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CORONARY ANGIOGRAM PLUS INVASIVE PHYSIOLOGIC TESTS IN WOMEN
WITH NONOBSTRUCTIVE CORONARY DYSFUNCTION

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

June 2021

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Abstract

Ischemic heart disease is the leading cause of death for women in the Western hemisphere. Women with ischemic heart disease typically present to the emergency department with acute coronary syndrome, and subsequently undergo coronary angiography. In 66% of women, no evidence of obstructive disease is found, and current standard of care recommends no further diagnostic testing. However, nonobstructive diseases cannot be ruled out with coronary angiography alone and therefore are frequently missed. **This study will examine whether invasive physiological testing with coronary angiography can impact multiple adverse cardiac events in adult women.** Using a prospective comparative effectiveness trial, we will compare the occurrence of these events at one year in adult women that undergo coronary angiography plus invasive physiological testing rather than standard of care. This study may help improve diagnostic accuracy and inform disease-specific treatment for women with nonobstructive coronary disease, as well as decrease healthcare utilization costs.

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List of Abbreviations

ACE-I Angiotensin Converting Enzyme Inhibitors
ACS Acute Coronary Syndrome
ARB Angiotensin Receptor Blocker
CFR Coronary Flow Reserve
CMR Cardiovascular Magnetic Resonance
CRT Coronary Reactivity Testing
CT Computed Tomography
cTn cardiac Troponin
CVDs Cardiovascular Diseases
DVT Deep Vein Thrombosis
ED Emergency Department
EMR Electronic Medical Record
LAD Left Anterior Descending coronary artery
MACE Major Adverse Cardiac Outcomes
MINOCA Myocardial Infarction with No Obstructive Coronary Artery disease
MPI Myocardial Perfusion Imaging
MRI Magnetic Resonance Imaging
NSTEMI Non-ST segment Elevation Myocardial Infarction
PCI Percutaneous Coronary Intervention
PET Positron Emission Tomography
STEMI ST segment Elevation Myocardial Infarction

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Chapter 1 – Introduction

1.1 Background

For women in the United States, and worldwide, as well, cardiovascular diseases (CVDs) remain the leading cause of death¹⁻⁴. Yet despite this staggering fact, CVDs are largely understudied in women and often thought of as primarily impacting men¹, leaving women out of critical research and a gaping hole in knowledge about how CVDs really impact women⁵. This is due largely in part to the fact that women often present differently from men with CVDs. While men present with the classic left-sided, crushing chest pain radiating to the left shoulder or arm, women tend to have more atypical symptoms such as dyspnea or weakness that can lead to a delayed presentation⁶⁻⁸. This delayed presentation can be as little as hours to days to present to the Emergency Department (ED), or even years later than men would typically present, and has been somewhat attributed to the decrease of estrogen with age and estrogen's analgesic property, as well as reluctance to seek care for their symptoms or barriers to access^{1,5,9}.

Additionally, women presenting with acute coronary syndrome (ACS) are often underdiagnosed¹⁰. This is partially attributed to studies that have shown that the diagnostic cutoff for troponin levels is too high for typically presenting women, as men more often present with higher levels¹⁰. With this underdiagnosis, women are also less likely to receive coronary angiography or pharmacological treatment than men are for their ACS, leaving the etiology of their ACS both undiagnosed and untreated^{1,10}. Patients have even been falsely told that there was nothing wrong with their heart when in fact further testing was not conducted to ensure this was true¹¹.

1.2 Statement of the Problem

When women are able to receive a coronary angiogram, they are more likely to have nonobstructive disease (<50% stenosis)¹²⁻¹⁵. There are various causes for nonobstructive disease that are not able to be determined from coronary angiography alone, including but not limited to microvascular dysfunction and vasospastic angina^{12,16-18}. Coming to the correct diagnosis is important for implementing an effective treatment plan for patients, and yet the standard of care in current practice is to pursue no further diagnostic testing after obstructive coronary artery disease is ruled out on coronary angiogram, often resulting in women being falsely reassured that they do not have coronary dysfunction when that may not be true^{19,20}. With only a diagnosis of nonobstructive disease and no further classification of disease, medical management is less likely to be used than in their obstructive coronary disease counterparts, in which there are evidence-based treatment guidelines including medications, revascularization, and cardiac rehabilitation²¹. There is no consistency across institutions in treating nonobstructive disease thanks in part to the lack of a well-classified diagnostic algorithm and an overall lack of research on these diseases^{21,22}.

Nonobstructive diseases have additionally been associated with higher rates of adverse cardiac events including stroke, myocardial infarction, heart failure, and even death, putting women disproportionately at risk for these adverse events and requiring further follow up/healthcare burden^{9,21-23}. According to the Women's Ischemia Syndrome Evaluation (WISE) study that has been conducted over the past 25 years, women with nonobstructive disease have a 13% overall mortality rate²⁴. Much of these adverse events are in the setting of microvascular dysfunction, underscoring the importance of further

research into these nonobstructive diseases²⁴. One crucial step in this process is to develop a diagnostic pathway for the various diseases that fall under the nonobstructive umbrella.

In the recent Coronary Microvascular Angina (CorMicA) trial, Ford et al. utilized an interventional diagnostic procedure in patients that were found to have ischemia and nonobstructive disease on coronary angiography to determine if there was a subsequent decrease in angina using the Seattle Angina Questionnaire²⁵. They found that by performing this interventional diagnostic procedure (which involves inserting a guidewire to infuse adenosine and acetylcholine into the great vessels of the heart) they were better able to diagnose nonobstructive diseases such as microvascular angina and vasospastic angina and stratify treatment more appropriately for each diagnosis. This subsequently led to improved angina and quality of life for patients that received this intervention²⁵. This study in addition to the WISE trial are pivotal steps in suggesting further diagnostic workup for patient with nonobstructive disease to further classify the etiology of the ischemia and filling the gap in research.

1.3 Goals and Objectives

The goal of this study is to evaluate if coronary angiogram with invasive physiologic testing is a viable option for improving diagnostic phenotyping in women with acute coronary syndrome and nonobstructive coronary dysfunction. We will accomplish this by determining if coronary angiography with invasive physiologic testing compared to historical data from Connecticut hospitals on the standard of care (coronary angiography

alone) in women with ACS found to have nonobstructive coronary dysfunction impacts the occurrence of MACE in the year following intervention.

The objectives of this study are to determine if coronary angiogram with invasive physiologic testing can lead to improved diagnostic phenotyping and personalized treatment strategies for women with ACS and nonobstructive coronary dysfunction, therefore leading to decreased subsequent MACE. Secondly, we will also evaluate if coronary angiogram with invasive physiologic testing impacts each individual component of MACE in the year following the intervention.

1.4 Hypothesis

We hypothesize that women over 18 years old with acute coronary syndrome who are found to have no obstructive coronary artery disease on coronary angiography and who subsequently undergo invasive physiologic testing to diagnose the mechanism of acute coronary syndrome will have a statistically significant difference in occurrence of MACE at one-year post-procedure as compared to historical data on those that undergo coronary angiography alone and do not receive a definitive diagnosis.

1.5 Definitions

ACS: Acute Coronary Syndrome. The American Heart Association defines ACS as “an umbrella term for situations where the blood supplied to the heart muscle is suddenly blocked.” Patients will have a high clinical suspicion as well as a rise or fall in cardiac markers (at least two consecutive cardiac troponins).

MACE: Major Adverse Cardiac Events including recurrent angina pain, development of heart failure, non-fatal infarction, presentation to the Emergency Department with cardiovascular-related illness, admission to the hospital for cardiovascular-related illness, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), stroke, and all-cause mortality.

Nonobstructive Disease: <50% vessel obstruction visualized on coronary angiogram

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Chapter 2 – Review of the Literature

2.1 Introduction

An extensive review of the relevant literature was performed with help from the Yale University School of Medicine librarians in July 2020 and from November 2020-December 2020. The databases utilized were Pubmed, Ovid Medline, Scopus, and The Cochrane Medical Library. Key search terms relating to our study population included “*acute coronary syndrome,*” *ACS,* *coronary,* *women,* *female,* *adult,* *sex,* *angina,* “*chest pain,*” and *NSTEMI.* Search terms related to our intervention included *angiography,* “*coronary angiogram,*” *adenosine,* *acetylcholine,* “*stratified therapy,*” *vasospasm,* *microvascular,* “*microvascular angina,*” *MINOCA,* and *INOCA.* Search terms relating to our outcome included “*major adverse cardiac events,*” *MACE,* *outcomes,* and “*one year.*” Finally, search terms related to our study type included “*comparative effectiveness*” and *prospective.* Searches were limited to adults over 18 and studies published in the last five years. Results were then screened for relevance to this study.

2.2 Review of Sex Differences in Coronary Artery Diseases

There is a generalized paucity of research on coronary artery diseases in women that has only begun to rectify itself over the past few years. This is likely due in part to the differing pathophysiology of coronary artery disease in women and the increased likelihood of a nonobstructive diseases such as coronary microvascular dysfunction^{26,27}. In 2015, Pepine et al. called attention to this gap in the literature with a position paper. They reference the Women’s Ischemia Syndrome Evaluation (WISE) study, which was a prospective cohort of 936 women with angina or suspicion for ischemia that underwent

coronary angiography, as the primary resource for data on nonobstructive disease in women²⁶. Their study made huge initial strides in the way of shrinking the gender gap in research by conducting a study with only women participants over several years. Some of their findings include that about 66% of women enrolled were found to have nonobstructive coronary dysfunction and that for this group of women there was a yearly risk of 2.5% that MACE would occur²⁶ with a 5 year rate of MACE around 11% ($p < 0.001$)¹⁹.

Although the WISE study is certainly impactful, it is not without limitations, as Pepine et al. point out, including a smaller sample size, selection bias including only women that have access to healthcare, and recall bias by utilizing a self-reporting system for MACE^{19,26}. The WISE study was able to spur other studies, though, and similar studies have replicated the same trend of women with ACS being more likely to have nonobstructive diseases as well as worse outcomes²⁶. Pepine et al. ended their position paper with a call to action to address further knowledge gaps going forward including being able to diagnose the mechanism behind ischemia as well as to stratify treatments specific to underlying etiologies of disease with more clinical trials²⁶.

In 2016, Kawamoto et al. published a review on sex differences in ACS to evaluate the available data and studies at the time⁵. In this, they highlighted the very prevalent disparities between women and men and the high mortality rate that heart diseases pose to women, especially those with comorbidities and to minorities⁵. They also ended their review with a call for more research so that better diagnostic modalities and treatment algorithms can be developed for these high-risk populations⁵. This same year, Mehta et al. published the first statement from the American Heart Association regarding

myocardial infarction in women. They report that although mortality for women with cardiovascular diseases has been declining in the past 15 years thanks to heightened awareness, it is still killing women at higher rates than men¹. They also highlight that women are undertreated with current guidelines and have worse outcomes than their male counterparts, further endorsing the need for more targeted research¹.

There is also copious evidence that women presenting with ACS are less likely than men to receive a coronary angiogram or to be diagnosed with any type of myocardial infarction^{1,10}. This is likely due in part to cardiac troponin (cTn) levels varying between women and men and women being less likely to reach the threshold for diagnosis¹⁰. However, in a 2018 study in Canada, researchers studied patients presenting to the Emergency Department with chest pain to evaluate if cTn levels could account for the differences in diagnosis and outcomes between men and women. They found that even in men and women that presented with ACS and met the cTn criteria for a myocardial infarction, women were still less likely to receive a coronary angiogram, be diagnosed with a myocardial infarction, had higher rates of MACE, and were less likely to be appropriately treated for their disease¹⁰. They do speculate that the higher rates of MACE may be related to the higher rates of comorbid conditions in women, as the difference did not persist and was no longer statistically significant when these conditions were corrected for¹⁰. However, this was a novel study with a large sample size (7,272 participants) that showed statistically significant sex differences, and though not without limitations such as lack of generalizability to patients without chest pain and use of coded data, it is a step in the right direction and emphasizes that further research is warranted to examine why these sex differences persist and what can be done about them¹⁰.

Conversely, in a 2018 study of patients with total obstructive coronary lesions evaluating MACE after receiving PCI found that male participants had a decrease in MACE over three years while female participants saw no change in MACE². They partially attribute this to complications that occurred during PCI being significant predictors of 3-year mortality on multivariate Cox regression for women but not for men². This indicates that even for women with obstructive disease, the mortality risk is higher after undergoing what is meant to be a lifesaving procedure, and continuing to treat women the same way men are treated is not sustainable and instead may be putting them at further risk. This is a German study that, while retrospective and not necessarily representative of the overall female population, spanned nine years and had a large sample size (2002 participants) making it important to consider. A similar study conducted in the US in 2019 did not find any sex differences in outcomes post-PCI for participants with total obstructive lesions⁷. This study, however, utilized a registry for reporting outcomes, only had 1000 participants (196 of which were women), and only evaluated MACE at 1 year as compared to the German study, subjecting this study to potential biases and limitations⁷.

Another study of 21,375 participants in India published this year examined sex differences in cardiovascular disease patients and found that women had more risk factors including diabetes and hypertension, had a later presentation to care, and were less likely to be treated²⁸. They additionally had a 53% increased risk of in-hospital MACE (adjusted RR 1.53, 95% CI 1.32-1.77, $p < 0.001$) and a 39% increased risk of MACE 30 days afterwards (adjusted RR 1.39, 95% CI 1.65-2.07, $p < 0.001$) than the men in the study²⁸. In terms of mortality, women were 67% more likely to die in the hospital

(adjusted RR 1.67, 95% CI 1.42-1.97, $p < 0.001$) and 48% more likely to die within 30 days (adjusted RR 1.48, 95% CI 1.29-1.70, $p < 0.001$) than men²⁸. This study found significantly worse outcomes for women all around, even when adjusting for baseline characteristics. Although India is a vastly different country than the United States, this just further highlights this staggering issue worldwide. The ultimate goal for sex differences in coronary dysfunction is to develop diagnostic algorithms that benefit women specifically, as the current standard of care throughout the world is not working well enough for women now⁸.

2.3 Review of Nonobstructive Coronary Dysfunction

The general consensus in the literature, and even from the European Society of Cardiology and the American Heart Association/American College of Cardiology, is that nonobstructive disease is considered to be $< 50\%$ vessel obstruction with elevated cardiac biomarkers (usually cTn)¹²⁻¹⁵. Another term that is often used in the literature is MINOCA, or myocardial infarction with no obstructive coronary artery disease. The specific nature of this terminology, though, implies there is a component of MI/ischemia occurring, which is not the case for all patients presenting with acute coronary syndrome, but is certainly one of the most dangerous diagnoses¹⁵. For the purposes of our study, we will continue to refer to our participants as those with nonobstructive coronary dysfunction rather than restricting them to the MINOCA umbrella.

The recent rise in nonobstructive coronary dysfunction, particularly in women, is likely multifactorial. Not only do we have an aging population in which NSTEMIs are more common than STEMIs, but also by relying more heavily on cTn as a biomarker of

ischemic disease rather than creatinine kinase-myocardial isoenzyme (CK-MB), more disease processes are being classified as NSTEMIs rather than unstable angina^{6,15,29}. In addition to this rise in prevalence is the theory that nonobstructive disease are more dangerous than originally thought, and with this danger comes an increasing need to further classify the underlying etiology⁹. In their 2018 review, Makarovic et al. proposed to classify nonobstructive disease by whether they are ischemic (Type I) or nonischemic (Type II) in which ischemic diseases are further differentiated as endothelium dependent (1A), endothelium independent (1B), or vasoconstrictive (1C) and nonischemic diseases are further differentiated as neurogenic afferent (2A), neurogenic efferent (2B), or habitual (2C)⁹. This proposed classification system is another step in the right direction and even suggests different clinical presentations patients may express, but ultimately is not useful without effective means of diagnosis, again highlighting the need for further studies proposing accurate diagnostic modalities.

In a recent statement from the American Heart Association, Tamis-Holland (Chair) et al. published in 2019 a proposed clinical algorithm called the “Traffic Light” Sequence to help diagnose nonobstructive disease that offers various diagnostic modalities depending on clinical presentation¹⁵. This algorithm includes considering non-cardiac causes of elevated cTn and nonobstructive disease as well as alternate diagnoses such as obstructive disease, dissection, Takotsubo cardiomyopathy, and myocarditis¹⁵. They recommend noninvasive techniques such as Echocardiogram or cardiac MRI if less suspicious for MINOCA, but for nonobstructive coronary dysfunction such as coronary vasospasm or microvascular disease, more invasive strategies are recommended instead¹⁵. This proposed algorithm is one of the first of its’ kind, and it carries a lot of

weight coming from the American Heart Association. It can help clinicians to make important strides in getting to the root cause of coronary dysfunction and then prescribe appropriate treatment regimens and improve overall outcomes¹⁵. Our proposed study would be applying part of this algorithm as our participants would have a high suspicion for nonobstructive dysfunction on presentation, being all women with ACS, and could provide further evidence for widespread implementation of this diagnostic algorithm or something similar.

This novel statement also suggests potential therapies for the variety of etiologies that could be diagnosed if this diagnostic algorithm was implemented, a field which is also in desperate need of further clinical trials as the diagnostic research is progressing^{15,30}. Some of their suggestions based on what research is currently available include aspirin and another antiplatelet agent for plaque disruption, calcium channel blockers for coronary vasospasm, and calcium channel blockers and beta blockers for microvascular dysfunction¹⁵. The Women's IschemiA Trial to Reduce Events in NonObstructive CAD (WARRIOR) trial is a new study currently in progress that aims to further examine the best treatment pathways for women with nonobstructive coronary dysfunction³¹. This trial is multicenter, prospective, and randomized with a blinded outcome evaluation, and is comparing intensive medical therapy with statins and angiotensin converting enzyme inhibitors (ACE-I) or receptor blockers (ARB) to the current standard of care on the occurrence of MACE³¹. Hopefully the results of this trial will help guide treatment in women with nonobstructive coronary dysfunction going forward.

2.4 Review of Diagnostic Modalities for Nonobstructive Coronary Dysfunction

Although there is no true consensus on the best diagnostic modality for nonobstructive coronary dysfunction, there have been more recent studies on noninvasive techniques such as cardiovascular magnetic resonance (CMR), computed tomography (CT), and functional stress testing^{8,32-34}. Additionally, Positron emission tomography (PET) myocardial perfusion imaging (MPI) can also quantify coronary flow reserve (CFR) of coronary vessels and is thought to be useful in prognosis and risk assessment, especially as more facilities are combining PET and CT⁸. These imaging techniques aim to do a similar job as a more invasive testing procedure with the added benefits of being less limited by cost and perhaps more accessible. However, for our study, the participants we are recruiting would be receiving an invasive coronary angiogram regardless, and the additional invasive procedure we propose would not add much time or effort to what is already being done. Patients that do not require coronary angiogram initially may be better served by these noninvasive techniques.

In the WISE study, one of the more invasive diagnostic modalities they tested was coronary reactivity testing (CRT) in which acetylcholine was infused in various concentrations into the coronary arteries (specifically the left anterior descending or LAD) of patients with ACS and nonobstructive coronary dysfunction and pressures were measured in the left ventricle and aorta to look for microvascular disease^{20,35-37}. They then examined subsequent adverse events and MACE, finding that only two participants (0.7%) had serious in-procedure events of dissection from the doppler wire not requiring intervention and a focal coronary spasm prior to acetylcholine infusion treated with nitroglycerin²⁰. Another two women (0.7%) had adverse events in procedure which were

a transient air microembolism that resolved with supplemental oxygen and a deep vein thrombosis (DVT) a month afterwards that resolved with anticoagulation²⁰. As for MACE in these participants, which included, death, MI, stroke, or hospitalization for heart failure, there was a rate of 8.2% in the following five and a half years²⁰. The low rates of serious and general adverse events in-procedure and right afterwards is reassuring for an invasive procedure in a high-risk population.

In the WISE trial, to discuss this first invasive intervention more specifically, assessing microvascular reactivity with CFR was measured by injecting adenosine in two increasing amounts into the coronary arteries and taking a ratio of peak velocity to rest velocity with each infusion (CFR ≥ 2.32 was considered normal)²³. When examining MACE with this technique, rates of MACE over 10 year follow-up were increased in participants with a low CFR (p = 0.008 for 3-component MACE and p = 0.028 for 4-component MACE) and low CFR levels independently, statistically significantly predicted the 4-component MACE even when corrected for baseline characteristics (HR 1.06, 95% CI 1.004-1.12, p = 0.035)²³. Although this trend of low CFR being a predictor of MACE has been previously established, and that CFR is often lower in women³⁸, this study was able to replicate it with longer-term follow-up. The authors again reiterate that although these procedures are invasive, they are fairly safe with low rates of complications or adverse effects, making them a considerable option for going women with ACS and nonobstructive coronary dysfunction^{23,39}.

Another invasive technique used to further evaluate the underlying etiology of nonobstructive coronary dysfunction in the WISE study is to infuse acetylcholine to assess for vessel reactivity and coronary vasospasm⁴⁰. They did this by infusing

acetylcholine into the coronary arteries for two three-minute periods then measuring blood flow, pressure, and vessel diameter to assess for changes²³. With this technique, the researchers found that decreases in coronary blood flow by 10% increased the mortality risk by 23% (HR 1.23, 95% CI 1.04-1.45, p = 0.015), as well as a 16% increase in both 4-component and 3-component MACE (HR 1.16, 95% CI 1.06-1.27, p = 0.001 and HR 1.16, 95% CI 1.05-1.28, p = 0.003 respectively)²³. All this is to say that this invasive, reasonably safe technique appears to be effective in identifying participants with coronary arteries prone to vasospasm that puts them at higher risk for MACE. The authors do reiterate here, though, that testing requires specific training and is not very cost effective, despite its diagnostic effectiveness. Additionally, results here may be skewed because even though coronary dysfunction was further characterized, because there is no universal treatment algorithm for these types of diseases yet, many of the participants went without treatment and this could have impacted the occurrence of adverse outcomes as well²³.

2.5 Review of Relevant Methodology

The following sections will review current literature and the methodology used relevant to this proposed study.

2.5.1 Selection of Intervention

As previously discussed, while more research is being conducted on less invasive testing recently, invasive testing such as the proposed additional physiologic testing after coronary angiogram seems to be effective in further characterizing nonobstructive

coronary dysfunction. Not only is this evident in the WISE trial, but another trial titled the CorMicA trial that was conducted in 2018 utilized a similar intervention in both men and women^{12,23}. They called their intervention an “interventional diagnostic procedure” in addition to coronary angiography which involved assessing the LAD coronary artery’s coronary flow reserve (CFR), index of microcirculatory resistance (IMR), and fractional flow resistance (FFR) (to determine a lesion’s functional significance⁴¹) while infusing adenosine to evaluate microvascular dysfunction, as well as evaluating for coronary vasospasm while infusing acetylcholine¹². They examined the effect of this on subsequent angina using the Seattle Angina Questionnaire, finding that angina was improved in those that received the procedure in their randomized controlled trial¹². This study was another, similar to the WISE study, that showed an invasive procedure that had a positive impact on outcomes for its nonobstructive coronary dysfunction participants. As there are many hospitals across the state of Connecticut with coronary angiography capability staffed by very capable interventional cardiologists that perform similar interventions daily, we chose to mimic our own intervention after Ford et al.’s in the CorMicA trial to build upon the data they have already compiled.

Additionally, a study conducted by Ahmed et al. on the safety of FFR and IMR measurements with adenosine found that adverse effects were self-limited and serious events such as STEMI, NSTEMI, and dissection were exceedingly rare, reinforcing the overall safety of our chosen procedure⁴². A study by Fearon et al. touted IMR as a widely available quantitative, and easily reproducible diagnostic strategy and found IMR > 40 to be stronger predictor of adverse outcomes⁴³. This same trend was recognized in a trial by Fahrni et al. in 2017⁴⁴. Garcia et al. advocated for the use of FFR and CFR together in

tandem to get the best picture of what is happening in the coronary arteries, as we propose to do in our study⁴⁵.

2.5.2 Selection of the Outcome

Many of the studies we have previously discussed have evaluated MACE as their outcome. While we are basing our intervention on the CorMicA trial, their primary outcome is the Seattle Angina Questionnaire and only examined angina in patients¹². By using MACE, we can include angina along with other adverse outcomes patients with ACS and nonobstructive coronary dysfunction are likely to have such as stroke, healthcare utilization, and even death from a cardiovascular cause. This is also a hard outcome that can be measured from hospital system EMR rather than a subjective questionnaire filled out by the patient themselves and not as subject to recall bias. Other studies that have chosen MACE as their primary outcome include a 2019 study in China by Abdu et al. examining MI in MINOCA patients and a 2020 study by Dreyer et al. examining Medicare patients with MINOCA compared to those with obstructive MIs^{46,47}. Both studies found that older patients with MINOCA had worse outcomes^{46,47}. Other studies using MACE as their outcome have found the opposite trend, that MINOCA patients had lower rates of MACE than obstructive disease patients, such as one study in Spain by Garcia-Blas et al. and another in Poland by Zandecki et al.^{48,49}. Regardless, though, using MACE as our primary outcome like many other studies have allows us to compare and contrast results with others in the field to ultimately contribute to a wider body of knowledge. Additionally, by breaking down each individual component of MACE as our secondary outcome, we can also compare data to other studies that use

various combinations of MACE because MACE is defined slightly differently for each specific study.

2.5.3 Selection of the Study Population

While several studies, including the CorMicA trial, recruited both men and women for their studies, the general trend is that nonobstructive diseases disproportionately impact women¹². Even in the CorMicA trial, about 74% of all patients were women¹² and the nature of the WISE study was to recruit only women, as well. As also previously stated, women and men have differing pathophysiology of disease, and by recruiting solely women, who are also understudied as a whole, we can minimize any sex differences that may have been playing a role in the outcomes of studies that recruited both sexes. This also contributes to the novelty of this study as a whole, being that there are so few studies that only recruited women.

As far as choosing baseline characteristics for our study population, we chose many that were similar to those in the CorMicA study such as age, medication usage, comorbid conditions such as diabetes and dyslipidemia, smoking status, and BMI. We also added some of our own that we thought may be interesting or potentially contributory and would need to be controlled for in multivariate analysis such as psychosocial factors, menopausal status, marital status, and prior therapies¹². Many of these baseline characteristics were also collected in other studies such as the WISE study^{19,23,50}.

2.5.4. Selection of Study Type

While much of the current literature consists of randomized clinical trials or cohort studies, we decided to go in a different direction and make our study a comparative effectiveness trial. By using this type of trial, we are able to rely on historical data from the hospitals we choose as our “control group” and enroll every eligible participant into the intervention we are proposing⁵¹. This eliminates the need for any blinding and helps us to achieve the appropriate sample size and power within the year-long time frame. This type of study also contributes to the novelty of our research, as in the literature searching, we were unable to find other studies that were conducted this way for female patients with nonobstructive coronary dysfunction. The closest study found was one by Kishi et al. in 2020 that examined the relationship between plaque burden in coronary arteries evaluated by cardiac CT and MACE that utilized a comparative effectiveness study design⁵². They found success through achieving statistical significance in their several of their results with this model and its feasibility of comparing a novel intervention to the current standard of care, just as we propose to do⁵².

2.7 Conclusion

Overall, there are very clear gaps in the literature as far as nonobstructive coronary dysfunction in women. Women as a whole are understudied in this field, as well as more likely to have nonobstructive disease rather than obstructive. Nonobstructive diseases additionally require diagnostic modalities that are not only accessible and feasible, but also that are effective enough to further characterize the underlying mechanism of disease so that patients can get appropriate treatment which should, in turn, improve outcomes such as MACE. The proposed study aims to do just that,

implementing additional invasive physiologic testing for women with ACS that are likely to have nonobstructive disease in hospitals across Connecticut to determine if there is an impact in MACE going forward.

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Chapter 3 – Study Methods

3.1 Study Design

The proposed study will be a multicenter, single-arm, prospective comparative effectiveness clinical trial. We will target hospitals in the state of Connecticut that have coronary angiography capability by working with the states' two largest healthcare systems, Yale New Haven Health and Hartford Healthcare. These hospitals would include Yale New Haven Hospital, Greenwich Hospital, Bridgeport Hospital, Lawrence and Memorial Hospital, and Westerly Hospital within the Yale New Haven Health System, as well as Hartford Hospital, Backus Hospital, The Hospital of Central Connecticut, St. Vincent's Hospital, and Windham Hospital within the Hartford Healthcare System. Because this is a comparative effectiveness trial, we would enroll every patient able to give informed consent and meeting inclusion criteria into the intervention and compare outcomes with historical data on MACE rates from the WISE trial for women that underwent coronary angiography alone without further physiologic testing¹⁹. The total proposed timeline for the study would be 24 months with an 11-month recruitment period and 12-month follow-up period to assess for occurrence of MACE. Hospital Electronic Medical Record (EMR) system will be used to monitor for MACE in the following year. Both hospital systems use Epic for their EMR.

3.2 Study Population and Sampling

Because women are frequently left out of clinical trials and the evidence-based medicine is tailored to male participants, our study would solely recruit women. The study population would include women over the age of 18 presenting to Connecticut

hospitals (with coronary angiography plus invasive physiologic testing capability) with acute coronary syndrome and found to have nonobstructive disease on coronary angiogram. We will sample using convenience sampling so that any woman coming through the hospital doors with acute coronary syndrome will be recruited, contingent upon their initial coronary angiogram results showing nonobstructive disease. Including all hospitals from the two largest health systems in Connecticut that have coronary angiogram capability increases the likelihood that we will have a representative sample for adult women in the state of Connecticut. These 10 hospitals are spread throughout the state, and if women with acute coronary syndrome presented to a smaller hospital within the same system, they would need to be transferred to a hospital with coronary angiography capability regardless, so these women would be accounted for as well. Additionally, the nature of a comparative effectiveness study is that every woman with the potential to be included will have the opportunity to be included, as the “control group” is historical data from prior patients at each participating hospital, making the data more generalizable than in a randomized controlled trial which can be subject to internal bias. Women will be excluded from the study if they are found to have non-cardiac angina, Takotsubo cardiomyopathy, or an ST-elevation myocardial infarction (STEMI).

3.3 Subject Protection and Confidentiality

Prior to the beginning of the study, institutional review board (IRB) approval will be obtained through the Yale University School of Medicine. The procedure described in section 100 PR.1 Review by a Convened IRB will be followed while submitting an application. This application will include a detailed protocol, a plan and materials for

recruiting, consent forms, Health Insurance Portability and Accountability Act (HIPAA) forms, and a funding application. Consent forms (Appendix 1) will be given at the time of recruitment on presentation to the Emergency Department to either the participant or their healthcare proxy with clearly outlined study protocols as well as any potential benefits and risks for participating in the study. While it may be challenging to obtain informed consent in an acute setting, the patient will already be consenting for a coronary angiogram to be performed, so we would come in afterwards to explain the additional testing and to answer any questions or concerns participants may have. All patient data will be stored on an encrypted server and de-identified of protected health information where possible, closely following all HIPAA guidelines.

Because our study has the potential to include pregnant patients and those of childbearing age, extra precautions will be taken to protect this vulnerable population. We will follow section 330.1 Requirements for Approval of DHHS-funded Biomedical or Behavioral Research Involving Pregnant Women or Fetuses to do so, as it is important to include potentially pregnant patients in our study population because MACE may cause significant harm to both mother and fetus, and the goal of this study is for our intervention to impact subsequent MACE. Additionally, the risks associated with a woman experiencing MACE outweigh those of performing additional physiologic testing, making it ethical to include these women in the study population.

3.4 Recruitment

By utilizing convenience sampling, we will recruit every adult woman over age 18 that meets inclusion criteria presenting with ACS to the aforementioned Connecticut

hospitals with coronary angiography capabilities. Participants will be consented prior to coronary angiogram and will remain in the study to receive the additional physiologic testing if they are found to have nonobstructive disease in their major coronary arteries. If a participant presents with a STEMI on EKG or is found to have obstructive coronary artery disease, Takotsubo cardiomyopathy, or a non-cardiac cause of ACS, they will also be removed from the study population and will not receive the intervention.

3.5 Study Variables and Measures

The intervention will be performing coronary angiogram plus invasive physiologic testing of the left anterior descending artery (LAD). The invasive physiologic testing involves inserting a pressure wire to measure coronary reserve flow (CRF), index of microcirculatory resistance (IMR) and fractional flow reserve (FFR) while infusing adenosine (to assess for functionally obstructive epicardial disease and microvascular dysfunction) and acetylcholine (to detect coronary vasospasm). This intervention is described in more detail by Ford et al. for the CorMicA trial, and we will be modeling our intervention after theirs¹².

The primary endpoint for our study will be occurrence of MACE at one year after the invasive physiologic testing is performed. This is a dichotomous variable, as participants will either have MACE occur, or they will not. Secondary outcomes will include the median number of each individual MACE component that occurs over one year to examine each component on its own as compared to any MACE as a whole.

3.6 Blinding

Our study does not have a control group and will instead be comparing the outcomes of our participants to historical data on adult female patients that presented with ACS, received a coronary angiogram, and was found to have nonobstructive disease from each participating hospital. Due to the lack of a control group, every participant will receive the intervention and therefore will not need to be blinded to it. Additionally, researchers and those evaluating the primary and secondary outcomes will not need to be blinded to the intervention the participant received, either, as all participants received the same intervention.

3.7 Adherence

Adherence for our study primarily relies upon the training of qualified interventional cardiologists to perform the additional invasive physiologic testing while participants are undergoing coronary angiogram. We will target interventional cardiologists at participating Connecticut hospitals that have copious experience performing coronary angiograms and train them in the procedure before the recruitment period, so they are comfortable performing it for the study itself. Each provider will be required to attend a day-long training session, for which they will be compensated for their time, where they will be educated on the potential benefits of the procedure and all other study details, as well as given the opportunity to practice in a simulation. The invasive physiologic testing is at a similar level of complexity as a typical coronary angiogram, so it should not take the providers very long to feel comfortable performing it. We will also have a researcher observe the first two procedures each provider performs to assure consistency.

As far as adherence for the participants, this is a one-time procedure, so the main factor will be reporting the occurrence of MACE, or any adverse effects experienced in the year following the procedure. As MACE are often events that would cause participants to seek healthcare⁵³, we can primarily monitor this through hospitals' EMR. Additionally, each participant will be given a researcher's contact information to report any occurrence of MACE, and researchers will be instructed to reach out to each participant monthly by phone and/or email (by participant preference) to ask if MACE has occurred, and to remind them what MACE consists of.

3.8 Monitoring of Adverse Events

In the CorMicA trial, there were very few adverse events recorded as a result of the intervention, and ones that did occur were considered minor or easily reversible¹². The immediate adverse effects that we will need to monitor for during the procedure would be persistent atrial fibrillation, and paroxysmal atrial fibrillation secondary to acetylcholine. In the CorMicA trial, transient bradycardia and sinus pauses were not considered adverse events, but rather expected physiologic reactions to the procedure¹². In the event that atrial fibrillation persisted and did not self-resolve within 30 minutes as occurred in the CorMicA trial for one patient, the interventional cardiologist would be advised to perform cardioversion with intravenous amiodarone while still in the cardiac catheterization lab to revert the patient back to sinus rhythm, which was successful in the CorMicA trial¹².

In the WISE trial, there were also very few adverse events. They reported one participant with a dissection from doppler wire insertion that did not require intervention,

one participant with a focal spasm prior to the invasive physiologic testing that resolved with nitroglycerin, one participant with a transient air microembolism that resolved with supplemental oxygen, and one participant that developed a DVT a month after the procedure that was effectively treated with anticoagulation²⁰. These are all very low risk of occurrence, and all amenable to treatments that any cardiac catheterization lab would have at their disposal and that the interventional cardiologists would be capable of administering.

Additionally, the nature of our outcome (MACE) is that they are adverse outcomes in and of themselves. However, these outcomes are associated with patients with acute coronary syndrome and nonobstructive coronary dysfunction in general and may or may not be a direct result of our intervention^{20,46,47}. Therefore, like any patient undergoing coronary angiogram, we will encourage our participants to both seek urgent medical attention in the setting of MACE occurring, as well as to later report this event to a researcher. As previously stated, we will also have researchers reaching out to participants monthly in addition to reviewing the EMR to assure we are aware of any occurrence of MACE.

3.9 Data Collection

Data collection will occur continuously throughout this study. When participants are enrolled in the study (or soon after the intervention, depending on timing and urgency of coronary angiogram) baseline characteristics (detailed below) will be recorded. To collect data on our primary outcome, participants will need to give permission for us to view their EMR to monitor for the occurrence of MACE in the year following the

intervention. We will also have researchers reach out monthly to the participants by phone or email to assess for occurrence of MACE. The researcher will be required to fill out the Participant MACE Form (Appendix 2) for each participant during these monthly check-ins and evaluation of the EMR. All data collection information will be recorded on encrypted servers. If at any time a participant wishes to withdraw from the study, their associated information and data will be permanently deleted.

3.10 Sample Size Calculation

To calculate sample size for this comparative effectiveness trial, we will be utilizing data from the WISE study and the Power and Sample Size Calculator provided online by the Department of Biostatistics at Vanderbilt University¹⁹. From the WISE study, their primary composite endpoint was cardiovascular events including MI, and hospitalization for heart failure, stroke, or cardiac mortality which is similar to our proposed MACE outcome¹⁹. They found that about 2% of the asymptomatic (control) group met the primary composite endpoint while the symptomatic group was split into normal coronary arteries and nonobstructive coronary artery disease for which 8% and 16% respectively met the primary composite endpoint¹⁹. To group these two symptomatic groups together, we found that 8% of 318 participants with normal coronary arteries is about 25 participants and 16% of 222 participants is about 35 participants, so added together, 60 of 540 participants or about 11% of symptomatic patients met the primary composite endpoint. We then calculated the sample size based on a power of 0.80 and a Type I (alpha) error of 0.05 estimating that the probability of the outcome for a control participant (p_0) to be about 2% and the probability of the outcome for an experimental

participant (p1) to be about 11%. This gives us a sample size of 117 participants to reach this statistical power and Type I error. Detailed images and information regarding our sample size calculation can be found in Appendix 3.

3.11 Statistical Analysis

Baseline characteristics (Table 1) for each participant that will be reported and analyzed will include age, comorbid conditions (history of CVD or stroke, diabetes, dyslipidemia, hypertension, severe COPD, overweight/obesity, or history of pregnancy complication such as hypertension, premature delivery, gestational diabetes, or preeclampsia), current medications (including statins, antihypertensives, antiplatelets, anti-ischemics, or cholesterol-lowering), cardiovascular risk factors (such as smoking), prior therapies (percutaneous coronary intervention or stents placed in the coronary arteries), psychosocial factors (such as perceived stress evaluated by the Perceived Stress Scale (PSS), depression evaluated by the Patient Health Questionnaire-9 (PHQ-9), anxiety evaluated by the General Anxiety Disorder-7 (GAD-7), household income, food security, housing security, or transportation security), marital status, and menopause status. Dichotomous, categorical, and ordinal variables, such as comorbid conditions, medications, cardiovascular risk factors, prior therapies, psychosocial factors, marital status, and post-menopausal status will all be analyzed as proportions. Continuous variables including age is assumed to be normally distributed and will be analyzed as a mean with a standard deviation.

Characteristic	Type of Variable	Number of Study Participants
Age	Continuous	
Comorbid Conditions – history of CVD or stroke, diabetes, dyslipidemia, hypertension, premature delivery, gestational diabetes, preeclampsia	Dichotomous	
Medications – statins, antihypertensives, antiplatelets, anti-ischemics, cholesterol lowering	Dichotomous	
Cardiovascular Risk Factors (i.e. smoking)	Dichotomous	
Prior Therapies (i.e. PCI/stenting)	Dichotomous	
Psychosocial Factors – perceived stress, depression, anxiety, household income, food security, housing security, transportation security	Categorical – Ordinal (stress, depression, anxiety, income) Dichotomous (food, housing, transportation security)	
Post-menopausal	Dichotomous	
Marital Status	Categorical - Nominal	

Table 1. Baseline Characteristics of enrolled participants

The primary outcome, MACE, is a dichotomous variable and will be analyzed as a proportion using a Chi-square test for bivariate analysis. To consider any potential confounding effects of baseline characteristics as well as differences in care patterns by hospital, we will employ a hierarchical multivariate analysis using a logistic regression. The secondary outcomes will be the median number of each individual MACE component (recurrent angina pain, development of heart failure, non-fatal infarction,

presentation to the Emergency Department with cardiovascular-related illness, admission to the hospital for cardiovascular-related illness, repeat PCI, CABG, stroke, and all-cause mortality) that occurs over the one-year, post-intervention period and these are continuous, not normally distributed variables. They will be analyzed as means with standard deviations using a Student t-test. Significance will be defined as $p \leq 0.05$.

3.12 Timeline and Resources

The timeline for this study will be a total of 24 months. After receiving IRB approval, we will aim to begin the study in January 2022. During the first month, we will properly train the interventional cardiologists that will be performing the invasive physiologic testing at each participating Connecticut hospital. There will be a day-long training at each hospital involving an overview of the study protocol, as well as a summary of potential benefits and adverse outcomes, followed by a question-and-answer session. There will then be an opportunity to practice the intervention through a virtual simulation. These clinicians will all be familiar with typical coronary angiogram, and because the procedure itself (infusing into and taking measurements of coronary arteries using a guidewire) is similar to standard practice, the one-day training period should be sufficient. However, we will have a researcher observe the first two sessions each provider conducts with study participants, as well as one subsequent random session, to assure consistency and that there are no further questions or clarifications. After this first month of training, we will begin the recruiting period for the next 11 months, cutting off enrollment at December 31, 2022 so as to allow for the full year of follow-up to assess

for the occurrence of MACE. From January 1, 2023-December 21 2023 there will be follow-up to assess for the primary and secondary outcomes.

Relevant personnel will include a principal investigator to oversee all areas of the study. Additionally, we will need one research assistant assigned to each of the 10 participating Connecticut hospitals respectively. They will be in charge of helping educate the interventional cardiologists prior to enrollment, the actual enrolling and consenting of participants at the beginning of the study, and monthly follow-up with patients and their EMR after the intervention to assess for occurrence of MACE. Lastly, there will be one physician assistant student assigned to fill in any gaps in data collection and to assist in statistical analysis and the writeup of the study afterwards.

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Chapter 4 – Conclusion

4.1 Advantages and Disadvantages

This study has several strengths. Through the nature of a comparative effectiveness trial with every enrolled participant receiving the intervention and by targeting the two largest health systems in the state of Connecticut, I believe we will be reaching a large, diverse sample that is representative of the target population. This also means that every participant that enrolls has the opportunity to achieve the potential benefits of the additional invasive physiologic procedure. All of these factors make our study highly generalizable. Additionally, as a one-time procedure, there is minimal follow-up required for participants other than reporting if MACE occurs within the year after the procedure, which can also be cross-checked using each hospital system's EMR. This decreases the likelihood that patients will be lost to follow-up as can be the case in studies that require more patient participation throughout the following year.

Despite the many strengths, this study is not without limitations. One limitation of this study is the cost. While the goal of this intervention is to decrease adverse outcomes in the long-term for patients, which may result in less healthcare utilizations and saving money in that respect later, the up-front costs will be high. Firstly, we will need to train the interventional cardiologists performing the intervention and compensate them for their time, as well as make sure each cardiac catheterization lab has access to the proper tools and materials necessary for the intervention. We also need to compensate 10 research assistants (one for each hospital site) and the primary investigator for the two-year duration of the study. This is important research, though, that has the potential to

have a large, lasting impact on many patients, and with the proper time to apply for grant funding, we will be able to fund this study.

Another potential limitation is obtaining informed consent in an acute environment. Although we are excluding patients with STEMIs that need to go to the cardiac catheterization lab urgently, we are recruiting patients that are in the ED for ACS and this can be a stress-inducing environment for patients and family members alike. However, as mentioned in Chapter 3, patients that qualify for our study will already be consenting to receive a coronary angiogram while in the ED regardless, and our researchers will be giving potential participants all study details including all known potential risks and benefits. They will also be sure to answer all questions and concerns the participant or healthcare proxy may have prior to enrollment to ensure they have all the information required to make an informed decision to participate or not. If at any time the participant chooses to leave the study after consenting, their information will be removed from encrypted servers, and they can be assured that they will continue to receive high quality care as per usual.

4.2 Clinical and Public Health Significance

This study has the potential to make a real difference, not just in the field of cardiology, but in clinical practice as a whole. As previously mentioned, CVDs are still the greatest cause of mortality for women across the world, and nonobstructive coronary dysfunction is more and more frequently the underlying cause^{1-3,12-15}. In recent studies, invasive physiologic testing with acetylcholine and adenosine infusion into the coronary arteries to assess for microvascular dysfunction or coronary vasospasm, like we propose

to implement here, has shown to be a safe, effective method of further characterizing the diagnosis of nonobstructive coronary dysfunction²³. For many patients, a diagnosis can be life changing. Not only is coming to the correct diagnosis a potential answer to what is causing the patient's symptoms, but it is also a critical step in getting the proper treatment for the underlying etiology of disease. With disease-specific treatment, we can impact overall outcomes for our patients, which can lead to less utilization of the healthcare system and decreased costs because adverse outcomes such as MACE are frequent reasons patients need to seek healthcare. If we can train interventional cardiologists across the country to perform this extra procedure while already doing a coronary angiogram in the absence of obstructive disease, women in every state could have decreased rates of MACE, including preventing unnecessary deaths. Admission to the hospital is a bad prognostic sign, and should be avoided where possible⁵⁴⁻⁵⁶.

Providers in any field are likely to come across these patients, and with sound, evidence-based research like this proposed study to back up proposed diagnostic algorithms such as Tamis-Holland et al.'s "Traffic Light" Sequence¹⁵, providers can feel confident in recognizing the signs symptoms of ACS with a potential nonobstructive etiology and knowing what type of testing to order or referral to make. This study can also lay a strong foundation for further research in disease-specific treatment algorithms for nonobstructive coronary dysfunction, which is another area of up and coming research that needs more clinical trials in the future.

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Appendix 1: EFIC Consent Form

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE YALE-NEW HAVEN HOSPITAL

Study Title: Coronary angiogram plus invasive physiologic tests in women with nonobstructive coronary dysfunction

Principal Investigator (the person who is responsible for this research): Megan McCauley

Phone Number: (413) 464-3510

Research Study Summary:

- We are asking you to continue being a part of our research study.
- The purpose of this research study is to determine whether coronary angiogram plus invasive physiologic testing for women with acute coronary syndrome found to have nonobstructive coronary dysfunction results in a decreased occurrence of major adverse cardiac events (MACE) in one year.
- Study procedures will include: Everyone in this study will receive a coronary angiogram and if there is less than 50% obstruction of the blood vessels in your heart by plaque buildup, you are considered to have “nonobstructive” coronary disease. You will then receive an additional invasive physiologic procedure that involves inserting a guidewire to infuse adenosine and acetylcholine to assess for any abnormalities and measuring pressures in the vessels. If you are found to have more than 50% obstruction, you will not qualify to participate in this study and will not receive the additional physiologic testing or be asked to follow-up with us. We will permanently delete all of your information from our encrypted servers.
- There risks to participating in this study are minimal and reversible. Because it is a one-time procedure, the risks often happen at the time of the procedure and include atrial fibrillation that is reversible on its own or atrial fibrillation that requires a very effective medication called amiodarone to reverse. Very few participants in prior studies experienced this adverse effect.
- Taking part in the continuation of this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to continue to participate; if so, you will have to sign this form.

Why is this study being offered to me?

We are asking you to take part in a research study because **you are an adult female that came to the Emergency Department (ED) and your ED provider believes you are having an Acute Coronary Syndrome requiring a coronary angiogram.**

Who is paying for the study?

Yale School of Medicine Physician Associate Program

What is the study about?

The purpose of this study is to evaluate if coronary angiogram with invasive physiologic testing is a viable option for improving diagnostic classification in women with acute coronary syndrome and nonobstructive coronary dysfunction. You have already consented to receive a coronary angiogram as part of your diagnostic workup for your acute coronary syndrome. The physician performing the angiogram will run a few extra tests if your coronary arteries show <50% obstruction. This includes infusing acetylcholine and adenosine into your coronary arteries and measuring pressures and taking measurements to observe for microvascular dysfunction or coronary vasospasm.

What are you asking me to do and how long will it take?

You are being asked to participate in this study because you are an adult female that met enrollment criteria by presenting to the ED with Acute Coronary Syndrome and are being referred for urgent coronary angiogram. While receiving a coronary angiogram in the cardiac catheterization lab, if your coronary arteries have from 0-49% obstruction with plaque, you are considered to have “nonobstructive coronary dysfunction” and qualify to continue participating in the study. While you are still in the catheterization lab under anesthesia, the interventional cardiologist that has been training in this procedure will perform additional invasive physiologic testing. This testing has been shown to be very safe with low risks of complications or adverse effects and has not increased hospital stay time.

The additional invasive physiologic testing specifically involves inserting a pressure wire through your radial artery into your Left Anterior Descending (LAD) coronary artery to measure coronary reserve flow (CRF), index of microcirculatory resistance (IMR) and fractional flow reserve (FFR) while infusing adenosine (to assess for functionally obstructive epicardial disease and microvascular dysfunction) and acetylcholine (to detect coronary vasospasm).

As this is a one-time procedure, the follow-up required would be reporting and Major Adverse Cardiac Events (MACE) that may or may not occur over the next year. MACE includes recurrent angina pain, development of heart failure, non-fatal infarction, presentation to the Emergency Department with cardiovascular-related illness, admission to the hospital for cardiovascular-related illness, percutaneous coronary intervention

(PCI), coronary artery bypass grafting (CABG), stroke, and all-cause mortality. You would give us access to your online medical record to determine if any of these events occurred to you and if so, how many. Additionally, you would allow a research assistant to reach out to you monthly to assess if one of these events occurred to you in the past month but did not cause you to seek medical care.

What are the risks and discomforts of participating?

There are minimal side effects associated with this additional invasive physiologic procedure reported in prior studies. Most reported were minor or easily reversible while still in the cardiac catheterization lab.

Potential Adverse Events Reported from Prior Studies:

One participant experienced a dissection (or false passage) of their coronary artery from pressure catheter insertion. This did not require any intervention as blood flow was not detrimentally impacted.

Another participant experienced a focal spasm of their coronary artery after the coronary angiogram and prior to the invasive physiologic testing that resolved soon after with the administration of intravenous nitroglycerin.

One other participant experienced transient air microembolism that resolved with supplemental oxygen.

One more patient developed a deep vein thrombosis 1 month after the procedure that resolved with guideline-approved anticoagulation.

A few patients also experienced transient atrial fibrillation that self-resolved. One patient had atrial fibrillation that persisted >30 minutes that resolved when give intravenous amiodarone while still in the cardiac catheterization lab.

These are the only risks we are currently aware of, but there is always a possibility of unforeseen risks.

Reproductive risks:

There have been no reports of harm to pregnant patients or their babies from this intervention, and the risks posed by MACE to the general population are considered worse, so we allow pregnant patients to be a part of this study if they so choose.

How will I know about new risks or important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study.

How can the study possibly benefit me?

This study may or may not help you, but we hope it will decrease your risk for subsequent MACE in the future. Less risk for MACE means less need to seek healthcare, and less cost for you due to seeking this healthcare. We also hope that this will give us further insight into what is causing your Acute Coronary Syndrome and Nonobstructive coronary dysfunction so we can correctly diagnose you and better treat the cause.

How can the study possibly benefit other people?

The benefits to science and other people may include implementing and making accessible this additional testing in hospitals across the country so that others may receive a clear diagnosis for their nonobstructive coronary dysfunction and also receive the best treatment possible so they also have decreased risks of MACE.

Are there any costs to participation?

You will not have to pay for taking part in this study.

Will I be paid for participation?

You will not be paid for taking part in this study.

How will you keep my data safe and private?

We will keep all information we collect about you completely confidential. We will only share it with others if you agree to it or when we have to do it because U.S. or state law requires it. We will keep all data related to your care password protected in a secure database.

When we publish the results of the research or talk about it in conferences, we will not use your name or other identifying information, such as your address or date of birth. We will also not share information about you with other researchers for future research.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called “Protected Health Information.” It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.

- The entire research record and any medical records held by **your other healthcare providers**
- Records about phone calls made as part of this research
- Records about your study visit
- Information obtained during this research regarding
 - Records about your medical condition
 - Records about the study intervention

How will you use and share my information?

We will use your information to conduct the study described in this consent form.

We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.

- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about **catheter, guidewire, and pressure-wire** involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor or manufacturer of study drug/device
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to continue to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to **Megan McCauley** at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctors outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. **This may occur if you are discovered to not meet enrollment criteria, such as if you are: under 18 years of age, a prisoner, or ward of state.**

What will happen with my data if I stop participating?

If you decide to stop participating in the study, all data and images associated with your name will be deleted from our database.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.
If you have questions later or if you have a research-related problem, you can call the

Principal Investigator at **(413) 464-3510**.

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

_____	_____	_____
Participant Printed Name	Participant Signature	Date
_____	_____	_____
Person Obtaining Consent	Person Obtaining Consent	Date
Printed Name	Signature	
_____	_____	_____
Legally Authorized Representative	LAR Signature	Date
Name		

Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only. If the interpreter is affiliated with the study team, the signature of an impartial witness is also required.

Print name of interpreter: _____

Signature of interpreter: _____ Date: _____

An oral translation of this document was administered to the participant in
_____ (state language) by an individual proficient in English and
_____ (state language).

Print name of impartial witness: _____

Signature of impartial witness: _____ Date:

Appendix 2: Participant MACE Form

Definition of MACE

Major Adverse Cardiac Events including:

- Recurrent angina pain
- Development of heart failure
- Non-fatal infarction
- Presentation to the Emergency Department with cardiovascular-related illness
- Admission to the hospital for cardiovascular-related illness
- Percutaneous coronary intervention (PCI)
- Coronary artery bypass grafting (CABG)
- Stroke
- All-cause mortality

Over the past month, did participant number _____ experience...

<u>Months</u> <u>Post-</u> <u>Intervention</u>	1 mo	2mo	3mo	4mo	5mo	6mo	7mo	8mo	9mo	10mo	11mo	12mo	<u>Total</u>
<i>MACE</i>													
<i>Recurrent angina pain</i>													
<i>Heart failure</i>													
<i>Non-fatal Infarction</i>													
<i>ED presentation (CV related)</i>													
<i>Hospital Admission (CV related)</i>													
<i>PCI</i>													
<i>Stroke</i>													
<i>All-cause mortality</i>													
<i>Total</i>													

***Directions: Please fill in the participant identification number in the blank above. Next, fill in which (if any) and how many MACE occur in the table above for each participant then calculate the total number of MACE.**

Appendix 3: Sample Size Calculation

Sample Size based on a dichotomous variable using the Power and Sample Size Calculator provided online by the Department of Biostatistics at Vanderbilt University (<https://vbiostatps.app.vumc.org/ps/>).

- **Type I error (alpha) = 0.05**
- **Power = 0.80 (beta = 0.20)**
- **Probability of outcome for control participant = $p_0 = 2\%$**
- **Probability of outcome for experimental participant = $p_1 = 11\%$**

Independent / Prospective / Two proportions /
Uncorrected chi-square test

Output: Sample size

+ Add line

Type I Error (α)



Sample size (Computed value)



Power



Probability of the outcome for a control patient (p_0)



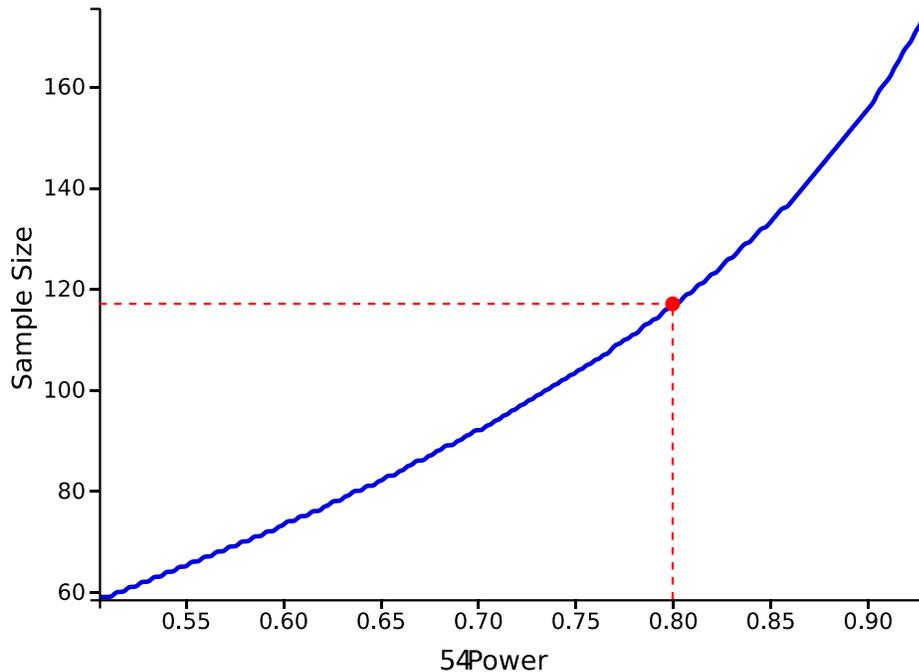
Probability of the outcome for an experimental patient (p_1)



Ratio of control/experimental subjects (m)



Sample Size vs. Power



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