Title: Importance of anticoagulation and postablation silent cerebral lesions: subanalyses of REVOLUTION and reMARQable studies

Short title: Post-ablation silent cerebral lesions

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Abstract

Background: Silent cerebral lesions (SCLs) are a potential complication of left atrial radiofrequency ablation (RFA) procedures for paroxysmal atrial fibrillation (PAF). We aimed to compare the incidence of SCLs in patients treated with irrigated RFA multielectrode catheters (nMARQ® Catheter group) and irrigated focal RFA catheters (NAVISTAR® THERMOCOOL® Catheter; TC group) after PAF ablation from subpopulation neurological assessment (SNA) cohorts of the REVOLUTION and reMARQable studies.

Methods: Data from SNA cohorts in the prospective, nonrandomized REVOLUTION study (March 2011 to September 2013) and the prospective, randomized, controlled reMARQable study (October 2013 to November 2015) were included. The incidence of SCLs was assessed pre- and post-ablation using magnetic resonance imaging. Neurological deficits were assessed using the National Institutes of Health Stroke Scale, modified Rankin Scale, and Montreal Cognitive Assessment.

Results: A total of 37 patients from REVOLUTION and 76 patients from reMARQable were included in the SNA cohort of each study. In the REVOLUTION SNA cohort, the incidence of SCLs was 21.1% (4/19) in the nMARQ® Catheter group and 5.9% (1/17) in the TC group. Findings from REVOLUTION helped inform the reMARQable study protocol’s stringent anticoagulation regimen. SCL incidence was subsequently reduced in both groups (nMARQ® Catheter, 7.9%; TC, 3.3%). No permanent neurological deficits were observed.

Conclusion: Adherence to a stringent anticoagulation regimen prior to and during ablation procedures appears to be an important factor in minimizing the risk of SCL.

Trial registration number: NCT01353586; NCT01824394
Keywords: atrial fibrillation; anticoagulation; focal radiofrequency ablation catheter; multielectrode catheter; silent cerebral lesion

Introduction
Symptomatic thromboembolic events (stroke and transient ischemic attack) following radiofrequency ablation (RFA) are rare (<1%). However, it has been reported that catheter ablation is associated with silent cerebral lesions (SCLs), diagnosed by brain MRI. Initial data suggest that the incidence of SCLs varies across different ablation technologies, with a higher incidence associated with non-irrigated, multielectrode phased radiofrequency (RF) catheters (38.9%) and a lower incidence for irrigated focal RF catheters and cryoballoon catheters (5.6%–8.3%). There is evidence that modifications to the ablation workflow—altering the management of anticoagulation and deactivating the distal or proximal electrode to avoid RF interaction—have led to a significant reduction in the incidence of SCLs.

The Clinical Workflow Study for the Evaluation of the Multi-Electrode Pulmonary Vein Isolation System for the Treatment of Paroxysmal Atrial Fibrillation (REVOLUTION) trial was an early study aimed at evaluating the workflow, safety, and effectiveness of the open-irrigated multielectrode nMARQ® Catheters in the treatment of paroxysmal atrial fibrillation (PAF). Since the initiation of the REVOLUTION trial, there has been an increased awareness of post-ablation SCLs. A subpopulation neurological assessment (SNA) cohort was included to determine the incidence of SCLs and any associated symptomatic neurological deficits pre- and post-ablation in the nMARQ® Catheter and focal NAVISTAR® THERMOCOOL® Catheter (TC) groups. The reMARQable trial incorporated the insights gained from the REVOLUTION trial and included an SNA cohort to further evaluate the incidence of SCLs under a more stringent anticoagulation regimen. This
sub-analyses of the SNA cohorts intends to understand the incidence of and possible factors associated with SCL occurrence.

Methods

Study design

REVOLUTION was a prospective, multicenter, nonrandomized study conducted at 8 sites across Europe between March 2011 and September 2013 to assess the early safety, effectiveness, and workflow of the open-irrigated, multielectrode nMARQ® Circular and Crescent Catheters (Biosense Webster, Inc., Diamond Bar, CA, USA) for the treatment of drug-refractory PAF. After amendments to the study protocol, a prospective, nonrandomized, controlled SNA cohort was included at 3-sites (France, 1; Belgium, 1; Italy, 1) to evaluate the incidence of SCLs and associated neurological deficits in comparison to a focal TC group (NAVISTAR® THERMOCOOL®; Biosense Webster, Inc., Diamond Bar, CA, USA). Patients were evaluated pre- and post-ablation with follow-up at 1, 3, 6, and 12 months.

The reMARQable study was a prospective, multicenter, randomized (1:1), controlled study involving 45 sites across the United States and Europe, including an SNA cohort at 12 sites, with the main objective to evaluate the safety and effectiveness of the nMARQ° Catheters compared to TC in the treatment of drug-refractory, symptomatic PAF. Patients were evaluated pre- and post-ablation with follow-up at 1, 3, 6, 9, and 12 months.

The study protocols were approved by the Institutional Review Board and Independent Ethics Committee at each center.
**Patient population**

In both studies, enrolled patients were 18 years or older, presented with symptomatic PAF with at least 1 documented AF episode within 12 months of enrollment, and had experienced failure of at least 1 antiarrhythmic drug for AF (class I, class III, or atrioventricular nodal-blocking agents). Inclusion criteria of the SNA cohorts were comparable to the main studies’ protocols. Patients with pacemakers, cardiac defibrillators, advanced renal disease, contraindications to the use of contrast agents for magnetic resonance imaging (MRI), or unresolved pre-existing neurological deficits were excluded. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice.

**Ablation procedure**

Ablation was performed with the nMARQ® multichannel RF generator and CARTO® 3 electroanatomical mapping system. The maximum setting for the nMARQ® Catheter RF power was 25 W at unipolar mode and 15 W at bipolar mode with an irrigation flow rate of 4 mL/minute when not delivering RF current; during RFA, irrigation flow rate was 60 mL/minute for the nMARQ® Circular Catheter and 42 mL/minute for the nMARQ® Crescent Catheter. Ablation with the control TC was performed with a Stockert generator (EP 70/SmartAblate, Shuttle). The ablation procedure was considered complete with confirmation of entrance block in targeted pulmonary veins. Additional RF lesions could be performed per the investigator’s discretion.
SCLs and neurological assessments

The primary safety endpoint of the SNA substudies was the incidence of post-ablation SCLs and associated neurological deficits (Supplementary Table 1), conducted on-site by certified, blinded neurologists from the same investigation site. Follow-up neurological assessments and MRI evaluations (Supplementary Table 2) were required only if neurologic symptoms or SCLs were identified in a prior evaluation.

Anticoagulation

In the REVOLUTION trial, the following anticoagulation regimen was recommended, but not mandated: a vitamin K antagonist was maintained for at least 4 weeks pre-ablation with an international normalized ratio (INR) of >2.0 at the time of ablation; sodium heparin (adjusted for body weight) was administered before and/or soon after the transseptal puncture to maintain an activated clotting time (ACT) >300–320 seconds throughout the procedure; and ACT was checked every 30 minutes. Post-ablation, patients were continued on warfarin for 3 months, with INR maintained between 2.0 and 3.0. Novel anticoagulants such as rivaroxaban, apixiban, or dabigatran were not allowed in the study.

In the reMARQable study, the anticoagulation regimen was further modified and was mandated for all procedures: warfarin was maintained for at least 4 weeks pre-ablation and 2 months post-procedure, with a mean INR ≥2.0 on the day of the procedure; a later amendment included subjects who were taking apixaban or rivaroxaban (approved February 2015; n=6 patients). Heparin was infused during the ablation to maintain ACT ≥325 seconds, with ACT checks at least every 30 minutes.
Statistics

Study results of REVOLUTION and reMARQable SNA cohorts were presented side-by-side and summarized descriptively.

Results

Patient disposition and baseline characteristics

A total of 37 and 76 patients were included in the SNA substudies of REVOLUTION (nMARQ® Catheter group, n=19; TC group, n=18) and reMARQable (nMARQ® Catheter group, n=38; TC group, n=30), respectively (Figure 1). In the REVOLUTION SNA substudy, there were more males in the TC group than the nMARQ® Catheter group (82.4% vs. 57.9%), as well as a higher prevalence of baseline comorbidities such as heart disease and diabetes, likely due to the absence of randomization. Baseline characteristics were more comparable between the 2 groups of the reMARQable SNA substudy, with the exception of a greater proportion of diabetic patients in the TC group (Table 1). One patient in the reMARQable substudy (nMARQ® Catheter group) died due to cardiac arrest approximately 1 year after ablation, which was not considered device- or procedure-related (Figure 1).

Procedural data

Procedural data are summarized in Supplementary Table 3. In comparison to the TC group, total procedure times were longer and RF application times were shorter in the nMARQ® Catheter group in both the REVOLUTION and reMARQable SNA substudies.
Primary safety endpoint

In the REVOLUTION substudy, 4 subjects (21.1%) in the nMARQ® Catheter group and 1 subject (5.9%) in the TC group experienced post-ablation SCLs without neurological findings (i.e. normal National Institute of Health Stroke Scale [NIHSS] scores) (Figure 2). One subject in the nMARQ® Catheter group had 3 lesions located in the left frontal lobe, right frontal lobe, and left periventricular frontal region. Single lesions (located in the right cerebellum, right frontal lobe, and right parietal lobe) were observed in the remaining 3 patients in the nMARQ® Catheter group, and in 1 patient (left cerebellar hemisphere) in the TC group. Average (standard deviation [SD]; range) lesion size in the nMARQ® Catheter group (n=6) was 3.7 (1.03; 2.0-5.0) mm. At the 1-month follow-up, all but one lesion in the nMARQ® group had resolved.

In the reMARQable SNA substudy, the incidence of post-ablation SCLs was 7.9% (3/38) and 3.3% (1/30) in the nMARQ® Catheter and TC groups, respectively (Figure 2). One patient had a pre-existing lesion that was not considered a new SCL. Among the 4 patients with new SCLs post-ablation, one patient in the nMARQ® Catheter group had 2 lesions in the right basal ganglia. Single lesions were observed in the other 2 patients in the nMARQ® Catheter group (located in the right cerebellum and right occipital lobe), and 1 patient in the TC group (left occipital lobe). The average (SD; range) size of the 4 post-ablation lesions in the nMARQ® Catheter group was 4.4 (1.5; 3.0-5.9) mm.

Anticoagulation management

In the REVOLUTION SNA cohort, patients without post-ablation SCLs had higher ACT during ablation than patients with post-ablation SCLs, both in the nMARQ®
Catheter group (431.7 vs. 335.2 seconds, respectively) and TC group (336.8 vs. 286.0 seconds, respectively). Patients with SCLs were either on low-molecular-weight heparin or fluindione pre-ablation, and either had an INR <2.0 at baseline and/or minimum ACT <300 seconds during the ablation procedure. No new SCLs were observed in the remaining SNA patients treated exclusively with warfarin with INRs ≥2.0 pre-ablation. Overall, 80% (4/5) of SCL cases occurred at a single study site, at which 33%-67% of the monitored procedural ACT values were <300 seconds.

Another site, which had 0 post-ablation SCLs among 23 patients, maintained all pre-ablation INR values >2.0, and 20 of 23 patients with available data had mean ACT values >300 seconds; only 11% of all measurements of ACT values at this site were <300 seconds.

In the SNA cohort of reMARQable, ACT during ablation was comparable between patients with and without SCL, and also between the nMARQ® Catheter and TC groups (Table 2).

Symptomatic neurological evaluation in the SNA cohorts

Of the 5 patients with SCLs in the REVOLUTION SNA cohort, all had pre- or post-ablation NIHSS scores of 0. Pre-existing minor neurological deficits presenting as NIHSS scores of 1 were documented in 1 patient in each group; however, NIHSS scores remained unchanged after ablation (Figure 3A). All other patients had pre- and post-ablation NIHSS scores of 0.

In the reMARQable SNA cohort, there were no changes in NIHSS scores pre- and post-ablation in the 4 patients with post-ablation SCLs. All patients had pre-ablation NIHSS scores of 0 with the exception of 2 patients, in whom scores either improved
or remained unchanged post-ablation (Figure 3B). Four patients that reported post-ablation scores >0 had no SCLs detected pre- or post-ablation.

*Change in Montreal Cognitive assessment (MoCA) and modified Rankin Scale (mRS) in reMARQable SNA cohort only were unremarkable and comparable in both groups (Supplementary Table 4)*

**Discussion**

The REVOLUTION and reMARQable SNA substudies, with stringent periprocedural anticoagulation regimens resulted in a substantial decrease in post-ablation SCLs. In addition, no patients with SCLs presented with any gross neurological deficits.

Careful analysis of the REVOLUTION SNA substudy suggested a relationship between anticoagulation regimen and occurrence of SCLs, such that lower INR and ACT were observed in patients with SCLs. Of note, the majority of SCL cases occurred at 1 site with less conservative periprocedural anticoagulation, in which 33%–67% of the procedural ACT levels were <300 seconds. At this site, over half of the treated patients developed post-ablation SCLs. At another site where the anticoagulation regimen was more tightly monitored, no patients experienced SCLs. These early observations suggest that stringent anticoagulation was crucial in reducing the incidence of SCLs. This finding is supported by results from a separate study reporting SCLs in 0/25 patients treated with nMARQ® Catheters with ACT >320 seconds throughout the procedure.11 The reduction in SCLs observed in the randomized, controlled reMARQable trial, in which anticoagulation regimens were more tightly monitored and followed, further supports the important role of periprocedural anticoagulation in minimizing SCLs.
The SCL rate reported for the nMARQ® Catheter group in the reMARQable SNA substudy is comparable to reported rates for irrigated RF focal catheters from the literature (7.4%-24.2%) and within range or lower than those reported for other technologies, such as pulmonary vein ablation catheter (1.7%-38.9%), cryoballoon (4.3%-18.2%), and laser balloon (11.4%-24.2%). One study with a less conservative ACT target of >250 seconds reported a higher incidence of SCLs for all technologies (focal RF, 24.2%; cryoballoon, 18.2%; laser balloon, 24.2%), while another study with a more stringent anticoagulation regimen similar to our study (targeted INR ≥2.0 on the day of the procedure, procedural ACT ≥350 seconds) reported a low SCL rate of 1.7% for non-irrigated multielectrode RF catheter ablations.

The importance of adequate periprocedural anticoagulation has been well documented. Intraprocedural ACT has been reported as an independent factor associated with the occurrence of SCLs with irrigated RFA catheters; an increase in each point of ACT value >320 seconds results in a 0.4% risk reduction for SCLs. Large variations in the incidence of SCLs have been observed in patients undergoing ablation with open-irrigated THERMOCOOL® Catheters, depending on the anticoagulation regimen: 2% (3/146) incidence of SCL in patients without warfarin discontinuation accompanied with heparin bolus before transseptal catheterization; 7% (10/134) in patients with subtherapeutic INR and/or failure to receive pre-transseptal heparin bolus infusion and/or ≥2 consecutive ACT measurements <300 seconds; and 14% (21/148) in patients with warfarin discontinuation bridged with low-molecular-weight heparin.

The clinical implications of SCLs are unclear. In our studies, MRI-detected SCLs were not associated with clinical neurological deficits, and there was no clear
relationship between the presence of SCLs and neurological assessments. It has been previously reported that lesions ≤10 mm in diameter are undetectable at a median 3-month follow-up examination. In this study, all SCLs were <6 mm in the REVOLUTION trial and <5 mm in the reMARQable trial; all but one SCL resolved without sequelae. In one REVOLUTION subject, a SCL persisted at the study exit, but did not produce symptoms/ neurological deficits. AF patients have an underlying risk of SCLs prior to ablation, and previous studies have similarly reported an absence of neurological symptoms associated with SCLs pre- or post-ablation. Further investigation is needed to better understand any potential long-term clinical presentations of SCLs.

Although not explored in this report, other factors may contribute to the incidence of SCLs, including but not limited to energy sources or catheters used, procedure duration, handling of sheath, and timing of cardioversion. Protocol workflow modifications, such as delayed electrical cardioversion after 4-week anticoagulation post-ablation, prevention of electrodes interaction, and careful sheath exchange to minimize air ingress, have been shown to reduce SCLs.

Study limitations: both the SNA sub-studies were not powered to detect SCL differences between different ablation technologies. Factors other than anticoagulation contributing to SCL formation must be taken into consideration during AF ablation. The stringent anticoagulation protocol from the reMARQable trial may not be generalizable to current practice. But it is an important consideration to improve patient safety for all catheter ablation procedures, especially in higher risk situations.
Conclusions

Adherence to a stringent anticoagulation regimen prior to and during ablation procedures appears to be an important factor in minimizing the risk of SCL.

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Author contributions: All authors contributed to data analysis/interpretation, and critical review of manuscript. MG additionally contributed to drafting the article. All authors approve the manuscript.

References


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Figure legend

Figure 1. Patient disposition.

SNA, subpopulation neurological assessment; SCL, silent cerebral lesion

Figure 2. Incidence of post-ablation SCL in SNA cohort of REVOLUTION and reMARQable studies

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Figure 3. Pre- and post-ablation NIHSS scores in the (A) REVOLUTION study and (B) reMARQable study

NIHSS, National Institutes of Health Stroke Scale
<table>
<thead>
<tr>
<th></th>
<th>REVOLUTION nMARQ® Catheter group (n = 19)</th>
<th>THERMOCOOL® Catheter group (n = 17)</th>
<th>reMARQable nMARQ® Catheter group (n = 38)</th>
<th>THERMOCOOL® Catheter group (n = 30)</th>
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<td>Male (%)</td>
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<td>14 (82.4%)</td>
<td>24 (63.2%)</td>
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<td>56.5 (9.86)</td>
<td>59.3 (10.7)</td>
<td>59.9 (11.0)</td>
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<td>1 (3.3%)</td>
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<td>Diabetes</td>
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<td>Direct current cardioversion in past 180 days</td>
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Table 2. Anticoagulant management

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<tr>
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<td>nMARQ®</td>
<td>THERMOCOOL®</td>
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<td>Mean (Standard deviation;</td>
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<td>THERMOCOOL®</td>
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<td>Catheter group</td>
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<td>Pre-ablation international</td>
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<tr>
<td>activated normalized ratio</td>
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<td>Activated clotting time during</td>
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<td>431.7 (133.0; 331, 737)</td>
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<td>ablation</td>
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