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Infarct Topography and Detection of Atrial Fibrillation in Cryptogenic Stroke: Results from CRYSTAL AF

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Key Words
Cryptogenic stroke · Atrial fibrillation · Brain infarction

Abstract
Background: Insertable cardiac monitors (ICM) have been shown to detect atrial fibrillation (AF) at a higher rate than routine monitoring methods in patients with cryptogenic stroke (CS). However, it is unknown whether there are topographic patterns of brain infarction in patients with CS that are particularly associated with underlying AF. If such patterns exist, these could be used to help decide whether or not CS patients would benefit from long-term monitoring with an ICM. ***Methods:*** In this retrospective analysis, a neuroradiologist blinded to clinical details reviewed brain images from 212 patients with CS who were enrolled in the ICM arm of the CRYptogenic STroke And underLying AF (CRYSTAL AF) trial. Kaplan-Meier estimates were used to describe rates of AF detection at 12 months in patients with and without prespecified imaging characteristics. Hazard ratios (HRs), 95% confidence intervals (CIs), and p values were calculated using Cox regression. ***Results:*** We did not find any pattern of acute brain infarction that was significantly associated with AF detection after CS. However, the presence of chronic brain infarctions (15.8 vs. 7.0%, HR 2.84, 95% CI 1.13–7.15, p = 0.02) or leukoaraiosis (18.2 vs. 7.9%, HR 2.94, 95% CI 1.28–6.71, p < 0.01) was associated with AF detection. There was a borderline significant association of AF detection with the presence of chronic territorial (defined as within the territory of a first or second degree branch of the circle of Willis) infarcts (20.9 vs. 10.0%, HR 2.37, 95% CI 0.98–5.72, p = 0.05). ***Conclusions:*** We found no evidence for an association between brain infarction pattern and AF detection using an ICM in patients with CS, although patients with coexisting chronic, as well as acute, brain infarcts had a higher rate of

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AF detection. Acute brain infarction topography does not reliably predict or exclude detection of underlying AF in patients with CS and should not be used to select patients for ICM after cryptogenic stroke.

Introduction

Approximately one-third of all ischemic strokes have no determined mechanism (cryptogenic stroke, CS) despite thorough diagnostic evaluation including vascular and cardiac imaging, hematological testing, and electrocardiographic (ECG) monitoring [1]. Atrial fibrillation (AF) is commonly associated with ischemic stroke [2]. Diagnosing AF after stroke is important, because long-term oral anticoagulation is extremely effective at preventing recurrent stroke in patients with AF [3], but has not been proven superior to antiplatelet therapy in patients without AF or other major cardiac sources of embolism [4]. AF may occur in brief, rare intervals that may not be detected with standard ECG monitoring in the days after a stroke ('occult' AF) [5]. This has led to the hypothesis that occult AF may underlie some CS, and that prolonged cardiac rhythm monitoring in these patients might detect this underlying AF.

Insertable cardiac monitors (ICM) perform continuous cardiac rhythm monitoring and have improved our ability to detect occult AF. The CRYptogenic STroke And underLying Atrial Fibrillation Study (CRYSTAL AF) showed that an ICM detects significantly more AF than standard monitoring in patients with recent CS [6]. In CRYSTAL AF, 441 patients with CS were randomized to either standard monitoring or at least 12 months of monitoring with ICM. By 12 months, the AF detection rate in the ICM arm was 12.4% [7]. The earliest patients enrolled in the study underwent up to 36 months of monitoring and of those, the AF detection rate in the ICM arm was 30%, approximately 9-fold more than was detected with standard monitoring techniques [7].

Strokes associated with AF have classically been described as severe, with higher rates of death and permanent severe disability than strokes from other mechanisms [8]. In clinical practice, physicians try to infer stroke mechanism by looking for brain imaging signs that are typically associated with AF. For example, the presence of multiple infarcts in different vascular territories, or very large ischemic lesions with cortical and deep components, has been associated with cardioembolic stroke (including AF) [9, 10].

The radiographic associations with AF described earlier were determined prior to the advent of ICMs, and therefore may only apply to patients with non-occult AF. It is unknown whether occult AF is associated with the same radiographic signs as AF that are detectable with routine monitoring strategies, or if there is any radiographic pattern associated with underlying occult AF. If the detection of occult AF were found to be significantly more frequent in patients with particular patterns of ischemic lesions, diagnostic resources could be directed specifically to patients with those patterns, and those with low-risk patterns might be spared invasive testing.

To determine if occult AF is associated with a particular radiographic pattern in patients with CS, we analyzed the brain imaging findings from the ICM arm of CRYSTAL AF. Our hypothesis was that among patients with CS who underwent continuous monitoring for ≥1 year, there would be a distinct set of imaging findings more frequently associated with the ultimate detection of occult AF.

Methods

The CRYSTAL AF trial design has been described in detail elsewhere [7, 11]. The study protocol was approved by all relevant institutional review boards or ethics committees, and all patients provided written informed consent before randomization. In brief, 441 patients with stroke of unknown mechanism were randomized to either standard monitoring according to local practice (n = 220), or ICM insertion (n = 221). The primary endpoint was time to first detection of AF by 6 months, and the key secondary endpoint was time to first detection of AF by 12 months. AF was defined as an episode ≥30 s in duration of an irregular rhythm without detectable P-waves. All first episodes of AF were independently adjudicated. Lacunar stroke was an exclusion criterion for CRYSTAL AF and was defined as a single acute ischemic lesion <1 cm in diameter occurring in the territory of a small penetrating artery in the basal ganglia, internal capsule, corona radiata, or thalamus. Local investigators determined eligibility and were relied upon to exclude lacunar stroke, and images were not reviewed centrally prior to enrollment and randomization. Importantly, the inclusion criteria for CRYSTAL AF mandated that patients have an acute brain infarction consistent with symptoms on brain computed tomography (CT) or magnetic resonance imaging (MRI), even when symptoms were transient (e.g. they all had stroke by current definitions) [12].

For this sub-study, images obtained as standard of care after the index stroke in the subjects randomized to ICM insertion were collected and analyzed. A neuro-radiologist blinded to clinical details determined the size, vascular distribution, and number of acute and chronic ischemic lesions. Lesions were classified as 'lacunar' if they were small, deep lesions in the territories of penetrating arteries in the basal ganglia or thalamus but there were no size restrictions. Lesions were classified as 'territorial' if they conformed to the territory of a first- or second-generation branch of the circle of Willis. Border-zone infarcts were those situated between the usual

territories of the anterior and middle cerebral artery or between the anterior and posterior cerebral artery.

Descriptive statistics were used to characterize the imaging findings. Kaplan-Meier estimates were used to describe the rates of AF detection by 12 months among patients with and without prospectively defined lesion characteristics. To compare the rate of AF detection between patients with different imaging characteristics, hazard ratios (HRs), 95% confidence intervals (CIs), and p values (from the score statistic) were estimated using Cox regression.

Results

Patient demographics and comorbidities have been published elsewhere [7]. Of 221 patients randomized to the ICM arm, 212 (95.9%) had ≥1 brain image sent to the core lab, while no image was provided for 9 patients (4.1%); these patients were excluded from further analysis. CT images were provided for 86 subjects (38.9%) and MRI were provided for 166 subjects (75.1%) (some patients had >1 image submitted). Of the MRI scans, diffusion-weighted imaging (DWI) was assessable in 63.3%. The average time between the index stroke and the image was 2.2 days, and 90% of images were obtained within 5 days of the index stroke. Details of imaging modalities and sequences provided are summarized in table 1. The imaging characteristics of acute and chronic ischemic lesions seen in the entire study population (ICM arm) are shown in table 2.

Table 3 shows the rate of AF detection in patients with or without particular imaging characteristics. There were no acute lesion characteristics that were significantly more likely to be associated with the detection of AF by 12 months. In particular, neither the type of lesion (cortical, subcortical, or both; border-zone, or lacunar), the size of lesion, nor the arterial distribution of acute lesions showed any significant association with the detection of AF at 12 months.

However, when chronic lesions were included in the analysis, we did note several significant associations of lesion type with the detection of AF. Specifically, we noted an increased rate of AF detection in patients with any chronic infarcts (15.8 vs. 7.0%, HR 2.84, 95% CI 1.13–7.15, p = 0.02), and the presence of leukoaraiosis (18.2 vs. 7.9%, HR 2.94, 95% CI 1.28–6.71, p < 0.01). The presence of chronic territorial infarcts was associated with AF detection at a borderline level of statistical significance, but we consider this a biologically and clinically plausible association (20.9 vs. 10.0%, HR 2.37, 95% CI 0.98–5.72, p = 0.05).

Table 1. Imaging studies reviewed by core lab

Images provided to core lab	ICM (n = 221)
Index event image type, n (%)	
Any image available	212 (95.9)
CT	86 (38.9)
MRI	166 (75.1)
No image available	9 (4.1)
Index event image type – CT, n (%)	
NCT	78 (35.3)
CT	11 (5.0)
CTA	29 (13.1)
Other	0 (0.0)
Index event image type – MRI, n (%)	
T1	53 (24.0)
DE	77 (34.8)
FLAIR	148 (67.0)
T2*	90 (40.7)
DWI	140 (63.3)
Other	57 (25.8)

Table 2. Brain lesion characteristics for ICM subjects for whom imaging studies were available

Image characteristics	ICM (n = 212)
Index event infarct type, n (%)	
Cortical	92 (43.4)
Subcortical	40 (18.9)
Both cortical and subcortical	48 (22.6)
Internal border zone	2 (0.9)
External border zone	0 (0.0)
Lacunar	54 (25.5)
Posterior circulation (excluding lacunar)	18 (8.5)
Not assessable	15 (7.1)
Size of stroke lesion, n (%)	
<5 mm	65 (30.7)
≤5 mm	156 (73.6)
Not assessable	15 (7.1)
Acute stroke lesion/infarct arterial location, n (%)	
Middle cerebral artery	128 (60.4)
Anterior cerebral artery	7 (3.3)
Posterior cerebral artery	39 (18.4)
Brainstem	6 (2.8)
Cerebellum	19 (9.0)
Not assessable	13 (6.1)
Old ischemic infarctions, n (%)	
None	89 (42.0)
Any	101 (47.6)
Territorial	31 (14.6)
Lacunar	35 (16.5)
Leukoaraiosis	70 (33.0)
Hemodynamic-watershed	1 (0.5)
Not assessable	17 (8.0)

Table 3. Association of imaging characteristics with AF detection rate among patients where an image was assessable

Variable	AF detection rate at 12 months, %		HR (95% CI)	p value
	with	without		
Patients with/without 1 or more acute lesion by type of infarct				
Cortical	14.0	8.9	1.60 (0.70–3.64)	0.26
Subcortical	13.1	10.8	1.38 (0.54–3.50)	0.50
Cortical and subcortical	17.4	9.3	2.09 (0.91–4.83)	0.08
Internal border zone	0.0	11.4	0.00 (0.00, N/A)	0.60
External border zone	N/A	11.3	N/A	N/A
Lacunar	5.7	13.4	0.38 (0.11–1.27)	0.10
Posterior circulation (excluding lacunar)	25.0	10.0	2.52 (0.86–7.42)	0.08
Patients with stroke lesions by size				
Any lesion <5 mm	15.1	9.5	1.66 (0.73–3.78)	0.23
Any lesion ≥5 mm	12.0	8.5	1.67 (0.50–5.63)	0.40
Patients with/without 1 or more acute lesion by arterial distribution				
Middle cerebral artery	9.9	14.7	0.65 (0.29–1.44)	0.28
Anterior cerebral artery	14.3	11.6	1.13 (0.15–8.40)	0.90
Posterior cerebral artery	18.6	10.0	2.13 (0.91–4.99)	0.07
Brainstem	16.7	11.5	1.39 (0.19–10.31)	0.74
Cerebellum	23.5	10.5	2.21 (0.75–6.47)	0.14
Patients with/without 1 or more chronic ischemic infarctions by type				
Any chronic lesion(s)	15.8	7.0	2.84 (1.13–7.15)	0.02
Territorial	20.9	10.0	2.37 (0.98–5.72)	0.05
Hemodynamic-watershed*	100.0	11.2	30.14 (3.63–250.34)	<0.01
Lacunar	12.6	11.5	1.60 (0.63–4.02)	0.32
Leukoaraiosis	18.2	7.9	2.94 (1.28–6.71)	<0.01

* 100% is based on a single patient (1/1).

Discussion

In a population of patients with rigorously defined CS who underwent ≥12 months of continuous cardiac monitoring to detect occult AF, we did not find any acute ischemic lesion characteristic that correlated significantly with the detection of occult AF. However, the presence of chronic infarcts, chronic territorial (as opposed to lacunar) infarcts, and leukoaraisosis were each associated with a 2–3-fold increased rate of AF detection. It is important to note that the hazard ratios associated with the presence of old lesions are moderate, and that many patients without chronic lesions were found to have occult AF.

The most important clinical implication of our findings is that among patients with CS defined as we did in CRYSTAL AF, brain imaging cannot be relied upon to select patients for long-term cardiac monitoring. Since detection of AF in this population has important treatment implications (and resulted in initiation of anticoagulation by the treating physicians in almost every case [7]), the conclusion from CRYSTAL AF that ICM insertion should be considered in all CS patients remains valid regardless of the results of brain imaging.

AF has classically been associated with large brain infarctions and correspondingly severe neurological deficits, and a high risk of death or permanent disability. Our results might be interpreted to mean that occult AF does not carry those associations. However, it is important to consider that patients enrolled in CRYSTAL AF had mild strokes. More than 83% of the CRYSTAL AF patients were independent at the time of enrollment and the mean NIH stroke scale in the ICM arm of CRYSTAL AF was 1.9. This indicates that patients with severe and disabling CS were not enrolled in CRYSTAL AF. To determine whether patients with disabling CS have clinical or radiological characteristics that are associated with underlying occult AF, a study specifically enrolling such a population would be required. However, the clinical utility of detecting AF in patients with devastating stroke is unclear.

The CRYSTAL AF study detected occult AF in a significant minority of patients with CS, but was not designed to show that the AF predated the stroke. The association we found of AF with the presence of chronic lesions (in addition to the index acute lesion) suggests that for many of our patients with occult AF, the AF was present prior to the stroke. Our patients did not have arterial lesions or known cardiac conditions that predisposed them to stroke, making alternate explanations for the chronic lesions unlikely. We acknowledge that this interpretation remains unproven, but the association we found is consistent with this interpretation. The radiographic associations we found could be used to select high-risk patients for trials of novel oral anticoagulants, since we did note some MRI features that were weakly associated with detection of AF. However, we do not think these radiographic associations are strong enough to justify empirical anticoagulation of cryptogenic stroke patients outside of a trial.

Strengths and Limitations

The strengths of this analysis include the prospective design of CRYSTAL AF (although this was a retrospective analysis of CRYSTAL AF), the review of images by a core lab, review of the imaging by a neuroradiologist who was blinded to clinical details, and a predefined hypothesis. Our study also has several weaknesses. First, the definitions of stroke lesion type used by our core lab may have differed from the definitions used by our enrolling physicians. This explains why our core lab scored approximately one-quarter of our patients as having acute lacunar infarction even though this was an explicit exclusion criterion for CRYSTAL AF [11]. Second, not all patients underwent MRI with DWI. DWI is the most sensitive modality for detection of acute lesions, and therefore some acute lesions may have not been detected. Additionally, there is uncertainty as to the clinical relevance of brief episodes of AF. We used a definition of 30 s of AF in the CRYSTAL study, but note that the majority of patients with AF had at least 1 day of 6 min or more of AF. It is possible that our small sample size prevented detection of infarct patterns that might have emerged in a larger cohort. Finally, CRYSTAL AF had a rigorous definition of CS which included a transesophageal echocardiogram that did not show a high-risk embolic source. Whether our findings apply to a population of CS patients who did not undergo this screening (e.g. the EMBRACE population [13]) is unknown.

In conclusion, we did not find an association of acute lesion size, location, or number with the detection of occult AF in a population of patients with rigorously defined CS. The presence of chronic lesions increased the chance of detecting AF, but the effect size was small. ICM should be considered in patients with CS regardless of the results of brain imaging findings.

Disclosure Statement

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