# ***COVER PAGE***

***OFFICIAL TITLE:*** SafeTy and Efficacy of Periprocedural Direct Oral Anticoagulant versus Aspirin Use for Reduction Of the RisK of CErebrovascular Events in Patients Undergoing Ventricular Tachycardia Radiofrequency Catheter Ablation (STROKE-VT)

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**SafeTy and Efficacy of Periprocedural Direct Oral Anticoagulant versus Aspirin Use for Reduction Of the RisK of CErebrovascular Events in Patients Undergoing Ventricular Tachycardia Radiofrequency Catheter Ablation (STROKE-VT)**



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## INTRODUCTION

Considerable research has sought to overcome the limitations of available anticoagulant and antithrombotic agents. This includes efforts to develop agents that target specific factors of the coagulation process, which in turn may improve efficacy and increase the therapeutic index. Warfarin acts through inhibition of multiple areas on the coagulation caseade and the direct oral anticoagulants (DOACs) like (Dabigatran/Rivaroxaban/Apixaban/Edoxaban) .Factor Xa is a primary target since this factor plays a pivotal role in the coagulation cascade at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is expected to exert anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation [1]. DOAC helps to anticoagulated and potentially decrease the risk of systemic thromboembolism .

### Overall Risk/Benefit Assessment

Atrial fibrillation (AF) is associated with 5 times increased risk of cerebrovascular events compare to patients in Sinus rhythm [2]. Even in patients undergoing Radiofrequency Ablation (RFA) for atrial fibrillation, the incidence of symptomatic cerebrovascular events (CVE) was 2.3% and 41% of those are from transient ischemic attacks and 25% are from ischemic CVEs, despite being on anticoagulation. The incidence of asymptomatic CVEs rises to 14% after the ablation for AF, detected by Flair enhancement MRI . Multiple trials have shown that the asymptomatic CVEs and/or micro infarcts can increase the odds of having dementia. The incidence of stroke immediately after ablation for left ventricular arrhythmias has ranged from 0 to 2.7% to 7.5% depending on the case series , but there aren't many studies to quantify this problem clearly. Interestingly, the amount of tissue ablated in the ventricles is not any smaller than what is done in the left atrium. Even though the stunning phenomenon that is seen with the left atrial appendage may not be relevant to the ventricular tachycardia ablation, the extensive endothelial denudation and subclinical thrombus formation at the sites of ablation is clearly under appreciated. No active strategies to prevent post ablation systemic thromboembolization are available in patients undergoing left ventricular arrhythmia ablation especially on the left side. Similar to AF, the projected incidence of asymptomatic CVEs may be much higher than the incidence of symptomatic CVEs given the multiple reasons like heat generated from the

ablation, possibility of necrosis of myocardium from ablation and manipulation of the left side of the heart, but currently there are no studies that have focused on the incidence of asymptomatic CVEs. It has been therefore recommended to perform cardioversion or ablation only at therapeutic levels of anticoagulation to decrease the risk of thromboembolism and stroke. So far, there are no trials evaluating the efficacy of unfractionated heparin or newer direct thrombin or factor Xa inhibitors in preventing or reducing symptomatic and also asymptomatic CVEs post-left ventricular arrhythmia ablation. Given the high incidence of symptomatic CVEs and possibility of higher incidence of asymptomatic CVEs which has many prognostic implications, this issue warrants further studies.

Use of oral anticoagulation after left ventricular arrhythmia ablation is not standard of care at this point and is anecdotally used in high risk patients with LV aneurysms and those with severe LV dysfunction. Even when used post ablation anticoagulation with warfarin is fraught with several practical issues including the time to therapeutic range and the need for bridging with unfractionated or low molecular weight heparin with implications to prolonged length of stay and increased bleeding complications. So, the novel non VKA agents probably are a better fit for this specific situation. Early experience with all four currently available agents (Dabigatran, Rivaroxaban , Apixiban and Edoxaban) for periprocedural anticoagulation seems to be safe and efficacious. DOAC is a direct oral inhibitor of Prothrombin/factor Xa inhibitor and thereby mediates its anticoagulation effect . In the recently published double blind randomized clinical trial DOAC was found to be superior to warfarin in decreasing the risk of stroke and also had fewer complications of bleeding and death in patients with atrial fibrillation/flutter .

We believe that peri-procedural DOAC use for left ventricular arrhythmia ablation will provide effective anticoagulation without increasing bleeding complications and may decrease the incidence of both symptomatic and asymptomatic cerebrovascular events, TIAs and strokes.

Magnetic resonance imaging (MRI) is the most commonly used imaging test to detect acute ischemic stroke and asymptomatic CVEs. There is a natural apprehension about the use of MRI scanning in patient with Cardiac Implantable Electrical Devices (CIEDs) . However, there are protocols in place showing MRI examination of patients with CIEDs with minimal or no side

effects . There is increasing data on the safety of the use of MRI in CIED patients which perhaps led to the participating institutions routine use of MRI in defining ventricular scar prior to RF ablation to optimize the treatment strategy and outcomes. The potential for adverse effects on the CIED during MRI of the head is far lower than imaging the chest as the device will not be in the direct MRI field as it is with head scanning. When performed with appropriate monitoring the post left ventricular arrhythmia ablation MRI scanning of the brain can be safe and help us examine an important issue that has not been well defined.

**Research Hypothesis**

We hypothesize that periprocedural anticoagulation with DOAC (an oral anticoagulation agent with rapid onset of action) for left ventricular arrhythmia ablation decreases symptomatic and asymptomatic cerebrovascular events compared to use of Aspirin only.

**Study Rationale**

Ventricular tachycardia (VT) is a complex arrhythmia with high mortality rate. ICDs have shown improvement in survival when placed for primary or secondary prevention in such patients, but they are not a cure for VT and they don't prevent recurrences. In addition, painful ICD shocks, not only impair quality of life and psychological health , but they are also associated with increased all-cause mortality. Antiarrhythmic therapy, even though moderately effective, with time and progressive remodeling recurrent VT and subsequent ICD therapies are common. Radiofrequency catheter ablation has emerged as an important therapeutic option to prevent VT recurrences and reduce the frequency of ICD shocks . Catheter ablation provides potential curative treatment in 77-95% of post MI patients presenting with monomorphic VT and around 60% in patients with VT arising from non-ischemic cardiomyopathy . With advancement in technology and newer saline irrigation catheters, the risks are very minimal, with high success rates . In a nationwide sample of 4653 patients who underwent ablation in the United States between 2002 and 2011 for post-myocardial infarction VT, the overall in-hospital complication rate was 11 percent with in-hospital mortality of 1.6 percent . The number of catheter ablations that are being performed for left ventricular arrhythmias continues to grow and varies from region to region and hard to quantify . Both retrograde transaortic approach and trans-septal approach are possible routes for endocardial radiofrequency ablation (RFA) with embolic risk associated with thrombus formation on the ablation catheters and sheaths, micro thrombus

formation at the ablation site during the procedure and after ablation as well. [3].Over the last decade left ventricular arrhythmia ablation techniques have evolved from being more focal targeted sites to the addition of extensive substrate modification targeting active channels as represented by mid diastolic potentials, late activation potentials etc. in the scar and scar border. This will change the surface area of the ventricular endocardium ablated significantly. The extensive denudation of the ventricular endocardium can obviously become a site of thrombus formation and subsequent embolization. Often times patients with Cardiomyopathy (CM) undergoing left ventricular arrhythmia ablation have poor LV function and have large segments of akinesis/dyskinesis/aneurysms making them more prone for stasis and thrombus formation. Treating them with periprocedural anticoagulation has a potential to significantly decrease the risk of systemic thromboembolization as measured by symptomatic and asymptomatic cerebrovascular events.

**STUDY END POINTS:**

**Primary Objectives**

Primary end point: To estimate the new symptomatic (Stroke and TIA) and asymptomatic CVEs (brain MRI lesions) and systemic thromboembolism in patients undergoing left ventricular arrhythmia ablation with a novel oral anticoagulant ( DOAC) when compared to aspirin only.

**Secondary Objectives:**

- To estimate the impact of DOAC on major peri-procedural bleeding in patients undergoing left ventricular arrhythmia ablation when compared to ASA. Assessment done up to 30 days post procedure.
- To estimate the impact of DOAC on minor peri-procedural bleeding in patients undergoing left ventricular arrhythmia ablation when compared to ASA. Assessments completed at 1week post procedure and up to 30 days post procedure.

**Institutional Review Board/Independent Ethics Committee**

Before initiation of the study, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information should be provided to subjects. The

investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects, and any updates.

The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

**Informed Consent**

Investigators must ensure that subjects or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Investigators must:

a) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

b) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

c) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

d) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

e) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.

f) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by

the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

**INVESTIGATIONAL PLAN**

**Study Design and Duration**

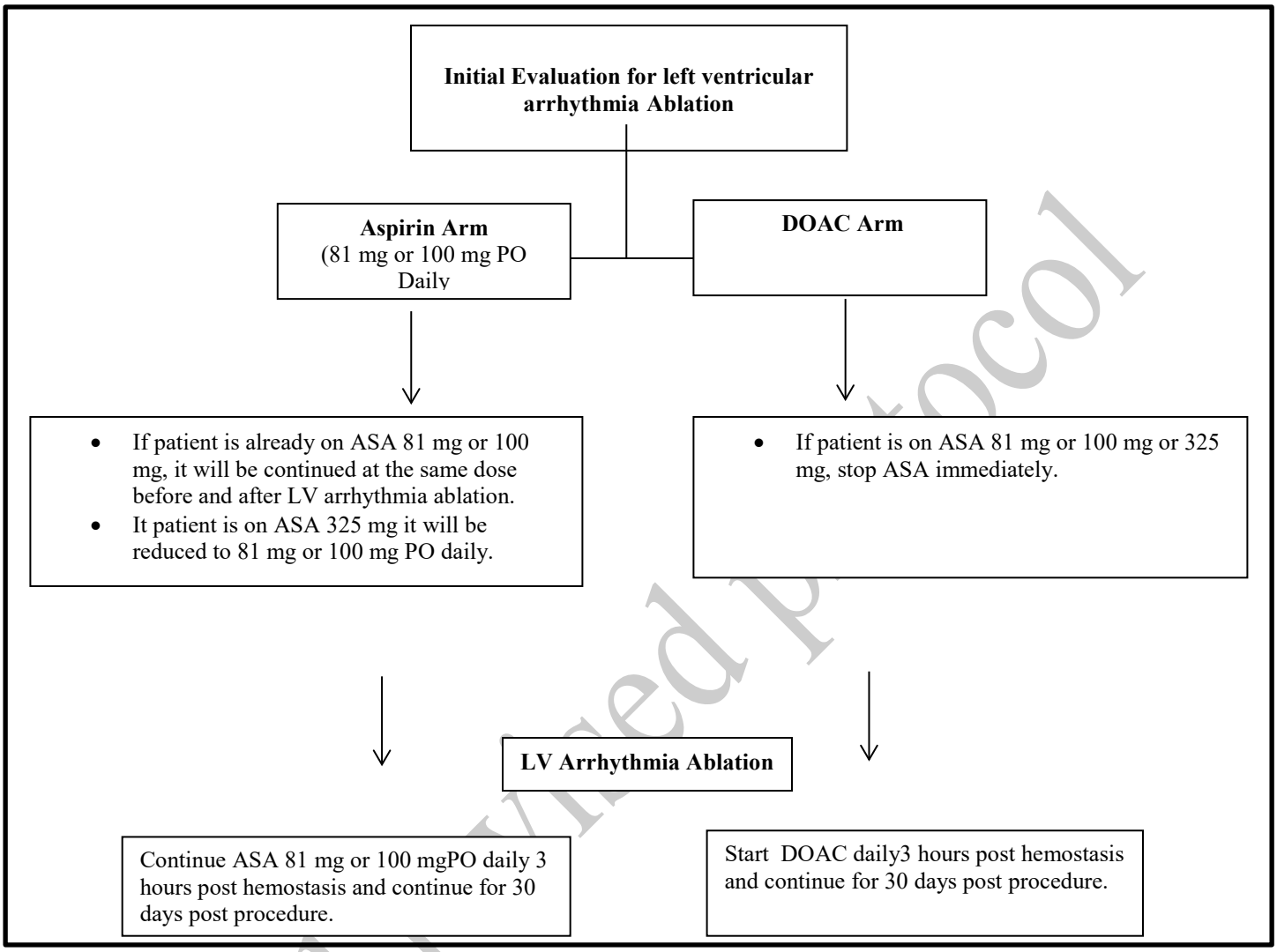
This is a multicenter, randomized, prospective study to determine, if DOAC can be used periprocedural in patients undergoing a scar left ventricular arrhythmia ablation. Patients will be screened from both the clinic setting and upcoming EP lab schedule. The patient's chart will be reviewed and those that meet inclusion/exclusion will be approached for the study. For this study, we intend to enroll 52 consecutive subjects who are undergoing a scar left ventricular arrhythmia ablation at participating institutions if they meet all other inclusion criteria and do not have any exclusion criteria. Patients will be randomized in a 1:1 fashion.

Figure 1 shows the use of ASA or DOAC for left ventricular arrhythmia ablation.

Patients undergoing left ventricular arrhythmia ablation will be consented and randomized to either ASA 81 mg or 100 mg daily or DOAC twice daily. Patients randomized to ASA will continue or start ASA 81 mg or 100 mg by mouth daily, and continue up to 30 days after the procedure. Patients randomized to DOAC group will stop the ASA if they are currently taking it; DOAC 5 twice daily will be started 3 hours after hemostasis and continue for 30 days post procedure.

The drugs to which they are assigned to will be continued at least for 30 days post left ventricular arrhythmia ablation. All subjects will be followed from baseline to 30 days post procedure. At this time they will have completed the study and can stop either DOAC and/or Aspirin at the physician′s discretion.

**Figure 1 Therapy initiation protocol for procedures.**




* In case of any two of the following: age ≥ 80 yrs, body weight ≤ 60 kg, or serum creatinine ≥1.5 mg/dL a dose of DOAC at a reduced dose will be initiated.

**Baseline Visit:**

Baseline visit will be conducted within 30 days prior to procedure (unless noted). This visit will include:

- A physical exam and medical history will be performed that includes: height, weight, BMI, NYHC evaluation, blood pressure, pulse, review of systems.
- Labs: Chemistry, CBC, Coagulation, Pregnancy test
- Echo: EF, LA size, Mitral Regurgitation, Aortic Regurgitation, Mitral Stenosis, Aortic Stenosis within 3 months of the procedure
- ECG, MRI, TEE, CT, Device interrogation − most recent within 6 months
- Procedural variables

**Oral Anti-Coagulation/Anti-Platelet Regimen:**

The initiation and stopping of the antiplatelet and DOAC regimens will be based on Figure 1. If subjects are on Aspirin 325 mg, the dose will be changed to 81mg daily. Once vascular access is obtained for ablation, the patient will be started on unfractionated heparin intravenously to maintain the ACT levels ≥ 300 msec during the procedure, as deemed appropriate by the operator. Subjects randomized to the DOAC group will be started on oral DOAC at the standard dose of 5 mg twice daily and continued for 30 days post procedure beginning 3 hours after hemostasis. In case of any two of the following: age ≥ 80 yrs, body weight ≤ 60 kg, or serum creatinine ≥1.5 mg/dL a dose of DOAC at reduced dose will be initiated for those randomized to the DOAC arm. For drug interactions occurring with DOAC, the concomitant use of the medications per the USPI should be avoided or dose should be adjusted accordingly.

**Ablation Protocol**

A standard left ventricular arrhythmia ablation protocol that is approved at the participating institution and which is in place will be followed. Endocardial ablation, access to the left ventricle is gain via trans-septal approach which is preferred access or via retrograde transaortic approach. When deemed necessary by the operator epicardial access will be obtained and used for mapping and ablation. Left ventricular arrhythmia ablation is performed targeting the clinical VT. A voltage map is created to assess the scar and scar border. If the VT is hemodynamically

stable it will be mapped and ablated using activation and entrainment mapping. If the VT is unstable, pace making, and substrate modification should be done in the target region. The non-clinical VTs are also targeted at the discretion of the operator. Substrate modification including ablation of potential sites of interest with mid diastolic and LAVA potentials should also be targeted. Standard definition for identifying the scar, scar border, pace match, induction protocol and substrate characteristics apply. Programmed stimulation will be repeated after the ablation to look for any inducible Ventricular Tachycardia. Hemodynamic support is used at the discretion of the operator. DOAC will be restarted only after the hemodynamic support has been removed and hemostasis has been achieved.

Hemostasis after procedure is defined as complete absence of any access site bleeding with ACT < 200 seconds and no further need for manual or artificial compression.

**Cerebral MRI (**as adopted from **)**

Study subjects will be screened for new asymptomatic CVEs, within 24 hours after the ablation procedure and again at 1month post procedure with 1.5 T MRI. A baseline is not done to minimize the number of imaging studies. The Flair sequencing has the ability to delineate a new embolic lesion from an old infarct. This will help reduce the patient exposure to repeated testing. The imaging protocol includes a sagittal T1-weighted spin echo sequence to obtain a better definition of the anterior and posterior cerebral commissures. The parameters of the T1-weighted spin echo sequence were as follows: repetition time/echo time 400/13; slice thickness 5 mm; distant factor 0%; field of view 230 mm; matrix 192×256; and acquisition time 59 seconds. An axial fluid-attenuated inversion recovery (FLAIR) sequence was then used. The parameters of the FLAIR sequence were as follows: repetition time/echo time 8500/112; TI 2500 ms; slice thickness 5 mm; distant factor 30%; field of view 240 mm; matrix 154×256; and acquisition time 3.24 seconds. A diffusion-weighted (DW) sequence, with the use of a single-shot spin echo with echo-planar imaging technique that combined the motion-probing gradient before and after the 180° pulse with echo-planar imaging readout, was obtained; The parameters of the DW sequence were as follows: repetition time/echo time 3200/99; slice thickness 5 mm; distant factor 30%; field of view 230 mm; matrix 128×128; bandwidth 1502 Hz; gradient strength 22 mT; duration of diffusion gradients 31 ms; gradient separation 42 ms in 3 orthogonal directions; and

acquisition time 43 seconds. For each DW sequence, the apparent diffusion coefficient map will be obtained.

On the post ablation MRI, an acute embolic lesion was defined as a focal hyper intense area detected by diffusion weighted sequence (DWI) with or without addition of delayed Fluid-attenuated inversion recovery (FLAIR) positive sequence. The size and localization of the focal lesions will be analyzed certified by radiologist blinded to the clinical status.

Subjects who have the Cardiac electrical implantable devices who are undergoing MRI examination will follow standard protocol which are in place in the institution.

**Neurology Evaluations**

Patients will undergo a NIHSS and EQ5D prior to procedure (within 24 hours) and post (12-48 hours). If changes in the NIHSS score of greater than 3 a neurologist will be consulted, and the patient will be evaluated and treated based on their recommendation. Asymptomatic Cerebrovascular emboli are defined as cerebral infarct present on MRI or CT scan for which no corresponding symptoms were documented [2]. Symptomatic Cerebrovascular emboli were defined as an episode of neurological dysfunction associated with a focal cerebral infarction in the region correlating with the dysfunction. .

**Study Population**

For entry into the study, the following criteria MUST be met.

***Inclusion Criteria***

**A. Signed Written Informed Consent**

Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

**B. Target Population**

- Patients undergoing radiofrequency catheter ablation for left ventricular arrhythmias secondary to ischemic cardiomyopathy and non-ischemic cardiomyopathy. Patients with normal heart VT, i.e. no clinical evidence of cardiomyopathic process will be excluded from the study.

- Patients undergoing radiofrequency catheter ablation for left sided VT based on initial clinical suspicion.

**C. Age and Reproductive Status**

- Males and Females, ages 18 to 80 years

- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

- Women must not be breastfeeding

- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with DOAC plus 5 half-lives of DOAC (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion.

- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with DOAC plus 5 half-lives 3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion.

- Azoospermia males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

**HIGHLY EFFECTIVE METHODS OF CONTRACEPTION**

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectable, implants and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

***Exclusion Criteria***

**A. Target Disease Exceptions**

- History or CVA/TIA in last 3 months
- Cardiac surgery or neurosurgery within 3 months of the intended procedure date

**B. Medical History and Concurrent Diseases**

- Ongoing ischemia or a prior coronary intervention requiring continued dual antiplatelet therapy
- Any active bleeding
- Severe hypersensitivity reaction to DOACs (including drug hypersensitivity, such as skin rash and anaphylactic reactions, such as allergic edema)
- Prosthetic heart valves; the safety and efficacy of DOACs have not been studied in patients with prosthetic heart valves.
- History or bleeding and clotting disorders
- Requires dual anti-platelet therapy
- Contraindications to Aspirin therapy
- Contraindication to oral anticoagulation
- Patients who have a continuing need for oral anticoagulation (i.e. patients with AF; DVT or a mechanical valve) Evidence of intracardiac thrombus
- Patient with Creatinine Clearance of $\leq$ 40 cc/min

**C. Sex and Reproductive Status**

***See Section on WOCBP above***

**D. Prohibited Treatments and/or Therapies**

- Participation in another investigational study related to oral anticoagulation, drug and/or device intervention.
- Claustrophobic patients
- ICD generator placement before the year 2000
- Has an ICD and is pacing dependent without underlying rhythm upon interrogation at baseline
- Patient has abandoned leads

**E. Other Exclusion Criteria**

- Prisoners or subjects who are involuntarily incarcerated.
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Patients with abnormal troponins or any evidence of a recent MI

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

***Women of Childbearing Potential***

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

***Discontinuation of Subjects from Treatment***

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or inter-current illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedures outlined above. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

**TREATMENTS**

**Study Treatment: DOAC or Warfarin**

**Definition of Investigational Product:** A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from

the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is DOAC.

**Definition of Non-Investigational Product:** Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care. In this protocol, the non-investigational products are none**.**

**Method of Assigning Subjects to a Treatment**

All subjects who have signed the study ICF and meet all inclusion and no exclusion criteria will be randomized in a 1:1 into one of the two study arms (1) Aspirin 81 mg or 100 mg or (2) DOAC recommended dose. For study purposes, subjects are considered enrolled in the study once they have signed the consent form and are randomized and stratified by individual sites.

**Selection and Timing of Dose for Each Subject**

DOAC should not be used if a patient has an allergy or has had active pathological bleeding where the use of the agent is contraindicated. Similarly, patients who are allergic and contraindicated to ASA should not use ASA.

If a dose of DOAC is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and then continue with twice daily administration as before. The dose should not be doubled to make up for a missed dose. DOAC can be taken with or without food.

DOAC is not recommended in patients with severe hepatic impairment. These patients will not meet the inclusion/exclusion criteria.

***Dose Modifications***

Dose modification per investigator recommendations and per current guidelines.

**Concomitant Treatments**

***Prohibited and/or Restricted Treatments***

Co-administration of the maintenance dose of DOAC is not recommended with drugs that increase the risk of bleeding (eg, other anticoagulants, heparin, thrombolytic agents, NSAIDs, SSRIs, serotonin norepinephrine reuptake inhibitors).

***Other Restrictions and Precautions***

DOAC should be discontinued 48 hours prior to elective surgery or invasive procedures. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Use DOAC with caution when co-administered with nonsteroidal anti-inflammatory drugs (NSAIDs), including ASA.

**Treatment Compliance**

Patient compliance will be reported by patient interview to assure no medications were missed. The DOAC bottle will be returned to the study coordinator at their 1 month follow up visit.

## STUDY ASSESSMENTS AND PROCEDURES

### Study Schematic

### Time and Events Schedule

| Procedure | Baseline (Within 30 days of the procedure) | Randomization (Within 48 prior to procedure) | Prior to Procedure (Within 24 hours of procedure) | Day of Procedure | 24-48 hours Post-Procedure | Discharge | Day 30 (+/- 7 days) Follow-Up |
|---|---|---|---|---|---|---|---|
| **Eligibility Assessments** | | | | | | | |
| Informed Consent | **X** | | | | | | |
| Medical History | **X** | | | | | | |
| Inclusion/Exclusion Criteria | **X** | | | | | | |
| **Study Assessments:** | | | | | | | |
| Physical Examination | **X** | | | **X** | **X** | **X** | **X** |
| Vital Signs | **X** | | **X** | **X** | **X** | **X** | **X** |
| Adverse Events Assessment | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Evaluation of Bleeding Events | **X** | | **X** | **X** | **X** | **X** | **X** |
| Laboratory Tests | **X** | | | | | | |
| Pregnancy Test | **X** | | | | | | |
| Ablation Procedure | | | | **X** | | | |
| Device Interrogation | | | **X** | | **X** | **X** | **X** |
| Cerebral MRI | | | | | **X** | | **X** |
| Neurology Evaluation NIHSS | | | **X** | | **X** | | **X** |
| EQ5D Survey | | | **X** | | **X** | | **X** |
| Randomization | | **X** | | | | | |
| Dispense Study Drug | | | | **X (3 hours post hemostasis** | | | |
| Drug Compliance | | | **X** | **X** | **X** | **X** | **X** |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

Schedule of Events

Baseline (to be completed within 30 days prior to the procedure)

- Informed Consent
- Medical History including medication review
- Inclusion/Exclusion Criteria reviewed
- Physical Exam
- Vital Signs
- Adverse Event Assessment
- Evaluation of Bleeding events − including TIMI evaluation
- Laboratory tests (including Chemistry, CBC, Pregnancy Test)
- Pregnancy Test (if applicable)

Randomization

- Adverse Event Assessment
- Randomization

Prior to Procedure (within 24 hours of procedure)

- Vital Signs
- Adverse Event Assessment
- Evaluation of Bleeding events − including TIMI evaluation
- Device Interrogation
- Neurology Evaluation − NIHSS
- EQ5D Survey

Day of Procedure

- Physical Exam
- Vital Signs
- Adverse Event Assessment
- Dispense Study Drug
- Evaluation of Bleeding events − including TIMI evaluation
- Ablation Procedure

Post Procedure (within 24-48 hours)

- Physical Exam
- Vital Signs
- Adverse Event Assessment
- Evaluation of Bleeding events − including TIMI evaluation
- Device Interrogation
- Cerebral MRI
- Neurology Evaluation − NIHSS
- EQ5D Survey

Discharge

- Physical Exam
- Vital Signs
- Adverse Event Assessment
- Evaluation of Bleeding events − including TIMI evaluation Device Interrogation

Day 30 Follow up (+/- 7 days)

- Physical Exam
- Vital Signs
- Adverse Event Assessment
- Evaluation of Bleeding events − including TIMI evaluation
- Device Interrogation
- Cerebral MRI
- Neurology Evaluation − NIHSS
- EQ5D Survey

**Safety Assessments**

| **STROKE VT**<br>**Non-CABG Surgery Related Bleeding Events Criteria** |
|---|

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|---|
| **TIMI Major Bleeding Events**<br>Any Symptomatic Intracranial Hemorrhage, or clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of >5 g/dL (or when the hemoglobin concentration is not available, an absolute drop in hematocrit of >15% or Fatal Bleeding (bleeding that directly results in death within 7 days post procedure) |
| **TIMI Minor Bleeding Events**<br>Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin concentration of 3 to < 5 g/dL (or, when hemoglobin concentration is not available, an absolute drop in hematocrit of 9 to < 15%) |
| **TIMI Bleeding Events Requiring Medical Attention**<br>Any bleeding event that requires medical treatment, surgical treatment, or laboratory evaluation and does not meet criteria for a major or minor bleeding event, as defined above |
| **Insignificant Bleeding Events** (ie, TIMI Minimal Bleeding Event)<br>A reported blood loss or bleeding event episode not meeting any of the above criteria |
| **Clinically Significant Bleeding Events**<br>The composite endpoint of TIMI major bleeding event, TIMI minor bleeding event, or bleeding event requiring medical attention is considered clinically significant for the TIMI scale |
| **Not a TIMI Bleeding Event** |

**Primary End Point Assessment**

Incidence of periprocedural embolic events –TIA/CVA/other systemic embolic events immediately after the left ventricular arrhythmia ablation up to 30 days post left ventricular arrhythmia ablation.

The incidence of new asymptomatic cerebrovascular events as documented by MRI at 24-48 hours post procedure and at 30 days after the left ventricular arrhythmia ablation.

**Secondary End Point Assessments**

A. Major bleeding events as defined above using TIMI criteria

B. Minor Bleeding events as defined by the TIMI criteria

C. Cardiovascular mortality

D. All-Cause mortality

E. Any other adverse events occurring during the study period

**ADVERSE EVENTS**

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

**Serious Adverse Events**

**Serious Adverse Event (SAE)** is any untoward medical occurrence at any dose that:

- results in death

- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see ***NOTE****: below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
- Potential drug-induced liver injury (DILI) is also considered an important medical event--see the DILI section below for a definition of a potential DILI event.
- Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

***NOTE:** The following hospitalizations are not considered SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected:

Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

***Serious Adverse Event Collecting and Reporting***

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form.

**SAE Email Address:** dlakkireddy@gmail.com

**SAE Fax Number:** 913-575-2157

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

All SAEs should be followed to resolution or stabilization.

***SAE Reconciliation***

The investigator will reconcile the clinical database SAE cases transmitted to the study team. The DSMB and study steering committee will adjudicate the adverse events in the event of disagreement.

**Non-Serious Events**

A non-serious adverse event is an AE not classified as serious.

***Non-Serious Adverse Events (NSAEs) Collecting and Reporting***

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Non-serious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

**Laboratory Test Abnormalities**

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, use the term anemia rather than low hemoglobin value).

Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

**Pregnancy**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will

be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

**Overdose**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

**Potential Drug-Induced Liver Injury (DILI)**

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

**Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious adverse event, as appropriate, and reported accordingly.

**DATA MONITORING COMMITTEE**

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring Board (DSMB) will monitor results during the study. The board consists of 2 physicians and 1 statistician who have no formal involvement or conflict of interest with the subjects or the investigators. Records will be reviewed after the first 50 patients and then at the completion of the study.

If the major bleeding events in the DOAC group occur at >15% but <30% (absolute event rate) of those in the ASA group during any of the assessments, a recommendation will be made to consider modifying the study by the members of the DSMB. First consideration to modify is to decrease the dose of the drug to 2.5mg PO twice daily. If the major bleeding events in the DOAC group occur at >30% (absolute event rate) of those in the ASA group during any of the assessments, a recommendation will be made to stop the study by the members of the DSMB.

**STATISTICAL CONSIDERATIONS**

***Study Management and Sample Size Justification***

This is a pilot study and 52 total patients will be enrolled in the study. We expect to analyze a total of 50 patients and each arm will consist of 25 patients. The additional 2 allows for attrition. Since this is a pilot study, the number needed to treat to achieve a pre-specified statistical significance cannot be calculated accurately. Exact sample size could not be given due to lack of pre-existing data on this subject. We hypothesize a 30% difference in outcomes can be seen with a total sample size of 50 patients.

**Data Collection Center**

The Kansas City Heart Rhythm Research Foundation will be the coordinating site for the study. A project manager (PM) with the help of the PI will create the study worksheets and create the CRFs. The sites will complete the paper CRF and submit via secure email to the project manager. The PM will assist the Database Manager (DM) with updating the access database and providing computer support for outside centers. All data will be submitted via secure email including de-identified patient data that is to be used as source.

Participant's data will be de-identified and a code will be assigned. The code will consist of Site Number, Patient Number and Patient Initials. The coordinator at that site will have access to the code; the linking list will be destroyed at the completion of the project.

**Statistical analysis:** Patients will be randomized in a stratified manner to control arm versus treatment arm. We will analyze the differences in secondary endpoints between the two groups for major, minor bleeding and cardiovascular mortality up to 30 days post ablation. Categorical variables will be reported as counts and percentages and continuous variables will be expressed as mean ± SD. Continuous variables will be compared using t-test for normally distributed data or Mann Whitney U test for non-normally distributed data as deemed appropriate. Categorical events will be compared using chi-square test for parametric data.

Univariate and multi-variate analysis will be performed to identify the predictors of systemic thromboembolic events and mortality. This is a pilot study to study the feasibility and safety of the study. A larger study will be done in the future if there is a positive signal.

**Compliance with the Protocol**

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by the study team.

## GLOSSARY OF TERMS

| Term | Definition |
|---|---|
| Adverse Reaction | An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product. |
| Expedited Safety Report | Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures. |
| Hemostasis | Defined by no further ooze from groin puncture sites after pressure hold is released. Typically, 3-4 hours post procedure. |
| SUSAR | Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC). |
| Unexpected Adverse Reaction | An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product). |
| Peri-Procedural Bleeding | Occurring prior to the procedure within 48 hours and up to 48 hours post procedure. |
| Recent MI | Recent is defined as within 30 days of the planned procedure. |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACE | Asymptomatic Cerebrovascular Event |
| AE | Adverse Event |
| AF | Atrial Fibrillation |
| ASA | Aspirin |
| DOAC | Direct Oral Anticoagulant |
| CIED | Cardiac Implantable Electrical Devices |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVA | Cerebrovascular Accident |
| CVE | Cerebrovascular Events |
| EP | Electrophysiology |
| ESR | Expedited Safety Report |
| FDA | Food and Drug Administration |
| FSH | Follicle-Stimulating Hormone |
| GCP | Good Clinical Practice |
| HCG | Human Chorionic Gonadotropin |
| HRT | Hormone Replacement Therapy |
| IB | Investigator Brochure |
| ICD | Implantable Cardioverter Defibrillator |

| | |
|---|---|
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| ISR | Investigator-Sponsored Research |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NIHSS | National Institute of Health Stroke Score |
| NSAE | Non-Serious Adverse Event |
| RFA | Radiofrequency Ablation |
| SAE | Serious Adverse Event |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TIA | Transient Ischemic Attack |
| TIMI | Thrombolysis In Myocardial Infarction |
| VT | Ventricular Tachycardia |
| VKA | Vitamin K Antagonist |
| WOCBP | Women of Child-Bearing Potential |

**Attachment A**

**Algorithm for subjects who have Cardiac implantable devices and who are undergoing brain MRI examination** (as adopted from [2])

**General:**

1. MRI scans will be performed in a 1.5 T scanner.
2. Subjects will undergo interrogation of the device (CIED) before and after the scan by experienced heart rhythm management personnel, outside the MRI room.
3. Patient height and weight will be recorded to determine the specific absorption rate (SAR) levels not to exceed the manufacturer's pre-specified limits, if in case, the parameters, repetition times, number of slices and angle will be changed accordingly.
4. A crash cart and ACLS trained health care professional will be available during the entire procedure.
5. Blood pressure, pulse oximetry and cardiac rhythm will be monitored. If any signs of hemodynamic instability (BP<90/60, HR<40) or ventricular fibrillation the procedure will be stopped and patient will be managed as per the ACLS protocol.

**Device (CIED) interrogation and monitoring:**

1. Device interrogation will include measurements of battery voltage, P- and R-wave amplitudes (if present), and lead impedance and pacing threshold for all leads.
2. Pacing threshold measurements will be performed at 10 beats/min above the programmed pacing rate (if pacemaker dependent) or, 10 beats/min above the patient's intrinsic rate. The pacing rate for testing can be increased by increments of 10 beats/min, if there is insufficient suppression of the patient's underlying rhythm.
3. The pacing rate will gradually be decreased to 40 beats/min, if the patient has an intrinsic rhythm of greater than 40 beats/min, the device will be programmed to pacing and sensing functions disabled (ODO) [Chamber paced-none; Chamber sensed--atria and ventricle; Mode of response –none] or OVO [Chamber paced-none; Chamber sensed-ventricle; Mode of response-none]). The patient will then be observed for 5 minutes before the scan. If symptoms are noted, the pacing function will be reprogrammed to an asynchronous pacing mode (DOO) [asynchronous pacing mode using both atrial and ventricular leads] or (VOO) [asynchronous pacing mode using only the ventricular lead]. If the patient has a device that does not allow permanent reprogramming to an ODO or OVO mode, the patient will be

reprogrammed to an asynchronous mode (DOO or VOO), and the pacing output for all active leads and pulse width will be set to a minimum value. If there is no intrinsic rhythm when the device is reprogrammed to 40 beats/min, the patient will be considered pacemaker dependent, and the device will be programmed to an asynchronous pacing mode (DOO or VOO). The patient will be observed for 5 minutes before the scan to ensure that the asynchronous pacing is well tolerated. If not, the original pacing parameters will be restored and the scan will not be performed.

4. Immediately after the scan, initial device parameters will be restored. Post scan device parameter interrogation will be performed using the pre-scan interrogation protocol. If there is a significant increase in pacing threshold (≥0.5 V at 0.4 ms or any increase at a wider pulse width) after the scan compared with before the scan, the pacing output will be increased to maintain a 2- to 2.5-times amplitude safety margin at the physician's discretion. If there is a significant decrease in the P- and R-wave amplitudes, the sensitivities will be adjusted to maintain adequate atrial and ventricular electrocardiogram detection.

**Implantable cardioverter-defibrillator interrogation and programming:**

1. The pacing rate will gradually be decreased to, 40 beats/min. If the patient has an intrinsic rhythm and is asymptomatic, the device will be programmed to no pacing (ODO or OVO). All tachycardia therapy and detection functions will be disabled. The patient will be observed for 5 minutes before the scan. If the patient does not have a stable intrinsic heart rate or symptoms are noted, the patient will be considered pacemaker dependent. Subjects with ICDs who are pacemaker dependent are excluded from the study.

2. Immediately after the scan, all tachycardia therapy and detection functions will be restored. Post scan interrogation will be performed as described earlier for pacemaker Subjects.

3. Subjects with 1 or more parameter changes will be asked to return for 3 follow-up interrogations over a six-month period, which will be scheduled less than 7 days after the procedure, again at 3 months (±30 days) after the MRI procedure, and at 6 months (±30 days) after the MRI procedure. If no parameter changes requiring multiple follow-up visits occur, the patient will require a single-device interrogation between 3 and 6 months (±30 days) after the MRI procedure.

**REFERENCES**


1. Cabral KP, Ansell JE. The role of factor Xa inhibitors in venous thromboembolism treatment. Vasc Health Risk Manag. 2015 Jan 30;11:117-23. doi: 10.2147/VHRM.S39726. eCollection 2015. Review. PubMed ID: 25673997.

2. Ghanbari H, Başer K, Jongnarangsin K, Chugh A, Nallamothu BK, Gillespie BW, Başer HD, Suwanagool A, Crawford T, Latchamsetty R, Good E, Pelosi F Jr, Bogun F, Morady F, Oral H. Mortality and cerebrovascular events after radiofrequency catheter ablation of atrial fibrillation. Heart Rhythm. 2014 Sep;11(9):1503-11. doi: 10.1016/j.hrthm.2014.05.003. Epub 2014 May 6. Erratum in: Heart Rhythm. 2015 Jan;12(1):253. Swangasool, Arisara [corrected to Suwanagool, Arisara]. PubMed ID: 24813379.