Preventing atrial fibrillation by combined right isthmus ablation and cryoballoon pulmonary vein isolation in patients with typical atrial flutter: PAF-CRIOBLAF study

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Abstract
Background: Although less common, typical atrial flutter shares similar pathophysiological roots with atrial fibrillation. Following successful cavo-tricuspid isthmus ablation using radiofrequency, many patients, however, develop atrial fibrillation in the mid-to-long-term. This study sought to assess whether pulmonary vein isolation conducted at the same time as cavo-tricuspid isthmus ablation would significantly modify the atrial fibrillation burden upon follow-up in patients suffering from typical atrial flutter.

Methods: This was a multicenter randomized controlled study involving typical atrial flutter patients with history of non-predominant atrial fibrillation (1 atrial fibrillation episode only, in 67% of population) who were scheduled for cavo-tricuspid isthmus radiofrequency ablation. Patients were randomly assigned to either undergo cavo-tricuspid isthmus ablation alone or cavo-tricuspid isthmus plus pulmonary vein isolation (CTI+). Pulmonary vein isolation was performed using cryoballoon technology. An outpatient consultation with ECG and 1-week Holter monitoring was performed at 3, 6 months, 1 year, and 2 years postprocedure. The primary endpoint was atrial fibrillation recurrences lasting more than 30 s at 2 years postablation.

Results: Of the patients enrolled, 36 were included in each group. At 2-year follow-up, the atrial fibrillation recurrence rate was significantly higher in the CTI vs CTI+ group (25/36, 69% vs. 12/36, 33% respectively; P < .001), with similar typical atrial flutter recurrence rates. There were no differences in undesirable events, except for transient phrenic nerve palsy reported from three CTI+ patients (8.3%).

Conclusion: Pulmonary vein isolation using cryoballoon technology was proven to significantly reduce the atrial fibrillation incidence at 2 years postcavo-tricuspid isthmus ablation.
1 | INTRODUCTION

Though typical atrial flutter (AFL) is less common than atrial fibrillation (AF), both arrhythmias likely share similar pathophysiological triggers. Despite the high success rates of AFL ablation, patients are nevertheless at risk of developing AF postablation, the incidence of which has been reported to be as high as 50% or even higher. Moreover, it must be stressed that the thromboembolic risk of AFL patients has been primarily linked to AF occurrence and the underlying cardiopathy. AF ablation using cryoballoon technology to isolate pulmonary veins has been reported to be as efficient as ablation by means of RF in managing paroxysmal AF, with very few complications reported worldwide.

Considering the performance and safety profile of cryoballoons, along with the high-risk of AFL patients to develop AF after successful AFL ablation, we designed and implemented the current study to primarily investigate the usefulness of performing a combined procedure of CTI ablation along with PVI using cryoballoon in patients referred to the participating centers for AFL ablation, with a documented non-predominant history of AF lasting at least 30 s.

2 | METHODS

This was a prospective, multicenter, open-label, randomized study with two parallel arms that was designed to assess the benefits of PVI +CTI (CTI+) vs CTI alone (CTI) in the prevention of AF recurrence in patients with an AF history who were referred to the electrophysiology laboratories for typical AFL ablation.

Patients were considered eligible for entry into the trial if the following inclusion criteria were met: (i) diagnosis of typical AFL confirmed by electrocardiography (ECG) or 24-h Holter monitoring, with AFL defined as negative F waves in the inferior territory, positive in V1, and negative in V6 lead, an F pattern with a characteristic "saw tooth" appearance, and an atrial cycle length comprised between 188 and 250 ms; with respect to patients arrhythmias, AF was neither the predominant (occasionally recorded) nor the targeted arrhythmia. The time duration spent by the patient in AFL should largely exceed that of AF; (ii) at least one AF episode lasting over 30 s documented on either the ECG or Holter recording; (iii) effective anticoagulant therapy comprising either new oral anticoagulants like rivaroxaban or dabigatran, or vitamin K antagonists (VKA) with an international normalized ratio (INR) ≥2 for at least 3 weeks; (iv) patient age between 18 and 75 years. Patients with contraindications to right-atrial catheterization or anticoagulant therapy were excluded from participation, as were those with predominant AF (or in AF at the screening/enrolment visit), known clotting disorders, or life expectancy <24 months.

The patients were screened after being referred to the electrophysiology laboratory for AFL ablation and only included in the trial after providing written informed consent.

The primary study endpoint was the recurrence of symptomatic or asymptomatic AF, documented on ECG or long-term Holter recording upon the 2-year follow-up (FU) beginning after the 12-week blanking period postablation, with AF recurrence defined as an atrial tachycardia episode of >30 s. Any episode of typical AFL >30 s between Day 1 and Month 24 was considered AFL recurrence and a secondary study endpoint. The patients’ quality of life was likewise assessed before and after the procedure, along with its evolution, the use of antiarrhythmic drugs, anticoagulants, and platelet inhibiting agents, and the rate of procedure-related complications, such as hematoma at the puncture site, thromboembolic events, and phrenic nerve palsy.

Prior to patient entry, we specified a 2-year recruitment period to enroll 170 subjects. Over the course of the study, however, owing to the much better outcome obtained using second-generation Advance cryoballoons, with 1-year AF recurrence rates of 20% instead of 30%–35%, a protocol amendment was forwarded to the national ethics committee requesting to reduce the total patient number to be recruited to 76 patients, ie, 38 per group. Based on an expected 55% AF recurrence rate in the CTI group vs 25% in the CTI+ group, a bilateral Chi-squared test would be able to detect a statistically significant between-group difference with an 80% statistical power and 5% risk level.

The study protocol, with its aforementioned amendment concerning the number of patients to be recruited, was approved by the national ethic committee and registered at clinicaltrials.gov under NCT 01 521 988.

Eligible patients were randomized using a 1/1 ratio by block, with stratification by center, to allocate an equal number of patients to each ablation therapy: CTI alone for Group 1 and CTI+ for Group 2. More blocks then necessary were created for any potential over-recruitment by a given investigator.

The RFA was performed under anatomic and electrophysiological guidance. Antiarrhythmic drugs were not systematically stopped before the procedure. Standardized procedures were employed, with the use of a quadripolar 6-F catheter positioned in the coronary sinus and a 4 mm tip irrigated RF catheter placed at the CTI. The RF ablation was conducted according to original research, with the main objective being to obtain a complete bidirectional isthmus conduction block 30 min (min) after the last RF application via recording widely spaced double potentials along the
ablation line, as well as inversion of the activation sequence opposite of the pacing site.

The procedure began with the CTI ablation, as described above. Thereafter, transseptal access was performed according to the centers’ practices, potentially guided by transesophageal echocardiography (TEE). Standardized procedures were employed. A balloon catheter of 23-28 mm in diameter was positioned in the left atrium, and, then, applied at the PV ostium for ablation, with a minimum of two cryo-applications of at least 4 min carried out at each PV ostium. The procedural endpoint of the PVI was the disappearance of the PV potentials or an electrical dissociation between the PV and the atrium assessed by a circular octopolar catheter (Achieve®, Medtronic Inc, Minneapolis, USA) inserted in the central lumen of the cryoballoon catheter. The remaining conduction gaps between the atrium and PV were ablated with the irrigated RF catheter used for CTI ablation.

During the hospital stay, cardiac rhythm monitoring was performed using continuous telemetry (scope) or 24-h Holter recording. AADs were continued for 3 months after the ablation as necessary, with the exception of amiodarone, which was discontinued in all cases postablation. Irrespective of the study arm, all patients received anticoagulant therapy 3 weeks before ablation that was maintained at least 3 months postablation. Antivitamin K (AVKs) agents were either maintained or replaced by heparin during the procedure. Managing new oral anticoagulants like rivaroxaban or dabigatran was left to the discretion of each center.

All patients were discharged home the day following the intervention. The patients were re-examined before discharge and at Weeks 12, 26, 52, and 104 (±2 weeks) postprocedure, with a clinical examination, cardiology evaluation, 12-lead ECG, quality of life questionnaire (SF 36), medical treatment recording, and 7-day Holter monitoring performed. Documentation of AF or AFL during the first 12-week period postablation was not considered a true recurrence unless it persisted beyond this frame.

Only one new AFL ablation was permitted during the first 3 months postablation, irrespective of the group. In the presence of symptomatic AF recurrence despite medical treatment in the combined group after Week 26, a second PVI procedure was recommended.

Continuous variables were expressed as mean ± standard deviation (SD) for normal data or median and interquartile range (IQR) for non-normal data, or counts and percentages for categorical variables. The analysis was carried out using the intent-to-treat method. Between-group comparisons were made using the Wilcoxon–Mann–Whitney test for categorical data and Fisher’s exact t test for qualitative data. Kaplan–Meier methodology was applied to determine the probability of AF (and AFL) recurrence postablation, ignoring the 12-week blanking period postablation. Univariate Cox regression analyses were performed to determine the clinical predictors of AF occurrence.

In the absence of homoscedasticity, the Welch test was applied. All tests were two-sided, with a P-value <0.05 considered statistically significant. All analyses were performed using the R 3.5.2 software (R Foundation for Statistical Computing).

3 RESULTS

The patient characteristics are summarized in Table 1. During the 2-year recruitment period, 76 patients fulfilling the inclusion criteria were recruited, four of whom were lost to FU, for a total of 72 patients analyzed, ie, 36 per treatment arm. All patients had either failed AADs administration or experienced intolerable undesirable effects. The Group 1 patients (n = 36, 65.6 ± 9.7 years, 72% male, 39% high blood pressure, 17% diabetic, and 8% heart failure New York Heart Association [NYHA] functional class ≥III) were assigned to undergo CTI only, whereas the Group 2 patients (n = 36, 62.1 ± 8.6 years, 83% male, 42% high blood pressure, 22% diabetic, and 28% heart failure) received the CTI+PVI intervention. The baseline patient characteristics were roughly similar between both groups (Table 1).

At the time of the intervention, 19 patients in Group 1 and 18 in Group 2 presented with typical AFL, with two and four exhibiting AF, respectively (Table 2). In the latter, patients cardioversion was performed before proceeding with ICT ablation. A normal sinus rhythm was obtained in all patients. Successful PVI was demonstrated in 100% of left common trunks (6/6), in 97% of left superior PVs (29/30), 100% of left inferior PVs (30/30), 94% of right superior PVs (34/36), and 89% of right inferior PVs (32/36). One RF application was delivered to isolate the left upper PV in one patient, and the right lower PV in another one. Expectedly, the ablation procedure duration was shorter in Group 1 vs Group 2 (62.5 vs 109.5 min, respectively).

Overall, 72 patients were followed-up, with the recurrence of AF and other cardiac events analyzed at 1-year and 2-year postablation. The data are summarized in Table 3 and illustrated in Figure 1. At the study’s end, 25 patients (69%) reached the primary endpoint in Group 1 vs 12 (33%) in Group 2, with the between-group difference being highly significant (P = 2.7e-04). Likewise, symptomatic AF occurred in 15 (Group 1) vs seven patients (Group 2), with a significant between-group difference as well (0.025). Due to the small sample size, no patient characteristics could be found as predictive of lack of AF recurrences after CTI alone (in particular, the introduction of AADs for occurrence of AF, which could have promoted later on, the development of AFL). The majority of the Group 1 patients (8/11 patients) without experiencing AF recurrences at the end of follow up were on AADs. Whereas patients under antiarrhythmic drugs and anticoagulants tended to be fewer in Group 1 vs Group 2 at 1 year (52% vs 67%, and 69% vs 86% respectively), this difference was no longer present at 2 years follow-up. No significant differences were noted concerning the other secondary endpoints.

The combined ablation in comparison with CTI alone was associated with a reduction in the HR to 0.19 (95% CI: 0.07; 0.43, P = 9e-5).

No between-group differences with respect to the overall SF36 quality of life score were observed nor were there any significant differences recorded with respect to the different score subitems (data not shown).
In the postintervention period, one Group 2 patient had a small pericardial effusion that did not require any drainage. One patient in each group developed a first-degree atrioventricular block, and another Group 1 patient exhibited a third-degree atrioventricular block resulting in pacemaker implantation. Three Group 2 patients exhibited phrenic nerve palsy that spontaneously disappeared within a few weeks. Two Group 2 patients displayed a groin hematoma that did not require any intervention. The number of hospitalization postablation was roughly similar between both groups, as was the number of new ablations required (Table 4). One Group 2 patient developed pulmonary vein stenosis following PVI, which was deemed not clinically relevant. One patient in each group developed stroke during the follow up period (9 and 20 months after the procedure).

### DISCUSSION

It must be emphasized once more that several studies have clearly revealed that, even with AFL being eliminated by means of CTI ablation, the postprocedural incidence of new-onset AF can reach ≥55% at 1-year postablation. In AFL patients, associated AF has also been found to be a strong predictive factor of new-onset AF following CTI ablation. Owing to these high AF rates, more comprehensive interventions have been developed over the last decade. In their randomized pilot study, Mohanty et al enrolled 216 patients with isolated AFL, yet no prior AF history, who were randomly assigned to undergo either CTI ablation alone (Group 1) or CTI+PVI ablation (Group 2). At 18 ± 6-month FU, 60% Group 1 patients were shown to be arrhythmia-free vs 71% Group 2 patients, with a statistically significant (P = .044) between-group difference. The 3-year follow-up data of the Prevent AF I study involving 50 AFL patients

### TABLE 1 Population characteristics

| Variable                | Flutter ablation n = 36 | Combined ablation n = 36 | P value |
|-------------------------|-------------------------|--------------------------|---------|
| Age                     | 65.6 (9.7)              | 62.1 (8.6)               | 0.066   |
| Gender                  |                         |                          |         |
| Male                    | 26 (72%)                | 30 (83%)                 |         |
| Female                  | 10 (28%)                | 6 (17%)                  |         |
| Body mass index         | 28.5 (6)                | 28.2 (5.5)               | ns      |
| High blood pressure     | 14 (39%)                | 15 (42%)                 | ns      |
| Diabetes                | 6 (17%)                 | 8 (22%)                  | ns      |
| Heart failure history   | 3 (8%)                  | 10 (28%)                 | ns      |
| Stroke history          | 3 (8%)                  | 1 (3%)                   | ns      |
| Transient ischemic attack history | 1 (3%)              | 2 (6%)                   | ns      |
| Distal embolism history | 2 (6%)                  | 0 (0%)                   | ns      |
| Lower limb arterial disease | 1 (3%)            | 1 (3%)                   | ns      |
| Carotid atheroma        | 0 (0%)                  | 1 (3%)                   | ns      |
| Paroxysmal AF           | 29 (81%)                | 25 (69%)                 | ns      |
| Antiarrhythmic treatment|                         |                          |         |
| Amiodarone              | 12 (33%)                | 18 (50%)                 |         |
| Sotalol                 | 2 (6%)                  | 0 (0%)                   |         |
| Ic antiarrhythmic drug  | 9 (25%)                 | 9 (25%)                  |         |
| Ia antiarrhythmic drug  | 2 (6%)                  | 1 (3%)                   |         |

Note: Quantitative data are expressed as median [min:max]. Qualitative data are expressed as rates (percentage).

### TABLE 2 Procedures, duration, and outcomes per group

| Heart rhythm at the beginning | Flutter ablation n = 36 | Combined ablation n = 36 |
|-------------------------------|-------------------------|--------------------------|
| Sinus rhythm                  | 15 (42%)                | 14 (39%)                 |
| Typical atrial flutter        | 19 (53%)                | 18 (50%)                 |
| Atrial fibrillation           | 2 (6%)                  | 4 (11%)                  |
| Heart rhythm at the end       |                         |                          |
| Sinus rhythm                  | 34 (94%)                | 35 (97%)                 |
| Unknown                       | 2 (6%)                  | 1 (3%)                   |
| Duration of procedure (min)   | 62.5 [23;146]           | 109.5 [38;227]           |
| Total radiofrequency ablation time (s) | 727 [69;2797] | 472 [61;2813] |
| Bidirectional complete isthmic block obtained | No | 2 (6%) | 0 (0%) |
|                                | Yes                     | 33 (92%)                 | 34 (94%) |
|                                | Unknown                 | 1 (3%)                   | 2 (6%) |

Note: Quantitative data are expressed as median [min:max]. Qualitative data are expressed as rates (percentage).
patients were published in 2018 by Romanov et al. Similarly, the study results revealed that in patients with typical AFL, adding PVI to CTI ablation turned out to be safe and effective in terms of AF freedom as compared with CTI alone. Indeed, at 3-year FU, freedom from any tachyarrhythmia was observed in 48% PVI + CTI patients as compared with 20% CTI-only patients (P = .01). Recently, in 2019, Koeber et al have published a meta-analysis involving four randomized trials with similar study designs. These authors also sought to better understand the effect of combined CTI + PVI vs CTI alone in patients scheduled for AFL ablation. Considering the 316 randomized patients in the analysis, AF freedom at 1-year postablation was significantly higher in the combined treatment group vs CTI ablation alone.

Based on the hypothesis that AF is chiefly initiated by triggers originating from the PVs, our data have further confirmed these aforementioned observations, ie, the clinical usefulness of combining PVI+CTI in AFL patients with at least 1 AF episode, despite the latter being not the predominant arrhythmia. In our study, AF recurrence was significantly less common when PVI was implemented at the time of CTI for typical AFL, in line with published data. In the Mohantly et al study, at 18 ± 6-month FU, about 40% patients developed AF in the CTI-only group vs 29% in the CTI+group. After carefully analyzing these published reports, we conclude that in patients with prior AF at the time of CTI ablation, as in our study population, or in those without prior AF, as in the Mohantly study, quite similar AF incidence rates (about 30%) were reported at 18-24-month FU in the combined treatment groups. These incidence rates, however, differed in the CTI-only groups. Whereas 70% AF recurrence rates were recorded in our study involving patients with prior AF, the rates of new onset AF were only 40% in the Mohantly study involving AF-naïve patients. The benefit of adding PVI to CTI was, thus, more convincing in our study. This differing outcome may possibly be explained by the observation that in our study, patients were required to display at least one prior 30 s AF episode to be eligible for study entry, whereas the Mohantly et al study recruited only AF-naïve patients.

Only limited data are available concerning the overall cost effectiveness of a combined PVI+CTI approach vs a sequential approach.

| TABLE 3 | Probability of arrhythmia events over the 2-year study period |
|---------|-------------------------------------------------------------|
|         | Group 1 n = 36 | Group 2 n = 36 | \( p \) value* |
| 30-s AF Overall frequency | 25 (69%) | 12 (33%) | 2.7e-04 |
| 1 year | 0.73 [0.53;0.84] | 0.23 [0.08;0.36] | 0.23 [0.08;0.36] |
| 2 years | 0.73 [0.53;0.84] | 0.38 [0.18;0.53] | 0.73 [0.53;0.84] |
| 1-min AF Overall frequency | 25 (69%) | 12 (33%) | 2.7e-04 |
| 1 year | 0.73 [0.53;0.84] | 0.23 [0.08;0.36] | 0.73 [0.53;0.84] |
| 2 years | 0.73 [0.53;0.84] | 0.38 [0.18;0.53] | 0.73 [0.53;0.84] |
| Symptomatic AF Overall frequency | 15 (42%) | 7 (19%) | .025 |
| 1 year | 0.4 [0.22;0.55] | 0.11 [0.02;0.21] | 0.4 [0.22;0.55] |
| 2 years | 0.44 [0.24;0.58] | 0.22 [0.06;0.36] | 0.44 [0.24;0.58] |
| Persistent AF Overall frequency | 5 (14%) | 8 (22%) | .32 |
| 1 year | 0.06 [0.01;0.14] | 0.14 [0.02;0.25] | 0.06 [0.01;0.14] |
| 2 years | 0.17 [0.02;0.29] | 0.25 [0.08;0.39] | 0.17 [0.02;0.29] |
| Typical AFL Overall frequency | 6 (17%) | 6 (17%) | .886 |
| 1 year | 0.15 [0.02;0.26] | 0.14 [0.02;0.25] | 0.15 [0.02;0.26] |
| 2 years | 0.19 [0.04;0.31] | 0.17 [0.04;0.29] | 0.19 [0.04;0.31] |
| Atypical AFL Overall frequency | 4 (11%) | 5 (14%) | .74 |
| 1 year | 0.09 [0.01;0.18] | 0.08 [0.01;0.17] | 0.09 [0.01;0.18] |
| 2 years | 0.13 [0.02;0.24] | 0.16 [0.02;0.28] | 0.13 [0.02;0.24] |
| Atrial tachycardia Overall frequency | 4 (11%) | 3 (8%) | .663 |
| 1 year | 0.09 [0.01;0.18] | 0.09 [0.01;0.17] | 0.09 [0.01;0.18] |
| 2 years | 0.13 [0.02;0.24] | 0.09 [0.01;0.17] | 0.13 [0.02;0.24] |

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter.
*Non-parametric log-rank test.
Referring to the 3-year FU data of Prevent AF I study, Romanov et al reported overall lower costs and procedural risks with a combined ablation procedure. These benefits were driven by a higher atrial arrhythmia recurrence rate at 3 years (80%), as well as a significantly higher rate of repeat procedures and hospitalizations in the CTI-only group. Contrarily, no significant differences in major complications requiring interventions were recorded with the combined procedure.

Further larger-scale, randomized studies including cost-efficacy analyses are still needed to better guide appropriate patient selection for ablation procedures in AFL management. If the combined approach would prove to be cost-effective in patients with "pure"
AFL in such larger-scale studies, we could then assume that a combined procedure would indeed be preferable as first-line therapy in patients with prior AF episodes.

The question as to whether AF and AFL could be initiated by the same electrophysiological triggers has previously been raised by numerous experts. A close pathophysiological relationship between AFL and AF is backed up by experimental studies and clinical data. As further outlined in the nicely written review paper by Waldo AL, AF is usually required for the development of a functional block between the venae cavae. This latter, in turn, seems to be necessary to enable a classical AFL to develop. According to Wazni et al, AF usually precedes the onset of AFL. Indeed, recent studies have demonstrated the key role that PVs play in initiating AF. As proposed by Roithinger et al and in line with Wazni et al, PV triggers initiate AF, transforming itself subsequently into AFL. According to Roithinger et al, PV triggers may be responsible for the development of AFL, under appropriate circumstances.

In agreement with this line of thoughts, the aforementioned publications, and the Navarrete et al’s report, our data likely confirm that it is rather logical to perform PVI in patients scheduled to undergo CTI for clinical AFL. In line with the conclusions drawn by Navarrete et al, that clinicians should be made aware of the robust link that exists between AFL and AF. That is to say, when CTI ablation is performed to interrupt AFL, it may be useful to assume that procedural PVI be carried out at the same time, at least in some selected patients, notably those with an AF history. The ultimate aim of this combined procedure would be to definitively diminish the high thromboembolic risk, even in the absence of clinically relevant AF. We should however underline that the potential increased risk of complications associated with PVI is likely the main reason physician would refrain to perform this procedure in this patient population. Unfortunately, the small patients sample size of our study precluded drawing any conclusion regarding complications. In any event, the still significant long-term risk of recurrent AF in this patient group is an incentive to adhere to general anticoagulation recommendations, regardless of the ablation strategy chosen and the presumed rhythm outcome, ie, high stroke risk patients should continue anticoagulation.

The results of this study should be interpreted in light of several methodological limitations, the major one being the limited number of patients per treatment group. Owing to constraints imposed by the ethic committee that requested patients to have experienced at least one 30 s AF episode to be eligible for study entry, recruiting sufficient patients proved very challenging, and a protocol amendment was thus issued. Keeping this limitation in mind, it is essential that our study results be further confirmed in larger-sized randomized comparative trials. Another limitation to be pointed out is that maintenance of AADs along the course of the study may have masked the presence of manifest AF, particularly in patients with persistent AF before the procedure. The patients most likely to benefit from this combined approach must still be better defined, in addition to in-depth cost-benefit analysis.

5 | CONCLUSIONS

The results of this prospective randomized study likely indicate that PVI in conjunction with CTI in AFL patients with history of non-predominant AF scheduled for AFL ablation significantly decreases the incidence of AF recurrence at both 1- and 2-year postablation periods.

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CONFLICT OF INTEREST STATEMENT

FA is consultant for and received lecture fees from Boston Scientific, Medtronic, and Microport CRM. AS received honoraria from Microport CRM. NC is consultant for and received lecture fees from Medtronic. PD received research grants and honoraria from Boston Scientific, Abbott, Microport CRM, and Medtronic. SB is consultant for Medtronic, Boston Scientific, Microport CRM, and Zoll. The other authors declare no conflicts of interest. The protocol for this research has been approved by a suitable constituted Ethics Committee of the institution under the approval number 2011-A00806-35, on July 21, 2011 and it conforms to the provisions of the Declaration of Helsinki. The ClinicalTrial identifier of this study is NCT01521988

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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