Protocol

1. Project Title
Pressure Assessment to Improve Outcomes after TAVR: a registry

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3. Abstract:
At the Malcom Randall Veterans Affairs Medical Center (MRVAMC), intra-cardiac pressures are routinely recorded after transcatheter aortic valve replacement (TAVR) procedures. Our research has disclosed that patients with abnormal hemodynamics (narrow aortic to ventricular end-diastolic pressure difference, indexed to heart rate) suffer from high long-term mortality, compared with patients with normal hemodynamics. Hypertension and diastolic dysfunction are highly co-morbid conditions among these patients. The selective aldosterone receptor antagonist eplerenone (Inspra) is approved for use in the treatment of hypertension. Research also supports that eplerenone may be able to improve diastolic function.

This prospective registry is interested in determining 1) the tolerability of eplerenone, and 2) feasibility of administering the Kansas City Cardiomyopathy Questionnaire (KCCQ) among patients with abnormal hemodynamics after TAVR. This registry will set the stage for a pilot randomized trial to evaluate eplerenone versus placebo among patients with abnormal hemodynamics after TAVR.

4. Background:
Our research has disclosed that patients who have abnormal hemodynamics (narrow aortic to ventricular end-diastolic pressure difference, indexed to heart rate) after TAVR suffer from poor long-term survival. This hemodynamic value can be referred to as the aortoventricular index (AVi). In a single center observational study, the 2-year mortality rate for patient with a value ≥0.6 mm Hg/bpm was 25% compared with 36% for patients with a value <0.6 mm Hg/bpm. An abnormal AVi was an independent predictor for poor survival. Hypertension and diastolic dysfunction are 2 highly co-morbid conditions among these patients. Currently, there is lack of appreciation that pressure measurements obtained at the time of TAVR can provide long-term prognostic value. There is also a lack of understanding on how to improve outcomes and quality of life among such patients.

Eplerenone is a selective aldosterone receptor antagonist approved for use for treatment of hypertension. Animal studies have shown that aldosterone receptor antagonists can decrease interstitial myocardial fibrosis. The non-selective aldosterone receptor antagonist, spironolactone 25 mg daily compared with placebo was shown to improve diastolic function, as assessed by echocardiography, among 28 elderly

subjects. A meta-analysis of eleven studies in 942 subjects found that aldosterone receptor antagonists improve diastolic function and markers of cardiac fibrosis without significant changes to left ventricular mass or dimensions. In a randomized controlled trial, eplerenone was found to be safely tolerated among asymptomatic patients with moderate to severe aortic stenosis.

The purpose of this registry is to set the stage for a pilot randomized trial to test our ultimate hypothesis that eplerenone versus placebo can improve survival and quality of life among TAVR patients documented to have abnormal hemodynamics. The KCCQ is a validated research tool to measure health status (physical limitation, symptom frequency, quality of life, and social limitation) among patients with aortic stenosis and heart failure symptoms.

5. Specific Aims:

1) Determine the tolerability of eplerenone among patients with abnormal hemodynamics and hypertension after TAVR.
2) Determine the feasibility of administering the KCCQ-12 at baseline and 8 weeks to asses quality of life.

6. Research Plan:

1) Enroll 25 subjects with hypertension and abnormal hemodynamics after TAVR.
2) Enrollment for non-local subjects will occur remotely with telephonic consent and mailing of the questionnaire and study drug. Enrollment for local subjects will occur remotely or in-person.
3) This is a greater than minimal risk study.
    a. Inclusion criteria:
        i. TAVR procedure performed at the Malcom Randall VA Medical Center within the last 2 years.
        ii. Intracardiac pressures recorded 5 to 10 minutes after TAVR and AVi < 0.6 mm Hg/bpm.
        iii. History of hypertension, taking anti-hypertensive medications, or recent systolic blood pressure ≥130 mm Hg.
    b. Exclusion criteria:
        i. Serum potassium >5.5 mEq/L at initiation.
        ii. Concomitant administration of strong CYP3A inhibitor (i.e. ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir).
        iii. Serum creatinine >2.0 for men and >1.8 for women.
        iv. Creatinine clearance <50 cc/min.
        v. Concomitant administration of potassium supplements or potassium-sparing diuretics.

4) Subjects who are eligible to participate and signed an informed consent will be given eplerenone 50 mg daily. Study drug (eplerenone) will be paid by the North Florida Foundation for Research and Education for the duration of the study.
    a. Down-titration or termination of non-essential anti-hypertensive agents is permissible so that eplerenone does not result in hypotension. Essential medications are as follows:
        i. Angiotensin converting enzyme inhibitors (ACE-inhibitors) or angiotensin receptor blockers, if intolerant to ACE-inhibitors are indicated for treatment left ventricular dysfunction (i.e. left ventricular ejection fraction ≤40%), diabetes, and proteinuric chronic kidney disease.
        ii. Beta-blockers are indicated 3 years after an acute myocardial infarction, unless there is persistent left ventricular dysfunction (i.e. left ventricular ejection fraction ≤40%).
5) Monitoring.
    a. Serum potassium within the last 30 days is required before initiating eplerenone. Repeat blood draw is required within the first week, and one month after the start of treatment with eplerenone.
    b. An order will be placed for the blood draws to be performed at the subject's local VA community-based outpatient clinic or hospital.
    c. Blood pressure will be recorded in the research office for local subjects and through the primary care provider for non-local subjects at 8 weeks.
6) Quality of life questionnaire.
    a. The Kansas City Cardiomyopathy Questionnaire (KCCQ-12) will be administered at baseline and 8 weeks. The KCCQ-12 instrument will be mailed to all subjects. Local subjects will be given the opportunity to complete the questionnaire in the research office, if they prefer. Study coordinator will call the subject at 8 weeks to confirm vital status, assess if any adverse reactions from eplerenone, and provide assistance to completing the KCCQ-12, if needed.

7. Possible Discomforts and Risks:

Blood draw:
The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure. The risk from a blood draw is considered top be minimal.

Study medication:
Eplerenone is a Food and Drug Administration approved medication for treatment of hypertension. Eplerenone was documented to be safely tolerated among patients with moderate to severe asymptomatic aortic stenosis. This medication can increase serum

potassium which will be monitored at baseline, 1 week and 4 weeks after initiation. Possible adverse reactions include: headache, dizziness, diarrhea, stomach pain, chest pain, nausea, cough or flu-like symptoms (such as fever, chills, body aches, or unusual tiredness), vaginal bleeding, breast swelling/tenderness, or rash.

Questionnaire: Possible emotional discomfort when answering some of the questions; however, this risk is exceeding small.

Confidentiality: Confidential information about subjects might be accidentally disclosed. We will use our best efforts to keep the protected health information secure. The risk of accidental disclosure is exceeding small.

8. Possible Benefits:

Subjects might breath better, have more energy, and have better control of their blood pressure from taking eplerenone. Subjects might also enjoy the satisfaction of participating in a research project that could ultimately help others.

9. Conflict of Interest:

No conflict of Interest