Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
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Main Title
BIOMARKER GUIDED THERAPY IN STAGE A, B HEART FAILURE

ClinicalTrials.gov Identifier: NCT02230891

Background Information
Among all cardiovascular diseases (CVD), heart failure (HF) incidence is projected to increase by the greatest extent over the next 2 decades, with estimates reporting that 8 million people (1 in 33) will have HF by the year 2030 resulting in an annual direct medical cost of ~$53 billion. These estimates may be even higher among the veteran population, in whom there is a high prevalence of cardiovascular risk factors which are the most important antecedent risk factors for HF incidence. While useful treatment options continue to emerge for the management of clinically manifest HF, the prognosis after the onset of clinically manifest HF remains poor. Therefore, prevention of HF is key and has been identified as a major need by the American College of Cardiology (ACC) and American Heart Association (AHA). The ACC/AHA therefore developed a staging system for HF in which they identified individuals at risk for the development of HF as Stage A (those with risk factors such as hypertension and diabetes) or Stage B (those with some structural myocardial changes [for example, left ventricular hypertrophy (LVH)] but without manifest HF) in the hope that early identification of risk would help in the prevention of HF. However, the ACC/AHA classification identifies the majority of the population (~65 75% of a middle-aged population in our analysis) as being at risk for HF. Clearly, not all these individuals develop incident HF. Therefore, further refinement of the ACC/AHA Stage A/B classification, so that the majority of the population is not classified as at risk, will be useful to test preventive strategies in clinical trials. Cardiac troponin T (cTnT), a marker of myocardial damage, has been shown to be associated with HF. Recently, we have shown that cTnT measured with a novel high-sensitivity assay (hs-cTnT) is strongly associated with incident HF (a finding confirmed by other groups) and can significantly improve prediction of HF risk among those with Stage A or B HF. Furthermore, in preliminary data, we show that hs-cTnT levels carry important HF prognostic information in every blood pressure (BP) range, such that individuals with normal BP,s (example systolic BP 120-150 mmHg) but elevated hs-cTnT (ongoing myocardial damage) have a higher HF risk than those with high systolic BP (example systolic BP 150-159 mmHg) with undetectable hs-cTnT, raising the possibility that hs-cTnT can be used to individualize HF prevention by aggressive treatment of risk factors such as BP in individuals with elevated hs-cTnT.
To pursue this further, we propose to evaluate if treating individuals with Stage A or B HF who have elevated hs-cTnT and a systolic BP between 120 and 155 mmHg (a range

where epidemiological studies suggest increased risk but drug studies have not shown any benefit) using 1 of 2 BP-lowering strategies (spironolactone or carvedilol) in a randomized fashion, will result in favorable changes in hs-cTnT and in surrogate markers of HF.
We chose the 2 anti-hypertensive medications for the following reasons:
Evidence to date suggests that an elevation in cTnT is reflective of structural injury to the myocardium (e.g., fibrosis) due to various causes. To make it easier for the myocardium to work and hence try to arrest/decrease the injury to the myocardium, possible approaches to be considered include improving the hemodynamics in the ventricular cavity or the arterial stiffness that the myocardium needs to overcome (i.e., ventricular vascular interaction). However, so far, no data have provided adequate guidance as to therapeutic strategies that may lower cTnT. Recently, we have shown that beta-blocker therapy is associated with marginal reductions/stabilization in hs-cTnT levels in a small population of subjects with prevalent HF. Furthermore, carvedilol has been shown to prevent HF in subjects receiving cancer chemotherapy. Therefore, therapy with beta-blockers, which have shown value in established HF, are associated with decreased cTnT levels, and have shown possible value in prevention of HF related to cancer chemotherapy, seems to be one potential strategy that should be tested.
Increased arterial stiffness has been associated with cardiovascular events including HF. Although no approved agents specifically target arterial stiffness, several agents that are used in the management of hypertension and HF do have an effect on arterial stiffness. Chief among these agents are those that affect the renin angiotensin aldosterone system, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and aldosterone (mineralocorticoid) antagonists, which have been shown to decrease the hypertrophy of vascular smooth muscle cells, result in relatively larger decreases in central BP, result in lesser decreases in diastolic BP, and overall are thought to have an antifibrotic effect. Furthermore, aldosterone antagonists have been shown to improve myocardial strain among hypertensive individuals and diastolic function among individuals who present with HFpEF. Therefore, physiologic and mechanistic studies support the choice of ACE-inhibitors/ARBs and mineralocorticoid receptor antagonists as a way to improve arterial stiffness, which in turn may lead to improvements in cardiac function. Given the routine use of ACE-inhibitors and ARBs as first-line antihypertensive treatment and given that the combination of ACE-inhibitors and ARBs has not shown to be successful, we opted to use aldosterone antagonists in our study.

Purpose and Objectives

Our hypothesis is: In carefully selected subjects with Stage A or B HF (i.e., subjects with elevated cardiac troponin T (hs-cTnT) and elevated 10-year HF risk), augmented therapy for 18 months with the aldosterone antagonist spiroloactone or the nonselective beta-blocker carvedilol will decrease hs-cTnT and be associated with improved cardiac and vascular function compared with subjects treated with usual care.
Our specific aim is to evaluate using a prospective randomized open label blinded end point evaluation (PROBE) study if subjects with stage A or B HF (i.e., individuals at risk for incident HF hospitalization), increased hs-cTnT levels (>5

ng/L), 10-year estimated HF risk >5% and a systolic BP between 120 mmHg and 155 mmHg who receive aggressive treatment with the addition of spironolactone or carvedilol have decreases in hs-cTnT and improved noninvasive measures of cardiovascular function (cardiac and vascular strain) compared with usual care.

Protocol Risks/Subjects
Risk Category

Category 3: Research involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.

Subjects

Gender:
Both
Age:
Adult (18-64 yrs), Geriatric (65+ yrs)
Ethnicity:
All Ethnicities
Primary Language:
English
Groups to be recruited will include:
Asymptomatic patients with chronic conditions, healthy

Which if any of the following vulnerable populations will be recruited as subjects? Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Pregnant woman/fetus
Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

Neonates
Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

Children
Will children be enrolled in the research?
No

Design/Procedure

Design

Select one category that most adequately describes your research:
u) Drug, Phase II, Single Center
Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.
We will use a prospective open label blinded end point (PROBE) design to allow us to conduct our proposed study.
Only veterans will be enrolled in this study. Eligible subjects will be recruited from primary care and cardiology clinics at the MEDVAMC and will include patients in Stage A or B HF whose risk factors (which led to their classification as Stage A/B) are adequately controlled and who have an hscTnT level greater than 5 ng/L and estimated 10 year HF risk greater than 5%.
Eligible indiviudals will be randomized (equal numbers in each group) to spironolactone, carvedilol or usual care.
Randomization will be performed by the research pharmacy at MEDVAMC supported by the Institution For Clinical and Translational research (ICTR) at Baylor College of Medicine using deidentified data.
Subjects who qualify will have hs-cTnT measured using a novel high sensitivity assay along with NT-proBNP. Those with cTnT greater than 5 ng/L and an estimated 10-year HF risk greater than 5%, estimated based on a lab result based model will be eligible to continue in the study and will then have an echocardiogram, carotid ultrasound imaging, and arterial stiffness assessment (pulse wave velocity). The echocardiogram will be interpreted to ensure that there are no clinically significant abnormalities that should be addressed by the subjects physician or that would exclude the subject from the study. The PI will review the images to ensure that they are of adequate quality to allow the measurement of cardiac strain (the primary end point). Those who meet all the inclusion criteria will then proceed to randomization.

RATIONALE FOR CHOICE OF STUDY POPULATION:
Our goal was to choose a population who were at higher risk among individuals with Stage A/B HF so that preventive therapies, if successful, would have a favorable risk vs. benefit ratio. Three important inclusion criteria were considered in the choice of our study population:
1. Systolic BP: We chose a systolic BP category (120 to 155 mm Hg) for many reasons. First, epidemiological data suggest that systolic BP in this range is associated with increased risk, yet studies that have targeted lower BP have not shown benefit. In a recent study describing the current epidemiology of heart failure with preserved left ventricular function (HHpEF), almost 75% of individuals with HFpEF had systolic BP between 110 and 160 mm Hg, and ~55% had systolic BP between 120 and 159 mmHg. Treating patients with systolic BP <120 mm Hg or withholding treatment from those with systolic BP greater than 150 mm Hg will be unethical, and hence we opted for the systolic BP range of 120 to 155 mm Hg.

2. Troponin T value: As we have shown in the ARIC study, hs-cTnT values (especially greater than 5 ng/L) have been associated with significantly increased risk for HF, even after adjusting for age, race, systolic BP, antihypertensive medication use, current smoking, former smoking, diabetes, BMI, prevalent CHD, heart rate (ARIC HF Model) and log NT-proBNP. In the ARIC population aged 55 to 75 years, 60% of the men and 27% of the women had hs-cTnT greater than 5 ng/L. Furthermore, for hs-cTnT values less than 5 ng/L, the reliability of the assay is lower. Therefore, an hscTnT value of greater than 5 ng/L seems to be an appropriate cut point for our study.

3. Estimated HF risk: We have also shown in the ARIC study that using a risk model that includes age, race, hs-cTnT, and NT-proBNP, ~61% of men and ~46.5% of women had an estimated 10-year risk of HF greater than 5%, and ~35% men and 20% women had a risk greater than10%. The inclusion criteria as listed, by requiring both hs-cTnT and estimated HF risk cut points, will result in a more selective group (rather than all Stage A/B HF) in whom the risk vs. benefit profile should be more favorable.

Inclusion Criteria:
1. Age greater than 40 years 2. One of the following in order to establish Stage A HF a. Hypertension b. Diabetes mellitus (controlled: defined as hemoglobin A1c less than 9%) c. Obesity (defined as BMI greater than 30 kg/m2) d. Metabolic syndrome (using the National Cholesterol Education Panel definition) e. Left ventricular hypertrophy (by ECG) f. Coronary or cerebrovascular arterial disease 3. Troponin T measured by the high sensitivity assay of greater than 5ng/L 4. Systolic BP 120-155 mmHg at PCP visit and prerandomization visit (i.e., 2 separate confirmations of the same). If there is dicordance between the PCP visit and pre-randomization we will use one of the following methods as the tie breaker:

1) Take an average of the 3 most recent BP measurements (within the past 6 months) in the subjects electronic medical record
2) Take a 5 day average of home BP measurements recorded by the subject.
3) Bring patient back to recheck their BP.

Not orthostatic with measurements (defined as a fall in systolic BP greater than 20 mmHg when subjects assumes an upright position). Note: If subjects systolic blood pressure is greater than 155 mmHg on date of randomization we will still include him/ her if he/ she meets the above blood pressure criteria.
5. Estimated 10-yr HF risk (based on ARIC HF Lab model) greater than 5% 6. Provides informed consent

Exclusion Criteria:
On the other hand, the exclusion criteria focus on individuals in whom the end point (echocardiogram based measures) will be difficult to ascertain (irregular rhythm, COPD, radiation to the neck/chest) or who have other major comorbidities
1. Current atrial fibrillation 2. History of chest/ neck radiation 3. High-risk chronic obstructive pulmonary disease (COPD) (GOLD classification 3-4 with greater than equalt to 2 COPD exacerbations in the last 12 months) 4. Known allergy to carvedilol or spironolactone 5. Renal insufficiency with eGFR less than 50 ml/min 6. Serum potassium greater than 5 meq/L 7. Current use of carvedilol, spironolactone, any other

beta-blockers or aldosterone antagonists 8. Signs of clinical HF on initial examination (pulmonary rales/crackles, elevated jugular venous pulse with S3/S4 on auscultation) 9. Left ventricular ejection fraction <50% by echo 10. Moderate or greater valve stenosis or regurgitation 11. Hypertrophic cardiomyopathy 12. Exposure to known cardiotoxic chemotherapy 13. Poor echo image quality 14. Right ventricular dysfunction more than mild 15. Any valvular dysfunction that is more than mild 16. Any life threatening disease expected to result in death within the next 2 years 17. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST greater than 3 x ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin greater than 2 x ULN). 18. Participation in another clinical trial involving an investigational agent within 90 days prior to randomization 19. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patients best interest 20. Drug or alcohol abuse within the past 6 months, and unable unwilling to abstain from drug abuse and excessive alcohol consumption during the study. Excessive alcohol consumption is on average greater than 2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80]proof alcohol for drinks. 21. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study. 22. Any immnuosuppressed condition where intercurrent illnesses may affect interpretation of study results 23. Pregnant women or any woman planning a pregnancy during the study period 24. Not meeting any of the inclusion criteria

Procedure

As per VA regulations, the health record of the subject will be flagged to indicate that he/she is participating in a research study.

Prerandomization Visit: During this visit, inclusion and exclusion criteria will be reviewed to ensure that subject eligibility. The informed consent document will be reviewed with those eligible for the study and willing to participate. We will answer all their questions and then if the subject is still interested have them sign the informed consent form. Baseline labs including a comprehensive metabolic panel, lipid panel, and hemoglobin A1C will be assessed (unless labs within 3 months are available). Additional blood will be stored for future biomarker analysis. These blood samples will be stored in the Research commons freezer or the Winters Center freezers located in building 110 at the MEDVAMC. The biomarker analyses to be performed will be based on additional funding that will be obtained as the current grant that supports this study will not have adequate funds to run additional biomarkers. Hence while related to the study in that all the data from this study will be used, the funding is to be obtained in the future and the biomarkers to be decided in the future. Blood from only those who meet the troponin inclusion criteria and who are ultimately randomized to this study will be stored. The others will be discarded.

Randomization visit and titration of medications: After the pre-randomization visit, those individuals who meet the inclusion criteria including hs-cTnT levels, HF risk score will come for the randomization visit. A history (medical, surgical, social, family and medication history and review of systems) and physical examination will be performed, and the findings will be documented on the case report form. The physical examination

would include BP measurements (3 taken 2 minutes apart). Orthostatic BP measurements will be performed as well. We will use calibrated BP machines in the clinic for the purpose of the study. They will have a 2D and 3D echocardiogram with Doppler. Those with adequate images for cardiac strain assessment will then be randomized to one of the 3 groups. Randomization will be achieved with the help of the research pharmacy and ICTR (institute for clinical and translational research). Randomization will be stratified for age, presence of CHD, ACE-inhibitor/ARB use, and hs-cTnT levels greater than14 ng/L. In addition to an echocardiogram, a carotid ultrasound and a pulse wave velocity assessment will be performed at the randomization visit

Subjects randomized to the spironolactone group will be started at 25 mg daily, and titration up to 50 mg daily will be attempted (blood pressure, potassium levels permitting). Briefly, subjects will start taking their medication and 2 weeks later return for a brief visit when BP and potassium will be checked. If BP is greater than 125 mm Hg, spironolactone will be increased to 50 mg daily. Once maximum dose is achieved, serum potassium will be measured to ensure stability. For those randomized to spironolactone who have eGFR between 50 and 60 ml, medication will be started at 12.5 to 25 mg daily and then potassium, renal function measured at 2 weeks and 6 weeks and medication titrated based on results. In addition for those subjects with blood pressure on the lower side (120-130 mmHg systolic) or per principal investigators discretion spironolactone may be started at 12.5 mg daily for the first few days to ensure safety/ tolerability and then increased to 25 mg daily.

Subjects in the carvedilol group will similarly be started at 6.25 mg PO 2 times daily and titrated up to a maximum dose of 25 mg PO 2 times daily, again monitoring BP. Titration will be continued provided the systolic BP is >125 mm Hg. In addition for those subjects with blood pressure on the lower side (120-130 mmHg systolic) or per principal investigators discretion carvedilol may be started at 3.25 mg two times daily for the first few days to ensure safety/ tolerability and then increased to 6.25 mg two times daily.

Subjects in the usual-care group will continue receiving treatment from their primary care physician. However they will be required to come to the research clinics at baseline, 6 months, 12 months and at the end of study when history, physical, blood biomarker collection and imaging will be done similar to the carvedilol/ spironolactone treatment groups.

Visit 2: Subjects randomized to the spironolactone or carvedilol groups will come back for a 2-week visit, when they will have their BP checked and medications titrated if required. Those in the spironolactone arm will also have their serum potassium measured. As noted above for those on spironolactone and eGFR between 50-60 ml, potassium and renal function will be repeated at 6 weeks as well. Subjects may be called by the research coordinators approximately every 8 weeks for the first 6 months to enquire about tolerability and compliance. In addition this may help with subject retention.

Visit 3: All subjects will return at 6 months. During the 6-month visit, all subjects will have a history and physical examination completed, and blood will be collected and part stored. Additionally, subjects will be interviewed about clinical events, including hospitalization, during the 6-month interval. Medication compliance will be assessed at this visit. Those on spironolactone will have their potassium checked

Visit 4: The 12 month visit will be identical to the 6 month visit

Visit 5: The final visit will capture details as in visit 3 and 4 but in addition also include all the imaging studies (echocardiogram, carotid ultrasound and pulse wave velocity measurement). Blood will be collected as well for biomarker assessment and additional samples stored for future research.
Subjects will be encouraged and requested to call/ notify us about any adverse events including side effects to medication, hospitalization, emergency room or urgent care visits. If there are any hospitalizations/ emergency room/ urgent care visits we will obtain information from the VA electronic medical record or from the hospital/ emergency room where they were cared for. There will be both paper and electronic data that will be nearly similar. The paper data will include the following HIPPA identifiers: name, date of birth, age, last four of the social security number, date of hospital admissions, date of discharge and any date of clinic visit during the duration of the study as well as participant address, phone number and email ID (if available). The electronic data stored at the VA will include name, last 4 of the social security number, date of birth, date of hospital admissions, date of discharge, any date of clinic visit and the research ID during the duration of the study. Electronic data stored in the BCM database which will be used for analysis will not have any HIPAA identifier and will include all other information. Data will be stored such that date of consent will be called "Day 0" and then other study events will be time stamped relative to the date of consent (example 6 month visit will be day 180 and so on). A date of birth will not be noted, but subject age will be recorded as this will be important in data analysis.

Sample Size/Data Analysis
Sample Size
How many subjects (or specimens, or charts) will be used in this study?
Local: 850 Worldwide: 850
Please indicate why you chose the sample size proposed:
Data on change in strain with various medications are limited. However, a 1 to1.5% absolute difference in longitudinal strain has been associated with outcomes.Therefore, assuming a conservative standard deviation of 3% (as described in studies), an alpha of 0.05, and a power of 0.8, we would require approximately 62 subjects per group. Therefore, a sample size of 205 210 subjects should be a reasonable estimate (accounting for an approximately 10% drop-out rate)

Data Analysis
Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance).

Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Primary analysis: To better inform the analyses planned, descriptive statistics (means and standard deviations of continuous variables and frequency of discrete variables) of subjects demographic characteristics and echocardiogram, vascular ultrasound, and biomarker variables will be computed at each measurement time and compared among the usual care and two drug treatment groups. All analyses will be conducted using the intention-to treat(ITT) principle. Statistical tests with a 2-sided P-value less than 0.05 will be considered statistically significant. When multiple comparisons are involved, Bonferroni correction for the type I error will be applied. Each continuous primary and secondary outcome will first be examined for its normality using the Shapiro Wilk test. When normality is verified, an analysis of variance (ANOVA) approach will be used to compare the mean change among the usual care and two drug treatment groups. Pairwise comparisons between the usual care and each of the drug groups will also be performed using the least significant difference method under the ANOVA framework. When the normality assumption is violated, the Kruskal Wallis nonparametric test will be applied.
Secondary Analysis: For each of the primary and secondary end points, the longitudinal mixed-effect model will be applied to compare the slope differences among the usual care and two drug treatment groups with and without adjusting baseline covariates. The main model can be described as mean outcome at time t = b0 + b1*t + b2* group + b3* t*group. The within-subject correlation structure will be assumed to follow spatial power correlation structure because of its uneven observational time intervals. The generalized estimation equation method will be used to perform the analysis. Secondary, exploratory analyses will be performed to evaluate prespecified subgroups; we will test changes in cardiac and carotid strain in responders (e.g., those whose cTnT levels stayed stable or decreased, those whose hs-cTnT levels were greater than 14 ng/L at baseline, those whose estimated HF risk was greater than 10%) in comparison with nonresponders.

Potential Risks/Discomforts

Potential Risks/Discomforts
Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

1. Medications: Carvedilol and spironolactone are clinically used, generally well tolerated with limited side effects. Both medications lower blood pressure which will be closely monitored. Spironolactone can lead to hyperkalemia (increased potassium levels) and at higher doses can cause gynecomastia (mostly reversible). However we are excluding individuals with renal insufficiency and using lower dose spironolactone which will decrease the risk of these occurrences. Furthermore for those on spironolactone we will check their potassium levels after starting the medication and during each study visit. With carvedilol other than lower blood pressures and possibly a slower heart rate no other significant side effects are anticipated. Idiosyncratic reactions such as allergies to medications etc. are possible

2. As with any clinical study despite our best efforts, loss of confidentiality is possible
3. The imaging tests are predominantly clinically used ultrasound based and have negligible side effects. Heating of tissue is a possibility with ultrasound imaging but we will not exceed the industry recommended standards. Subjects will be lying down when the studies are done and given that we will require approximately 40-45 minutes to complete the studies physical discomfort from lying down is possible in some of the subjects. The arterial stiffness measurement (pulse wave velocity) just involves tracking the pulse with a hand held tonometer in the arm and the groin (femoral artery) and has no known side effects other than momentary discomfort
4. Some individuals may be allergic to the stickers used to connect ECG leads and if placed in a hairy area of the chest may result in some pain when removing them
5. Given this is a study that will include individuals greater than 40 years of age, women of child bearing potential will be eligible for recruitment. Any woman who has child bearing potential and is interested in participating in the study will need to undergo a pregnancy test (urine) and only if negative will be eligible for the study. Furthermore, we will discuss and require that they have a contraception plan in place in order to participate
6. Finally with blood draws the usual possibilities including feeling faint/ fainting/ infection and pain exist but not any more than that which will happen during routine clinical care

Safety measures: The study drug will be discontinued in subjects with any allergic reaction to the study drugs or side effects from these drugs. In subjects receiving spironolactone, serum potassium will be monitored prior to each dose change and within 7 to 14 days after a dose change. Potassium supplements will be stopped before the start of spironolactone and will be allowed only if the serum potassium is less than 4.0 mEq/L after the study drug is started.
The spironolactone dosage will be adjusted based on the following algorithm which has been used in other clinical studies: if serum potassium is greater than or equal to 5.0 mEq/L but less than 5.5 mEq/L, the dose will not be increased; if serum potassium is greater than or equal 5.5 but less than 6.0 mEq/L, the dose will be reduced by half; if serum potassium is greater than or equal to 6.0 mEq/L, spironolactone will be stopped but could be restarted at the lowest dose if a correctable underlying condition for hyperkalemia is readily identified and serum potassium is reduced to less than 5.0 mEq L. For those individuals with eGFR between 50 and 60 ml, an additional lab test will be done at 6 weeks to follow up on renal function and potassium For subjects receiving carvedilol, any symptomatic bradycardia or atrioventricular blocks greater than first degree will result in stopping the medication. Additionally, any symptom of low BP (e.g., dizziness) that is bothersome to the subject will result in stopping the medication. A data safety monitoring board has been assembled (VA hospital, Chicago) and will oversee the study safety.

Data and safety monitoring plan
Do the study activities impart greater than minimal risk to subjects?
Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H – Data and Safety Monitoring Plan' as an attachment in Section S.
H3. Coordination of information among sites for multi-site research
Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?
No or Not Applicable
Is BCM the COORDINATING CENTER for this multi-site research?
No or Not Applicable

Potential Benefits
Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.
There are NO direct benefits to the subject that are anticipated.

Describe potential benefit(s) to society of the planned work.
Cardiac troponin T has been identified as an excellent marker of incident cardiovascular disease including heart failure. Currently there is no known therapeutic strategy in which asymptomatic individuals with elevated troponin T. Our strategy aims to test 2 anti-hypertensive medications at blood pressure ranges where treatement is not pursued usually. If positive this study may in the future help identify a strategy that could be valuable in the prevention of incident CHF

Do anticipated benefits outweigh potential risks?

Discuss the risk-to-benefit ratio.
Overall the 2 medications being used (spironolactone and carvedilol) are routinely used medications in the management of hypertension/ heart failure with a good safety record. The only additional risk in our study is that the blood pressure ranges where we initiate the medications are not ranges where treatment is usually recommended.
However, prior studies have used anti-hypertensive medications in this range of Blood pressures with no serious adverse consequences. Additionally we have a data and safety monitoring board who will be monitoring the study. Identification of approaches to lowering troponin T levels or at least identifying approaches in those with elevated troponin levels is an important step in finding ways to prevent heart failure. The benefit from a scientific stand point is therefore large.
Therefore, in sum, the overall benefits outweigh the risks.

Consent Procedures

J1. Waiver of Consent
Will any portion of this research require a waiver of consent and authorization?
Yes
Please describe the portion of the research for which a waiver is required. (Example: chart review to determine subject eligibility)

A waiver of consent is being requested ONLY for eligibility screening. It is anticipated that the recruitment of subjects will take place in the clinics of the principal investigator and co-investigators.

Explain why the research and the use or disclosure of protected health information involves no more than minimal risk (including privacy risks) to the individuals.
If a subject is not eligible, only limited information (last name, first name, last 4 of social security number and reason for ineligibility) will be noted and stored in a password protected folder on the drive. Only the PI and the research coordinator(s) will have access to this folder. Medical record review will be conducted by the PI and/or the research coordinators only to assess for eligibility.

Explain why the waiver will not adversely affect the privacy rights and the welfare of the research subjects.
If a subject is not eligible, only limited information (last name, first name, last 4 of social security number and reason for ineligibility) will be noted and stored in a password protected folder on the drive. Only the PI and the research coordinator(s) will have access to this folder. Medical record review will be conducted by the PI and/or the research coordinators only to assess for eligibility.

Explain why the research could not practicably be conducted without the waiver and could not practicably be conducted without access to and use of the protected health information.
Given the number of inclusion and exclusion criteria and the number of subjects to recruit it would not be feasible to obtain our analysis power without the use of medical record screening
Describe how an adequate plan exists in order to protect identifiers from improper use and disclosure. PHI will be stored in a password protected database on MEDVAMC's research drive in which only the coordinator and PI will have access. The primary analysis (cardiac strain) will be done using a software (Tomtec) which is loaded on a laptop which has been purchased for the study. The laptop is password protected. The laptop will be stored in a locked cabinet in the office of the PI

Describe how an adequate plan exists in order to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
VA has not yet obtained an approved Records Control Schedule for facility research data, data collected in this VA research study, including identifiers will be maintained indefinitely by the VA facility until an applicable schedule is approved by NARA.

Describe how adequate written assurances exist in order to ensure that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
The requested information will be protected from improper use and disclosure and will not be reused or disclosed to any other person or entity, except as required by law, for

authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule.
Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes
Specific information concerning alcohol abuse:
Yes
Specific information concerning drug abuse:
Yes
Specific information concerning sickle cell anemia:
No
Specific information concerning HIV:
No
Specific information concerning psychiatry notes:
No
Demographic information (name, D.O.B., age, gender, race, etc.):
Yes
Full Social Security #:
No
Partial Social Security # (Last four digits):
Yes
Billing or financial records:
No
Photographs, videotapes, and/or audiotapes of you:
No
Other:
No
Will additional pertinent information be provided to subjects after participation?
No
If No, explain why providing subjects additional pertinent information after participation is not appropriate.
Subjects will not be provided any information as this is only a screening for inclusion/ exclusion criteria to determine eligibility. Those not eligible will not be contacted while those eligible will be contacted to determine interest in the study. Those interested will then be provided with the informed consent form and will be provided with study details.

Waiver of requirement for written documentation of Consent
Will this research require a waiver of the requirement for written documentation of informed consent?
No
Consent Procedures
Who will recruit subjects for this study?
PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.
We will screen for subjects at 3 main clinic areas: a. the medicine clinics at MEDVAMC and b. the cardiology clinics at MEDVAMC. c. the endocrinology clinics at MEDVAMC
Our research co-ordinators will review daily out patient visits at the clinics of the PI and his co-investigators and identify potential subjects to approach and discuss the study. In addition we will describe the study and its goals to various primary care providers and ask them to inform their patients about our study so that interested individuals can contact us. Then, the research co-ordinators will approach the subject and ask if they are interested in learning about the study. To those interested a description of the study, its requirements, and details related to subject participation, visits and risks will be discussed in detail. They will be provided with the consent form and have an opportunity to review the same. The consent form will also be discussed by the study co-ordinator with the subject. Any questions that may arise will be answered by the co-ordinators. Then the subject will, if interested, be asked to come to the pre-randomization visit when we will answer any other questions they have. Then we will request the subject to sign the consent form.
Then their blood will be sent to the Atherosclerosis laboratory at BCM where the high sensitivity troponin assay will be done. We anticipate that these lab assays will be done on a weekly or bi-weekly (once in 2 weeks) basis. Then, if the patient qualifies based on this we will randomize them. The biomarkers to see if the subject qualifies for the study and also to study the effect of therapy (namely troponin T and NT proBNP) will have to be done at the Atherosclerosis labs at BCM as troponin assay we use (a high sensitivity assay) is currently only research and not available clinically.
Similarly other future markers done as research may need to be done at Baylor.
Samples sent to BCM will only have a research ID and study week. There will be no HIPAA identifiers. For example, subject #1,s coding on the blood sample
may read VAHFP0001W1 where VAHFP is the general study ID, 0001 is the subject ID and W1 states that it is the first sample. A code for this to identify the subject will be maintained at MEDVAMC under password protection. Please note that we may change the general study ID (i.e. VAHFP) to a similar alternative if other similar stems already exist to avoid confusion.

Are foreign language consent forms required for this protocol?
No
J3. Privacy and Intrusiveness
Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No
J4. Children
Will children be enrolled in the research?
No
J5. Neonates
Will non-viable neonates or neonates of uncertain viability be involved in research?

No
J6. Consent Capacity - Adults who lack capacity
Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No
J7. Prisoners
Will Prisoners be enrolled in the research?
No
Section K: Research Related Health Information and Confidentiality
Will research data include identifiable subject information? Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes
Specific information concerning alcohol abuse:
Yes
Specific information concerning drug abuse:
Yes
Specific information concerning sickle cell anemia:
No
Specific information concerning HIV:
No
Specific information concerning psychiatry notes:
No
Demographic information (name, D.O.B., age, gender, race, etc.):
Yes
Full Social Security #:
Yes
Partial Social Security # (Last four digits):
Yes
Billing or financial records:
No
Photographs, videotapes, and/or audiotapes of you:
No
Other:
No
At what institution will the physical research data be kept?
Physical research data will be stored and locked in the research/PI offices at MEDVAMC. Physical Data will be kept in locked cabinets which only the PI/ research staff have access to via key
How will such physical research data be secured?
Sensitive paper data will be stored and locked in the research/PI offices in the section of Cardiology at MEDVAMC

At what institution will the electronic research data be kept?

The electronic data will be stored at MEDVAMC and on web based platform hosted by BCM. Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
Yes
Such electronic research data will be secured via
Other:
Yes, (describe below):
Data will be kept secure in password protected files behind a secure VA network server Strain analysis and pulse wave analysis are done through independent software on laptops. These laptops will be secured in locked cabinets in the PI's office or research office.

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
Yes, identify the classes of the persons:
People who ensure quality from the institutions where the research is being done, federal and other regulatory agencies will have access to all of the research data.
Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
All data entered into the eCRFs are transmitted over secure encrypted channels to the ICTR database server.
For statistical analysis- data will be transferred. Data will be transferred through email for statistical analysis and will be as EXCEL spreadsheets (echocardiogram data analyses, pulse wave data analysis, biomarker data as obtained from Baylor College of Medicine, subject baseline and follow up characteristics including labs, AE/ SAE).
Only subject research ID (example HB 01, HB 02 along with possibly a suffix A or B to identify randomization visit vs. end of study information) will be there as an identifier. No specific patient/ subject related ID (example date of birth, social security number) will be included in the data transferred
A copy of the data will be sent to the MEDVAMC Privacy Officer to confirm no identifiers are present before transferring to sponsors and/or collaborators.

Will you obtain a Certificate of Confidentiality for this study?
No
Please further discuss any potential confidentiality issues related to this study.
Research records, including identifiers will be destroyed 6 years after cutoff (at the end of the fiscal year) after completion of the research project, but may be retained longer if required by other federal regulations or sponsor archive requirement.
The purpose of collecting information covered under 38 U.S.C. 7332 is to conduct scientific research and no personnel involved in this study will identify, directly or indirectly, any individual patient or subject in any report of such research. It is understood by the PI that data will not be used or shared with others outside the scope of the research study as documented in the protocol approved by the IRB and MEDVAMC R&D committee. Removal of access to research study data will be accomplished for all study personnel when they are no longer part of the research team.

An Accounting of Disclosure (AOD), will be created and maintained for any disclosure of individually identifiable information (III), outside the VA. The manual spreadsheet will include the data of the disclosure, nature or description of the III disclosed, purpose of each disclosure and the name and address of the person or agency to which the disclosure was made.

Cost/Payment
Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
There will be no costs to the subject. This study is sponsored through a VA MERIT grant award and subjects will be recruited exclusively at the MEDVAMC. The echocardiogram, measures of pulse wave velocity, drug (spironolactone/ carvedilol), measurement of troponin and BNP tests are all research
If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.
Dollar Amount:
125
Distribution Plan:
There are 5 visits. For each visit we will provide the subject with $25 to defray the expenses of travel and food. The money will be paid by cash after the subject has completed the visit

Genetics
How would you classify your genetic study?
Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.
Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Sample Collection
SAMPLE: Blood
What is the purpose of the sample collection?
The purpose of sample collection is 1. Biomarker assay which will qualify the patient for the study and is required to see the effect of therapy 2. Storage of blood for future possible biomarker studies. The biomarkers to see if the subject qualifies for the study and also to study the effect of therapy (namely troponin T and NT proBNP) will have to be done at the Atherosclerosis labs at BCM as troponin assay we use (a high sensitivity

assay) is currently only research and not available clinically. Similarly other future markers done as research may need to be done at Baylor. Samples sent to BCM will only have a research ID and study week. There will be no HIPAA identifiers. For example, subject #1,s coding on the blood sample may read VAHFP0001W1 where VAHFP is the general study ID, 0001 is the subject ID and W1 states that it is the first sample. A code for this to identify the subject will be maintained at MEDVAMC under password protection. Please note that we may change the general study ID (i.e. VAHFP) to a similar alternative if other similar stems already exist to avoid confusion.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
Blood will be collected at baseline, after starting spironolactone, any titration of dose, at 6 months, 12 months and study end. At baseline, 12 months and study end we will collect 8 teaspoons while after starting spironolactone/ titration of dose/ 6 months we will draw adequate blood to check a basic metabolic panel (~ 2 teaspoons). In all this makes the total blood collection during the study period to be 24-30 teaspoons

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Clinical Labs, Other: Research co-ordinator
Will the sample be stripped of identifiers?
No

If sample will be released outside the hospital:
Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
There are no plans at this time to release the samples to investigators not on the protocol

Will sample material be sold or transferred to any third parties? Will the information be de-identified?
No sample will be sold

If sample will be banked for future use:
Where will the sample be banked and for how long?
The samples will be stored in the freezer farm at the VA research buildings and will be stored for the duration of the study. Additional biomarker testing may be done (depending on obtaining funding) by the research team involved in this study

Does the banking institution have an approved policy for the distribution of samples?
NA: there will be NO distribution of samples. Future research will be done only by this study team

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
The samples will be stored for the duration of the study and the extra sample (if any) will be discarded

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:
Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
If the subjects withdraws/ revokes authorization his/ her sample will not be used and will be discarded

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
If the subject has not completed the study the sample will be deleted for analysis. If the subject completed the study and revokes authorization we will not use the data for analysis

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
The results of the potassium will be available on the patients chart (CPRS). Other research specific data/ biomarker will not be available to other subjects

Please identify all third parties, including the subject's physician, to receive the test results.
Anyone with authorized access to the patients chart on CPRS (the electronic medical record) will be able to review the potassium result when spironolactone is started/ dose changed and at 6, 12 and 18 months. No other data will be made available to the subjects physician

SAMPLE: Urine
What is the purpose of the sample collection?
Urine will be collected for a pregnancy test only in women of child bearing potential.
For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
Not applicable
Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Clinical Labs
Will the sample be stripped of identifiers?
No
If sample will be released outside the hospital:
Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
The sample will not be released
Will sample material be sold or transferred to any third parties? Will the information be de-identified?
The sample will not be sold or transferred to anyone else
If sample will be banked for future use:
Where will the sample be banked and for how long?
The urine sample will not be banked
Does the banking institution have an approved policy for the distribution of samples?
Not applicable
If the entire sample will NOT be used during the course of this research study:
Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
The remaining sample will be discarded per VA lab policies
Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No
If a subject withdraws from the study:
Will subject have the option to get the remaining portion of their sample back?
No
Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
Samples will be discarded immediately after the urine pregnancy test is completed as per VA lab policies (as with any other clinical sample)
Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
The results of the test will be part of the medical record in CPRS and will not be deleted
Will study data or test results be recorded in the subject's medical records?
Yes

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
The urine pregnancy test result will be discussed with the patient and since available in the medical record can be accessed by the patients physicians

Please identify all third parties, including the subject's physician, to receive the test results.
The test results will be available to anyone who accesses the patients medical records

Drug Studies
Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a
pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)
Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?
No
O1. Current Drugs
Drug : carvedilol
Drug : spironolactone
Is this study placebo-controlled?
No
Will the research involve a radioactive drug?
No

Device Studies
Does this research study involve the use of ANY device?
No

Advertisements
None