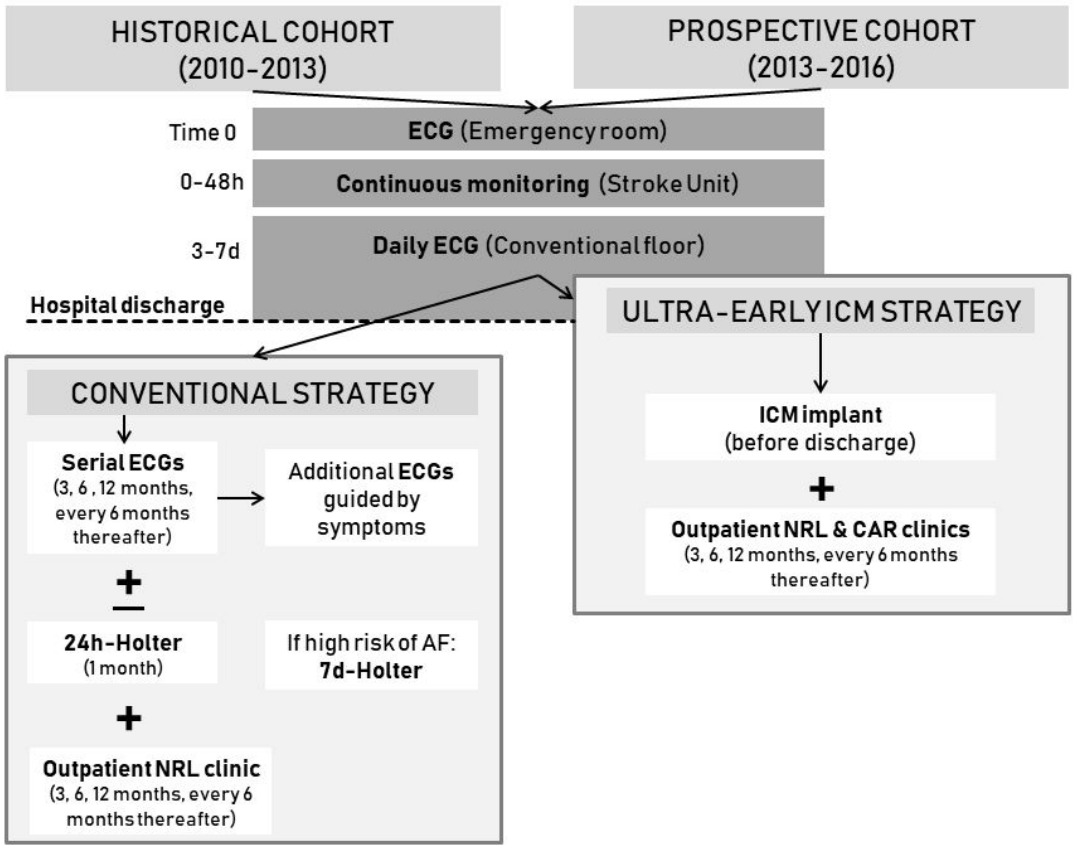


Figure 2

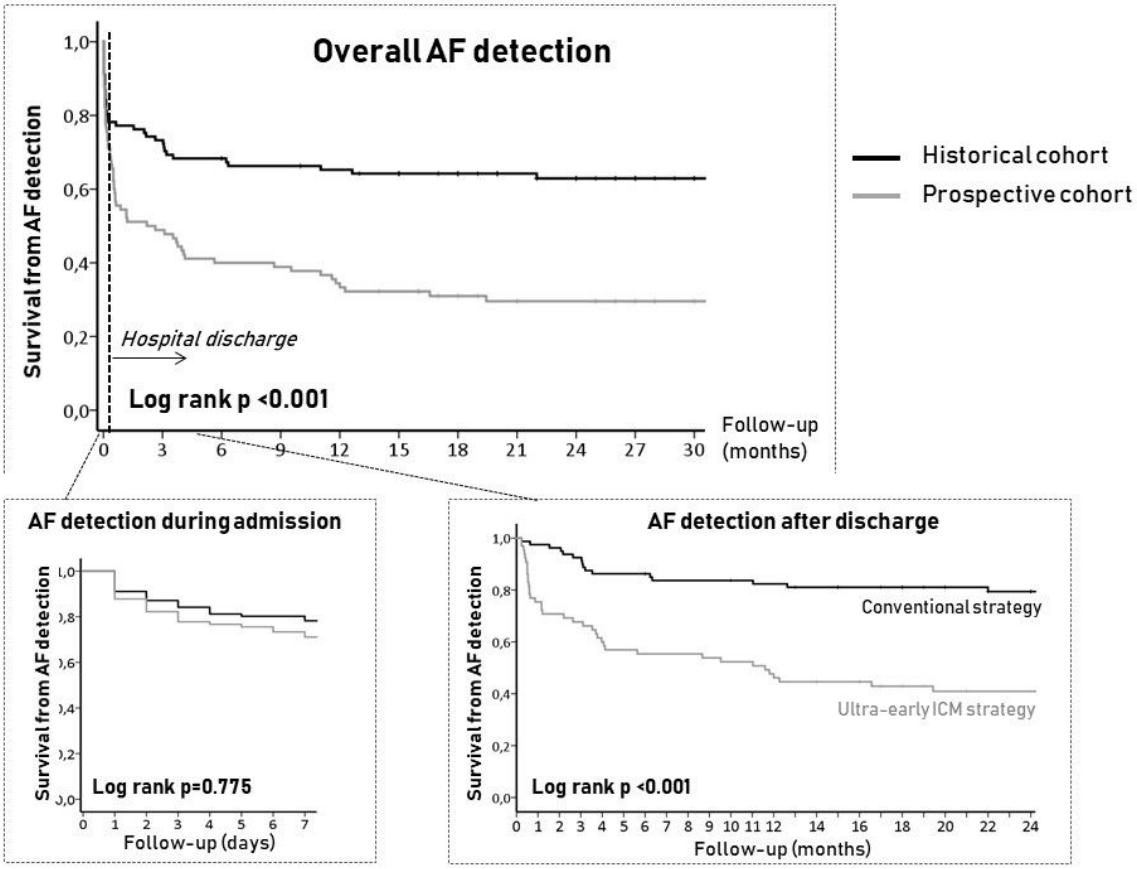
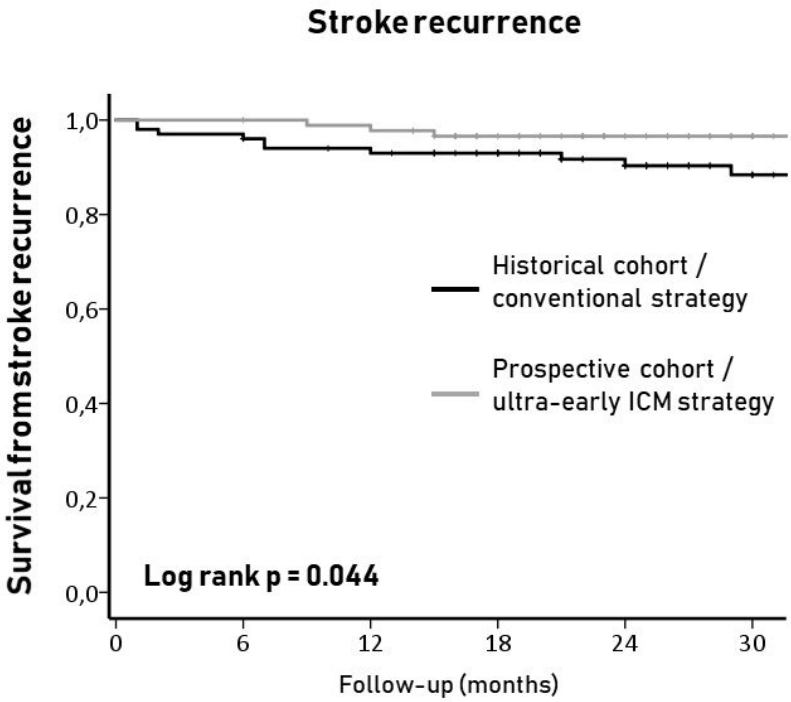
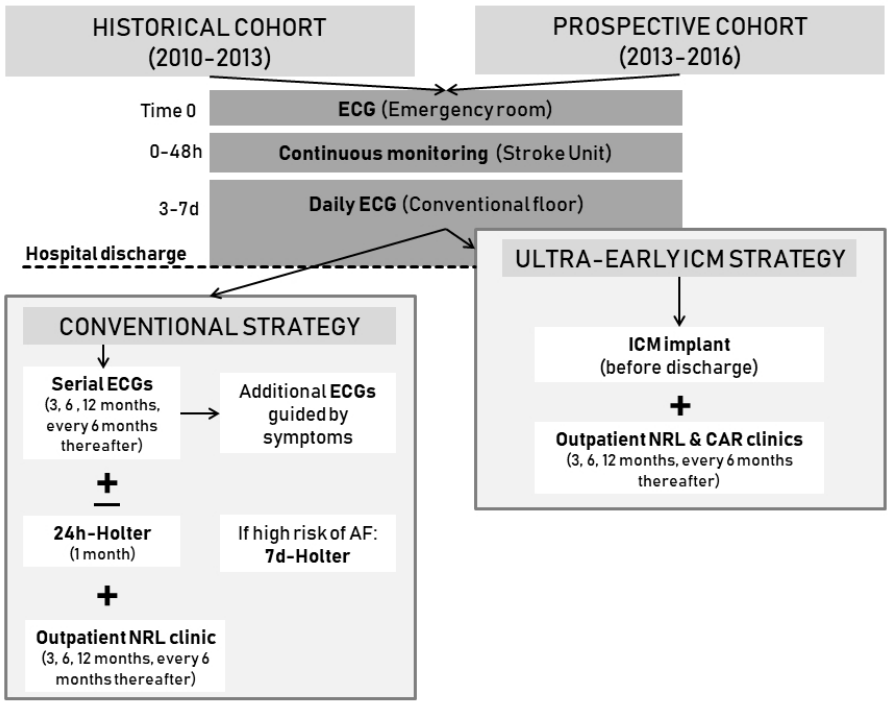


Figure 3





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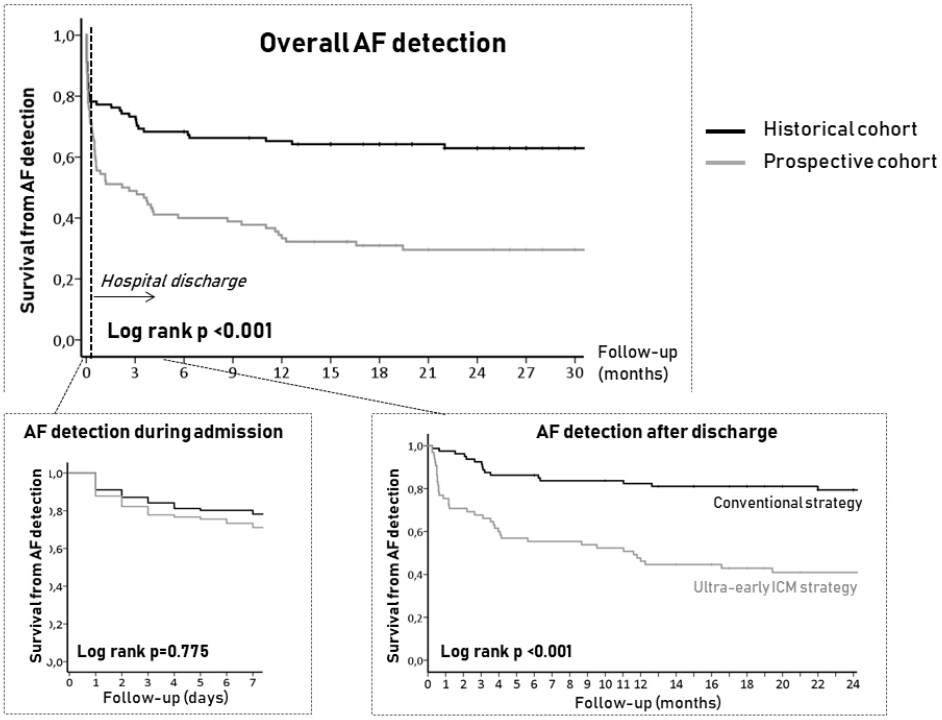

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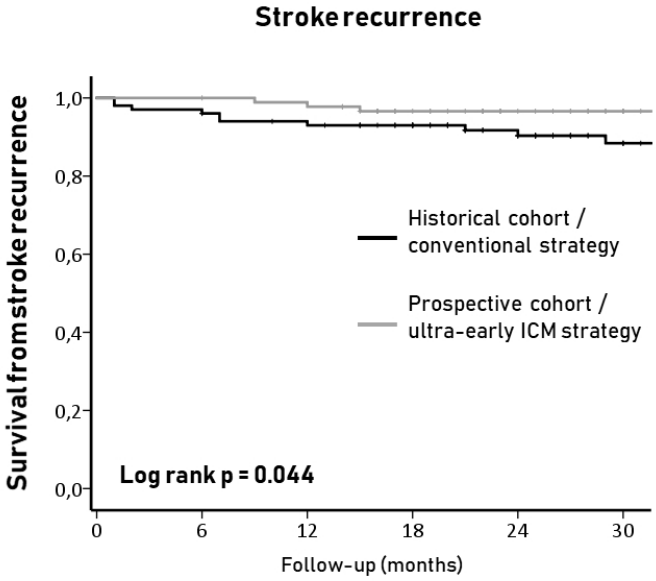

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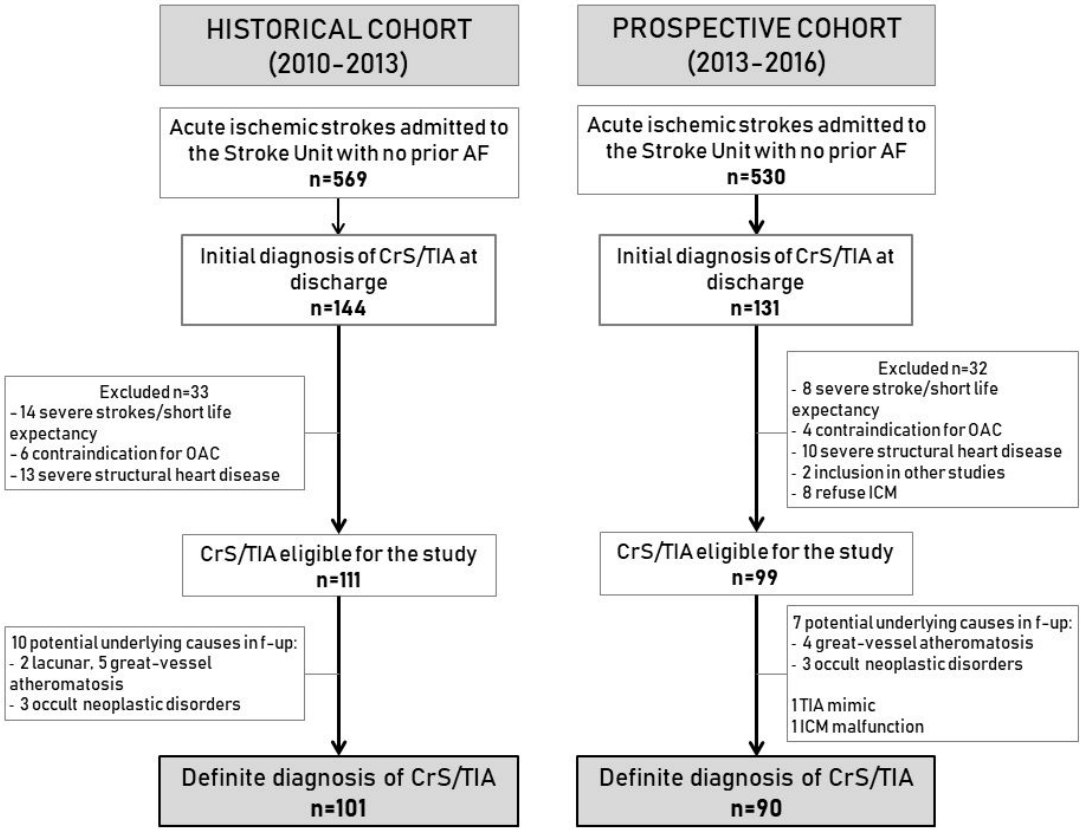
Supplemental Figures:

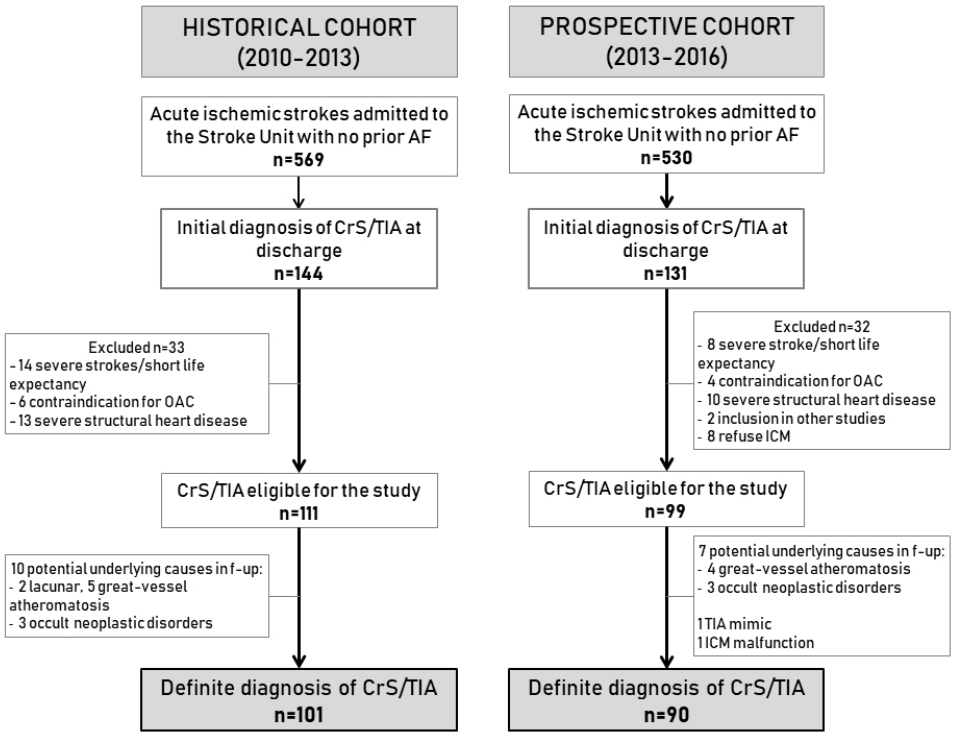
Legend to Figure S1. Flowchart of patients included in the historical and prospective cohorts, depicting those diagnosed of potential cryptogenic stroke (CrS) during admission, those who were excluded as per exclusion criteria and those who were not eligible due to subsequent identification of potential underlying causes of stroke, including great-vessel atheromatosis(1) and conditions known to be associated with hypercoagulability and arterial thromboembolic events, such as occult malignancies(2).



References:

1. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: The causative classification of stroke system. Stroke. 2007;38(11):2979–84.

2. Navi BB, Iadecola C. Ischemic Stroke in Cancer Patients: A Review of an Underappreciated Pathology. Ann Neurol. 2018;83(5):873–83.



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