Rationale

Atrial fibrillation (AF) is the most common arrhythmia requiring medical treatment, with a lifetime risk for development of AF approximately 25% in the general population[1]. AF confers an increased risk of thromboembolism and stroke. About 1/6 of all strokes are attributable to AF and this fraction increases with age. AF is the likely cause for over 25% of strokes in patients over 70 years old.

Heart failure (HF) is among the greatest contributors to morbidity and mortality and currently afflicts approximately 5 million Americans.

These two cardiac disorders are inextricably linked; patients with either disorders are at substantially increased risk of developing the other and when combined carry a substantially worse prognosis than either alone[2]. Numerous studies have confirmed that HF further increases the risk of stroke. The Atrial Fibrillation Investigators[5] reported that the annual risk of stroke was 1.03% in patients with AF who had no underlying cardiovascular disease, but the risk increased to 3.6%/year in the presence of HF. In the SPAF trials, recent HF (within 3 months) in patients with AF was associated with a 2.5-fold greater risk of stroke[6]. Most episodes of AF in that study were symptomatic and of substantial duration (days to weeks).

The $CHADS_2$ risk stratification scheme (Table 1) is a scoring system increasingly accepted as a practical way to estimate the risk of stroke in patients with AF[7], and as a guide to determining which patients warrant anticoagulation therapy[8].

Risk factor	Number of points assigned
C—CHF	1
H—Hypertension	1
A—Age ≥ 75	1
D—Diabetes mellitus	1
S—Stroke or TIA	2

Table 1: $CHADS_2$ risk score assessment

Patients must present a history of any of the risk factors listed above (except age) in order to count as points in the thromboembolic risk scheme. The $CHADS_2$ score may be used to estimate the yearly risk of stroke. For every 100 patients with AF in whom the $CHADS_2$ score is 2, about 4 will suffer a stroke each year unless anticoagulation is employed. A score of 6 results in more than a four-fold increase in risk per year (18.5).

It is well established that anticoagulation therapy reduces the risk of stroke in patients with AF. Multiple published clinical practice guidelines call for anticoagulation in patients with paroxysmal or persistent AF, and oral vitamin K antagonist agents such as warfarin are the standard therapy used to prevent stroke in AF patients at risk[9]. One of the major limitations of the current approach to prevention of stroke in patients with AF is that many cases of AF are asymptomatic and the occurrence and remission of paroxysmal AF (PAF) are not readily identified over time.

The current generation of sophisticated CRT-D and ICD devices offer real-time remote monitoring, making it possible to detect virtually every episode of AF, including the frequency and duration, regardless of the absence or presence of symptoms. Additionally, the total burden of AF in individual patients can be quantified, expressed as the percentage of time per day AF is present.

The Mode Selection Trial (MOST) was a 6-year prospective, randomized, multicenter trial designed to compare VVIR with DDDR pacing in patients whose sinus node dysfunction required permanent pacing for bradycardia. A limited secondary analysis comprising 312 patients found that 51.3% (160) patients had at least one atrial high rate episode (AHRE) of at least 5 minutes duration over a median follow-up of 27 months. Death or nonfatal stroke was reported in 33 (20.6%) of the AHRE patients as compared to 16 (10.5%) patients without AHRE. Cox analysis showed that detection of AHRE was an independent predictor of both mortality and stroke in the AHRE cohort[14].

Presently, there are no published guidelines regarding anticoagulation for patients with AF documented by device data, and whether early anticoagulation in patients with AF documented by remote monitoring can reduce the stroke rate in this population has not been established. Consequently, remote monitoring may be particularly relevant in patients with asymptomatic AF by allowing timely intervention as compared to conventional periodic office device evaluation.

Objectives

The IMPACT Study will investigate the clinical benefit of the combined use of BIOTRONIK Home Monitoring (HM) technology and a predefined anticoagulation plan compared to conventional device evaluation and physician-directed anticoagulation in patients with implanted dual-chamber defibrillators or cardiac resynchronization therapy devices.

The IMPACT Study Summary

Study Design

This is a prospective, multi-national, multi-center, single-blind, parallel group, and randomized trial. Up to 2718 patients at 100 clinical sites worldwide will be enrolled and followed for up to 36 months. Participants in the study will be implanted with BIOTRONIK Lumax DR-T/ HF-T devices or future legally marketed BIOTRONIK dual chamber ICD and CRT-D with HM and IEGM-Online technology.

Eligible patients will be randomized (1:1) to the Intervention Arm (Group 1) or the Control Arm (Group 2). Post-enrollment, all patients will be followed by conventional office visits at subsequent 3-month intervals for up to 36 months. At any time, interim follow-up visits may be scheduled based on HM notifications, patient-initiated calls or other clinical developments.

At enrollment visit, patients randomized to the Intervention Arm will receive a prescription for warfarin. HM must be fully enabled and data from continuous remote surveillance will be available to clinicians. The total duration of AF and/or atrial flutter (AFL) will trigger the start, stop, and re-start of anticoagulation and is stratified based on $CHADS_2$ risk score. The investigators will actively monitor for AF/AFL, and if the total duration over 48 consecutive hours reaches the predefined anticoagulation condition, an automatic notification (email, fax, etc.) will be sent to the physician. To **start** anticoagulation, after confirming the atrial arrhythmia using IEGM online, the site will instruct the patient by telephone to initiate warfarin therapy.

Laboratory testing of anticoagulation intensity (INR) should be scheduled shortly after initiating therapy with warfarin to guide dose adjustment. Warfarin anticoagulation management will be coordinated outside the study site by each patient's respective primary care physician, in accordance with current guidelines. Data on INR values and warfarin doses will be collected at scheduled study visits.

Clinicians will continue to monitor patients using HM, and if freedom from AF/AFL reaches the predefined interval, **stop** of warfarin therapy will be requested over the telephone. Following stop of anticoagulation, recurrence of AF/AFL (any duration) requires **re-start** of warfarin. Based on active HM alerts, the cycle may repeat indefinitely.

Patients assigned to Control Arm will have HM active (BIOTRONIK monitoring for safety), but the AF/AFL data will not be revealed to the patient or treating physician. These patients will receive physician-directed anticoagulation therapy based on conventional criteria.

Study Endpoints

The study hypothesis states that early detection of AF/AFL based on BIOTRONIK HM technology combined with a predefined anticoagulation plan will reduce the rate of the composite endpoint of stroke, systemic embolism and major bleeding.

In addition to the primary objective, the IMPACT clinical trial will evaluate eight secondary objectives. These include assessment of the impact of randomized treatment group assignment on rates of all-cause mortality, stroke (ischemic and hemorrhagic, disabling and non-disabling, cardioembolic and non-cardioembolic), and major bleeding, as well as the AF burden, quality of life, and mean heart rate reduction.

Blinding

To minimize bias associated with the assessment of the composite endpoint, a blinded neurologist and general cardiologist/internal medicine specialist co-investigator will evaluate the stroke, systemic embolism and major bleeding events.

Study Specific Inclusion Criteria

- Candidates for implantation of, or already implanted with, a BIOTRONIK Lumax HF-T or DR-T device
- Documented P wave mean amplitude ≥ 1.0 mV (sinus rhythm) or ≥ 0.5 mV (AF) at enrollment, if previously implanted
- Class I or II CRT-D or ICD implant indication
- $CHADS_2$ risk score ≥ 1
- Able and willing to follow anticoagulation therapy if the indication develops during the course of the trial
- Able to utilize the HM system throughout the study
- Ability to provide informed consent
- Geographically stable and expected ability to return for regular follow-up visits for 36 months
- At least 18 years old

Study Specific Exclusion Criteria

- Patients who do not fulfill all inclusion criteria
- Permanent AF
- History of stroke, TIA or systemic embolism and documented AF or AFL
- Currently requiring anticoagulant therapy for any indication
- Patients who underwent successful AF ablation (sinus rhythm restored) and have not completed a minimum of 3 months of warfarin
- Known, current contraindication to use of warfarin

- Long QT or Brugada syndrome as the sole indication for device implantation
- Pregnancy
- Life expectancy less than 3 years
- Currently enrolled in any other cardiovascular clinical research trial

Data collection

Original data will be collected from each investigational site and recorded into a secure Electronic Data Capture (EDC) application audited and monitored by BIOTRONIK and MedNet Solutions.

Study Organization

- Steering Committee – Responsible for protocol development and overall guidance of the trial.
- Sponsor – Responsible for protocol and regulatory compliance.
- Clinical Events Committee – Responsible for adjudication of clinical endpoint events.
- Data Safety Monitoring Board – Responsible for monitoring safety and effectiveness of the study

Sponsor

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References

Refer to the protocol for a complete list of references.

$CHADS_2$–warfarin anticoagulation algorithm