**Introduction**

Heart failure with preserved ejection fraction (HFpEF) constitutes up to half of heart failure hospitalizations with a similar prognosis as heart failure with reduced ejection fraction. Despite multiple randomized clinical trials over the last decade, there have been no identified therapies that improve mortality in HFpEF. A possible explanation for this is heterogeneous nature of the disease with multiple associated co-morbidities and often multiple organ systems affected. Developing a phenotypic framework to better understand HFpEF has been an area of active investigation with proposed strategies including stratification based on clinical presentation to more sophisticated methods such as machine learning techniques.

Beginning in 2014, the JHU HFpEF Clinic has been clinically phenotyping HFpEF patients based on their predominant co-morbidity profile, with common phenotype classifications including: hypertension (HFpEF-HTN), metabolic syndrome (HFpEF-MetS), coronary artery disease (HFpEF-CAD), pulmonary hypertension (HFpEF-PH), and chronic kidney disease (HFpEF-CKD). Within this cohort, cardiac amyloidosis (HFpEF-CAM) is now increasingly recognized as a relevant HFpEF phenotype, diagnosed in 14% of HFpEF patients referred for right heart catheterization and endomyocardial biopsy. To date, the concept of clinical HFpEF phenotyping has been proposed in the literature, however there have been no studies to assess differences in clinical presentation, functional capacity, frailty, and clinical outcomes by HFpEF phenotypes. And while dyspnea and exercise intolerance are ubiquitous in HFpEF, the mechanisms underlying these key symptoms are poorly understood across different HFpEF phenotypes.

The overarching goal of this proposal is to compare differences in baseline characteristics, clinical presentation, functional capacity, frailty, imaging, and rest and exercise hemodynamics across clinically based HFpEF phenotypes and assess for correlation of these parameters with clinical outcomes. With greater insight into clinically relevant HFpEF phenotypes, it may be possible to better target HFpEF therapies.

**Specific Aims**

**Aim 1:** To compare demographics, clinical presentation, echocardiographic parameters, rest hemodynamics, 30-D heart failure hospitalization, and 1-y survival in 3 HFpEF phenotypes: HFpEF-HTN, HFpEF-MetS, and HFpEF-CAM.

**Hypothesis 1:** We hypothesize that HFpEF-MetS patients will be younger, have a greater burden of co-morbidities, however comparable outcomes to HFpEF-HTN. We hypothesize that HFpEF-CAM patients will be older, with fewer co-morbid conditions, more structural left-sided heart disease on echocardiogram, and worse outcomes (survival at 1 year) compared to other HFpEF phenotypes.

**Methods 1:** We will retrospectively analyze data in RedCap from the JHU HFpEF Clinic Registry (N=221). HFpEF-HTN was defined by systolic blood pressure $\geq 150$ mmHg or taking $\geq 2$ anti-hypertensive medications (not including diuretic), no history of diabetes mellitus, and a BMI $\leq 35$ kg/m$^2$. HFpEF-MetS was defined by BMI $\geq 35$ kg/m$^2$, diabetes mellitus, and without refractory hypertension. HFpEF-CAM was diagnosed based on the presence of amyloid deposition on endomyocardial biopsy with further mass spectrometry-verified tissue typing performed at Mayo Medical Laboratories. Variables collected include demographics, medications, physical exam, laboratory measures, ECG, echocardiography, and rest hemodynamics. Continuous variables will be examined using percentages or means and standard deviations for normally distributed variables; medians and interquartile ranges for skewed variables. Categorical variables will be examined with contingency table arrays. Associations with HFpEF phenotypes will be analyzed using t-tests or Kruskal-Wallis tests for continuous variables and chi-squared or Fisher’s exact tests for categorical variables.
Aim 2: To compare measures of functional capacity (6-minute walk test, fraility, Global Well-Being and Dyspnea) across 3 HFpEF clinical phenotypes: HFpEF-HTN, HFpEF-MetS, and HFpEF-CAM and determine if there are associations between with these measures and 30-D heart failure hospitalization or 1-y survival.

Hypothesis 2: We hypothesize HFpEF-MetS will have worse 6MWT and measures of overall well-being compared to the other two HFpEF-phenotypes. HFpEF-CAM will have a significantly higher burden of frailty compared to the other HFpEF-phenotypes. Measures of functional capacity and frailty will be strongly associated with clinical outcomes in all HFpEF phenotypes.

Methods 2: We will retrospectively analyze data collected in RedCap. Assessments were completed at time of the initial clinic visit as part of a standardized clinic protocol. Global well-being and dyspnea were measured by visual analog scales and will be quantified as an area under the curve. 6MWT was performed in JHOC along a pre-specified course by trained research coordinators. Pre and post-vital signs were obtained and a Borg scale of energy expenditure was performed after walk completion. Frailty was assessed by the JHU Frailty Index, which is a validated tool designed by the Johns Hopkins Aging Institute. Patients with and without the outcomes of interest (30-D heart failure hospitalization and mortality at 1 year) will be compared with respect to baseline characteristics and measures of functional capacity and frailty (e.g. 6MWT) collected for the cohort at baseline. Hazard ratios for each outcome will be estimated using Cox proportional hazards regression models, adjusted for age and sex.

Aim 3: To perform prospective exercise right heart catheterizations in HFpEF patients referred from JHU HFpEF clinic to assess exercise hemodynamic differences and determine if there is any association with functional capacity and clinical outcomes. We will analyze these differences across 3 HFpEF phenotypes: HFpEF-MetS (N=20), HFpEF-HTN (N=10), and HFpEF-CAM (N=5).

Hypothesis 3: We hypothesize HFpEF-MetS will have worse measures of RV function with exercise (including higher mRAP, higher RA:PCWP, and lower RVSWI) with a higher burden of exercise-induced PH compared to other HFpEF phenotypes. HFpEF-CAM will have worse CO augmentation with exercise compared to other HFpEF phenotypes. There will be a high burden of chronotropic incompetence across all HFpEF phenotypes.

Methods: HFpEF patients will be referred to undergo exercise right heart catheterization. After placement of Swan-Ganz catheter, patients will exercise via supine cycle ergometry at 60 rpm starting at 15 Watts (W) workload, increasing by 10W every 3 minutes to maximum tolerated levels. Hemodynamics (including RA, PAP, PCWP, CO/Ci, SVR, PVR, MVO2, TPG, RVSWI, LVSWI) and vital signs (including HR, NIBP, and O2 sat) will be obtained at rest, at the completion of each exercise stage, and at peak exercise. Clinical outcomes including heart failure hospitalization and survival will be collected at 30-D and 1-year. HFpEF phenotype groups will be compared with respect to exercise hemodynamics, measures of functional capacity, and clinical outcomes. Associations with HFpEF phenotype groups will be analyzed using Kruskal-Wallis tests for continuous variables and Fisher’s exact tests for categorical variables.

Conclusion
HFpEF is a heterogeneous disease associated with significant symptom limitation. Despite advancements in understanding different HFpEF phenotypes over the past several years, there is currently no comparison of clinical features, functional capacity, frailty, and outcomes by different HFpEF phenotypes. With our work, we hope to address this gap in HFpEF literature which may have therapeutic implications.
Atrial Fibrillation in HFpEF: Bystander or Modifiable Risk Factor?
Fellow: Eunice Yang M.D.
Mentors: Hugh Calkins M.D., Kavita Sharma M.D, David Spragg M.D.

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are two age-related cardiovascular epidemics increasing in prevalence worldwide. For the estimated 6 million Americans who will have HFpEF by 2030, the 5-year median survival following first heart failure hospitalization is only 35%, and there are currently no therapies for HFpEF with proven mortality benefit.\textsuperscript{1-3} Large observational studies suggest that one-third of patients with HFpEF also have AF. HFpEF patients with AF demonstrate poorer exercise capacity and reduced life expectancy in comparison with their counterparts without AF.\textsuperscript{4-8} Thus, the goals of this proposal are to further investigate the interplay between AF and exercise capacity in HFpEF, and to determine whether treating AF can improve exercise capacity and clinical outcomes in the HFpEF population.

Though early studies on AF in the general population demonstrated no difference in rate versus rhythm control, HFpEF patients frequently suffer from chronotropic incompetence and have many medical comorbidities, both of which make them poor candidates for beta-blockers and anti-arrhythmic medications. While treatment of AF has traditionally involved medical management, advances in electrophysiology over the last 30 years has greatly expanded the therapeutic options available for AF. For example, pulmonary vein isolation (PVI) has been developed and refined over the last two decades and is now a standard therapy for individuals with both paroxysmal and persistent AF. This procedure has been associated with high levels of safety and has demonstrated superior efficacy to medications in attaining rhythm control.\textsuperscript{9} Recent studies using PVI for rhythm control in patients with heart failure with reduced ejection fraction (HFrEF) have shown improvement in systolic function, exercise capacity, quality of life,\textsuperscript{10-12} and a significant reduction in all-cause mortality.\textsuperscript{13,14} With respect to HFpEF, the PVI procedure has been shown to be safe and comparably effective in attaining rhythm control\textsuperscript{15,16}, but no studies have investigated the effects of PVI on exercise capacity or clinical outcomes in this population.

The overall objective of the work proposed herein is to determine whether there is a dose-dependent relationship or pathologic threshold of AF burden—defined as the proportion of time an individual is in atrial fibrillation relative to total ECG monitoring time—associated with exercise capacity in HFpEF, and to set the foundational work to pursue research that will determine whether reducing AF burden can lead to improved exercise capacity. Our central hypothesis is that AF is a modifiable risk factor that contributes to exercise intolerance and clinical decompensation in HFpEF patients, and that reducing AF burden leads to enhanced exercise capacity.

Aim 1: To determine the prevalence of undiagnosed AF in HFpEF. We hypothesize that there is a substantial proportion of AF that has evaded conventional screening in HFpEF patients. Our approach will use a non-invasive continuous electrocardiographic (ECG) monitor to screen for subclinical AF in HFpEF patients.

Aim 2: To investigate whether AF burden is negatively associated with reduced exercise capacity in HFpEF. We hypothesize that exercise capacity is negatively associated with AF burden, independent of heart rhythm during time of exercise capacity evaluation and demographic characteristics. Our approach will use non-invasive continuous ECG monitors in participants with HFpEF with a diagnosis of paroxysmal AF to quantify their AF burden. Participants will undergo metabolic exercise stress testing to evaluate exercise capacity which will be measured using peak VO\textsubscript{2} extraction.
Aim 3: To conduct a pilot study comparing PVI with medical management of AF in HFpEF. We hypothesize that individuals randomized to the PVI arm will demonstrate significantly greater AF burden reduction in comparison with subjects randomized to receiving pharmacologic AF therapy. We further hypothesize that the reduction in AF burden seen in the PVI arm will be significantly associated with improvement in exercise capacity. Our approach will be a prospective, single-center randomized control pilot study to determine whether using PVI to reduce AF burden leads to improvement in exercise capacity in HFpEF. We will use our findings on changes in exercise capacity to determine appropriate power for subsequent larger scale clinical studies.

Understanding how modifying the natural history of AF affects symptoms and clinical outcomes in the HFpEF population is a pressing public health concern and carries the potential for great clinical impact. The interdisciplinary team assembled for this proposal is uniquely positioned to address these specific aims, which utilize clinical research methods commonly used in both electrophysiology and heart failure. Ultimately, these preliminary studies will serve as the cornerstone from which I plan to launch my career as an independent investigator, and will be crucial to initiating a larger-scale randomized control trial comparing PVI with medical management in HFpEF.
References:


Title: Pregnancy: A Harbinger of Future Cardiovascular Events?
Fellow: Anum Minhas
Mentors: Allison Hays, Robert Weiss, Arthur (Jason) Vaught, Sammy Zakaria

**Background:**
Cardiovascular disease remains the leading cause of mortality in women, with approximately one woman dying per minute in the United States. Although declines in heart disease mortality have been observed over the last three decades, more recent data suggest stagnation in improving heart disease mortality in women, specifically in younger age groups (<55 years). Hypertensive disorders of pregnancy such as preeclampsia have emerged as an important contributor to heart disease in younger women, and confer increased cardiovascular disease (CVD) risk that persists into later life, far beyond the pregnancy period. **A better understanding of how preeclampsia affects cardiovascular health is critical to guide new treatment approaches to reduce CVD risk in women.**

Hypertensive disorders occur commonly in pregnancy and place both women and fetuses at risk for complications during pregnancy and long-term. Preeclampsia is one of the most deadly hypertensive complications of pregnancy, and is marked by both hypertension and end organ dysfunction occurring in up to 10% of all pregnancies. Over a woman’s lifetime, preeclampsia confers a 2-4 fold increased risk of CVD, including hypertension, ischemic heart disease and stroke. While the exact mechanism of this increased risk is unknown, prior studies have suggested that uteroplacental ischemia drives maternal inflammation and endothelial dysfunction, which appear to persist postpartum. Endothelial dysfunction is a known contributor to atherosclerosis and predicts future CVD events, and its measure is an important index of vascular health. Recent studies show that endothelial dysfunction present during preeclampsia and after may be mediated in part by increased sensitivity to angiotensin II through agonistic angiotensin II type 1 receptor autoantibodies (AT1-AA), which develop during pregnancy. Although the association between preeclampsia and increased risk for cardiovascular events is recognized, the mechanism for this is poorly understood. Non-invasive means to measure endothelial function of the coronaries and systemic vasculature offer the opportunity to better understand the link between preeclampsia, inflammation and vascular dysfunction that may shed important insights into the markedly elevated CVD risk in women with a history of preeclampsia. Furthermore, this pilot study will provide critical preliminary data to inform sample size estimates for a larger intervention trial designed to target angiotensin and improve endothelial function.

**Our overarching hypothesis is that adverse changes that occur during preeclampsia, such as increased systemic inflammation and the development of maternal angiotensin II type 1 autoantibodies (AT1-AA), persist in the postpartum period and impair endothelial function and increase cardiovascular risk.**

We propose to use novel MRI methods to measure both coronary endothelial function (CEF) and systemic endothelial function (SEF) in postpartum women with preeclampsia and matched controls (normotensive pregnancies) to test the hypothesis that CEF/SEF is impaired and that inflammation/AT1-AA levels are increased in women with preeclampsia compared to the control group. Furthermore, we hypothesize that abnormal levels of systemic inflammation and AT1-AA levels are related to the degree of impaired endothelial vasoreactivity in women with preeclampsia.
Specific Aims:

Aim 1
To characterize and quantify, using MRI, measures of coronary and systemic endothelial function in postpartum women with preeclampsia compared to controls (women with normotensive pregnancies), matched for age and risk factors.

Hypothesis 1
We hypothesize that women with preeclampsia as compared to age-matched healthy postpartum controls will have abnormal coronary and systemic endothelial function.

Methods 1
For Aim 1, we will study two groups: 25 women three months postpartum with a history of preeclampsia during pregnancy and 25 women three months postpartum with normotensive pregnancies. The two groups will be matched for age, gender, body mass index (BMI), and blood pressure. Both groups will have no prior history of hypertension, autoimmune disease, or cardiac disease (coronary disease, cardiomyopathy, valvular disease), and will be off all antihypertensives at the time of study enrollment. Patients will undergo detailed history and physical exam, including measurements of blood pressure, weight, BMI, and waist/hip ratio. Patients will also undergo MRI for CEF and SEF (coronaries and internal mammary arteries) and visceral adipose tissue (for visceral and subcutaneous fat quantification).

Aim 2
To evaluate the relationship between preeclampsia, systemic inflammation, and endothelial function by measuring biomarkers and AT1-AA levels.

Hypothesis 2a
We hypothesize that inflammation/AT1-AA levels are increased in women with preeclampsia compared to controls.

Hypothesis 2b
Abnormal levels of systemic inflammation and AT1-AA are related to the degree of impaired endothelial vasoreactivity in women with preeclampsia.

Methods 2
We will measure systemic inflammatory markers (hs-CRP, IL-1B, IL-6, IL-10), markers of cardiac dysfunction (hs-troponin, NT-proBNP, BNP), lipid panel, and agonistic angiotensin II type 1 autoantibody (AT1-AA) levels in all participants.

Implications:
We propose to conduct a pilot imaging study investigating the possible mechanisms of increased CVD, specifically evaluating coronary and systemic endothelial function and potential contributing factors (i.e. residual inflammation and autoantibodies) in women with a history of preeclampsia. This study will provide critical data that may provide background for further trials investigating use of medications to reduce the risk of cardiovascular disease in women with history of preeclampsia and perhaps mitigate the risks of preeclampsia in future pregnancies in women at risk. Importantly, this will further my career goal to become an academic Cardiologist with a research and clinical focus on Women’s Cardiovascular Health.
Title: Accuracy of Ultra-High-Resolution CT Coronary Angiography for Detecting Hemodynamically Significant Coronary Artery Disease
Fellow: Jacqueline M. Latina, MD, MS
Mentors: Armin Zadeh, MD, MPH, PhD, and Joao Lima, MD

Introduction
Coronary angiography by conventional CT (CTA) is a promising technology for noninvasively identifying patients with coronary heart disease (CHD). However, diagnostic accuracy of CTA is less favorable in the setting of severe coronary calcification or for the assessment of in-stent restenosis, limiting its application to lower risk patients. Recently, ultra-high-resolution CTA (U-HRCT) has been introduced which lowered the smallest available detector width from 0.5 to 0.25 mm.1,2 In conjunction with image reconstruction techniques, this allows a nominal spatial resolution of 0.1mm, similar to conventional angiography (Figure 1). U-HRCT, therefore, may be positioned to challenge conventional angiography as a routine tool for identifying patients with obstructive CHD. The criterion for assessment in patients with CHD, however, has evolved from simply determining an anatomical stenosis threshold, e.g., >50 or >70%, to identifying coronary lesions associated with ischemia, for example, by fractional flow reserve (FFR).3-7 FFR, however, requires adenosine administration and wire insertion, which can be time-consuming, and is problematic in the setting of multi-vessel disease. Quantitative flow ratio (QFR) combines computational fluid dynamics and conventional angiography to predict coronary ischemia.8-10 QFR has demonstrated promise as a cost and time saving alternative to FFR.11,12 Furthermore, QFR allows assessment of the entire coronary artery tree, making it an accessible reference standard for assessing CHD as an alternative to FFR.

Hypothesis
In adults with coronary artery disease undergoing invasive angiography, U-HRCT is not inferior to conventional coronary angiography for identifying patients with CHD, as defined by abnormal QFR findings.

Specific Aims
Aim 1
Determine the diagnostic accuracy (AUC) ultra-high-resolution CT to identify patients with obstructive coronary artery disease as compared to QFR by conventional coronary angiography.

Aim 2
Determine the comparative radiation doses of conventional angiography as compared to U-HRCT, adverse events, and costs associated with testing/interventions.

Aim 3
Determine the diagnostic accuracy (AUC) of QFR in the United States as compared to conventional FFR in patients with borderline lesions in which FFR is also performed for internal validation of QFR.

Study Design
This will be a prospective, single center diagnostic study in participants referred for invasive coronary angiography (Figure 2).
Inclusion criteria: Age 25 years of age and higher with coronary artery disease referred for invasive angiography.

Exclusion criteria: Ostial left main disease, previous coronary artery bypass surgery, renal failure with creatinine >2, ST elevation myocardial infarction, contraindication to nitroglycerin, inability to take dual anti-platelet therapy or other contraindication to drug-eluting stents, significant psychiatric illness.

Assuming an AUC of approximately 0.8, with 70% power and an inferior margin of 10%, the sample required will be approximately 42 participants. Assuming 10% drop out and 10% participants without any coronary artery disease, the goal enrollment will be 50 participants. FFR data will be collected if available. Demographics, comorbid conditions, medical therapy, and physical exam information will be collected. Echocardiographic data will be collected if available. Statistical analyses will be performed with SAS software (Cary, NC, USA).

Figure 1. An example of in-stent resolution in U-HRCT as compared to conventional CTA.

Figure 2. Enrollment pathway. Patients can be enrolled prior to invasive angiography and are willing to have a UHR-CT at least 24-48 hours prior to catheterization.
References

**Title:** Magnetic resonance coronary angiography revisited – a comparison against computed tomography coronary angiography

**Fellow:** Karan Kapoor, MD

**Primary Mentors:** Yoko Kato, MD, PhD; Bharath Ambale-Venkatesh, PhD; Joao Lima, MD, MBA

**Introduction:** Despite steady progress in the application of CMR to other disease states, to date, magnetic resonance coronary angiography (MRCA) has lagged behind CT angiography (CTA). However, MRCA holds several key advantages over CTA, including superior soft-tissue contrast, less hindrance from calcium blooming, and no exposure to ionizing radiation or iodinated contrast. The technical challenges to MRCA, in addition to those germane to the coronary arteries themselves (small caliber, significant tortuosity and near-constant motion), include lengthy acquisition time, low spatial resolution and absent consensus regarding quantitative assessment. Compressed sensing (CS) and deep learning reconstruction (DLR) are emerging technologies applicable to MR image acquisition and post-processing, respectively, that may help overcome the lengthy acquisition time and low spatial resolution. Regarding quantitative assessment, one study showed that measuring the MR signal intensity (SI) across a lesion may allow quantification of stenosis severity\(^1\), although a subsequent analysis showed that plaque characteristics (and not luminal area alone) may also impact the SI profile of a vessel\(^2\).

**Hypotheses:** (1) MRCA acquired with CS and post-processed with DLR will overcome the major shortcomings of prolonged image acquisition time and low spatial resolution to enable diagnostic image quality. (2) The predominant driver of the SI profile along a vessel is the percent luminal stenosis, with plaque characteristics only somewhat contributory.

**Specific Aims:**
- **Aim 1:** To demonstrate the feasibility of MRCA as a diagnostic alternative to CTA in the evaluation of CAD
  - **Aim 1a:** To semi-quantitatively assess MRCA image quality obtained using CS and DLR
  - **Aim 1b:** To correlate variations in SI profile on MRCA to plaque characteristics on CTA
  - **Aim 1c:** To quantify the degree of SI drop on MRCA against corresponding cross-sectional CTA slices, and establish threshold categories for differing degrees of stenosis

**Methods:** Our study protocol has been approved the Johns Hopkins Institutional Review Board. We have planned a prospective, non-randomized study in which 50 participants will be recruited over a 12-month period. Study participants are patients who have undergone clinical CTA at JHH within the preceding 6 months with the intent of ruling out obstructive CAD. Individuals with prior CABG and PCI to >2 vessels will be excluded (other inclusion/exclusion criteria, not shown, are standard). We intend to recruit a balanced representation of patients covering the spectrum of stenosis severity. Eligible candidates will be identified through surveying the electronic medical record and will undergo a telephone screening questionnaire prior to recruitment. Participants will
undergo non-contrast, whole-heart MR with T2-prepared, segmented fast low-angle shot (FLASH), 3D spoiled gradient echo (SGRE) sequencing with ECG- and diaphragm-navigator-gating, compressed sensing and fat suppression. All MR scans will be performed with a 3Tesla Vantage Galan scanner (Canon Medical Systems). After acquisition, MRI data will undergo post-process denoising through DLR. DICOM images will be anonymized and stored for interpretation within the JHH network. Study images will be independently interpreted by at least three observers (K.K, under supervision of Y.K, with at least 8 years MR and CT experience and J.L, >20 years MR and CT experience), blinded to all clinical data. Visual and quantitative assessment will be performed on the basis of the 16-coronary-artery segment model put forth by the American Heart Association. Quantitative assessment of stenosis severity by MR will be performed by analyzing the SI profile curve obtained from stretched multiplanar reconstruction of the vessel in question. Corresponding cross-sections on CT will be then be analyzed to determine the percent stenosis correlative to the referenced SI drop. This analysis will be repeated along the entire visualized vessel length (ideally in 5 mm increments, if available). To address intraobserver variability, quantitative assessments of MR and CT scans will be performed twice by the same observer at least 2 months apart to mitigate recall bias. Area under the ROC curves will be calculated to evaluate the diagnostic performance of MRCA against CTA. From this analysis, the optimal SI threshold to detect a significant (>50%) stenosis will be determined and the sensitivity, specificity, positive and negative predictive values will be ascribed. Per-segment, per-vessel and per-patient analyses will be performed.

Future Directions: High fidelity MRCA imaging obtained via CS and DLR may enable downstream physiologic assessment of coronary flow.

Select References:
Introduction
Atrial fibrillation (AF) is the most common arrhythmia encountered in adults and affects 3-6 million Americans. By 2050, estimates suggest that more than 15 million Americans will have AF. Traditional cardiovascular risk factors such as obesity, diabetes, hypertension, and sleep apnea have been implicated as contributors to AF. In addition, being overweight or obese is also associated with an increase in epicardial adipose tissue (EAT), which may confer a further increase in risk for the development of AF. Weight loss can reduce these traditional risk factors; in addition, it has been shown to decrease the volume of EAT as well decrease AF burden in a dose-dependent manner.

A new class of medications called glucagon-like 1 receptor agonists (GLP-1 RAs) has recently been approved for the treatment of type 2 diabetes and shown to decrease major adverse cardiovascular events. GLP-1 RAs have also been shown to significantly decrease weight in patients with and without diabetes and decrease EAT. In a canine model, administration of a GLP-1 RA has been shown to decrease AF inducibility.

A recent meta-analysis of GLP-1 RAs and AF showed the class as a whole did not have any effect on the incidence of atrial fibrillation. However, the effects on the burden of AF in patients known to have AF and treated with a GLP-1 RA remains unknown.

The purpose of this study is to establish a link between AF burden and GLP-1 RA use. To do so retrospectively, patients with implanted cardiac devices will be assessed.

Hypothesis
Use of GLP-1 receptor agonists will reduce atrial fibrillation burden and increase time in sinus rhythm for patients with paroxysmal atrial fibrillation.

Specific Aims
Aim 1: Show within a population of patients with atrial fibrillation and an implanted cardiac device that there is a decreased burden of atrial fibrillation following initiation of a GLP-1 RA.

Aim 2: Assess the change in weight, blood pressure, and A1c after initiation of a GLP-1 RA agonist within this population.

Aim 3: Use the results from this study to pursue future prospective studies with the upcoming release of oral semaglutide (first oral medication in this class; all others are subcutaneous injections).
Methods
Patients who followed at the Johns Hopkins Medical Institute for cardiac device interrogations and were prescribed a GLP-1 RA will be identified. Within this group, patients with at least 6 months of device clinic interrogations before initiation and at least 12 months of device clinic interrogations after initiation of the GLP-1 RA will be included. The burden of atrial fibrillation as measured by the implanted cardiac device prior to initiation of a GLP-1 RA will be compared to the burden of atrial fibrillation after starting the GLP-1 RA for each patient in this cohort. Changes in weight, blood pressure, and heart rate will be assessed after starting the GLP-1 RA.

References


Title: Influence of Modifiable Risk Factor Levels on the Development of HF and Subsequent Outcomes
Fellow: Carine E. Hamo, MD
Mentor: Chiadi E. Ndumele, MD, PhD

Heart failure (HF) is a growing public health concern with a prevalence of 6.5 million in the United States\textsuperscript{1,2} and is associated with marked morbidity, mortality, and health care costs.\textsuperscript{3,4} There is therefore growing emphasis on refining strategies for preventing HF onset. The progression of the obesity epidemic and related cardiometabolic comorbidities have contributed to the burgeoning rates of HF, particularly HF with preserved ejection fraction (HFpEF), which comprises half of all HF cases and to date, has no known pharmacologic therapy to improve survival.\textsuperscript{1} Several risk factors for HF are in fact modifiable, including obesity, physical activity and the related comorbid conditions diabetes mellitus (DM) and hypertension (HTN). This presents a potential opportunity, through modulation of risk factor levels, for affecting the burden of HF in the population. Thus far, the degree to which optimization of modifiable risk factors, individually and collectively, might impact the incidence of HF has not yet been fully defined.

We recently performed a prospective analysis of 13,534 participants in the Atherosclerosis Risk in Communities (ARIC) study, examining HF risk associations at different cutpoints of body mass index (BMI), glycemia (HbA1c), systolic blood pressure (SBP), and physical activity, all simultaneously included in a regression model. We found a graded association between more uncontrolled levels of each of the risk factors and incident HF. When we considered HTN, DM, and obesity in composite, we found significantly greater risk with less collective risk factor control (Figure), with those with severely uncontrolled levels of 2-3 of these risk factors having a greater than 3-fold higher HF risk than those with controlled levels (BMI < 30, SBP <130 mmHg, HbA1c <7%).

This work indicates the potential benefits for HF prevention of addressing the control of these risk factors. What remains unknown is whether levels of control of these modifiable risk factors have a differential association with the development of HFpEF versus HF with reduced ejection fraction (HFrEF), two HF subtypes with markedly different underlying pathophysiology. Additionally, beyond risk factor assessments at one time point, the cumulative impact of longitudinal levels of risk factors on myocardial dysfunction and HF risk are undefined. Furthermore, the implications of risk factor levels may differ after the onset of clinical HF.

To address these knowledge gaps, we will perform prospective analyses within the ARIC cohort in order to: assess the associations of levels of modifiable risk factors with incident HFpEF versus HFrEF; determine the cumulative impact of long term risk factor levels on incident HF; and define the morbidity and mortality implications of risk factor levels among persons with prevalent HF. We propose the following Specific Aims:

**Aim 1:** To determine whether levels of modifiable risk factors (obesity, DM, HTN and physical activity) have a differential risk association with the development of incident HFpEF versus HFrEF.

**Hypothesis 1:** We hypothesize that more optimal levels of modifiable risk factors, particularly BMI and physical activity, will have stronger risk associations with HFpEF than HFrEF, and that a greater proportion of HFpEF than HFrEF cases will be attributable to uncontrolled risk factor levels.

**Methods 1:** We will relate levels of BMI, HbA1c, SBP and physical activity to incident HF, utilizing adjudicated HF cases from ARIC Visit 4 (1996-98) through 2016. We will construct Cox proportional hazards models simultaneously including categorized risk factors to estimate hazard ratios and associated 95% CIs for individual and collective risk factor associations with HF. We will formally compare the magnitude of risk factor associations with HFpEF and HFrEF by using the technique of seemingly unrelated regression. We will additionally compare the proportion of HFpEF and HFrEF cases attributable to modifiable risk factors by using risk associations and prevalence data to calculate population attributable risks.
Aim 2: To determine the associations of longitudinal risk factor control with echocardiographic assessments of myocardial remodeling and incident HF.

Hypothesis 2: We hypothesize that greater cumulative exposure to uncontrolled risk factors, taking into account both the severity and the duration of poor risk factor control, will be associated with a greater likelihood of adverse cardiac remodeling and incident HF.

Methods 2: We will utilize measurements of each risk factor across multiple visits for evaluating risk associations of modifiable risk factors. For assessments of HF risk, we will utilize Visit 4 as the baseline for incident HF events and utilize risk factor assessments from ARIC Visits 1 through 4 (9 year interval). For assessments of echocardiographic remodeling (performed at Visit 5), we will utilize risk factor assessments from ARIC Visits 1 through 5 (20+ year interval). For risk factors not assessed at all visits (e.g., physical activity at Visits 1, 3 and 5), we will use multiple imputation techniques to estimate values at the intervening time points. We will center risk factor levels at the optimal threshold for control (e.g., SBP 130 mmHg), and use the difference between each risk factor measurement and that optimal level of control as well as the follow-up interval to assess cumulative exposure to uncontrolled risk factors. We will also perform sensitivity analyses using historical levels for risk factor control (e.g., SBP 140 mmHg), given changes in treatment thresholds over time. Additional analyses will consider medication use. We will use Cox regression to estimate risk associations with incident HF, and logistic and linear regression to assess associations with echocardiographic categories of remodeling and with continuous echocardiographic parameters (such as LV mass, LA size, Doppler measures of mitral inflow [E and A waves], mitral annular relaxation velocity [E’], ejection fraction and peak longitudinal and circumferential strain).

Aim 3: To determine the association of levels of modifiable risk factors with recurrent HF hospitalizations and mortality among ARIC participants with existing HF.

Hypothesis 3: We hypothesize a U-shaped association between modifiable risk factors and outcomes among individuals with prevalent HF. Very high levels of weight, glycemia, blood pressure, and physical inactivity will reflect the deleterious effect of those risk factors on myocardial health, whereas very low levels of these risk factors could reflect their control or the severity of their underlying clinical HF.

Methods 3: We will examine levels of risk factors measured at the visit following HF diagnosis and use Cox regression models to estimate associations with recurrent HF hospitalization and mortality. We will examine risk associations for both individual risk factors and groups of risk factors (e.g., 2-3 severely uncontrolled). We will construct restricted cubic spline models to assess the continuous associations between risk factor levels and the outcomes of interest, to assess for deviations from linearity in the risk relationships.

By demonstrating how baseline and longitudinal risk factor levels are linked to HF risk, and elucidating whether risk factor associations change after HF onset, we anticipate this work will help to inform strategies to reduce the burden and consequences of HF.

REFERENCES:


**Title:** Aortic Valve Calcification and Progression to Aortic Stenosis Outcomes

**Fellow:** Rhanderson Cardoso

**Mentors:** Seamus P. Whelton, MD, MPH; Michael J. Blaha, MD, MPH

**Introduction.** Calcific aortic stenosis (AS) is a highly prevalent degenerative valvular heart disease that affects up to 1 in 8 individuals after age 75 years.\(^1\) Despite remarkable advances in aortic valve replacement (AVR),\(^2\)-\(^5\) preventive therapies have thus far failed to slow the progression of mild-moderate AS to severe AS.\(^6\)-\(^8\) It is conceivable that such interventions were studied too late in the disease course, since nearly all patients with mild to moderate AS ultimately progress to severe AS.\(^9\)

Non-contrast cardiac-gated computed tomography (CT) can identify calcium deposits in the aortic valve leaflets at its earliest stages with high sensitivity and accuracy. AVC can be quantified by the Agatston method of area-density products (AVC score).\(^10\) This method has high intraobserver and interobserver reproducibility.\(^11,\)\(^12\) In data from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, baseline AVC score was a strong predictor of AVC progression over a median follow-up of 2.4 years.\(^13\)

There are several knowledge gaps in the natural history of AVC. First, differences in AVC prevalence in healthy individuals based on age, sex, and race have not been described. Second, the long-term progression of AVC and its determinants are not known. And third, the relationship of baseline AVC and AVC progression to clinical AS and AS-related outcomes has not been explored.

We hypothesize that a better understanding of the initiation and progression of AVC will allow personalized risk prediction for the progression of AVC and for AS-related outcomes. Furthermore, this knowledge may serve as the basis to identify target populations for future studies aimed at AS prevention.

**Specific aim 1.** To calculate AVC age, sex, and race percentiles in a healthy population

**Hypothesis.** There will be significant heterogeneity in the AVC score across age, sex, and ethnicities.

**Methods.** The MESA cohort includes over 6,800 individuals aged 45 to 84 years old at the initial study visit from July 2000 to August 2002. Participants were free of clinically-evident cardiovascular disease at baseline. CT-derived AVC score is available for all patients at the initial study visit. In this population, we will calculate population percentiles with locally weighted scatterplot smoothing (LOWESS) regression, according to the methods described by McClelland and colleagues for computing coronary
artery calcium (CAC) percentiles. First, AVC scores undergo logarithmic transformation given the skew in data towards lower results. Second, the population is divided in sex and race categories. Third, within each category, linear regression computes the mean log transformed AVC score as a function of age. Fourth, the residuals (fitted minus observed values) are weight-ranked and their percentiles are calculated. Finally, the percentiles are added to the fitted value, yielding a log transformed AVC percentile that can be exponentially transformed into an AVC percentile. This technique accounts for age as a continuous variable, and provides reliable estimates for the extremes of the distribution.

Understanding this data is critical for the clinical interpretation of AVC scores. A given absolute AVC score will likely have different long-term implications depending on patient age, sex, and ethnicity. This is the case for CAC, where there is substantial heterogeneity based on these parameters. Any CAC in young people, even at low scores, predicts an elevated lifetime risk of coronary heart disease.

**Specific aim 2.** To characterize the progression and incidence of AVC Agatston score over 10 years

**Hypothesis.** The AVC Agatston score at baseline will be a stronger predictor of AVC progression as compared to traditional cardiovascular risk factors.

**Methods.** For this analysis, we will use novel data on AVC score obtained at MESA visit 5, which was completed between April 2010 and December 2011 (Figure 1). We will perform stepwise multivariable linear regression modeling to determine the association of baseline AVC and traditional cardiovascular risk factors (diabetes mellitus, hypertension, chronic kidney disease, tobacco smoking, elevated lipoprotein (a), hyperlipidemia, and inflammatory markers) with AVC progression, measured in absolute values, relative terms, and percentile changes.

**Specific aim 3.** To investigate the association of baseline and progression of AVC with clinical AS events

**Hypotheses.** Individuals with AVC Agatston score of 0 at baseline will have a negligible risk of downstream aortic valve events over a 15-year follow-up. An AVC Agatston score ≥75th percentile at baseline will be strongly predictive of downstream AS clinical events.

**Methods.** We will adjudicate an outcome of ‘clinical AS events’ in MESA. This endpoint will be a composite of severe AS; heart failure with AS; death including AS as a contributing cause; aortic valvuloplasty; or AVR. Our pilot analysis identified 147 participants in MESA with ICD9, ICD10, or
CPT codes for this composite endpoint. We will perform an independent two-physician adjudication review of individual medical records to confirm each clinical outcome.

There are 2,354 individuals age ≥75 years old who have completed 15 years of follow-up of in MESA. Based on a 3.4% expected prevalence of severe AS in individuals ≥75 years old,¹ we estimate there will be 70 to 80 cases of severe AS in our study population (Figure 1). This number of events would allow us to detect a significant hazards ratio of ≥2.0 between those with AVC≥1 vs. AVC=0 at baseline, with an α of 0.05 and β (power) of 0.8 (Table 1).

We will perform progressively adjusted Cox proportional hazard modeling to examine the association between baseline AVC score and other risk factors with clinical AS events. We will also perform Kaplan-Meier survival analysis in order to describe the long-term survival free from a clinical AS event for patients with AVC=0, AVC≥1, and different AVC quartiles.

To the best of our knowledge, this study represents the first time an endpoint of incident clinical AS will be adjudicated in an NHLBI cohort of individuals free of cardiovascular disease at baseline and with an extended follow-up period (>15 years). Our expectation is that effective risk prediction tools for the development of AS-related clinical endpoints will inform patient selection for future studies of novel therapies aimed at preventing severe AS.

Figure 1. Flow diagram of MESA visits and aortic valve calcium evaluation

Table 1. Sample size and power calculations

<table>
<thead>
<tr>
<th>Comparison</th>
<th>AVC ≥1 vs. AVC=0</th>
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<td>Hazard Ratio</td>
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References


Title: The systematic assessment of novel peptides that mimic cooling protection in cardiac arrest.
Fellow: Daniel Ambinder, MD
Mentor: Henry Halperin, MD

Introduction
Sudden cardiac death (SCA) a leading cause of death in the United States. It affects 500,000 people annually with an overall survival rate less than 10-20%.1 2 3 There is a critical need, therefore, for improved CPR strategies, since each 1% improvement in survival rate would result in at least 5000 additional survivors.

Cooling is one of the few treatments that effectively improves cardiac and neurological function, and survival. However, it takes hours to reach the targeted temperature even if it is only a few degrees drop from 37°C to 34-36°C. Survival benefit is lost if active cooling is delayed just 20 min, suggesting that an important therapeutic window exists during CPR for affecting SCA outcome.4 Physical cooling during CPR is difficult to achieve clinically. Moreover, no medications currently exist for improving survival. Therefore, there is a compelling need to develop life-saving SCA medications. Agents that mimic cooling mechanisms of protection and gain quick access to tissues post-cardiac to improve survival would represent a significant advance in resuscitation medicine.

Signaling and metabolic mechanisms of CPR cooling protection
CPR cooling has been associated with enhanced activity of cardiac protein kinase B, also known as Akt. Akt is a ubiquitous and central player in regulating metabolism, cell growth and survival. It is a soluble cytosolic protein and, in the setting of hypothermic conditions is activated by PI3K via the key second messenger PIP3 in the plasma membrane that binds to Akt resulting in a conformational change in Akt which facilitates its phosphorylation on threonine308 and serine473 by the upstream kinases. Akt activity is negatively regulated by abundant phosphatases including PH domain leucine-rich repeat phosphatase (PHLPP). PHLPP regulates Akt activity by dephosphorylating Akt which stabilizes Akt conformation needed for Akt full activation (Fig 1).5 6

Cooling during and after resuscitation protects against the metabolic phase of injury caused by several minutes of untreated SCA.7 8 Activation of Akt enhances glucose utilization through multiple effects including the immediate translocation of GLUT4 to the plasma membrane9 10 together with the stimulation of glycolysis at phosphofructokinase 1 via PFK2 activation.11 Furthermore, Akt activation has been reported to increase pyruvate dehydrogenase (PDH) activity12 13 and thereby enhances the coupling between glycolytic activity and glucose oxidation which may be key to recovery. Other related metabolic events, such as glucose shunting to sorbitol, likely contribute to SCA injury and death. Taurine is concentrated primarily in the heart, important for antioxidant defense and calcium handling, and released during osmotic stress induced by sorbitol accumulation.14 15 16 Because it is not easily replenished, its release within minutes after CPR could greatly amplify cardiac reperfusion injury and stunning, with decreased tissue perfusion and brain injury. Furthermore, a similar compensatory release of brain glutamate increases excitotoxicity and worsens brain edema and injury.17 18 19 20 Thus, blood taurine and
glutamate concentration likely to reflect the injury of heart and brain following SCA and will be evaluated in the mouse and swine, and validated in SCA patients.

Two peptides, TAT-PHLPP9c and TAT-PIF, have been designed to duplicate critical mechanisms of cooling protection without the need for physical cooling (Fig. 1). Combination of these two peptides is proposed to induce maximal activation of Akt and enhancement of PDH activity. Reduced glucose shunting to sorbitol will diminish osmotic injury and release of taurine and glutamate into blood, with further improvement of cardiac stunning and improved neurologically intact survival.

In pilot studies, ventricular fibrillation (VF) was induced in 14 swine. After 5 min of no treatment, vest CPR was started and ACLS protocols were followed. In 8 animals, no peptide was given and in 6 animals, TAT-PHLPP9c was given during CPR (7.5 mg/kg x 4). Defibrillation was attempted and if return of spontaneous circulation was achieved, the animals were monitored for 24 hours or until they expired. Neurologic outcomes were then quantified along the lines of the modified Rankin score. Outcomes were much improved in the animals that received TAT-PHLPP9c (0/8, 24 hr survivors for no peptide vs 5/6, 24 hr survivors for peptide). An increase in blood taurine and glutamate concentrations was detected as early as 2 min following CPR. TAT-PHLPP9c decreased both taurine and glutamate concentrations in plasma at CPR 2 min.

Our overall aim is to determine whether these novel peptides improve swine SCA survival as well as cardiac and neurological outcome measured at 24 hours when given intravenously during CPR.

**Aim 1a:** Confirm the efficacy of TAT-PHLPP9c given during CPR in a pre-clinical 5 min VF swine model. **Hypothesis 1a:** TAT-PHLPP9c given during CPR improves ROSC rate, cardiac function and 24 hour neurologically intact survival when compared to traditional CPR.

**Protocol:** A total of 16 pigs (30 ± 4 kg) will be tranquilized with ketamine 22 mg/Kg IM, and intubated and mechanically ventilated with 100% O2 and 1 - 2.5% isoflurane for anesthesia. Percutaneous access to both femoral veins and arteries will be established, as well as one carotid artery, and 8 Fr sheaths will be placed. A pigtail catheter will be placed in the descending thoracic aorta for aortic blood pressure measurements and microsphere withdrawal. A pigtail catheter will be placed through the carotid sheath into the LV for injection of microspheres. External defibrillator electrodes will be placed on either side of the chest. All pigs will be studied in the supine position, and will be given 0.5 to 1 liter of normal saline, intravenously, to achieve mean right atrial pressures of 3 to 5 mm Hg to maintain a euvolemic state. Pigs will undergo 5 minutes of VF induced by delivering 60 Hz alternating current via a temporary pacing wire followed by vest CPR with periodic defibrillation, and administration of control (inactive) or active TAT-PHLPP9c (7.5 mg/kg x 4 at 1 minute intervals).

Adequacy of carotid and coronary blood flows and coronary perfusion pressure in all groups will be determined, along with return of spontaneous circulation. Absolute blood flow per gram of tissue will be measured via neutron activated microsphere blood flow.21 Serial blood concentrations of lactate, taurine and glutamate will be taken at selected times and correlated with ultrasound measurements of cardiac strain and function. Changes in ICP will be monitored using ocular ultrasound for detection of optic nerve sheath diameter. Cardiac stunning will be assessed by echocardiographic determination of systolic and diastolic function. A certified and licensed veterinarian will provide a blinded neurologic assessment at 24 hours post return of spontaneous circulation. Data analysis will be via simple descriptive analyses. Results will be reported as means ± standard deviation. ANOVA and two-tailed t-tests will be performed.
P<0.05 will be considered significant. For each group studied, we assume that there will be a 50% difference between groups, which is what is expected for the effects being investigated, based on prior studies of hypothermia using other technologies. For an alpha of 0.05 and a power of 80%, using “Power and Sample Size Calculation” (Version 2.1.31; Vanderbilt University); 8 animals will be needed for each group to show differences in peptide vs placebo across groups.

**Aim 1b:** Examine the additive benefit of combined peptides, TAT-PHLPP9c and TAT-PIF in improving swine SCA outcome. **Hypothesis 1b:** The combined treatment of TAT-PHLPP9c and TAT-PIF given during CPR improves cardiac function and 24 hour neurologically intact survival more so than TAT-PHLPP9c alone.

**Protocol:** In 8 additional animals, the protocol for Aim 1a will be followed for those receiving peptide, except that both TAT-PIF and TAT-PHLPP9c will be administered at 1 minute intervals during CPR, each at 7.5 mg/kg. The control group of 8 animals for this Aim will be the treatment group from Aim 1a.

**Aim 1c:** Examine if the additive benefit of combined peptides will allow for improvement in swine SCA in the setting of prolonged VF arrest (10 minutes) which is further comparable to clinical out of hospital SCA. **Hypothesis 1c:** The combined treatment of TAT-PHLPP9c and TAT-PIF given during CPR improves cardiac function and 24 hour neurologically intact survival in the setting of a prolonged VF arrest (10 minutes) when compared to traditional CPR.

**Protocol:** 16 animals will undergo the same protocol for Aim 1b except that the time of untreated VF will be increased to 10 minutes. 8 of these animals will receive inactive peptides and will serve as the control group for this aim.

**Aim 1d:** Examine if the additive benefit of combined peptides at higher doses will allow for improvement in swine SCA in the setting of a prolonged VF arrest (10 minutes). **Hypothesis 1d:** The treatment of higher doses of both TAT-PHLPP9c and TAT-PIF given during CPR improves cardiac function and 24 hour neurologically intact survival in the setting of a prolonged VF arrest (10 minutes) more so than lower doses of TAT-PHLPP9c and TAT-PIF.

**Protocol:** In 8 additional animals, the protocol for Aim 1c will be followed for those receiving peptide except TAT-PHLPP9c and TAT-PIF doses will be doubled. The control group of 8 animals for this Aim will be the treatment group from Aim 1c.

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Abstract

Improving Cardiovascular Care Access In Resource Limited Settings By Optimizing Outpatient Referrals in Chile

Bolanle Akinyele, MD; Sammy Zakaria, MD, MPH; Diana Prieto, PhD

Background

Cardiovascular disease (CVD) is the leading global cause of death.\(^1\) Over 75% of cardiovascular deaths take place in low- and middle-income countries (LMIC); however, LMICs have less access to effective and equitable health care services.\(^1\) Hence, many people are detected late in the course of the disease and die younger, often in their most productive years.\(^1\) Chile has been a country plagued by similar statistics. In Chile, the mortality rate from CVD is 29%, with coronary artery disease accounting for 31% of deaths. According to the National Health Survey in Chile, the prevalence of risk factors for CVD includes: sedentary lifestyle (90%), cigarette smoking (42%), hypercholesterolemia (35%), hypertension (33%) and obesity (23%). In Chile, the predominant health system is the National Health Insurance (public system) which serves 78% of the population.\(^6\) However, there are long waiting lists for most sub-specialty care prompting the government in 2005 to pass the Health Explicit Guarantees (GES) Act, which guarantees access to health care (diagnosis, treatment, follow-up, and rehabilitation) for every Chilean citizen for prioritized health conditions. For other non-government prioritized conditions, Chileans remain subject to long wait lists, and there remains a strong association between prolonged waiting times and increased risk of death among patients not prioritized by the GES Act.\(^11\) In particular, referrals for non-prioritized CVD conditions have a ~ 365 days wait time, mainly due to a lack of cardiologists.

Long wait lists to see CVD specialists is not unique to Chile and can be seen in other resource-limited settings. One of the reasons for delays are inefficient and antiquated referral and triaging processes. Previous work has identified several problems with referral processes; including a lack of information about the referral reason; missing or insufficient clinical information; patients unaware of the reason for referral; and unnecessary referrals. In contrast, efficient referral processes include structured referral sheets which prompt PCPs to conduct pre-referral tests or treatments and pre-appointment management and triaging of referrals by subspecialists.\(^9\) In the developed world, triaging of referrals has successfully been done in other subspecialties such as rheumatology where there are personnel shortages causing delayed access to care. In some academic and community practices, board-certified rheumatologists review documents sent by a referring provider and assign acuity scores such as: (1) urgent; (2) emergency; (3) next available; and (4) lowest priority.\(^10\) Patients without a demonstrated need for rheumatologic services are not scheduled, and timing of appointments depends on the pre-appointment acuity score. Using this standardized referral system, only 59% of referred patients required a rheumatology consultation.\(^10\) They concluded that pre-appointment management could be a key strategy for reducing health care costs, addressing personnel shortages, and improving access to and coordination of rheumatic disease care.\(^11\) This system could potentially be implemented for cardiology services, especially in areas with limited resources and providers, such as in Chile; other low- and middle-income countries, and within developed countries with limited cardiology sub-specialists.
Hypothesis

Triaging new outpatient cardiology referrals in the CRSHPC health system with a standardized questionnaire will help determine patients’ acuity level and reduce the cardiology waiting list in Santiago, Chile. Shorter wait times in the CRSHPC health system will be associated with improved cardiovascular outcomes.

Specific Aims

1. Develop a symptom-based questionnaire for the top 4 referral reasons to cardiology and triage them into urgent (< 14 days), priority (< 30 days), routine (>30 days) or no appointment.
2. Retrospectively validate the questionnaire using the CRSHPC electronic health records.
3. Create a prediction model using machine-learning algorithms to automatically triage patients.
4. Analyze the association between the cardiology waiting list and mortality prior to the institution of standardized referral tool and compare the data post-institution of the standardized referral tool.

Methods

The study will be conducted within the Centro de Referencia Hospital Provincia Cordillera (CRSHPC) health system in Santiago, Chile, which is one of the largest health systems in Chile. Our study investigators include a multi-disciplinary team from the Johns Hopkins Carey School of Business (Operations and Data Analytics), Johns Hopkins Medicine (Division of Cardiology and Department of Emergency Medicine), CRSHPC health system and the Universidad de Chile. Our source of funding for the implementation phase is provided by an Impact grant from the Johns Hopkins Alliance for Healthier World.

Using ACC/AHA/ESC guidelines and previously validated risk assessment tools, we will develop a symptom-based questionnaire for each of the 4 commonly encountered reasons for new outpatient cardiology referrals in the CRSHPC network. Using electronic health records in the CRSHPC system, we will retrospectively complete the standardized questionnaires and determine acuity levels. Then, we will compare the prior assigned acuity levels to the questionnaire determined acuity level. Finally, we will use data for all new cardiology patients on the CRSPHC waiting list for non-prioritized health problems from 2013 to 2017 to construct hierarchical multivariate survival models to predict mortality risk and other cardiovascular outcomes at three years after registration.