DIGITAL HOME BLOOD PRESSURE MONITORING IN TYPE B AORTIC DISSECTION PATIENTS (DISSECT-BP) STUDY

A RANDOMIZED CONTROL TRIAL

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PROTOCOL SIGNATURE PAGE

I have carefully read the DISSECT-BP protocol. I agree to conduct this study as outlined herein. Furthermore, I understand that the Cleveland Clinic and the IRB must approve any changes to the protocol in writing before implementation.

Table of Contents

Study Synopsis……Page 4

1.0 Introduction……...Page 5

5.0 Statistical Analysis and Endpoint……..Page 11

6.0 Safety Reporting……Page 12

6.1 Adverse Events……..Page 13

7.2 Informed Consent……..Page 14

8.0 Monitoring Plan……Page 15

9.0 Reference……...Page 18

Study Synopsis

Title	Digital home blood pressure monitoring in type B aortic dissection patients (DISSECT-BP) study
Purpose	The primary objective of this study is to determine the effectiveness of home digital blood pressure monitoring in aiding providers to maintain blood pressure within a therapeutic range in high risk type B aortic dissection patients upon discharge from the hospital
Design	A single-center, prospective, randomized study
Number of Subjects	Approximately 100
Inclusion Criteria	Patients who present to the Cleveland Clinic Main Campus with a principal diagnosis of uncomplicated type B aortic dissection or intramural hematoma who receive no surgical intervention during the index hospitalization
Exclusion Criteria	Patients who receive/planned to receive a surgical intervention for type B dissection, patients who do not own a smart phone and/or unable to transmit, or patients whose arm circumference is not conducive.
Duration of Participation	Approximately 4 weeks post discharge from the hospital
Study Centers	Cleveland Clinic Main Campus
Primary Endpoint	Change in mean 24-hour systolic blood pressure (mmHg) at month 1 from discharge mean 24-hour systolic blood pressure (mmHg).
Secondary Endpoints	Number of patients at the end of 4 weeks who are able to achieve a mean 24 hour systolic BP of less than 120 mmHg. Other secondary endpoints include increase in size of aorta as assessed by CT scan, hospitalizations for symptoms from dissection or uncontrolled hypertension, hospitalizations for hypotension, all-cause mortality, need for unplanned surgical intervention (open or endovascular), and questionnaire at the end of the study

1.0 INTRODUCTION

1.1 Purpose of this Study:

The purpose of this study is to examine the effectiveness of home digital blood pressure (BP) monitoring in discharged uncomplicated acute type B aortic dissection patients. Patients admitted to the Cleveland Clinic Main Campus with a diagnosis of type B aortic dissection who do not receive a surgical intervention during their index hospitalization, or planned intervention on follow up, and are discharged on medical therapy consisting of strict heart rate control and BP control will be included in the study. They will be either randomized to the standard therapy consisting of instructions to measure BP at home (standard of care) or intervention arm consisting of Withings Wireless Blood Pressure Monitor™ which will track and transmit home BP recordings from smartphone to MyChart/EPIC (test arm). All patients will first receive a 24 hour ambulatory monitor regardless of treatment assignment to establish baseline BP pattern. Following this, patients randomized to the intervention arm will utilize their Withings Wireless Blood Pressure Monitor. Providers on the study team will then adjust the patient's anti-hypertensive medications to ensure their BP is below a systolic goal of 120 mmHg utilizing the downloaded recordings available in the electronic medical record.

The primary clinical endpoint is the change in mean 24-hour systolic blood pressure between the start of the study and the end of the study period (4-week period). Secondary outcomes will include the number of patients able to achieve a therapeutic systolic blood pressure of 120 mmHg with both mean BP cuff and in office visit at the end of 4 week period, increase in size as measured by computed tomography (CT) scan of the aorta, hospitalization or emergency room (ER) visits for symptoms from dissection or uncontrolled hypertension,

hospitalization or ER visits for hypotension, all-cause mortality, and need for surgical intervention (open or endovascular).

1.2 Importance and Rationale of Study

Hypertension is one of the leading medical diagnoses and affects close to 30 percent of Americans.[1] Furthermore, data from the NCHS previously illustrated that only 53 percent of Americans had their BP well controlled with medications.[1] Uncontrolled hypertension leads to coronary artery disease, cerebrovascular accidents, congestive heart failure, chronic kidney disease, and retinopathy. The SPRINT trial showed that lowering BP to a goal systolic of less than 120 mmHg reduced both cardiovascular events and deaths.[2] Because of this, it remains a large public health problem that requires effective interventions that can decrease the prevalence of the disease and increase the number of patients with well controlled hypertension.

An intervention that has gained more attention over time is home BP monitoring performed by patients with adjustment of medications made over the phone or at follow-up office visits. In fact, home BP monitoring is a class 1 recommendation in most recent American BP guidelines.[3] Green *et. al* randomized patients with hypertension to either usual care, home monitoring of BP and web site training, or home monitoring of BP, web training, and pharmacist adjustment of medications.[4] They found that patients who received home monitoring, web training, and pharmacist adjustment of medications had significantly better controlled BP than patients who did not receive all three parts of the intervention.[4] Because of studies like this and increasing use of the smart phone, companies such as Withings have created digital BP monitors that directly transmit BP recordings to patients' providers so that they can maintain a log of

recordings performed at home and adjust antihypertensives. However devices like this have not been validated in well-designed randomized controlled trials.

Aortic dissection is one of the most feared complications of uncontrolled hypertension. Patients present with sharp chest pain that radiates to the back and frequently have systolic BP greater than 150 mmHg. While the prevalence is low, it has a very high mortality rate of close to 27 percent.[5] Patients presenting with dissection are classified into two types given their differences in treatment strategies. Type A dissections involve the ascending aorta while type B dissections are defined as originating distally from the left subclavian artery. While type A dissections require emergent surgery, type B dissections are managed medically managed in the absence of complications.

Current guidelines from the thoracic aorta 2010 ACC and AHA state that type B aortic dissection patients should be medically managed with antihypertensives unless they develop "malperfusion syndrome, progression of dissection, enlarging aneurysm, or inability to control blood pressure or symptoms".[5] The guidelines also advocate for a heart rate less than 60 bpm and systolic BP between 100-120 mmHg.[5] However the guidelines do not have any recommendations on how patients' BP should be monitored or controlled once they are discharged from hospital. Currently at our center, we discharge patients with uncomplicated type B dissection with oral antihypertensives and have them return in 6-8 weeks for a follow-up appointment. However, patients do not receive BP cuffs, and therefore upon follow-up visits frequently have systolic BP measurements well above the goal of 120 mmHg systolic.

1.3 Brief summary of relevant literature:

A Medline literature search with the following unique search terms; type B aortic dissection, blood pressure monitoring, home blood pressure was completed in the preparation of this protocol.

The relevant literature was summarized in the rationale section above. Briefly, it is well-established that home BP monitoring improves adherence to antihypertensives and outcomes in patients with hypertension. Furthermore, it is well known that patients presenting with type B dissection have improved outcomes with tighter BP control. However what is unknown is whether digital BP monitoring via a smart phone can improve outcomes in type B aortic dissection patients.

2.0 Study Design, Objective, and Clinical Endpoints

This is a single-center, prospective, randomized study which plans to enroll approximately 100 patients discharged with a principal diagnosis of type B aortic dissection who do not receive a surgical intervention during their index hospitalization and are discharged on medical therapy. All 100 patients will receive a 24 hour home blood pressure cuff with use instructions, at the start of the study. 50 patients will be randomized to standard of care which involves discharge to be performed by discharging team with a prescription for obtaining BP cuff, instructions to take antihypertensives, measure BP at home 3 times a day, call their provider with BP information, follow-up in 2 weeks with a nurse practitioner or physician assistant and follow-up in 4 weeks with a study physician. Nurse practitioners and physician assistants will be given a protocol of the study with in-servicing. 50 patients will be randomized to treatment arm. They will receive a Withings Wireless Digital Blood Pressure Monitoring System with proper instruction of use and training as well as and adjustment of medications done by the study team. Patients will be asked to transmit BP recordings 3 times a day and members of the study team

will call patients and adjust medications on Monday and Thursday of every week. Medications will be adjusted based upon the IRAD registry data with aim of having patients on beta-blockers first line and then the addition of calcium channel blockers, with addition of thiazide diuretics, loop diuretics, or ACEi/ARBS depending on comorbidities and investigator discretion. These patients will have an office visit in 2 weeks with a nurse practitioner or physician assistant and at 4 weeks with a study physician. At the 4 week office-visit all 100 patients will again receive a 24 hour home blood pressure cuff with use instructions. Once these results are sent in, this marks the completion of the study.

2.1 Primary Objective

The primary objective will be evaluating the change in mean systolic 24 hour ambulatory BP measurement from the start of the study to the end of the 4 week period. We will also measure an in office BP measurement at the end of 4 weeks. The protocol for the office BP measurement will be similar to that done in the SPRINT trial, in which the patient will be resting for 5 minutes in a chair and then use the arm with higher systolic pressure with 3 consecutive measurements done from that arm 90 seconds apart. We will use the appropriate circumference cuff and standard digital BP device.

2.2 Secondary Objectives

The secondary objectives include the following:

A) Mortality in 4 weeks

B) Surgical intervention (open or endovascular)

C) Hospitalization or Emergency Room Visit for uncontrolled hypertension or symptoms from dissection

D) Hospitalization or Emergency Room Visit for hypotension

E) Increase in size or progression of dissection as measured on cardiac CT

F) Questionnaire describing patients experience in the study

3.0 Selection of Subjects

3.1 Inclusion/Exclusion Criteria

A) 100 patients discharged from Cleveland Clinic Main Campus with a principal diagnosis of type B aortic dissection (defined as distal from left subclavian artery) who do not receive a surgical intervention during their hospitalization

B) We will include patients only with arm circumference of 9-17 inches

C) We will exclude patients who do not have a smart-phone

4.0 Study Procedures

Prior to the initiation of participation, a signed and dated informed consent and permission to use protected health information must be obtained

4.1 Study Evaluations

Study Procedures	Time Point 1- Baseline (all patients)	Within 24 hours after hospital discharge (all patients)	Time Point 2- Home Monitoring (Hospital discharge thru week 4 clinic appointment) (all patients)	Time Point 3 2 week Follow-Up	Time Point 3 4 week Follow-Up
Informed Consent	X				
Medical History	X				

Review of Baseline CT scan	X				
Review of Last Blood Pressure Measurement Before Hospital Discharge	X				
Review of Medications Before Hospital Discharge	X				
24 hour ambulatory BP monitor		X (Begin next morning after hospital discharge)			X (Begin next morning after 4 week clinic visit)
Blood Pressure Monitoring (as per randomized study group)			X		
Medications Before Discharge	X				
Adverse Event /SAE assessment				X	X
Mean BP performed in Office				X	X
Review lab results				X	X
Vital status/Hospitalizations				X	X
Need for Surgery				X	X
Review repeat CT scan if performed				X	X
Patient Questionnaire					X

5.0 Statistical Analysis and Endpoints

5.1 Sample Size:

This randomized control trial will aim to prospectively enroll 100 patients who are hospitalized with a diagnosis of type B dissection. All patients will be followed for 4 weeks to review vital status, hospitalizations, and BP measurement at the end of the study period.

5.2 Primary Endpoints

The primary endpoint that we will assess will be the mean difference in 24 hour ambulatory SBP from the end of 4 weeks to the start of the study. We will also measure the number of patients in both arms who achieve a mean 24 hour ambulatory systolic BP and in office systolic BP of less than 120 mmHg at the follow-up visit 4 weeks from start of the study. We will perform a student's t test for changes in mean 24 hour BP. We will also perform a Chi-squared analysis to determine the effectiveness of the intervention on BP control in this patient population.

5.3 Secondary Endpoints

Additional endpoints to be considered include:

A) Mortality
B) Surgical intervention (open or endovascular)
C) Hospitalization or Emergency Room Visit for uncontrolled hypertension or symptoms from dissection
D) Hospitalization or Emergency Room Visit for hypotension
E) An decrease in estimated GFR by greater than 30 percent
F) Increase in size or progression of dissection as measured on cardiac CT
G) Mean difference in BP from final BP at discharge to follow-up visit 4 weeks later
H) Patient Responses to Questionnaire completed at the end of the study

5.4 Analytical Plan

Descriptive statistics will be generated for all baseline patient characteristics, complications, and endpoints. Frequency counts and percentages will be used to summarize binary and categorical data. Continuous data will be summarized using means ± standard

deviation, median and interquartile range, and minimum/maximum values. A Chi-squared test will be performed for our primary measurement to examine how many patients meet the systolic BP target of less than 120 mmHg. An $\alpha < 0.05$ will be considered significant.

6.0 Safety Reporting

6.1 Definitions

6.1.1 Adverse Events

An adverse event (AE) is any event, side effect, or untoward medical occurrence in a subject in a clinical trial whether or not it is considered to have a causal relationship to the study drug, device or procedure. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory finding outside of normal range, physical examination finding, or disease temporally associated with the use of the study drug, device or procedure whether or not the event is considered related to the study drug, device or procedure.

6.1.2 Serious Adverse Events

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is defined as any adverse event occurring that results in any of the following outcomes:

1) Death

2) A life-threatening experience

3) Inpatient hospitalization

4) A persistent or significant disability or incapacity

5) A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.3 Documenting and Reporting of Adverse Events

For the purposes of this registry study adverse events that are in the opinion of the investigator, thought to be both serious and unexpected should be recorded in the database.

7.0 Administration

7.1 Maintaining the Security of Patient Data

Data will be stored on in a REDCAP database. There is an instance of this database maintained as a resource at Cleveland Clinic. REDCAP is maintained by Cleveland Clinic but is accessible on and off campus in secure fashion. We will analyze the data using SAS, version 9.4 or other programs as the discretion of the investigators or statisticians. The data will be entered into the database after completion of the procedure. This will be entered in by the investigators. The study principle investigator, co-investigators, statistician(s) and study monitoring staff are the only individuals that will have permission to access the data, and will be able to do so by request.

7.2 Informed Consent

This is a minimal risk, study. The only risk involves the potential risk that patient's BP could be too aggressively well controlled and lead to hypotension. Patients could also have adverse effects from increasing antihypertensives. Patients will be asked to consider enrolling in

this study before discharge from the hospital. They will be provided with written information regarding the purpose of the study and the risk with up titrating antihypertensives. Once all their questions have been answered, patients will be asked to sign an informed consent document prior to agreeing to enroll in the study.

.7.3 Investigator Assurances

The Registry/Database PI is responsible for reviewing and authorizing all requests from others to obtain data from this database. Any additional users, known as Sub-Investigators, must submit to the PI a written request along with a signed Sub-Investigator Statement of Assurance. The PI is responsible for authorizing the release of data to Sub-Investigators and tracking these uses with a brief description of their activity.

The PI confirms no data from this database will be released without a written request from the sub-investigator and that the data provided will not contain identifiers unless consent from subjects has been obtained.

8.0 Monitoring Plan

- Review of all original signed ICFs for completeness and accuracy, including review of the version signed.

- Verify adequate documentation of the informed consent process and perform 100% SDV of the same.

- Source verify CRFs.

- Verify compliance with current regulations and GCP guidelines.

- Review all inclusion and exclusion criteria, SAEs and endpoints for 100% subjects.

Research staff from HVIR will provide monitoring for this study. The below monitoring plan will be implemented once the first subject is enrolled.

The first regular monitoring is to occur within 10 days of the second enrolled patient's baseline visit time point. The primary goal of this monitoring is to assure the study is conducted in compliance with ICH-GCP, ensure subject safety, and validate clinical data against source documents. 100% SDV will be performed on the 1st, 2nd, 3rd, 7th & 10th patients enrolled and then continue with every 5th patient enrolled after that.

Subsequent monitoring will occur on the same patient's listed above once the week 4 study visit is completed.

Monitoring Activities

- Review of all original signed ICFs for completeness and accuracy, including review of the version signed.

- Verify adequate documentation of the informed consent process and perform 100% SDV of the same.

- Source verify data entered into Red Cap.

- Verify compliance with current regulations and GCP guidelines.

- Review all inclusion and exclusion criteria, SAEs and endpoints for the above listed subjects.

- Verify protocol compliance and note any issues for follow-up with the site.

- Verify appropriate subjects are enrolled in the study at the expected accrual rate.

- Review the Signature and Delegation Logs, Subject Identification Logs, Enrollment Logs and Screening Logs.

- Verify that any new staff have been appropriately trained and have signed a Training Log.

- Facilitate data query resolution.

- Verify timely reporting and follow up of adverse events (AEs), serious adverse events (SAEs) and any protocol deviations/violations.

- Verify submission of any SAE to the Institutional Review Board.

- Review of site regulatory files and IRB communication.

- Review of compliance with CC policies and procedures as well as HVIR guidelines..

- Review communication memos sent to the site from the project team.

Data Base-Case Report Form Completion

Only site staff listed on the Signature and Delegation Log are authorized to enter data or make corrections to CRFs/

CRF review will include review for legibility, completeness and consistency with source documents. CRFs should be completed on all subjects that have been randomized.

9.0 References

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