Title: A Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy of Ivabradine Initiated at the Time of Discharge from the Observation Unit. (OBSERVE-IVA)

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1.0 Summary

Prospective, randomized (1:1), placebo-controlled, double blind, study of ivabradine (Corlanor®) begun at the time of discharge from the hospital or observation unit after a stay of < 48 hours from the time of admission, for a total of 28 (+/-2) days in a cohort of predominantly (but not exclusively) African American patients with acute heart failure (HF). The primary endpoint will be change in heart rate from discharge to 28 (+/-2) days. Secondary endpoint will be heart rate change in African Americans from discharge to 28 (+/-2) days. Exploratory endpoints include change in NT-proBNP, change in hs-cTnT each comparing baseline to 28 (+/-2) days. Key safety endpoints will be the rate of unplanned medical care (presentation to ED or urgent care, unplanned hospitalization, unplanned medical office visit) and days alive and out of hospital over the 28 (+/-2) days of treatment.

2.0 Rationale

Ivabradine (IVA) has been shown to decrease the risk of hospitalizations for worsening HF and was associated with a trend towards improved mortality in the SHIFT[1] trial. SHIFT[1] excluded patients within 4 weeks of hospital discharge, so the efficacy and safety of IVA in this setting is less clear. In today's health care environment more and more patients that present to the ED for mild AHF are being placed into observation unit and subsequently discharged, or discharged outright from the ED. This is not only a growing segment of patients, but also represents an important window of opportunity to intervene with a potentially effective therapy.

Moreover, at this point in a patient's experience (being discharged after getting treated for exacerbation of HF), its not clear that beta blockers (BB) should yet be increased/started due to the recent state of exacerbation. Standard treatment of worsened heart failure presenting to the ER or urgent care includes diuresis and vasodilators (e.g. ACE-I), but according to usual standard of care, titration of beta blockade is often reserved for outpatient follow up after a period of demonstrated stability (in the ambulatory setting). This is in contradistinction to hospitalized patients, where patients have been observed by the treating team for days, presumably show stability and improvement, and starting low dose BB at the time of hospital discharge has been shown to be safe (IMPACT-HF[2] trial). As such these ED/Observation discharge patients are often not optimal candidates for intensification of BB at the time of release, and could be considered to be at maximally tolerated BB dose (for at least for 2-4 weeks). This may represent a vulnerable period for these patients; it's unknown in the setting of Observation discharge but evidence from hospitalized patients indicates that the highest daily risk of rehospitalization is in the days just after discharge. IVA may be effective post observation unit management (where lower risk HF patients are typically placed), to reduce heart rate (without decreasing contractility, such as a BB would) to help reduce the risk of hospitalization or emergency care, but safety and efficacy (in terms of heart rate lowering) in this setting has not been previously explored.

Additionally, the SHIFT[1] trial lacked African Americans and this unique patient population has not been previously studied with IVA. The investigating sites serve a predominantly African American patient

population. Therefore the proposed study represents an important opportunity to gather data on IVA effect in this understudied group of patients.

3.0 Setting

Four medical centers in Detroit (Henry Ford Hospital, Detroit Receiving Hospital, Sinai Grace Hospital, and Harper University Hospital) with a single coordinating center (Wayne State University). The emergency departments of these two hospitals treat >100,000 patients annually each. The patient population is majority African American. This makes a perfect setting to execute the proposed study. In addition, both hospitals are affiliated with Wayne State University, which has a highly functional Clinical Research Service Center that is under the direction of one of the co-investigators (Dr. Levy), enabling facilitated outpatient follow-up.

4.0 Eligibility Criteria

Inclusion Criteria:

1) Age >18 and <90.
2) Established HF with reduced ejection fraction (EF ≤35 %), assessment done within 12 months of index visit.
3) Admitted to the observation unit or inpatient ward for management of AHF.
4) Heart rate ≥70 beats per minute, with sinus rhythm.
5) Receiving guideline based medical therapy in the judgement of the treating physician.
6) Patient currently on a Beta Blocker regimen.
7) Achieved clinically determined stabilization during treatment under observation unit or during hospital admission within 48 hours from the time of admission.

Exclusion Criteria:

1) Known intolerance to study drug.
2) End stage renal disease.
3) Plan to titrate BB at the time of discharge from the observation unit.
4) Any condition that in the opinion of the investigators will interfere with the ability to complete the study (e.g. history of extreme non-adherence, extreme psychosocial instability).
5) Inability to provide written informed consent.
6) Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (women of childbearing age will be included only if they agree to use adequate contraceptive methods or engage in sexual abstinence).
7) Systolic Blood pressure less than 100 mmHg.
8) Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present.

9) Severe hepatic impairment.
10) Pacemaker dependence (i.e. heart rate maintained exclusively by the pacemaker).
11) Concomitant use of strong CYP3A4 inhibitors. Examples of strong CYP3A4 inhibitors include azole antifungals (e.g., itraconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone.
12) Concomitant use of diltiazem or verapamil that are not planned for discontinuation.
13) Severe, left sided valvular abnormalities (severe aortic stenosis, severe mitral stenosis, severe aortic insufficiency or severe mitral regurgitation.
14) Documented, prior to or at the time of randomization, restrictive amyloid cardiomyopathy, or acute myocarditis, or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy.

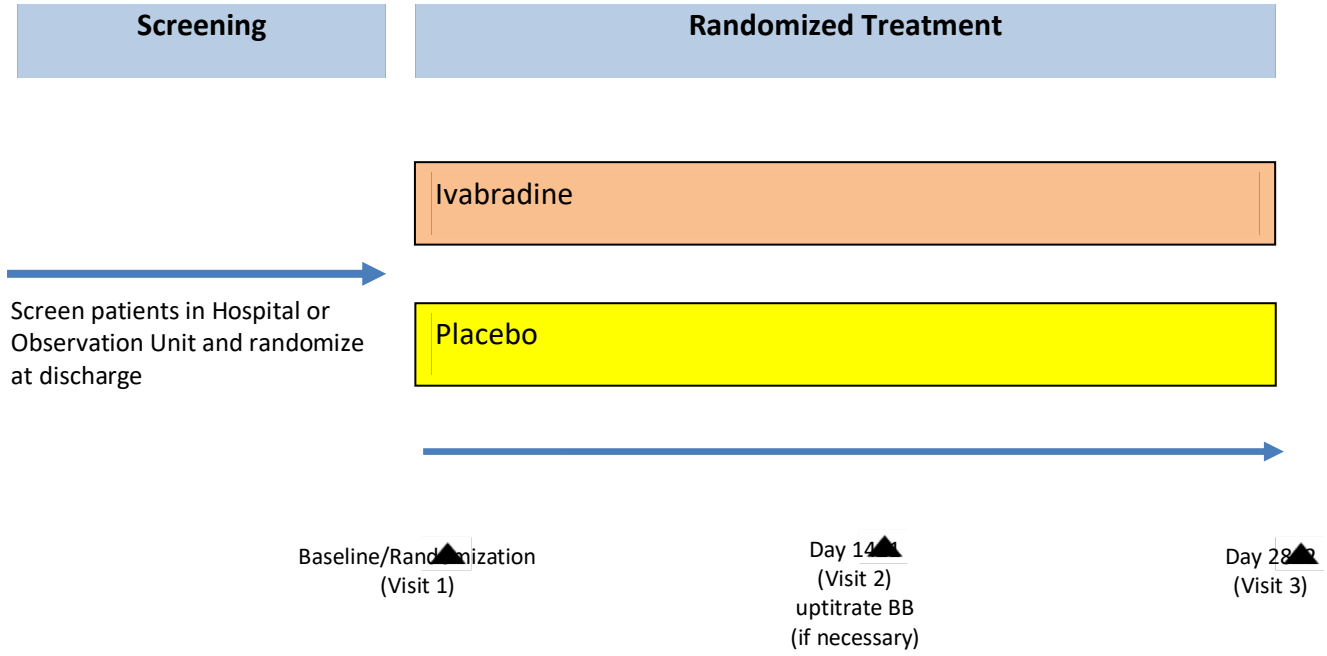
5.0 Endpoints

Efficacy:

- Primary - Change in heart rate (Day 28 (+/-2) - baseline), measured by 12-lead ECG and Zio® patch (Day 14 (+/-1) - baseline).
- Secondary - Change in heart rate in self-identified African Americans (Day 28 (+/-2) – baseline), measured by 12-lead ECG and Zio® patch[3](Day 14 (+/-1) - baseline).
- Exploratory:
    1) Change in NT-proBNP (Day 28 (+/-2) – baseline)
    2) Change in hs-cTnT (Day 28 (+/-2) – baseline)

Safety: Presentation for unplanned medical care in any setting within 28 (+/-2) days.

6.0 Study Design & Timeline



7.0 Post-Discharge Management

Subjects will be enrolled at the time of discharge from the hospital or observation unit (visit 1), all baseline procedures will be performed at this time, these would include blood draw for biomarker assessments, vitals, physical examination, Zio patch[3] placement and IP dispensation. At the baseline visit, the study team will schedule a follow-up appointment post Day 28 +/- 2 (Visit 3) with the subject's primary care physician(PCP)/cardiologist, if the subject does not have their own PCP/cardiologist the study team will schedule and facilitate this appointment with the Gateway Clinic. A list of current medications and doses will be provided. At Day 14 +/-1 (visit 2) the subject will return for a follow up visit for IP accountability and titration (if needed), BB uptitration (if needed), collection of the HR monitor (Zio patch[3]), assessment of any adverse events, ECG, vital signs, and will undergo a physical examination. At Day 28 +/-2 (visit 3), the patient will return for study exit procedures, which include blood draw for biomarker assessments, vitals, physical examination, assessment of adverse events (if any), and IP return.

As with any clinical trial, no un-blinding will occur unless there is a concern for patient safety, as this could affect the integrity of data. We will provide the patient and their PCP/cardiologist a clinical summary, inclusive of ECGs. On-going management for the patient's condition will be at the discretion of their PCP/cardiologist and will not be influenced directly by participation in this study.

8.0 Schedule of Events

	Baseline - Visit 1[a]	Day 14 (+/- 1) - Visit 2	Day 28 (+/- 2) - Visit 3
Screening (I/E)	**X**		
Informed consent	**X**		
Medical History	**X**		
Medication History	**X**		
Concomitant Medications	**X**	**X**	**X**
Physical Exam	**X**	**X**	**X**
Vitals, including Height and Weight	**X**	**X**	**X**
12-lead ECG	**X**	**X**	**X**
Zio® XT patch HR monitoring	**X**	**X**	
Echocardiogram	**X**[b]		
Biomarker Assessment (NT-proBNP and hs-cTnT)	**X**		**X**
Urine Pregnancy Test	**X**		
Randomization	**X**		
IP Dispensation	**X**		
IP Titration (if needed)		**X**	
IP Accountability		**X**	**X**
Beta Blocker uptitration (if needed)		**X**	
Assessment of AEs	**X**	**X**	**X**
[a]Baseline procedures will be done at discharge from the hospital or observation unit. [b]Assessment done at index visit or within 12 months of index visit.			

9.0 IP Dosage and Titration

At Randomization the initial Ivabradine dose will be 5 mg BID. If at any time during the study the patient's HR <50 **AND** suggestive symptoms such as lightheadedness or hypotension are present: Discontinue study drug immediately.

At Day 14 (+/-1) follow up, medication adjustments will be made based on the following criteria:

1) If patient has signs or symptoms of continued volume overload diuretic dose will be doubled for 3 days and vasodilators (ACEi/ARB/H+N) reassessed for potential increase, and BB continued at current dose. Regarding IP:
    a. If HR <50 bpm decrease study dose by 2.5 mg BID.
    b. If HR between 50-60 AND possible signs/symptoms of bradycardia (i.e. light headedness or hypotension), decrease study dose by 2.5 mg BID.
    c. Otherwise (i.e. neither above criteria present) no adjustment to study drug.
2) If patient appears stable and euvolemic:
    a. If HR >60 bpm and patient on target BB dose (i.e. total daily of 50mg carvedilol OR 200mg metoprolol succinate OR 10mg Bisoprolol): Increase study drug dose by 2.5 mg BID, to the maximum dose of 7.5 mg BID.
    b. If HR >60 bpm and patient receiving less than target BB dose: Double BB daily dose.
    c. If HR 50-60 bpm: Maintain study drug dose at 5 mg BID (and no BB change).
    d. If HR <50 bpm: Decrease study drug by half (2.5 mg BID). If IP is at the lowest dose i.e. 2.5mg BID, it will be stopped.

At Day 28 (+/-2) follow up, IP will be permanently stopped and no unblinding will occur unless for safety reasons. Other medications dose adjustments (if needed) will be made according to standard of care practice (GDMT).

10.0 Beta Blockers Dosage and Titration

Subjects will be assessed for BB therapy uptitration at Day 14 (+/-1) follow up.

11.0 Adverse Events or Unanticipated Problems involving Risk to Participants

All incidence of AE, AE leading to withdrawal of IP, and SAE will be reported to the IRB per institutional policies and procedures. IP will be stopped in treatment emergent clinically relevant events such as hypotension, significant dizziness, loss of consciousness, atrial fibrillation, 3rd degree AV block, and QTc prolongation. If IP is stopped, no re-challenging will be done. In case of any events between the scheduled study visits, subjects will be instructed to call the 24/7 phone number of the study team, and if clinically relevant, subjects will be asked to come in to follow up clinic for an unscheduled visit.

11.1 Unblinding Procedure

In the case of an emergent medical event, where the unblinding of a subject is deemed medically necessary by the study PIs, the unblinded study personnel will consult the randomization key to unblind study treatment. Once a subject has been unblinded, the date, time and reason(s) for un-blinding will be recorded in the source documents and eCRF.

11.2 MedWatch Reporting

If in the study PIs assessment, an unexpected SAE is related to subject's participation in the study, the event will be reported to MedWatch.

11.3 Data Safety and Monitoring Board

A safety analysis and review by an independent 3-member data safety and monitoring board (DSMB) will be done halfway through recruitment (after 66 subjects have been enrolled). Based on the outcomes of the review, the DSMB may propose amendments to the study protocol. The study PIs will review these proposals prior to amending the protocol and submitting to the IRB.

12.0 Biomarker Assessments

Once patients have been enrolled they will have their blood drawn using proper phlebotomy procedures. Standard gold top serum vacutainer and green top Lithium Heparin gel vacutainer, approximately 10mL (about 2 tsp) of blood, will be drawn at baseline as well as at the day 28 (+/- 2) (visit 3) follow-up. Plasma vacutainers will be placed in the refrigerator (2°-8°C) while serum sample is coagulating for 30-60 minutes. Immediately after the serum sample has coagulated for at least 30 minutes the vacutainers will be centrifuged in a swing bucket horizontal centrifuge for 10 minutes at 1100 to 1300 g. Samples will be qualitatively assessed for hemolysis after centrifugation. These characteristics will be recorded in the source documents. Plasma and serum will be aliquoted using transfer micro pipettes into as many 0.5 mL aliquots possible; aseptic techniques will be utilized throughout processing. These aliquoted samples will be frozen in a -80°C freezer onsite within three hours of blood draw. Samples will be batch shipped on dry ice in thermally-insulated containers to the University of Maryland. Good Laboratory Practices and national regulations regarding biohazardous materials will be followed. NT-proBNP and hs-TnT levels will be quantified.

13.0 Statistical Analysis

The primary outcome (change in heart rate i.e. the value at Day 28 (+/-2) - the value at baseline) will be analyzed as two sample t-test. Secondary outcomes that are continuous variables will be analyzed as two sample t-test. The safety endpoint of unplanned visits will be compared as the number of unplanned medical visits over the study period tested using Poisson regression.

14.0 Sample Size And Power

Based on the SHIFT[1] study, the mean heart rate reduction with IVA is 8 bpm with a standard deviation of 13 bpm. A sample size of 57 in each group will have 90% power to detect a difference in means of 8.0 assuming that the common standard deviation is 13.0 using a two group t-test with a 0.05 two-sided significance level. To account for a projected dropout rate of 15%, 66 subjects will be enrolled in each group (132 total for the study over a 2-year period). Furthermore, we expect that our centers will recruit a cohort that is 75% self-identified African Americans. This number (n=99) will provide 80% power to detect the same effect size when analyzed in African Americans only.

For the safety endpoint (unplanned presentation for medical care), assuming an event rate of 25% at 1 month (estimated based on local hospital readmission rates), our sample size will provide 80% power to detect a doubling of the relative risk. If the Control group event rate is higher there will be greater power; for example, with an event rate of 35% we would have 98% power for risk ratio of 2.0 and 83% power for risk ratio of 1.75.

15.0 Institutional Review Board

The conduct of this study will conform to the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and applicable regulations. A copy of the protocol (including protocol amendments), and all versions of informed consent forms will be sent to IRB for approval of both of the participating centers prior to implementation of the study. The investigator will also obtain IRB approval of the annual continuing review throughout the duration of the study and will notify the IRB of deviations from the protocol.

16.0 Informed Consent Process

All participants or their family members will be given detailed oral and written information about the study. Consent forms describing in detail the study procedures and risks will be given to each participant or their family members and written documentation of informed consent is required prior to enrollment. Participants or their family members must sign an informed consent document that has been approved by the IRB. The informed consent form will be signed and dated by the participant, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the participant's study file and a copy will be provided to the participant. Participants may withdraw consent at any time during the course of the study. Deciding to not be part of the study will not change the patient's regular medical care in any way.

17.0 Participant Confidentiality

All subject related information including Case Report Forms, and biological specimens will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each

subject. All computerized databases will identify subjects by numeric codes only, and will be password protected.

18.0 Data Management and Source Documentation

Research staff will collect data on study specific case report forms (CRFs). Source documentation will support the data collected on the CRFs. Source documents include all recordings of observations or notations of clinical activities and all reports in the EMR. All de-identified data will be entered in the password-protected, HIPAA compliant, REDCap database (Research Electronic Data Capture http://project-redcap.org/).

19.0 References

1. Böhm M, Robertson M, Borer J, et al. Effect of Visit-to-Visit Variation of Heart Rate and Systolic Blood Pressure on Outcomes in Chronic Systolic Heart Failure: Results from the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) Trial. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2016;5(2): e002160. doi:10.1161/JAHA.115.002160.
2. Gattis W, O'Connor C, Gallup D, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol, 2004. 43(9): p. 1534-41
3. Zio®Patch. 2016 iRhythmTechnologies, Inc. www.zioreports.com/Application.html#XT_PATCH_INFO_ANONYMOUS