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This document below is the Study Protocol including the Statistical Analysis of The Clinical Impact of Stress CMR Perfusion Imaging in the United States (SPINS): A Global CMR Registry Substudy (NCT03192891).

Sincerely,

Raymond Y. Kwong, MD MPH

The Clinical Impact of Stress CMR Perfusion Imaging in the United States (SPINS): A Global CMR Registry Substudy

Last approval date: October 29th, 2018

Background

Numerous single-center studies have indicated gadolinium-enhanced stress CMR perfusion imaging has excellent diagnostic accuracy for coronary artery disease and negative clinical event rates, with its diagnostic accuracy exceeding nuclear scintigraphy. However, current prognostic evidence supporting clinical use of stress CMR is limited by study size, single-center settings with a predominance of academic centers, and a lack of "real-world" study design. Large-scale multicenter real-world evidence from a registry will provide the much needed information to guide evidence-based clinical adaptation that benefits patient care.

The Global Cardiac Magnetic Resonance Registry (GCMR) registry effort by the Society for Cardiovascular Magnetic Resonance (SMCR) constitutes the only current global effort that includes multiple international CMR programs that span academic, community hospital, and private practice settings (http://www.gcmr-scmr.org/). This is also the only CMR registry that includes a large number of CMR sites in the United States. The GCMR is currently lead by Prof. Raymond Kwong under the direction of the SCMR Executive Committee, the Chief Executive Officer, and the Board of Trustees. This leadership structure within the SCMR guarantees continuity and consistent quality for many years into the future. All of the data contributed by participating sites and the web database structure (http://www.gcmr-scmr.org/) are owned by the SCMR.

Based on a recent survey of the current 68,500 studies contributed from US-based CMR programs in the GCMR, there have been approximately 10,700 stress CMR perfusion studies performed since 2007. The US sites and their investigators that contributed these studies are listed in Table 1.

Investigating Team (this list may expand)
Raymond Kwong (PI)(BWH), Rory Hachamovitch (CCF), Subha Raman (OSU), Andrew Arai (NIH), Scott Bingham (UCC), Ted Martin (OHI), Scott Flamm (CCF), Nat Reicheck (SFH), Chris Kramer (UVA), James Pottala PhD, PStat (USD - Statistician).

Table 1

Site	Site Name	PI	stress CMR (estimated)
BWH	Brigham and Women's Hospital, Harvard University	Kwong	1,500
OSU	The Wexner Medical Center, The Ohio State University	Raman/Simonetti	2,000
NIH	National Institutes of Health	Arai	1,500
UCC	Central Utah Clinic Cardiology	Bingham	2,500
OHI	Oklahoma Heart Institute	Martin	1,000
CCF	Cleveland Clinic	Flamm, Kwon, Hachamovitch	1,000
UVA	University of Virginia School of Medicine	Kramer	700
SFH	Saint Francis Hospital, New York	Reicheck	500
USD	University of South Dakota	Pottala (statistician)	
		total number	10,700

Dr. Kwong has experience in developing web-based database infrastructures essential in conducting multicenter trials using CMR technology. His lab in Boston currently serves as the CMR core laboratory for several large-scale NHLBI-funded international trials. Dr. Kwong and the members of the investigating team have published key articles in the current literature about the clinical adaptation, strength and challenges, of stress CMR perfusion and they have extensive understanding of the needs and challenges of stress CMR perfusion in the US. The ISCHEMIA trial is the largest (US$85M) clinical trial funded by the NIH/NHLBI currently using multimodality imaging to detect moderate-high risk patients to study for potential benefits of coronary revascularization. Dr. Kwong has been intimately involved in the study design as well as the development and performance of the CMR core laboratory for the ISCHEMIA trial; he is extremely qualified to recommend the trial that best provides the needed evidence to clinically advance stress CMR perfusion in the US.

Rationale and the Expected Deliverables of this Project
This proposal (Project 1) aims to assess the clinical impact of stress CMR perfusion guided treatments on patient outcomes in a 2,200 consecutive multicenter patient cohort, referred for assessment of myocardial ischemia in the United States. In the 3 specific aims presented below, we aim to obtain real-world evidence in patient outcomes including mortality and non-fatal cardiac outcomes, downstream cardiac procedures, invasive and non-invasive testing, costs in health care dollars based on national averages, and cardiac event-weighted quality adjusted life years (QALY). We believe these specific aims will provide the *core evidence that medical insurance agencies and industries most sought after in making their reimbursement and payment decisions* in the United States, towards the use of stress CMR perfusion imaging in patients with chest pain syndromes. At the end of the funding period, we expect multiple publications to result from each of the 3 specific aims which represent these core evidence.

Study Cohort and Enrollment Criteria
Consecutive patients who underwent stress CMR perfusion imaging for evaluation of myocardial ischemia between 2008-2013.

Inclusion Criteria: all of the following at time of imaging:

a) male or female at age 35-85 years,
b) presence of either of the following sign/symptom that led to stress CMR imaging
   1) Symptoms suspicious of ischemia, or
   2) abnormal ECG with a suspicion of coronary artery disease
c) Intermediate or high risk of significant coronary disease based on <u>at least 2</u> of the following conditions:
   a. patient age > 50 for male, 60 for female
   b. Diabetes: by either history or medical treatment
   c. Hypertension: by either history or medical treatment
   d. Hypercholesterolemia: by either history or medical treatment
   e. family history of premature coronary disease: first degree relative at age <= 55 male and <=65 female
   f. Body mass index > 30
   g. Any medical documentation of peripheral artery disease
   h. Any history of myocardial infarction or percutaneous coronary intervention

Exclusion Criteria: any of the following at time of imaging:

a) Prior history of coronary artery bypass surgery (CABG)
b) Acute myocardial infarction within the past 30 days prior to CMR
c) any significant non-coronary cardiac conditions confirmed by medical documentation
   a. severe valvular heart disease,
   b. non-ischemic cardiomyopathy with LVEF <40%,
   c. infiltrative cardiomyopathy,
   d. hypertrophic cardiomyopathy,
   e. pericardial disease with significant constriction, or
d) active pregnancy,
e) any competing conditions leading to an expected survival of < 2 years
f) Known inability to follow-up due to logistical reasons (e.g. patient lives in another country where follow-up is not feasible)

Study Endpoints and Hypotheses to Test

Study Endpoints

<u>Primary outcomes</u> include all-cause mortality, acute myocardial infarction (AMI), and late coronary revascularization (PCI or CABG beyond 60 days after CMR).

<u>Secondary outcomes</u> include non-fatal cardiac events (including cardiac hospitalizations for unstable angina or heart failure, heart transplant, significant ventricular arrhythmias, and strokes), alteration of diagnostic and therapeutic decision, and cardiac event-weighted QALY.

The specific aims of this project are listed below:

Specific Aim 1 – Association of CMR ischemic burden with clinical outcomes in the real-world

To test the hypothesis that stress CMR perfusion imaging adds predictive stratification of clinical outcomes over known risk factors for patients presenting with chest pain syndromes, at moderate pre-test risk, in a multicenter real-world setting in the US. Endpoints of interests include both primary and secondary outcomes. This aim is important because it provides the prognostic association of key CMR variables of ischemia with the observed primary and secondary events without and with adjustments to known clinical markers of patient risks, annualized event rates of primary and secondary outcomes either annualized across the entire study period or at specific intervals of study follow-up (e.g. first, second, third year of follow-up etc), net reclassification index by CMR metrics of ischemia towards current guideline-supported treatments, and potential alteration of diagnostic and therapeutic thinking.

Specific aim 1 will assess the prognostic association of presence of ischemia and percent ischemic myocardium (both by CMR) with the primary and secondary clinical outcomes. In the multi-variable analyses, key known risk markers such as patient age, patient sex, left ventricular and systolic volume (LVESV), validated pretest coronary disease probability, and validated risk score (Diamond and Forrester) will be considered for inclusion in a multivariable model, and then presence or extent of ischemia by stress CMR will be added to the model to test the null hypothesis that CMR assessment of ischemia do not add prognostic value, versus the alternative hypothesis that stress CMR assessment of ischemia do add predictive value. A significance level of 0.05 will be used. Since CMR findings will affect patient management, which in turn, will affect the clinical outcomes, in a secondary analysis, cardiac treatment (e.g. revascularization) received within 60 days of the CMR will be added to the above model to account for treatment effects on the relationship between extent of ischemia and outcome. Annualized event rates of the primary and secondary outcomes, stratified by CMR ischemia (present or absent), and CMR ischemic burden (mild, moderate, high), will be determined, both unadjusted and adjusted for cardiac treatments received. We also plan to calculate net reclassification index of these CMR metrics to event-free survival (primary and secondary outcomes).

Interim analysis at the end of the 2-year study period
The study investigators agree with collaborators from Siemens and Bayer that an interim analysis at the end of the 2-year study period, of the proposed N=2,200, will inform the magnitude of the risk reduction rate. We firmly believe that the current proposed study of N=2,200 will lead to important and publishable results and we plan to publish manuscripts based on results obtained from the cohort of 2,200 patient subjects. However, this interim analysis will help to infer towards the planning of future studies and preparation of manuscripts that will provide key additional evidence regarding the clinical impact of stress CMR in the US. These actions include the possibility of proposing another study aiming at a larger sample size.

Specific Aim 2 – Assessment of the impact of CMR-guided invasive coronary revascularization, compared with medical therapy, on primary outcomes
Sub-aim 2.1 Using a propensity score-matching analysis, test the hypothesis that in real-world clinical practice that stress CMR perfusion imaging-guided use of invasive coronary revascularization (INT) (defined by INT performed within 60 days after CMR) offers *AMI-free, coronary revascularization-free, survival benefits* over medical therapy (MED) in patients with suspected ischemia. We will estimate the # lives saved per 100 patients treated with INT versus MED (based on predicted primary outcome rate amongst MED)−(predicted primary outcome rate amongst INT)
Sub-aim 2.2 Using a propensity score-matching analysis, test the hypothesis that in real-world clinical practice that stress CMR perfusion imaging-guided use of INT offers *survival benefits free of primary or secondary outcomes* over MED in patients with suspected ischemia.
Sub-aim 2.3 The preferred initial treatment for patients with stable ischemic heart disease (SIHD) is the best available medical therapy. The benefits of using physiologic ischemia-based guidance to performing INT has been shown in the FAME and FAME-2 trials where fraction-flow-reserve was used to assess physiological significance of coronary stenosis. In FAME (multi-vessel SIHD) and FAME 2 (single or multi-vessel SIHD) trials: a 29% and 66% relative risk reduction of primary outcome at 2-years were reported, respectively. CMR perfusion assessment had demonstrated remarkable correlation to FFR based assessment of coronary physiologic significance. For sub-aim 2.3, test the hypothesis that comparing to the FAME-2 primary outcome rate of patients managed by medical management alone, CMR-guided INT patients have a relative risk reduction of 2-year primary outcomes >= 30%.

Specific Aim 3 – Cost-effectiveness analysis

Using a propensity score-matching analysis, test the hypothesis that in real-world clinical practice that stress CMR perfusion imaging-guided use of INT offers *cost-effectiveness benefits* over MED in patients with suspected ischemia.

Database Infrastructure of Database and DICOM Storage

A HTTP secure web database focusing on collecting clinical data in CMR (CMR Cooperative) (https://cmrcoop.partners.org/) has been established and collecting CMR data since 2008. There are currently 45 US centers using this web-based HIPAA compatible database which allows complete de-identification of all patient information, multicenter research, and DICOM anonymized linkage and storage. In addition, this web-tool was designed to facilitate detailed but simple-to-use interface in collecting all data (below) relevant to this multicenter study. Several pages of this web-tool are displayed in the Appendix Section.

Data to Collect

a) **Patient Demographics**

Basic patient demographic data including age, gender, cardiac and non-cardiac medical history, and medications in use at the time of imaging. Detailed collection of cardiac symptoms and reasons for imaging referral including the Diamond and Forrester symptom scores, New York Heart Association Grade, pre-test CAD risk scores will be determined. Key demographic variables (amongst others) are shown in Appendix A2.

b) **CMR Imaging**

Detailed contrast uses including types, brands, dosages, and methodology of contrast injections will be collected. Retrospective review of site-reported extent of myocardial ischemia by CMR, based on a 17-segment AHA nomenclature, as "mild" (<=3 segments), "moderate" (4-7 segments), or "severe" (>=8 segments). CMR based LVEF, infarct location and number of segments with LGE. Please refer to Appendix A3 for subset of the examples of the web-based data collection.

c) **Clinical Outcomes within 4 years after CMR**

Primary outcomes: a) All-cause including cardiac mortality, b) new acute MI, within 4 years after CMR imaging, and c) late coronary revascularization (PCI or CABG beyond 60 days after CMR);

Secondary outcomes: heart failure hospitalization, unstable angina hospitalization, heart transplantation, significant ventricular arrhythmias, and strokes, within 4 years after CMR. Times to all of the above events will be collected. Other supportive data: angiographic reports including PCI details, CABG operative reports. Repeat events of all non-fatal outcomes will be collected using our web-based data structures (Appendix A4).

d) **Costs**

Please see the attached word file figure 3 and the excel file budget (GCMR stress perfusion budget).

All costs of imaging tests, medical care, and cardiac procedures will be based on regional national average inflated to the year of study analysis.

Imaging: Initial and downstream performance of any imaging studies (stress CMR, stress nuclear imaging including SPECT or PET, coronary CTA, stress echocardiography, and stress treadmill exercise test without imaging).

Medical care: any treatment of acute MI, heart failure or unstable angina admissions, and heart transplantation.

Cardiac procedures: coronary angiography with and without intervention, CABG, ICD and pacemaker implantation.

e) **Effectiveness**

Quality-adjusted life years (QALY) over a 4-year period calculated by validated utility-weighting (www.cearegistry.com).

Core Lab DICOM Reads

Participating sites will be asked to provide DICOM images for a random sample of trial-eligible CMR studies (10% of eligible cases at the site). The core lab will review rest perfusion, stress perfusion, and LGE images. The purpose of the DICOM reads is to assess the quality of images and not to dispute the site's interpretation of cases.
DICOM images read by the core lab will be shared with the vendors (Siemens and Bayer).

Number of Sites
It is expected that a range of 6-15 US centers will participate. Each site will be screened by a sample survey and is required to provide a limited dataset to verify the existence of the stress CMR studies, completeness of key pulse sequences (cardiac function, stress perfusion, and LGE imaging), and diagnostic quality for ischemia assessment. To qualify for the study, a site needs to demonstrate:

a) Willingness/ability to provide a screening dataset
b) Can contribute at least 100 studies
c) <10% of the consecutive cohort were deemed diagnostic inadequate by the site

Sample Size
<u>For sub-aim 1:</u>
The rate of cardiac hard events (death and acute MI) is estimated based on reported evidence of 0.5% and 6% per year for patients who have absence and presence of ischemia on CMR perfusion imaging, respectively. We plan to collect follow-up events for a 4-year period after CMR. Based on prior evidence, prevalence of ischemia on CMR perfusion was 23% in referred patients.
With a sample size of 2,200 patients, 506 (23%) are assumed to be with presence of ischemia and 1694 (77%) with absence of ischemia. With incidences of 6% and 0.5% per year and a 4-year follow-up, a total of 124 of 506 patients with ischemia and 36 of 1694 patients with no ischemia are expected to experience an event, i.e. a total of 150 patients with event.

A sample size of 2,200 patients overall and 150 patients with event in a 4-year follow-up is regarded sufficient to run multivariable analysis with up to 10 variables.

With regards to the sample size considerations on the time-to-event analysis, the following settings and assumptions were used:

- Power = 80%
- Level of significance (two-sided) = 5%
- Assumed proportion in control group (i.e. no revascularization)= 77%
- Total sample size = 2,200 patients
- Number of events = 150 in total sample
- 4-year follow-up for all patients available
- The hazard ratio is estimated by a Cox proportional hazard model

With a sample size of 2,200 patients and an event rate of 124 in group 1 and 36 in group 2, a hazard ratio of 0.59 can be detected with the above mentioned settings and assumptions (i.e. 41% risk reduction rate).

For sub-aim 2.3 (comparison to the historical FAME 2 study
As reported in published data (own BWH dataset and Hachamovitch et al Circulation 2011 Apr 12;123(14):1509-18), the event rate of patients who underwent revascularization guided by CMR ischemia (i.e. CMR physiologic guidance) is about 5% per year, i.e. 10% in a 2-year follow-up. In the

historic fame-2 study, the 2-year event rate of patients who did not use physiological guidance (N=441), was 19.5%. With a power of 80%, a two-sided alpha of 5% and an assumed difference under H1 of -9.5%, the sample size of patients in this registry needs to be at least 180 patients.

Bias considerations

The minimization of biases and confounding are major tasks when conducting a cohort study. By the nature of this type of study, randomization cannot be introduced to minimize these. Therefore, in the patient selection, major efforts have to be taken to minimize any type of bias. Special care has to be taken with regard to selection bias, i.e. the selection process to decide whether a patient is eligible for the study entry.

In order to minimize selection bias and treatment bias over time across the centers, we plan to select the 2,200 consecutive cases from GCMR registry using a search criteria of stress CMR studies performed between 2008-2012. We plan to restrict the contribution from each of the sites to between 100-500 consecutive studies. Unsuccessful cases (technical failures or patient factors) during the same time interval will also be recorded for the purpose of a separate analysis of study success rate.

A large selection of possible confounders will be collected to assess any differences between the two groups of patients (patients with and without ischemia) to assess any differences between the groups with regard to e.g. medical history, demographics and baseline characteristics.

Statistical Analyses

Specific aim 1

Unadjusted and multivariable survival analyses associating presence of ischemia and percent ischemic myocardium (both by CMR), with the primary and secondary clinical outcomes will be performed. In the multi-variable analyses, key known risk markers such as age, patient sex, left ventricular and systolic volume (LVESV), validated pretest coronary disease probability, and validated risk score (Diamond and Forrester) will be modeled, and then extent of ischemia by stress CMR studies will be added to the model to test the null hypothesis that CMR findings do not add predictive value, versus the alternative hypothesis that stress CMR findings do add predictive value. A significance level of 0.05 will be used. Since CMR findings will affect patient management, which in turn, will affect the clinical outcomes, in a secondary analysis, cardiac treatment (e.g. revascularization) received within 60 days of the CMR will be added to the above model to account for treatment effects on the relationship between extent of ischemia and outcome. Annualized event rates of the primary and secondary outcomes, stratified by CMR ischemia (present or absent), and CMR ischemic burden (mild, moderate, high), will be determined, both unadjusted and adjusted for cardiac treatments received. We also plan to calculate net reclassification index of these CMR metrics to event-free survival (primary and secondary outcomes). In addition, we will examine the annual event rates of primary and secondary outcomes in each of these subgroups and perform corresponding comparative analyses.

Interim analysis at the end of the 2-year study period

The study investigators agree with collaborators from Siemens and Bayer that an interim analysis at the end of the 2-year study period, of the proposed N=2,200, will inform the magnitude of the risk reduction rate. In addition, it will provide reasonable guidance to what actions will be appropriate, if necessary, to further evaluate specific aim 1. These actions include the possibility of proposing another study aiming at a larger sample size.

Specific aim 2 (2 separate analyses for sub-aims 2.1 and 2.2, respectively)

We structured the present study's analysis of observational data to mimic a randomized clinical trial: a patient's assignment to a treatment was based on the therapy selected in the first 60 days after stress CMR perfusion study and nonrandomized treatment adjusted for via a propensity score. This time point of 60 days was selected from previous work indicating that revascularization performed within this timeframe resulted from the noninvasive imaging study, whereas referrals after 60 days tended to be attributable to worsening clinical status. Based on our pilot data, approximately 10-15% of patients undergo early coronary revascularization within the first 60 days after CMR. We therefore anticipate that 85-90% of the study cohort received MED whereas 10-15% received INT.

We plan to examine the assumptions of proportional hazards in each of the Cox models. In addition, performance of the propensity score model will be tested by comparing the prognostic associations between treatment and clinical outcomes, without and with that propensity score matching. Key risk markers will be compared between the treatment groups, without and with inclusion of the propensity score matching.

Step 1: Propensity Score to Treatment We plan to structure the study analysis of observational data in SA1 to mimic a randomized clinical trial: a) assignment of coronary intervention (INT) vs. medical therapy (MED) is based on the therapy selected in the initial 60 days after imaging and b) nonrandomized treatment adjusted for via a propensity score. Either PCI or CABG will define coronary revascularization. Follow-up time begins at the time of the index stress CMR imaging. To adjust for non-randomization of treatment, a single propensity score will be developed using logistic regression to model the decision to refer to revascularization considering all factors known to influence the referral decision. This single composite propensity score represents the probability of treatment assignment, which will be included in all subsequent survival models (step 2) associating stress CMR perfusion guided-treatment with the respective endpoints in each of the 3 sub-aims. This adjustment reduces the bias introduced by nonrandomized referral to INT in practice. While all factors known to influence this referral decision will be considered for entry into this logistic regression model, based on existing literature, the most likely predictors of referral to INT include % ischemic myocardium (% myocardial mass based on number of segments, by CMR), typical angina symptoms (yes if positive response to 2 of 3 Diamond and Forrester qualities, else no), infarct size (LGE size, grams of myocardial mass), ischemic ST changes on rest ECG (yes/no), pre-test coronary disease probability (ordinal), and prior cardiac catheterization (yes/no).[2] We anticipate that 10-15% of patients (~n=300) received INT so model over-fitting will not occur when constructing this logistic regression model.

Step 2: Multivariable survival analyses for treatment's impact incorporating the propensity score (sub-aims 2.1 and 2.2). A Cox proportional hazards model will be used to assess the association of treatment with the primary outcome (sub-aim 2.1) and secondary outcome-free survival (sub-aim 2.2). For each of sub-aim 2.1 and 2.2, we plan to build a survival model using Cox proportional hazards regression to control for the effects of baseline patient differences. Key known risk markers to be included in these models are age, sex, diabetes, and % ischemic myocardium. Major Treatment (INT or MED) and the propensity score will then be entered into the model to assess for any survival advantage from INT vs MED adjusting for the nonrandomized referral pattern. Any potential impact by any covariate in the model onto the survival benefit from INT, will be tested by adding an interaction term between treatment and the covariate of interest.

Specific aim 3

A decision analysis will be performed and it compares stress CMR perfusion imaging based on all cost and outcome data obtained in this study, against the current cost-effectiveness data from SPECT imaging and coronary CTA. It has been shown recently that coronary CTA-only strategy demonstrated a favorable incremental cost effectiveness ratio (ICER) of $20,429 per QALY, which is

both cheaper and more effective than SPECT imaging (dominated) for evaluation of intermediate-risk chest pain patients without known coronary artery disease.

Using CMR data collected from the current proposal study, we anticipate that a base-case model (a 55 year-old male with 30% CAD prevalence) of comparative cost-effectiveness analysis can be constructed using published diagnostic performance of CAD diagnosis from other modalities: coronary CTA (95% sensitivity, 83% specificity, equivocal rate 0.12), SPECT (87% sensitivity, 73% specificity, equivocal rate 0.09), and invasive coronary angiography (100% sensitivity, 100% specificity).[3]

We plan to perform a decision analysis and compare the following strategies (a) coronary CT angiography followed by invasive coronary angiography for positive or equivocal findings for CAD at coronary CT angiography (coronary CT angiography only), *(b)* coronary CT angiography followed by invasive coronary angiography for positive findings for CAD at coronary CT angiography and myocardial perfusion SPECT for equivocal findings for CAD at coronary CT angiography (coronary CT angiography first), *(c)* myocardial perfusion SPECT followed by invasive coronary angiography for positive or equivocal findings for CAD at myocardial perfusion SPECT (myocardial perfusion SPECT only), *(d)* stress CMR perfusion followed by invasive coronary angiography for positive or equivocal findings for CAD at CMR perfusion (myocardial perfusion CMR only), and *(e)* direct invasive coronary angiography. Using costs and QALY data we collect from the current proposed study, a base-case model (55 year-old male with 30% CAD prevalence) of cost-effectiveness analysis can be constructed using published diagnostic performance of CAD diagnosis: coronary CTA (95% sensitivity, 83% specificity, equivocal rate 0.12), SPECT (87% sensitivity, 73% specificity, equivocal rate 0.09), and invasive coronary angiography (100% sensitivity, 100% specificity). From published meta-analyses, stress CMR perfusion had reported a 89-92% sensitivity, and 80-90% specificity.

Project Period
12/01/2016 - 11/30/2018 (2 years)

Potential Impact
If stress CMR performs in this large observational real-world cohort as well as predicted by previous single-center trials, this study will provide robust evidence that stress CMR perfusion should become standard of care world-wide.

References

1: Wagner A, Bruder O, Schneider S, Nothnagel D, Buser P, Pons-Lado G, Dill T, Hombach V, Lombardi M, van Rossum AC, Schwitter J, Senges J, Sabin GV, Sechtem U, Mahrholdt H, Nagel E. Current variables, definitions and endpoints of the European cardiovascular magnetic resonance registry. J Cardiovasc Magn Reson. 2009 Nov 5;11:43. doi: 10.1186/1532-429X-11-43. PubMed PMID: 19891768; PubMed Central PMCID: PMC2779181.

2: Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003 Jun 17;107(23):2900-7. Epub 2003 May 27. PubMed PMID: 12771008.

3: Min JK, Gilmore A, Budoff MJ, Berman DS, O'Day K. Cost-effectiveness of coronary CT angiography versus myocardial perfusion SPECT for evaluation of patients with chest pain and no known coronary artery disease. Radiology. 2010 Mar;254(3):801-8. doi: 10.1148/radiol.09090349. PubMed PMID: 20177094.

Appendix Section

A1: Diamond and Forrester Chest Pain Prediction Score to restrict enrollment to intermediate (moderate) to high risk pre-test likelihood of disease.

III. Interpretation

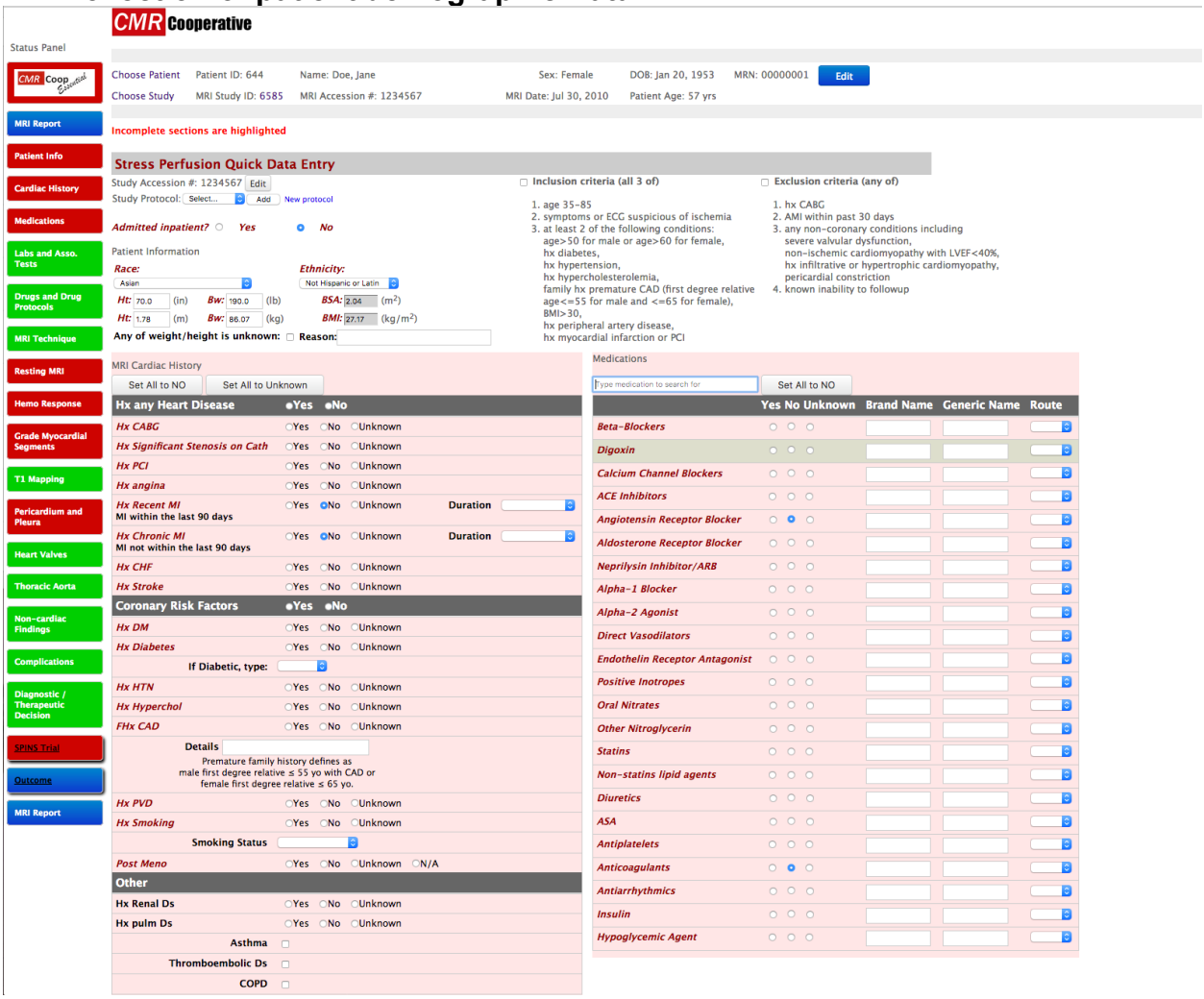
A. Typical Angina: 3 criteria from above
   1. Age 30-39: 76% likelihood (intermediate) in men and 26% in women (intermediate)
   2. Age 40-49: 87% likelihood (high) in men and 55% in women (intermediate)
   3. Age 50-59: 93% likelihood (high) in men and 73% in women (intermediate)
   4. Age 60-69: 94% likelihood (high) in men and 86% in women (high)

B. Atypical Angina: 2 criteria from above
   1. Age 30-39: 34% likelihood (intermediate) in men and 12% in women (low)
   2. Age 40-49: 51% likelihood (intermediate) in men and 22% in women (low)
   3. Age 50-59: 65% likelihood (intermediate) in men and 31% in women (intermediate)
   4. Age 60-69: 72% likelihood (intermediate) in men and 51% in women (intermediate)

C. Non-Anginal Chest Pain: 1 criteria from above
   1. Age 30-39: 4% likelihood (low) in men and 2% in women (low)
   2. Age 40-49: 13% likelihood (intermediate) in men and 3% in women (low)
   3. Age 50-59: 20% likelihood (intermediate) in men and 7% in women (low)
   4. Age 60-69: 27% likelihood (intermediate) in men and 14% in women (intermediate)

D. No criteria present
   1. Risk is low to very low for both men and women

A2: Collection of patient demographic Data



A3: Database display of hemodynamic and ventricular functional parameters

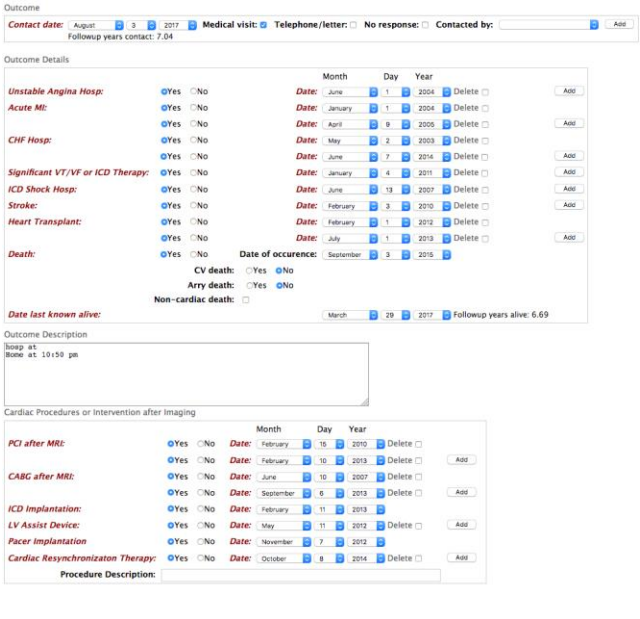
	Heart Rate (Beats/M)	SBP (mmHg)	DBP (mmHg)
Rest:			
Peak Stress:			

Any of HR/SBP/DBP is unknown: ☐ Reason:

Resting MRI

	LV		RV	
Cine not acquired	☐		☐	
Cannot quantify	☐		☐	
EDV	300.0	mL		mL
ESV	100.0	mL		mL
Mass		g		
Anteroseptum diameter		mm		
Postlateral diameter		mm		
EDD		mm		
ESD		mm		

A4: Collection of patient clinical outcomes


Outcome

Contact date: August 3 2017 **Medical visit:** ☑ **Telephone/letter:** ☐ **No response:** ☐ **Contacted by:** Add

Followup years contact: 7.04

Outcome Details

		Month	Day	Year	
Unstable Angina Hosp:	◉Yes ○No	**Date:** June	1	2004	Delete ☐ Add
Acute MI:	◉Yes ○No	**Date:** January	1	2004	Delete ☐
	◉Yes ○No	**Date:** April	9	2005	Delete ☐ Add
CHF Hosp:	◉Yes ○No	**Date:** May	2	2003	Delete ☐
	◉Yes ○No	**Date:** June	7	2014	Delete ☐ Add
Significant VT/VF or ICD Therapy:	◉Yes ○No	**Date:** January	4	2011	Delete ☐ Add
ICD Shock Hosp:	◉Yes ○No	**Date:** June	13	2007	Delete ☐ Add
Stroke:	◉Yes ○No	**Date:** February	3	2010	Delete ☐ Add
Heart Transplant:	◉Yes ○No	**Date:** February	1	2012	Delete ☐
	◉Yes ○No	**Date:** July	1	2013	Delete ☐ Add
Death:	◉Yes ○No	**Date of occurence:** September	3	2015	
	CV death: ○Yes ◉No				
	Arry death: ○Yes ◉No				
	Non-cardiac death: ☐				
Date last known alive:		March	29	2017	Followup years alive: 6.69

Outcome Description

```
hosp at
Home at 10:50 pm
```

Cardiac Procedures or Intervention after Imaging

		Month	Day	Year	
PCI after MRI:	◉Yes ○No	**Date:** February	15	2010	Delete ☐
	◉Yes ○No	**Date:** February	10	2013	Delete ☐ Add
CABG after MRI:	◉Yes ○No	**Date:** June	10	2007	Delete ☐
	◉Yes ○No	**Date:** September	6	2013	Delete ☐ Add
ICD Implantation:	◉Yes ○No	**Date:** February	11	2013	
LV Assist Device:	◉Yes ○No	**Date:** May	11	2012	Delete ☐ Add
Pacer Implantation	◉Yes ○No	**Date:** November	7	2012	
Cardiac Resynchronizaton Therapy:	◉Yes ○No	**Date:** October	8	2014	Delete ☐ Add
Procedure Description:					

Hide definitions

Unstable Angina	Worsening chest pain or anginal equivalent (chest tightness, shortness of breath, arm or neck pain) **AND** Unscheduled hospitalization **AND** Evidence of myocardial ischemia by cardiac imaging (abnormal nuclear perfusion imaging, stress echocardiogram, stress MRI, exercise treadmill test, and/or angiogram (CT or conventional) with >=50% left main or >=70% lesion in any other coronary artery) **AND** Negative cardiac biomarkers (CK, CK-MB, troponin I/T/high-sensitivity)
Acute MI	Chest pain or anginal equivalent (chest tightness, shortness of breath, arm or neck pain, new onset fatigue/weakness, syncope) **AND/OR** Acute electrocardiographic changes (ST/T segment changes, LBBB, development of pathological Q waves) **AND** Cardiac biomarker rise and /or fall >99th percentile of the upper reference limit
CHF Hospitalization	Admission to hospital with primary diagnosis of HF with new or worsening symptoms/signs of HF **AND** Length of stay >24 hours **AND** Initiation or intensification of treatment for HF **Symptoms:** exertional shortness of breath (NYHA classification), paroxysmal nocturnal dyspnea, orthopnea, leg swelling **Signs:** elevated JVP, reduced breath sounds at lung bases, end-inspiratory crackles at lung bases, peripheral edema and/or ascites, CXR - enlarged cardiac silhouette, pulmonary edema, pleural effusions, PA catheter - increased RA and LA wedge pressures
ICD Therapy	ICD shock or antitachycardia pacing to terminate ventricular tachycardia or ventricular fibrillation **AND** Appropriate (therapy administered by ICD deemed to be appropriate by interrogating electrophysiologist)
ICD Shock Hospitalization	Hospitalization due to recurrent ICD Therapy
Heart Transplantation	Heart transplantation for any reason
Death (Cardiac)	Death caused: acute MI, arrhythmic, HF, stroke, pulmonary embolism, peripheral arterial disease, or cardiovascular procedure
Death (Acute MI)	Death caused by any cardiovascular mechanism (arrhythmia, sudden death, HF, stroke, pulmonary embolism peripheral arterial disease, cardiovascular procedure) within 30 days after an acute MI **AND** acute MI verified by above criteria and/or autopsy findings showing recent MI or recent coronary thrombosis
Death (Arrhythmic)	Witnessed sudden death without new or worsening symptoms **OR** Witnessed death within 60 minutes of the onset of new or worsening symptoms unless symptoms suggest acute MI **OR** Witnessed death attributed to an identified arrhythmia (electrocardiographic or ICD review) **OR** Death after unsuccessful resuscitation from cardiac arrest **OR** Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac cause **OR** Unwitnessed death whereby patient was seen alive + stable <=24 hours and no evidence to support an alternative cause of death **AND** not within 30 days of an acute MI
Death (Heart Failure)	Death associated with clinically worsening symptoms and/or signs of HF (regardless of etology) and not occuring within 30 days of an acute MI
Death (Non-Cardiac)	Any death not caused by a cardiac etiology (please see above)
Stroke	Acute episode of focal or global neurologic dysfunction (weakness, paralysis, speech difficulty, loss of/blurred vision, loss of balance, reduced level of consciousness, confusion, difficulty swallowing) **AND** Caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage (bleeding) or infarction documented by imaging (CT and/or MRI)
Transient Ischemia Attack (TIA)	Acute episode of focal or global neurologic dysfunction (weakness, paralysis, speech difficulty, loss of/blurred vision, loss of balance, reduced level of consciousness, confusion, difficulty swallowing) **AND** Transient (<24 hours) Caused by brain, spinal cord, or retinal ischemia without acute infarction by imaging (CT and/or MRI)
Cardiogenic shock	Sustained (>30 min) episode of systolic **BP** <90 mm Hg and/or cardiac index <2.2 L/min/m2 secondary to cardiac dysfunction (systolic or diastolic dysfunction documented by cardiac imaging) **AND/OR** requirement for parenteral inotropic or vasopressor agents or mechnical support to maintain BP and cardiac index above specified levels
Percutaneous coronary intervention (PCI)	Placement of angioplasty guidewire, balloon, stent, or thrombectomy into a native coronary artery or bypass graft for the purpose of mechanical coronary revascularization
Coronary artery bypass surgery (CABG)	Cardiac surgery for placement of one or more coronary artery bypass grafts (including internal thoracic artery or arteries)

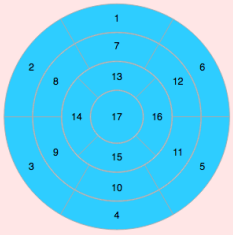
A5: Collection of Segmental Analyses Data

Grade Myocardial Segments

Perfusion | Viability

Normal | Abnormal | Possible Subendo | Mild Subendo | Moderate Subendo | Severe Subendo | Possible Transmural | Mild Transmural | Moderate Transmural | Severe Transmural | Non-diagnostic | Not Done

Stress

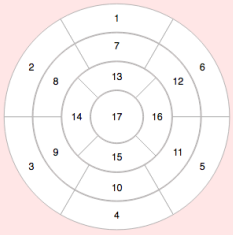


Stress Perfusion: Normal

17 Normal | 16 Normal | Clear All

Not Done | Non-Diag

Rest



Rest Perfusion:

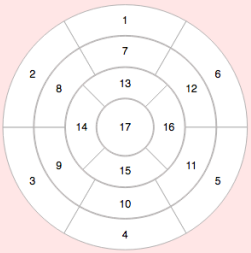
17 Normal | 16 Normal | Clear All

Not Done | Non-Diag

Grade Myocardial Segments

Perfusion | Viability

Normal | 1= 1-25 | 2= 26-50 | 3= 51-75 | 4= 76-99 | 5= 100
Subsegmental | Diffuse | Epicardial | Midwall | Focal | RV Insertion | Other | Non-diagnostic | Not Done



17 Normal | 16 Normal | Clear All | Not Done | Non-Diag | 17 Diffuse

MDE LV:

MDE RV:

MDE consistent with:

Ablative Scar:	Amyloidosis:
Arrhythmogenic CMP:	Chagas Disease:
Fabry's Disease:	Hypertensive CMP:
Hypertrophic Cardiomyopathy:	Myocardial Infarction - Acute:
Myocardial Infarction - Chronic:	Myocardial Infarction - unspecified:
Myocarditis:	Non-ischemic CMP:
Pericardial Disease:	Sarcoidosis:
Other Infiltration:	Other:
Non-specific:	Uncertain Etiology:

Describe MDE pattern:

A6: Collection of Downstream Cardiac Tests