HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2023 February 22.

Published in final edited form as:

J Am Coll Cardiol. 2022 February 22; 79(7): 651–661. doi:10.1016/j.jacc.2021.11.052.

Predictors of Left Main Coronary Artery Disease in the ISCHEMIA Trial

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ClinicalTrials.gov **Identifier:** NCT01471522;

https://clinicaltrials.gov/ct2/show/NCT01471522

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Abstract

Background: Detection of ≥50% diameter stenosis left main coronary artery disease (LMD) has prognostic and therapeutic implications. Noninvasive stress imaging or an exercise tolerance test (ETT) are the most common methods to detect obstructive coronary artery disease, though stress test markers of LMD remain ill-defined.

Objectives: We sought to identify markers of LMD as detected on coronary computed tomography angiography (CCTA), using clinical and stress testing parameters.

Methods: This was a post hoc analysis of ISCHEMIA, including randomized and nonrandomized participants who had locally determined moderate or severe ischemia on nonimaging ETT, stress nuclear myocardial perfusion imaging, or stress echocardiography followed by CCTA to exclude LMD. Stress tests were read by core laboratories. Prior coronary artery bypass grafting was an exclusion. In a stepped multivariate model, we identified predictors of LMD, first without and then with stress testing parameters.

Results: Among 5146 participants (mean age 63 years, 74% male), 414 (8%) had LMD. Predictors of LMD were older age ($p<0.001$), male sex ($p<0.01$), absence of prior myocardial infarction ($p<0.009$), transient ischemic dilatation (TID) of the left ventricle on stress echocardiography ($p=0.05$), magnitude of ST-segment depression on ETT ($p=0.004$) and peak metabolic equivalents achieved (METs) on ETT ($p=0.001$). The models were weakly predictive of LMD (C-index 0.643 and 0.684).

Conclusions: In patients with moderate or severe ischemia, clinical and stress testing parameters were weakly predictive of LMD on CCTA. For most patients with moderate or severe ischemia, anatomic imaging is needed to rule out LMD.

Condensed Abstract

Detection of ≥50% diameter stenosis left main coronary artery disease (LMD) has both prognostic and therapeutic implications. In this post hoc analysis of 5146 ISCHEMIA randomized and non-randomized participants, we assessed clinical and stress testing predictors of LMD on coronary CT angiography. Models for LMD demonstrated suboptimal prediction overall. Thus for most patients with moderate or severe ischemia, exclusion of LMD will require anatomic imaging with either CCTA or coronary angiography.

Keywords

Stress testing; coronary CT angiography; stable ischemic heart disease; coronary artery disease

Introduction

Detection of significant (≥50%) left main disease (LMD) has major prognostic and therapeutic implications.(1) While the detection of obstructive coronary artery disease (CAD) is important, this is especially true of LMD because current guidelines recommend revascularization to improve survival when LMD is present.(2)

The ISCHEMIA trial, which randomized patients with moderate or severe ischemia to guideline-directed medical therapy vs guideline-directed medical therapy plus optimal revascularization, showed no statistical difference between the groups for the primary composite outcome or the secondary outcome of cardiovascular death or myocardial infarction.(3) However, patients with LMD ≥50% on computed coronary tomographic angiography (CCTA) were excluded from randomization. Hence, detection of LMD during the initial evaluation of patients with myocardial ischemia is important as revascularization remains the guideline-recommended management strategy in these patients. Previous studies that evaluated clinical or functional tests (i.e, stress test) criteria for the identification of LMD are sparse and mostly performed in small populations.(4)

The aim of this post hoc analysis of ISCHEMIA(5) was to explore the markers of LMD using clinical and noninvasive functional parameters and to identify whether functional testing modalities can predict LMD on CCTA.

Study Population

In brief, the ISCHEMIA cohort comprised patients with stable ischemic heart disease and moderate or severe ischemia on clinically indicated stress imaging or severe ischemia on exercise tolerance test (ETT) as determined by enrolling sites and read later at centralized trial core laboratories. Patients were eligible if they were clinically stable, including stable angina or silent ischemia. CCTA was performed to confirm the presence of obstructive CAD and to rule out LMD. Major exclusion criteria included estimated glomerular filtration rate (eGFR) less than 30mL/min/ 1.73m^2, myocardial infarction (MI) or unstable angina within 2 months of randomization, left ventricular ejection fraction less than 35%, LMD ≥50% on CCTA, New York Heart Association class III to IV heart failure or exacerbation of chronic heart failure within 6 months, or unacceptable angina despite maximally tolerated medical therapy.(5) Enrolled patients that were not confirmed to be eligible for randomization after additional testing and core laboratory review were excluded from the trial. ISCHEMIA was funded by the National Heart, Lung, and Blood Institute. IRB approval was obtained at the Clinical Coordinating Center (NYU Grossman School of Medicine IRB) and at each coordinating center and site. All participants provided informed consent.

For this analysis, enrolled ISCHEMIA participants with available CCTA interpretation for the presence or absence of LMD and available core laboratory interpretation of ischemia

severity were analyzed. Patients with prior coronary artery bypass grafts (CABG) were excluded from this analysis. Patients who had CCTA done before the study were also excluded. Figure 1 depicts how the study population was derived. Stress imaging and ETT eligibility criteria for the ISCHEMIA trial have been previously described.(5) Stress testing details are mentioned in brief below.

Stress testing

Sites were directed to screen and enroll patients with moderate or severe ischemia, as determined locally on a stress test performed for clinical indications, preferably within the prior 3 months. Stress test data (e.g., images and ECG recordings for those undergoing ETT) were transferred electronically to the relevant core laboratory. The core laboratories independently interpreted baseline stress tests for all trial participants. For stress nuclear imaging (single-photon emission computed tomography or positron-emission tomography), mild ischemia was defined as reversible ischemia affecting <10% of the myocardium (summed difference score <7 segments), moderate ischemia was defined as reversible ischemia affecting ≥10% but <14.9% of the myocardium (summed difference score ≥7–9) and severe ischemia was defined as >15% ischemia (summed difference score ≥10). For stress echocardiography, mild ischemia was defined as <3 segments with reversible wall motion abnormalities in a 16 segment left ventricular model, moderate ischemia was defined as 3 segments with severe inducible wall motion abnormalities and severe ischemia as ≥ 4 segments with severe inducible wall motion abnormalities. Exercise testing entry criteria for severe ischemia required all of the following: (1) history of stable or exercise test-induced typical angina; (2) an interpretable resting ECG (e.g., no resting ST segment depression ≥1 mm); (3) at least 2 leads showing new exercise-induced ST segment depression ≥1.5 mm or a single lead ≥2 mm as compared to the baseline tracing occurring at ≤7 METs or peak heart rate <75% of age-predicted maximum confirmed by the ECG core-lab laboratory and (4) anatomic>70% stenosis of a major coronary artery on CCTA. We did not analyze cardiac magnetic resonance (CMR) data in relation to LMD due to the low number of patients enrolled after this stress test modality.

CCTA

CCTA was interpreted centrally by a core laboratory, without regard to stress test findings or clinical information. At least two readers evaluated the presence and severity of LMD, with any disagreements resolved by the core laboratory director.

Statistical Analysis

Presence of LMD was defined as LMD stenosis ≥50%. Continuous variables are presented as medians (Q1, Q3) and differences compared using the Wilcoxon rank-sum test or Student’s t-test, as appropriate. Categorical variables are presented as counts (raw percentages) and differences compared using Pearson’s chi-square test or Fisher’s exact test if cell frequencies were not sufficient. A multivariable logistic regression model was used to assess the association between the following clinical characteristics and LMD: age at enrollment, sex, race/ethnicity, hypertension, diabetes, smoking status, prior MI and eGFR (ml/min). An additional multivariable logistic regression model assessed the association between imaging and stress test variables and disease status, adjusting for the clinical

characteristics. Specific imaging and stress test variables included: the number of ischemic segments on SE, number of infarcted segments on SE, summed differences score on nuclear, TID on nuclear, TID on SE, ST depression on ETT, peak exercise METs on ETT, severe or moderate anterior ischemia on nuclear or SE and LAD and LCX ischemia on nuclear or SE. Both models combined data from imaging and ETT patients and the latter model included a sex by modality interaction term. Multiple imputation by chained equations was used to impute missing covariates for the logistic regression models. Imaging and stress test variables were set to a constant value for patients that did not undergo the particular test; the odds ratios for the imaging and stress test indicators are not reported due to lack of interpretability. The model's ability to distinguish between patients with relatively high versus low likelihood of LMD > 50% was assessed by calculating the C-index and by plotting the distribution of predicted probabilities of LMD > 50% within each modality. Predicted probabilities of LMD >50% from the full model were further analyzed with the goal of identifying non-rare subgroups with a low average probability of LMD >50%. The search for subgroups was performed both in the combined cohort and separately within each modality. In the combined cohort, candidate subgroup factors included all predictor variables with a p-value <0.2 in the full multivariable model plus the core-laboratory determined degree of ischemia (none/mild/moderate/severe). In modality-specific analyses, we used modality-specific predictors in place of the degree of ischemia. Subgroups were identified by calculating the average predicted probability of LMD >50% across patients within each level of each candidate subgroup factor and within groups formed by the cross-classification of 2 or more candidate subgroup factors. Subgroups were reported here if they included at least 350 patients and if the average predicted probability was ≤2.5%. To account for statistical uncertainty in these estimates, we present results along with 95% bootstrap confidence intervals.

RESULTS

A total of 5146 patients were enrolled after stress testing who underwent CCTA, who did not have prior CABG, and had interpretable ischemia testing using a modality other than CMR imaging (Figure 1), of whom 414 (8.0%) had LMD. The median age was 63 years and 74% were males (Table 1). Participants with LMD were older, more likely to be male, of Asian ethnicity, and had a lower prevalence of prior MI and lower median eGFR. There was no meaningful difference between those with or without LMD in the prevalence of diabetes mellitus, systemic hypertension and history of smoking. The proportion of LMD patients undergoing nuclear imaging, stress echocardiography and ETT were 38%, 22% and 40%, respectively (p<0.001 vs. without LM). Those with LMD had a greater degree of inducible ischemia than those without LMD, on all stress test modalities. Transient ischemic dilatation (TID) was observed more often in patients with as compared to those without LMD among those undergoing stress echocardiography but not significantly more often in patients undergoing nuclear imaging. Patients with LMD had a lower exercise capacity on ETT than those without LMD. The proportion of LMD patients with moderate or severe anterior ischemia was higher among patients undergoing stress echocardiography and nuclear imaging. The proportions of patients with ischemia in both the left anterior descending (LAD) and circumflex (LCX) territories were not different

in patients with and without LMD by nuclear imaging but were significantly more in LMD group by stress echocardiography. Among patients who underwent nuclear imaging, 45% underwent exercise testing and 55% received pharmacological agents; the proportions in stress echocardiography were 77% and 23%, respectively. Exercise hemodynamics were not routinely available for stress imaging tests.

Logistic regression analysis (Table 2) indicated that among clinical factors, older age, male sex, Asian race and lack of prior MI were the only significant predictors of LMD. The C index for the clinical logistic model was 0.643. Among imaging and exercise parameters, after adjusting for clinical factors (Table 3), significant predictors of LMD were older age, male sex, lack of prior MI, greater ST depression and lower peak METs on ETT and TID on stress echocardiography. Nuclear imaging parameters were not independently associated with LMD. The C index for this model was only marginally but statistically significantly improved compared with the clinical model, to 0.684 ($p<0.001$). Sensitivity analysis performed after excluding patients with prior MI showed that TID on stress echocardiography was no longer significant, with no change in C-index.

Analysis was also performed based on ≥70% LMD (n=82 patients). The proportion of enrolled participants with ≥70% LMD was 1.1% with nuclear imaging, 1.3% with stress echocardiography and 2.7% with ETT ($p<0.001$). Due to the limited number of patients with LMD, only modality-specific variables were included in the models; clinical characteristics were not included as adjustment variables. ETT parameters of ST depression ($p=0.02$) and lower peak workload ($p=0.04$) were associated with ≥70% LMD, but neither nuclear nor stress echocardiography data provided incremental information over clinical parameters in ≥70% LMD prediction.

Figure 2 illustrates the distribution of the predicted risk estimates of LMD, ranging from less than 2% through over 30%, by stress test modality. Tables 4 and 5 depict the subgroups defined by combinations of clinical and imaging parameters that were associated with less than 2.5% probability of LMD on average. Table 4 shows the combined effect of nuclear and stress echocardiography on the model, with ischemia categorized as severe, moderate, mild or none. The variables considered were age, sex, prior MI and the degree of ischemia. The simplest combination of clinical features that excluded LMD with more than 97.5% probability on average in an adequately sized subgroup was female sex with mild or moderate ischemia (Central Illustration). Among remaining participants (women with severe ischemia, and men), the prevalence of LMD was 8.9%. Table 5 shows the modality-specific parameters (nuclear, stress echocardiography, ETT) associated with LMD. Clinical variables were the same as in the clinical analysis in Table 4. There were no ETT subgroups of the specified size with ≤2.5% predicted likelihood of LMD.

Discussion

This large study assessed commonly used non-invasive stress modalities for the prediction of significant LMD as assessed by CCTA among patients with a relatively high likelihood of LMD, approximately 8%. We demonstrated that stress testing offered only modest incremental value over clinical parameters for prediction of LMD in this cohort of

patients with moderate or severe ischemia as determined by sites on clinically indicated stress testing before enrollment in the ISCHEMIA trial. Overall, the predictive value was suboptimal. ISCHEMIA showed that high-risk stable ischemic heart disease patients with significant inducible ischemia on noninvasive testing did not have a statistically lower rate of the composite primary outcome or of cardiovascular death and MI when routine revascularization was added to guideline-directed medical therapy as compared to guideline-directed medical therapy alone.(3) Application of these results to clinical practice, however, may be challenging when LMD status is not known, since patients with LMD were excluded from randomization in the ISCHEMIA trial. Though the results of ISCHEMIA and other strategy trials(6,7) indicate that the majority of patients without LMD can be managed conservatively, it is nonetheless important to exclude LMD. Available studies indicate that patients with LMD benefit from revascularization, though these trials predated effective medical therapy for risk reduction.(8) A pre-trial survey of cardiologists indicated a lack of equipoise regarding revascularization for LMD.(9)

Previous studies have identified stress testing parameters that are associated with higher likelihood of LMD. To our knowledge, this is the first study attempting to identify predictors of LMD among patients with clinically diagnosed moderate or severe ischemia, a group with a relatively high likelihood of LMD. In contrast, the prevalence of LMD in the CONFIRM registry in patients with suspected angina without known CAD was only 0.9%. (10) We found that stress test parameters were not adequate for ruling out LMD. Though TID on stress echocardiography and severe ST depression and low workload on ETT were independent predictors of LMD beyond clinical variables and independent of other imaging markers of LMD disease, their incremental predictive value was modest. The imaging findings are consistent with other, smaller studies(4) and can be explained by the fact that in LMD, hyperemic blood flow is rarely affected to the same degree in the LAD and left circumflex territory. Indeed, distal LMD disease may preferentially reduce blood flow in the LAD as the plaque frequently extends into the LAD vs left circumflex territory.(11) Furthermore, it is recognized that it may be difficult to discriminate LMD from the disease in the LAD and left circumflex coronary arteries without LMD commonly known as left main equivalent.(12) Patients with LMD have a high prevalence of associated multivessel disease. This is highly relevant in the ISCHEMIA trial, in which 66% of patients undergoing CCTA had multivessel CAD.(3)

There are also imaging specific issues that may have affected the discriminatory power of the imaging modalities. Nuclear imaging (particularly SPECT, which was the major nuclear modality in the ISCHEMIA trial) depends on a relative myocardial blood flow difference of at least 2:1 ratio to detect reduced perfusion. Thus, differential reduction in flow in the LAD vs left circumflex territory may not be detected. On the other hand, a similar reduction in perfusion in large areas of the left ventricle (balanced ischemia) may result in normalization of tracer uptake in ischemic segments and thus may underestimate ischemia.(13) Perfusion defect patterns in these studies identified only 19%−29% of patients with LMD.(14) The sensitivity of SPECT compared to stress echocardiography for the detection of LMD tended to be lower for the same reasons as stated above.(4,14). Exercise stress echocardiography has previously been reported to have similar high sensitivity for the detection of LMD compared to dobutamine stress echocardiography.(15) In our study,

neither stress echocardiography nor SPECT demonstrated a significant relationship between increasing ischemia severity and LMD.

Transient ischemic dilation as detected by stress echocardiography, but not SPECT, was independently associated with LMD. Transient ischemic dilation was more commonly observed during stress echocardiography than during nuclear imaging in this study, perhaps related to a greater proportion of patients undergoing exercise rather than pharmacological stress with stress echocardiography in contrast with the proportions used for nuclear imaging.(15) It is noteworthy that exercise-induced ST depression and reduced workload by ETT was associated with LMD. Unfortunately, we could not analyze exercise time and hemodynamics in patients undergoing stress imaging in this study, and therefore cannot comment on whether these parameters would have refined risk prediction.

Given that the presence of LMD is a critical factor in selection for revascularization, particularly after publication of the main ISCHEMIA results, we explored clinical and stress test variables that could be used in combination to rule out LMD. Female sex alone was significantly associated with lower likelihood of LMD in patients with moderate or severe ischemia on either nuclear imaging or stress echocardiography, but female patients undergoing exercise tolerance testing had a slightly higher probability of LMD not meeting our predetermined threshold. Further, there was substantial variability in predicted risk of LMD even within the lower risk female subsets. There was no subgroup of men with low likelihood of LMD meeting our predetermined sample size, regardless of stress testing results. The subgroups with the lowest average risk of LMD were female sex with induced ischemia with <10 score by stress nuclear and female sex with <5 segments by stress echocardiography. Unfortunately, these two subgroups were small, 7.6% and 7%, respectively. Our finding of lower likelihood of LMD in patients with prior MI may be related to anatomic coronary imaging at the time of the prior MI; if LMD was found then, the patient would not be considered eligible for the trial.

Limitations

We analyzed left main stenosis using the 50% threshold, but not all 50–70% left main stenosis may be flow limiting. The population studied was comprised of patients who were enrolled following site-interpreted moderate or severe ischemia by imaging or severe ischemia ETT criteria, and on core laboratory review, 24% of stress imaging tests submitted by sites showed mild or no ischemia, and 23% of ETTs showed less than severe ischemia.(16)These proportions were higher than in the randomized trial cohort.(16) Exercise hemodynamic data were not available in enough patients with stress imaging to permit inclusion into this analysis. We used CCTA to define LMD. It is known that CCTA and invasive coronary angiography may not yield identical results due to inherent differences in the techniques. CCTA may overestimate stenosis severity(12). Calcification may also obscure stenosis assessment by CCTA. Our sites did not use echocardiography to identify flow in the LM coronary artery, though movement artifact can compromise its ability to consistently image the LM(17). In another post-hoc analysis of the ISCHEMIA trial despite high concordance (97.1%), when the 1728 patients in whom CCTA showed no significant left main disease underwent invasive coronary angiography, 2.9% of patients had ≥50%

LMD, which may have implications regarding which anatomic testing may be performed for the exclusion of LMD.(12)

Conclusions

In patients with moderate or severe inducible ischemia who underwent CCTA in this analysis, the prevalence of left main stenosis ≥50% was 8%. Transient ischemic dilation by stress echocardiography, and the magnitude of ST depression and low achieved workload by ETT, were associated with LMD independent of clinical factors, but the discriminatory capacity of the model was modest. Women with a lower burden of ischemia by either stress nuclear or stress echocardiography had a very low predicted likelihood of LMD, on average 2.3%. Thus for most patients with moderate or severe ischemia, exclusion of LMD will require anatomic imaging with either CCTA or invasive coronary angiography.

Clinical Implications

It is desirable for clinicians to know whether a patient with stable ischemic heart disease has significant left main stenosis because guidelines recommend revascularization to improve survival in patients with LMD. Among patients with moderate-severe ischemia who were considered for initial conservative therapy, clinical and stress testing parameters were inadequate for ruling out LMD with a high degree of certainty overall. There was high concordance of CCTA and invasive angiography for LMD in ISCHEMIA. Thus for most patients, exclusion of LMD will require anatomic imaging, with CCTA or conventional invasive angiography.

Sources of Funding:

NIH grants U01HL105907, U01HL105462, U01HL105561, U01HL105565

Disclosure Statements:

Dr. Roxy Senior reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Harmony R. Reynolds reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; non-financial support from Abbott Vascular, non-financial support from Siemens, non-financial support from BioTelemetry, outside the submitted work;

Dr. James K. Min reports grants from National Heart, Lung and Blood Institute during the conduct of the study; also receives grants from CLEERLY INC., GE HEALTHCARE ARINETA, outside the submitted work.

Dr. Daniel S. Berman reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; reports grants from GE, CSMC Heartflow, and Bayer; receives software royalties from Cedars-Sinai Medical Center outside the submitted work.

Dr. Michael H. Picard reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Bernard R. Chaitman reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; personal fees from Merck, NovoNordisk, Lilly,Johnson and Johnson, Daiichi Sankyo, Imbria, Xylocor, Sanofi, Tricida, and Xylocor outside the submitted work;

Dr. Leslee J. Shaw reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Courtney B. Page reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Sajeev C. Govindan reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Jose Lopez Sendon reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; grants from Bayer, Merck and Amgen; grants and personal fees from Pfizer, Menarini, Sanofi, Boeringher Infleheim outside the submitted work. Dr. Jesus Peteiro reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Gupreet S. Wander reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Jaroslaw Drozdz reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Jose Marin-Neto reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Joseph B. Selvanayagam reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Jonathan D. Newman reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Christophe Thuaire reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Johann Christopher reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. James J. Jang reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Raymond Y. Kwong reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Sripal Bangalore reports grants from National Heart, Lung, and Blood Institute, during the conduct of the study; grants and personal fees from Abbott Vascular, personal fees from Biotronik, Pfizer, Amgen, and Reata outside the submitted work.

Dr. Gregg W. Stone reports grants and personal fees from National Heart, Lung, and Blood Institute, during the conduct of the study; personal fees from Terumo, personal fees from Amaranth, personal fees from Shockwave, personal fees and other from Valfix, personal fees from TherOx, personal fees from Reva, personal fees from Vascular Dynamics, personal fees from Robocath, personal fees from HeartFlow, personal fees from Gore, personal fees from Ablative Solutions, personal fees from Matrizyme, personal fees from Miracor, personal fees from Neovasc, personal fees from V-wave, personal fees from Abiomed, personal fees from Claret, personal fees from Sirtex, personal fees and other from Ancora, personal fees and other from Qool Therapeutics, other from Cagent, other from Applied Therapeutics, other from Biostar family of funds, other from MedFocus family of funds, personal fees and other from SpectraWave, personal fees from MAIA Pharmaceuticals, personal fees and other from Orchestra Biomed, other from Aria, personal fees from Vectorious, other from Cardiac Success, outside the submitted work;

Dr. Sean M. O'Brien reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. William E. Boden reports grants from National Heart, Lung, and Blood Institute, during the conduct of the study; grants from Abbvie, grants from Amarin, grants from Amgen, personal fees from Amgen, personal fees from Cleveland Clinic Clinical Coordinating Center, personal fees from Janssen, outside the submitted work;

Dr. David J. Maron reports grants from National Heart, Lung, and Blood Institute during the conduct of the study.

Dr. Judith S. Hochman is PI for the ISCHEMIA trial for which, in addition to support by National Heart, Lung, and Blood Institute grant, devices and medications were provided by Abbott Vascular; Medtronic, Inc.; Abbott Laboratories (formerly St. Jude Medical, Inc); Royal Philips NV (formerly Volcano Corporation); Arbor Pharmaceuticals, LLC; AstraZeneca Pharmaceuticals, LP; Merck Sharp & Dohme Corp.; Omron Healthcare, Inc, Sunovion Pharmaceuticals, Inc. Espero BioPharma; and Amgen, Inc; and financial donations from Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP.

Disclaimer:

This article refers to work supported by National Heart, Lung, and Blood Institute grant U01HL105907, U01HL105462, U01HL105561, U01HL105565; device donations from Abbott Vascular; Medtronic, Inc.; St. Jude Medical, Inc.; Volcano Corporation; and Omron Healthcare, Inc.; medications provided by Amgen Inc; Arbor Pharmaceuticals, LLC; AstraZeneca Pharmaceuticals, LP; Merck Sharp & Dohme Corp.; and by financial donations from Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP. The content of this manuscript is solely the responsibility of the authors and does not necessarily reflect the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the United States Department of Health and Human Services.

This project was supported in part by Clinical Translational Science Award Nos. 11UL1 TR001445 and UL1 TR002243 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences, the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the Department of Health and Human Services.

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Subcommittee: PCI—David Williams (Co-Chair)

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Jim Blankenship

Sorin Brener

Chris Buller

Antonio Colombo

Bernard de Bruyne

Philippe Généreux

Robert Harrington

Dean Kereiakes

Thierry Lefevre

Jeffrey Moses

Clinical Events

Endpoint Definition Panel—Bernard R. Chaitman (Chair)

Karen P. Alexander

Judith S. Hochman

Ken Mahaffey

David J. Maron

Gregg W. Stone

Harvey White

Clinical Event Review Committee—Bernard R. Chaitman (Chair)

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Jelena Celutkiene

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Radmila Lyubarova

Deirdre Mattina

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Sripal Bangalore

T. Bruce Ferguson

David Williams

(Philippe Genereux, former Chair, Angiography Subcommittee)*

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David J. Maron (Co-Chair)

Jerome Fleg

Jonathan Newman

Biorepository—Jeffrey Berger (Chair)

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Harmony R. Reynolds

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William Boden (US-VA Regional Leader)

Jonathan Newman (Optimal Medical Therapy CCC Director, Regional Leader)

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Wanda Parker*

Wayne Pennachi

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Susanna Stevens

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ISCHEMIA Imaging Coordinating Center (ICC)

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Abhinav Goyal

Holly Hetrick

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Sean W. Hayes (Co-Director)

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Louise Thomson

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Matthias Friedrich (Director)*

Francois Pierre Mongeon (Co-Director)

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Judy Hung

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Reza Arsanjani

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Andrea Lorimer

Marco Magnoni

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Laura Sarti

Martinia Tricoli*

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Renato Lopes (Country Leader)

Lilian Mazza Barbosa

Tauane Bello Duarte

Tamara Colaiácovo Soares

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Natalia de Carvalho Maffei

Flávia Egydio*

Anelise Kawakami*

Janaina Oliveira*

Elissa Restelli Piloto*

Jaqueline Pozzibon*

Canadian Heart Research Centre (CHRC) - Canada

Shaun Goodman (Country Leader)

Diane Camara

Neamat Mowafy

Caroline Spindler

China Oxford Centre for International Health Research - China

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Jia Li

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Lihua Zhang

Liping Zhang

Ning Zhang

Hui Zhong

Estudios Clínicos Latino America (ECLA) - Argentina

Rafael Diaz*

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Maria Eugenia Martin*

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Foundation for Biomedical Research of La Paz University Hospital (FIBHULP) - Spain

José Lopez-Sendon (Country Leader)

Paloma Moraga

Victoria Hernandez

Almudena Castro

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José Luis Narro Villanueva

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French Alliance for Cardiovascular Trials (FACT) - France

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II.: Site Personnel

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Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
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	Steven Weitz, MD	Lori Pritchard, RN	Schenectady,	NY
Associates of Schenectady P.C. (17)				
	Suzanne Arnold, MD	Rosann Gans, RN		
	James Henry O'Keefe, Jr, MD (PI from 2012–2016)	Paul Kennedy, RN	Kansas City, MO	Saint Luke's Hospital (17)
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	Steven A. Fein, MD	Wendy L. Stewart, MS		
	Mikhail T. Torosoff, MD, PhD	Kristin M. Salmi, BS	Albany, NY	Albany Medical Center Hospital (16)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
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	Krzysztof Drzymalski, MD			
	Edward O. McFalls, MD, PhD			
	Santiago A. Garcia, MD			
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	Ronnell A. Hansen, MD			
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	Richard Goldweit, MD	Sallie Canada Meghana Kakade Patricia Mieses Stanley E. Cobos, BA Raven R. Dwyer, MPH	Englewood, NJ	Englewood Hospital and Medical Center (13)
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	Brooks Mirrer, MD	Kirsten J. Quiles, MS	Brooklyn, NY	NYU-HHC Woodhull Hospital (12)
	Victor Navarro, MD	Magdalena Rantinella, BS Jessica Rodriguez, BS		
		Olivia Mancilla, BS		
	David E. Winchester, MD, MS	Susan Stinson, RN	Gainesville, FL	Malcom Randall VAMC (11)
	Marvin Kronenberg, MD	Terry Weyand		
	Philip Rogal, MD Christopher McFarren, MD	Sherron C. Crook	Nashville, TN	Vanderbilt University Medical Center (11)
	John F. Heitner, MD	Jean Ho Saadat Khan Mahmoud Mohamed Mary R. Soltau, RN Delsa K. Rose, RN	Brooklyn, NY	New York - Presbyterian/Brooklyn Methodist Hospital (10)
	Ira M. Dauber, MD	Rebecca J. Wimmer, RN Kathy E. Siegel, RN Susan Derbyshire	Littleton, CO	South Denver Cardiology Associates, P.C. (10)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
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	Puja K. Mehta, MD Michael McDaniel, MD	Fauzia Rashid, PhD		
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	Arshed Quyyumi, MD	Keyur Patel		
	Nanette K. Wenger, MD			
	Chester M. Hedgepeth, MD, PhD	Jennifer Gillis, APRN		
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	David Booth, MD	Yvonne Taul, RN		
	Steve Leung, MD	Jennifer Isaacs, MS		
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	Khaled Ziada, MD			
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	Khaled Dajani, MD	Carol M. Kartje, BSN	Maywood, IL	Loyola University Medical Center (8)
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		Viktoria Bulkley		
	Bob Hu, MD	Renee Kaneshiro	Palo Alto, CA	Palo Alto Medical Foundation Research Institute (4)
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	Philip Rogal, MD	Nhi N. Tran, MS		
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	Christiano Caldeira, MD David J. Maron, MD			
	Fatima Rodriguez, MD, MPH	Reem Yunis, PhD		
	Ingela Schnittger, MD William F. Fearon, MD	Jhina Patro	Stanford, CA	Stanford University School of Medicine (4)
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		Hugo Bloise-Adames		
	Joseph Sweeny, MD	Santa Jimenez Nicole Saint Vrestil Reyna Bhandari	New York, NY	Icahn School of Medicine at Mount Sinai (4)
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	Claudia P Hochberg, MD	Paula Beardsley	Boston, MA	Boston Medical Center (4)
		Denise Fine Jana Tancredi, RN, MA/ MSN, CCRN		
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		Deborah O'Neill Joy Burkhardt, CCRP		
	Ray Wyman, MD	Suellen Hosino, RN, BSN, CCRP	Torrance, CA	Torrance Memorial Medical Center (4)
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				Coastal Heart Medical Group (4)

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		Diana Parra Tri Tran		
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	Jeffrey C. Milliken, MD	Andrea M. Lundeen, MA		
	Pranav M. Patel, MD	Edgar Karanjah, MD		
	Arnold H. Seto, MD Kevin T. Harley, MD	Wanda C. Marfori, MD Eduardo Hernandez-Rangel, MD	Orange, CA	University of California Irvine Medical Center (3)
	Michael A. Gibson, MD Byron J. Allen, MD	Pam Singh		
	Rita Coram, MD	Anne Marie Webb, BSN	Louisville, KY	University of Louisville (3)
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	Sabu Thomas, MD, MSc	Angela Kim, BS		
	Ronald G Schwartz, MD, MS Wei Chen, MD, MS	Patrick Wilmot, BS	Rochester, NY	University of Rochester (3)
	Mahfouz El Shahawy, MD	Ramona Stevens	Sarasota, FL	Cardiovascular Center of Sarasota (3)
	James Stafford, MD	Loriane Black	Baltimore, MD	University of Maryland Medical Center (3)
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		Tia Cauthren Trish Tucker		
	Andrew Zurick, MD	Hollie Horton Jan Orga	Nashville, TN	Saint Thomas Hospital (3)
	Thomas M. Meyer, MD Ronald G. Morford, MD	Joyce R. White, MSN NP-C Cynthia Baumann, RN	Lynchburg, VA	Stroobants Cardiovascular Center (3)
	Bruce Rutkin, MD	Vidya Seeratan	Manhasset, NY	Northwell Health - Manhasset (3)
	Sabahat Bokhari, MD	Magnolia Jimenez	New York, NY	Columbia University Medical Center (3)
	Seth I. Sokol, MD Jay Meisner, MD	Cidney Schultz, RN Jeanne Russo, RN	Bronx, NY	Jacobi Medical Center (3)
	Ihab Hamzeh, MD Arunima Misra, MD	Zohra Huda, RN, BSN, CCRP		
	Matthew Wall Jr., MD Veronica Lenges De Rosen, MD Mahboob Alam, MD	Araceli Boan	Houston, TX	Baylor College of Medicine (3)
	Michael C. Turner, MD Thomas J. Mulhearn, MD	Christine R Hinton	Lake Charles,	Cardiovascular Specialists of Southwest Louisiana (3)
		Beth A. Archer, BSN, RN Julia S. Dionne, BA	LA	
	Arnold P. Good, MD	Cheryl A. Allardyce, BSN, RN Lindsey N. Sikora, BSN, RN Jennifer H. Czerniak, RN	Columbus, OH	Ohio Health Grant Medical Center (3)
		Jennifer A. Mull, MSN, RN Elizabeth Ferguson Frances Laube		
		Gail A Shammas, BSN, RN		Midwest
	Nicolas W. Shammas, MD, MS	Lori Christensen Holly Park	Davenport, IA	Cardiovascular Research Foundation (3)
	Robert Chilton, MD	Joan Hecht	San Antonio, TX	Audie Murphy V.A. (2)
	Patricia K. Nguyen, MD	Davis Vo, BS James Hirsch	Palo Alto, CA	VA Palo Alto Healthcare System (2)
	Matthew Jezior, MD	Jody Bindeman Sara Salkind Dalisa Espinosa, MBS Lori-Ann Desimone, BSN	Palo Alto, CA Bethesda, MD	VA Palo Alto Healthcare System (2) Walter Reed National Military Medical Center (2)
	Paul C. Gordon, MD Thomas Crain, MD	Lina Felix-Stern Jassira Gomes Catherine Gordon, BSN	Providence, RI	Miriam Hospital (2)
	Robert Stenberg, MD	Aimee Mann	Johnstown, PA	Conemaugh Valley Memorial Hospital (2)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Ronald P. Pedalino, MD	Theresa McCreary Stanley E. Cobos, BA Raven R. Dwyer, MPH Dalisa Espinosa, MBS Kirsten J. Quiles, MS Stanley E. Cobos, BA	Brooklyn, NY	NYU-HHC Kings County Hospital Center (2) New York University - Langone
	Joseph Wiesel, MD	Raven R. Dwyer, MPH Dalisa Espinosa, MBS Kirsten J. Quiles, MS Candace Gopaul, BS	Flushing, NY	Cardiovascular Associates (2)
	George J. Juang, MD	Karen Hultberg Tauqir Huk Afshan Hussain Yesenia Zambrano, BS	Brooklyn, NY	Coney Island Hospital (2)
	Mohammed Al-Amoodi, MD	Sarah Medina Rodriguez Trudie Milner Abbey Mulder, RN	Yuma, AZ	Yuma Regional Medical Center (2)
	David Wohns, MD	Stacie Van Oosterhout, MEd	Grand Rapids, MI	Spectrum Health (2)
	Ellis W. Lader, MD	Martha Meyer, RN, MSN Nancy L. Clapp, RN, BA, CCRC	Kingston, NY	Mid Valley Cardiology (1)
	Michael Mumma, MD	Heather Barrentine Jenne M. Jose, PA	Sarasota, FL	Sarasota Memorial Hospital (1)
	Lekshmi Dharmarajan, MD	Stanley E. Cobos, BA Raven R. Dwyer, MPH Dalisa Espinosa, MBS Kirsten J. Quiles, MS	Jenne Manchery	Bronx, NY
NYU-HHC Lincoln Medical and Mental Health Center (1)				
	Joseph F.X. McGarvey Jr, MD Thomas R. Downes, MD (till Dec. 2016)	Vera McKinney, RN Linda Schwarz, RN Scott M. Kaczkowski	Doylestown, PA	Doylestown Health Cardiology (1)
	Gary J. Luckasen, MD (from Dec. 2016)	Adam J. Jaskowiak Joel Klitch	Loveland, CO	Medical Center of the Rockies (1)
		Joel Klitch		
	Benjamin Cheong, MD Srinivasa Potluri, MD	Debra Dees Precilia Vasquez	Houston, TX Plano, TX	Baylor St. Luke's Medical Center (1) Baylor Research Institute at Legacy Heart Center (1) **
	Ronald A. Mastouri, MD			
	Jeffery A. Breall, MD, PhD George E. Revtyak, MD Jonathan W. Bazeley, MD	Elise L. Hannemann, RN,CCRC Judy Mae Foltz, RN,CCRC	Indianapolis, IN	Indiana University/ Krannert Institute of Cardiology (1)
		Emily DeRosa		

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Dayuan Li, MD	Beth Jorgenson Joyce Riestenberg-Smith	St. Paul, MN	HealthEast Saint Joseph's Hospital (1)
	Kenneth Giedd, MD		New York, NY	Beth Israel Medical Center (1)
	Wayne Old, MD Francis Burt, MD	Rebecca Bariciano	Chesapeake, VA Bethlehem, PA	Cardiovascular Associates, Ltd. (1) Saint Luke's Hospital and Health Network (1)
	Kozhaya Sokhon, MD	Jessica Waldron	Sugar land, TX	Medicus Alliance
		Michelle Mayon		Clinical Research Org., Inc. (1)
	Deepika Gopal, MD		Plano, TX	The Heart Hospital Baylor (1)
	Uma S. Valeti, MD	Gretchen Ann Peichel, RN Brandy Starks	Minneapolis, MN	University of Minnesota (1)
	Jon Kobashigawa, MD	Rajesh Gopalan Nair, MD, DNB, DM	Lucilla Garcia Maria Thottam	
India (941) Country Leader				
Balram Bhargava, DM				Anjali Anand, MSc
	Sajeev Chakanalil Govindan, MD, DNB, DM, PhD		Janitha Raj, B.Tech Reshma Ravindran, MSc	
Beverly Hills, Cedars Sinai Medical CA Center (1)				
Calicut Government Medical College (208)				
		Rajalekshmi VS, MSc, MScCRRA		
	Cholenahally Nanjappa Manjunath, MD, DM Nagaraja Moorthy, MD, DM	Nandita Nataraj, BE(Biotech) PGDICRCDM Soundarya Nayak, BE(Biotech) PGDICRCDM		
	Satvic Cholenahally Manjunath, MD,DM	Mahevamma Mylarappa, GNM (General Nursing)	Bangalore	Sri Jayadeva Institute of Cardiovascular Sciences and Research (149)
	Suryaprakash Narayanappa, MBBS Neeraj Pandit, MD, DM	Sheromani Bajaj		
	Ranjit Kumar Nath, MD, DM	Vandana Yadav, Msc,PGDACR Girish Mishra, Msc, PGDACR	New Delhi	Dr Ram Manohar Lohia Hospital (101)
	S.K. Dwivedi, DM V.S. Narain, DM	Roma Tewari, PG Meenakshi Mishra, PG		King George's
	Sharad Chandra, DM	Shivali Patel Suman Singh, PG	Lucknow	Medical University, Department of Cardiology (100)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Gurpreet S. Wander, DM Rohit Tandon MD			
	Sarju Ralhan, M.Ch (CTVS)	Baljeet Kaur, MSc (Biotechnology)	Ludhiana	Hero DMC Heart Institute, Dayanand Medical College and
	Naved Aslam, DM	Sonika Gupta, MBA, B. Pharmacy		Hospital (83)
	Abhishek Goyal, DM Balram Bhargava, DM G.Karthikeyan, DM			
	S.Ramakrishnan, DM			
	Sandeep Seth, DM			
	Rakesh Yadav, DM Sandeep Singh, DM			
	Ambuj Roy, DM Neeraj Parakh, DM	Chandini Suvarna, BDS	New Delhi	All India Institute Of Medical Sciences (67)
	Sunil Kumar Verma, DM Rajiv Narang, DM Sundeep Mishra, DM Nitish Naik, DM Gautam Sharma, DM			
	Shiv Kumar Choudhary, M.Ch Chetan Patel, DNB Gurpreet Gulati, MD			
	Sanjeev Sharma, MD V K Bahl, DM			
	Anoop Mathew, MD	Binoy		MOSC Medical
	Eapen Punnoose, MD	Mannekkattukudy Kurian	Kolenchery	College Hospital (39)
	Milind Avdhoot Gadkari, MD	Sheetal Rupesh Karwa, BHMS		
	Siddharth Gadage, MD DNB Tapan Umesh Pillay, BHMS MSc	Suvarna Kolhe, MSc	Pune	KEM Hospital Pune (35)
	Santhosh Satheesh, MBBS, MD, DM	R. J. Vindhya, B.Sc. (Bio-Technology), MSc(Bio-Informatics)	Pondicherry	Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER) (31)
		Peeyush Jain, MD Ashok Seth, MD		
		Zile Singh Meharwal, MD		
	Atul Mathur, MD Upendra Kaul, MD	Atul Verma, MD Mona Bhatia, MD Ankush Sachdeva, MD Thounaojam Indira Devi, RN Nungshi Jungla, RN	New Delhi	Fortis Escort Heart Institute (31)
	Johann Christopher, MD, DNB	K. Manjula Rani, MSc.		
	Rajeev Menon, MD, DNB	M. Sowjanya Reddy, BSc	Hyderabad	Gurunanak CARE Hospital (27)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Nirmal Kumar, MD, DNB	K. Preethi, BSc		
	Abraham Oomman, MD,DM,DNB	Rinu R sidh, MSc(Clinical Research)		
	Robert Mao, MD, DM	Ramakrishnan T., B.Tech(Biotechnology)	Chennai	Apollo Research and Innovation (23)
	Hilda Solomon, PhD	Rajesh Francis, MSc(Clinical Research)		
	Sudhir Naik, MD, DM			
	Sajeeda Parveen Khan, MBBS, (Dip.Card)	Vamshi Priya P., MSc	Hyderabad	Apollo Research & Innovations (13)
	Johann Christopher, MD Nirmal Kumar, MD	Kotiboinna Preethi	Hyderabad	CARE Nampally (11)
	Purvez Grant, MD	Shweta Hande, BHMS, PGDCR Poonam Sonawane, B.ScMicrobiology, ACCR	Pune	Ruby Hall Clinic,Grant Medical Foundation (10)
	Ranjan Kachru, MD	Abhishek Dubey Kavita Rawat	New Delhi	Fortis Healthcare Fl.t Lt. Rajan Dhall Hospital (4)
	Ajit Kumar VK, MD, DM			
	Sanjay Ganapathi, MD, DM			
	Jayakumar K, MS, M.Ch	Vineeth CP		
	Harikrishnan Sivadasanpillai, MD, DM	Manas Chacko, RN	Trivandrum	Sree Chitra Tirunal Institute for Medical Sciences and Technology (3)
	Bijulal Sasidharan, MD, DM Kapilamoorthy TR, MD	Suresh Babu		
	Johann Christopher, MD	Sowjanya Reddy		
	Praneeth Polamuri, MD	Manjula Rani	Hyderabad	CARE Hospital (3)
		Priyadarshani		Batra Hospital and
	Upendra Kaul, MD	Arambam Bebek Singh	New Delhi	Medical Research Centre (BHMRC) (3)
United Kingdom (539) Country Leaders				
Roxy Senior, MBBS, MD, DM Keith AA Fox, MBChB *(past)* Country Coordinators				
Grace M. Young, MSc, BSc (Hons)				
Kathryn Carruthers *(past)*				

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Roxy Senior, MBBS, MD, DM Ahmed Elghamaz, MB BCh Sothinathan Gurunathan, MBChB		Harrow	Northwick Park Hospital Harrow/ Royal Brompton Hospital London (202)
	Nikolaos Karogiannis, MBBS	Grace M. Young, MSc, BSc (Hons)		
	Benoy N Shah, MD, MBBS, BSc (Hons) Richard HJ Trimlett, MBBS, CCST	Christopher Kinsey Raisa Kavalakkat, MSc, BSc, RN		
	Michael B Rubens, LRCP, MRCS, MBBS, DMRD	Jo Evans, RN		
	Edward D Nicol, MD, BMedSci, MBBS, DTM&H Tarun K Mittal, MD	Ikraam Hassan, RN		
	Reinette Hampson, BSc (Hons), BA (Hons)			
		Sarah Williams, RN		
	Reto Andreas Gamma, MBBS	Kim Holland, RN Karen Swan, RN	Chelmsford	Broomfield Hospital (39)
	Mark A de Belder, MD Jeet Thambyrajah, MD	Bev Atkinson, RN	Middlesbrough	The James Cook University Hospital, Middlesbrough (37)
	Thuraia Nageh, BSc(Hons) MBBS MD MRCP John R Davies, MBBS, PhD	Swapna Kunhunny, MRes Clin Res, BSc (N), RN	Westcliffe on Sea	Southend University Hospital (34)
	Steven J. Lindsay, MD	Craig Atkinson, RN		
	John Kurian, MD Haqeel Jamil, MD	Carita Krannila, RN Manitha Vinod, RN	Bradford	Bradford Royal Infirmary (20)
	Osama Raheem, MD			
	Angela Hoye, MD	Lisa Chaytor		
		Leanne Cox Julie Morrow Kay Rowe	Cottingham	The University of Hull/Castle Hill Hospital (19)
	Patrick Donnelly, MD	Stephanie Kelly, RN		
	Bernardas Valecka, MD	Susan Regan, RN	Belfast	South Eastern Health and Social Care (17)
		Dawn Turnbull Catherine Fleming		
	Anoop Chauhan, MD	Arijit Ghosh Karen Gratrix	Blackpool	Blackpool Teaching Hospitals (16)
		Stephen Preston		
	Craig Barr, MD	Anne Cartwright	Dudley	Russells Hall Hospital (15)
	Khaled Alfakih, MBBS, MD Jonathan Byrne, PhD Ian Webb, PhD, MA	Abigail Knighton, BSc., PG Dip. Katherine Martin, RGN, Dip. N, MSc	London	King's College NHS Foundation Hospital (14)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Peter Henriksen, PhD, MB ChB, BSc(Hons)	Laura Flint, RGN James Harrison, BSc(Hons), PG dip	Edinburgh	Royal Infirmary of Edinburgh (13)
	Peter OKane, MD	Nicki Lakeman	Bourneouth	Royal Bournemouth Hospital (13)
	Ramesh de Silva, MB ChB, MD	Anja Ljubez	Bedford	Bedford Hospital NHS Trust (11)
	Dwayne S. G. Conway, MD	Judith Wright Donna Exley	Wakefield	Pinderfields Hospital (11)
	Alexander A Sirker, MB BChir, PhD	Mervyn Andiapen, RN Amy J. Richards, BSc	London	University College London Hospitals NHS Foundation Trust BartsHealth NHS Trust (11)
	Stephen P Hoole, MD	Lisa Wong, MSc	Cambridge	Papworth Hospital (10)
	Fraser N. Witherow, MD	Melanie J. Munro, RGN	Dorchester	Dorset County Hospital (8)
	Nicola Johnston, MB, Bch BAO, MRCP, MD	Michelle McEvoy, RN		
	Mark Harbinson, MB, Bch BAO, MRCP, MD Simon Walsh, MB, Bch BAO, MD	Caroline Brown, RN	Belfast	Belfast Trust (7)
	Hanna Douglas, MB, Bch BAO, MRCP, MD			
		Thabitha Charles		Central Manchester
	Matthew Luckie, MD	Laurel Kolakaluri Hannah Phillips Louise Morby, RN	Manchester	University Hospital (7)
	Jolanta Sobolewska, MD	Karen Hallett, RN Carolyn Corbett, RN Lynne Winstanley	Oldham	The Pennine Acute Hospitals NHS Trust (6)
	Paramjit Jeetley, MD			Royal Free London
	Niket Patel, MD Tushar Kotecha, MBChB, Mpharm Christopher Travill, MBBS, MD Iqbal Karimullah,		MBBS	Angelique Smit, RN London Susan Gent, SRN
RGN Nafisa Hussain, BSc	Luton	NHS Foundation T rust (6)		
		Luton and Dunstable University Hospital NHS FT (5)		
	Mahmud Al-Bustami, MBBS			
	Denise Braganza, MD	Fiona Haines	Peterborough	Peterborough City Hospital (5)
	Robert Henderson, MD	Joanne Taaffe Jane Burton		
	Kate Pointon, MBBS	Maria Colton	Nottingham	Nottingham University Hospitals (4)
	Surendra Naik, PhD Thomas Mathew, MBBS, MD, DM	Rachel King		

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
		Ammani Brown, MSc BA RN Andrew Docherty, RN		
	Colin Berry, BSc MB ChB, PhD Damien Collison, MB ChB Giles Roditi, MB ChB	Lisa McCloy, RN Kate Robb, RN Craig Paterson, PhD	Clydebank	University of Glasgow (4)
		Wenda Crawford, RN Joanne Kelly, RN		
		Lorraine McGregor, RN		
	Andrew J Moriarty, BSc MB PhD	Anne Mackin, RN, BSc	Craigavon	Cardiovascular Research Unit, Craigavon Area Hospital (2)
	Jason D. Glover, MBBS Jiwan Pradhan, MBBS	Janet P Knight, RN	Basingstoke	Hampshire Hospitals NHS Foundation Trust (2)
	Ghada Mikhail, MD			Imperial College
	Darrel P. Francis, MD, MA	Tuhina Bose	London	IHealthcare NHS Trust (1)
*Canada (447) Country Leaders Vladimir Dzavik, MD				
Shaun G. Goodman, MD, MSc Gilbert Gosselin, MD		Anna Proietti, RN Myriam Brousseau, RN		
	Gilbert Gosselin, MD	Magalie Corfias, RN Patricia Blaise Luc Harvey	Montreal, QC	Montreal Heart Institute (90)
	Ariel Diaz, MD Philippe Rheault, MD		Trois-Rivieres, QC	Centre Hospitalier de Regional Trois-Rivieres (71)
	Miguel Barrero, MD Carl-Éric Gagné, MD	Patricia Alarie		
	Yanek Pépin-Dubois, MD	Linda Arcand		
	Ricardo Costa, MD	Isabelle Roy		
	Ying Tung Sia, MD	Estelle Montpetit		
	Catherine Lemay, MD			
	Alejandro Gisbert, MD			
	Pierre Gervais, MD			
	Alain Rheault, MD			
		Katia Drouin, RN		
	Denis Carl Phaneuf, MD	Christine Bergeron, RN	Terrebonne, QC	CISSSL - Hopital Pierre-Le Gardeur (42)
	Gilbert Gosselin, MD	Christine Shelley		
		Christine Masson Sandy Carr, RN		
	Pallav Garg, MBBS, MSc	Catherine Bone, RN	London, ON	London Health Sciences Centre (35)
	Benjamin J.W. Chow, MD	Ermina Moga		

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Renee C. Hessian, MD	Janetta Kourzenkova	Ottawa, ON	University of Ottawa Heart Institute (29)
	Rob S. Beanlands, MD	Olga Walter		
	Richard F. Davies, MD			
	Kevin R. Bainey, MD, MSc	Norma Hogg, RN Suzanne Welsh, RN	Edmonton, AB	University of Alberta (28)
	Asim N. Cheema, MD, PhD			
	Akshay Bagai, MD, MHS			
	Ron Wald, MDCM, MPH			
	Shaun G. Goodman, MD, MSc	Khrystyna Kushniriuk, HBSc, MD	Toronto, ON	St. Michael's Hospital (27)
	John Joseph Graham, MRCP, MB ChB, BSc	Mohammed Hussain		
	Mark Peterson, MD, FRCSC, PhD	Olugbenga Bello		
	Chi-Ming Chow, MD, CM, MSc			
	Beth Abramson, MD, MSc			
	Asim Nazir Cheema, MD	Ishba Syed, MBBS	Mississauga, ON	Dixie Medical Group (24)
	Mohammad Tariq Vakani, MD	Mohammed Hussain, BSc(H)		
		Khrystyna Kushniriuk, MBBS		
		Judy Otis, CRC		
	James Cha, MD	Rebecca Otis, CRC Michelle M Seib, RN	Oshawa, ON	Dr. James Cha (21)
	Andrew G Howarth, MD, PhD	Sandra M Rivest, RN	Calgary, AB	University of Calgary (15)
		Rosa Sandonato, BSCN		
	Graham Wong, MD	Jackie Chow Andrew Starovoytov Naomi Uchida Ngaire Meadows	Vancouver, BC	Vancouver General Hospital (15)
	Amar Uxa, MD	Nadia Asif Suzana Tavares	Toronto, ON	University Health Network (14)
	Paul Galiwango, MD	Bev Bozek, RN, CCRC		
	Saleem Kassam, MD	Maria Shier	Scarborough, ON	Scarborough Cardiology Research (9)
	Ashok Mukherjee, MD	Lori-Ann Larmand		
	A. Joseph Ricci, MD	Amir Janmohamed		
	Andy Lam, MD	Brenda Hart Jane Marucci Sharon Tai Sonya Brons, RN Chris Beck, RN	East Grimsby, ON	West Lincoln Memorial Hospital (8)
	Shamir Mehta, MD	Glenda Wong, RN Krystal Etherington	Hamilton, ON	Hamilton General Hospital (7)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
		Thippeekaa Arumairajah Maria Aprile		
	Jacob Udell, MD	Sara Karlsson Susan Webber	Toronto, ON	Women's College Hospital (7)
	Philippe Généreux, MD	Chantale Mercure	Montréal, QC	Centre Intégré Universitaire de Santé et de Services Sociaux du Montréal (2)
	Adnan Hameed, MD	Nancy Aedy	St. Catharines, ON	Saint Catharines General Hospital (2)
		Fran Farquharson		Northwest GTA
	Ledjalem Daba, MD	Anam Siddiqui	Vaughan, ON	Cardiovascular and Heart Rhythm Program (1)
Brazil (399)				
Country Leaders				
Antonio Carlos Carvalho, MD, PhD				
Renato D. Lopes, MD, PhD				
	Whady A. Hueb, MD			
	Paulo Cury Rezende, MD Expedito Eustáquio Ribeiro Silva, MD	Myrthes Emy Takiuti, RN	Sao Paulo	Heart Institute (InCor) University of São Paulo (127)
	Alexandre Ciappina Hueb, MD Paola Emanuela Poggio Smanio, MD, PhD	Leonardo Pizzol Caetano, PhD	São Paulo	Instituto Dante Pazzanese de Cardiologia (98)
	Alexandre Schaan de Quadros, MD			
	Renato Abdala Karam Kalil, MD	Aline Peixoto Deiro		
	José Luiz da Costa Vieira, MD	Alice Manica Muller		
	Gabriel Grossmann, MD Pedro Píccaro de Oliveira, MD	Maria Antonieta Pereira de Moraes Bruna Maria Ascoli	Porto Alegre	Instituto de Cardiologia de Porto Alegre (41)
	Leonardo Bridi, MD	Sílvia Zottis Poletti		
	Simone Savaris, MD			
	João V Vitola, MD, PhD			
	Rodrigo J Cerci, MD, Msc Fabio R Farias, MD, Msc	Sandra S. Zier, BSc Vilmar Veiga Jr, BSc	Curitiba	Quanta Diagnostico & Terapia (33)
	Miguel M Fernandes, MD, PhD			
	José Antonio Marin-Neto, MD, PhD			

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	André Schmidt, MD, PhD Moysés de Oliveira Lima Filho, MD, PhD Ricardo Mendes Oliveira, MD João Reynaldo Abbud Chierice, MD	Diego Franca da Cunha	Ribeirao Preto	Hospital das Clinicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (31)
	Carísi A. Polanczyk, MD Mariana V. Furtado, MD	Guilherme G Rucatti, PsyD Fernanda Igansi, BSc	Porto Alegre	Hospital de Clínicas de Porto Alegre (12)
	Luis F. Smidt, MD	Mauren P Haeffner, BSc		
	Antonio Carlos Carvalho, MD	Viviane Almeida	Sao Paulo	Unifesp - Hospital Sao Paulo (9)
	Gustavo Pucci, MD	Gabriela Sanchez de Souza		
	Flavio Lyra, MD Alvaro Rabelo Alves Junior, MD Marianna D. A. Dracoulakis, MD, PhD	Mayana Almeida Viviane dos Santos	Salvador	Fundacao Bahiana de Cardilogia (9)
	Rodolfo G. S. D Lima, MD	Natalia S Oliveira, RN	Salvador	Hospital da Bahia (8)
	Estevao Figueiredo, MD	Bruna Edilena Paulino Azevedo Marco Bizzaro Santos	Belo Horizonte	Hospital Lifecenter (8)
	Paulo Ricardo Caramori, MD	Amanda Germann Vitor Gomes Rosa Homem Ellen Magedanz	Porto Alegre	Hospital Sao Lucas da Pontificia Universidade Catolica do Rio Grande do Sol (7)
	Rogerio Tumelero, MD	Rosane Laimer Alexandre Tognon	Fundo	Hospital Sao Vicente de Paulo (5)
	Frederico Dall'Orto, MD		Pocos de Caldas	Hospital Maternidade e Pronto Socorro Santa Lucia (4)
	Claudio T. Mesquita, MD Alexandre S. Colafranseschi, MD Amarino C. Oliveira Jr., MD Luiz A. Carvalho, MD Isabella C. Palazzo, MD Andre S. Sousa, MD Expedito Eustáquio Ribeiro da Silva, MD, PhD	Roberta P Santos, RN	Botafogo	Hospital Pró-Cardiaco (3)
	Pedro Gabriel Melo de Barros e Silva, MD, PhD	Mariana Yumi Okada, RN		

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Luciana de Pádua Silva Baptista, MD, PhD	Ana Paula Batista, RN	Sao Paulo	Hospital TotalCor (2)
	Marcelo Jamus Rodrigues, MD	Aline Nogueira Rabaça, BS		
	Marcos Valério Coimbra de Resende, MD, PhD			
	Jose Francisco Saraiva, MD	Larissa Miranda Trama	Sao Paulo	Hospital Celso Pierro (1)
		Talita Silva Camila Thais de Souza Ormundo Carla Vicente		
	Costantino Costantini, MD, PhD	Caroline Pinheiro Daniele Komar	Curitiba	Hospital Cardiologico Costantini (1)
Poland (333)				
Country Leaders				
Witold Ruzyllo, MD, PhD				
Hanna Szwed, MD, PhD				
Country Coordinator				
Radoslaw Pracon, MD, PhD				
	Marcin Demkow, MD, PhD			
	Radoslaw Pracon, MD, PhD			
	Cezary Kepka, MD PhD			
	Anna Teresinska, MD PhD	Olga Walesiak	Warsaw	Coronary and Structural Heart Diseases Department, Institute of Cardiology (127)
	Karolina Kryczka, MD PhD	Katarzyna Malinowska		
	Jan Henzel, MD PhD			
	Mateusz Solecki, MD PhD			
	Edyta Kaczmarska, MD PhD			
		Jakub Maksym, MD		
		Karolina Wojtera, MD		
	Tomasz Mazurek, MD, PhD	Anna Fojt, MD	Warszawa	Medical University of Warsaw (48)
		Ewa Szczerba, MD		
		Szymon Jonik, MD		
	Jaroslaw Drozdz, PhD			
	Bartosz Czarniak, MD			
	Malgorzata Frach (formerly Stasiak), MD		Lodz	Cardiology Clinic, Medical University in Lodz (43)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Konrad Szymczyk, MD			
	Iwona Niedzwiecka, MD			
	Sebastian Sobczak, MD			
	Tomasz Ciurus, MD			
	Piotr Jakubowski, MD			
	Magdalena Misztal-Teodorczyk, MD			
	Dawid Teodorczyk, MD	Marta Swiderek, MA		
	Aleksandra Fratczak, MD	Ewelina Wojtala, MA		
	Marcin Szkopiak, MD			
	Patrycja Lebioda, MD			
	Michal Wlodarczyk, MD			
	Anna Plachcinska, MD			
	Jacek Kusmierek, MD			
	Magdalena Miller, MD			
	Halina Marciniak, MD			
	Karolina Wojtczak-Soska, MD			
	Katarzyna Łuczak, MD			
	Tomasz Tarchalski, MD			
	Anna Cichocka-Radwan, MD			
	Hanna Szwed, MD, PhD	Jaroslaw Karwowski, MD	Warsaw	National Institute of Cardiology, Warsaw (35)
	Grazyna Anna Szulczyk, MD			
	Adam Witkowski, MD, PhD			
	Krzysztof Kukuła, MD, PhD		Warsaw	Department of Interventional Cardiology & Angiology, Institute of Cardiology (20)
	Małgorzta Celińska-Spodar, MD			
	Joanna Zalewska, MD			
	Grzegorz Gajos, MD, PhD		Krakow	Department of Coronary Disease, John Paul II Hospital, Jagiellonian University Medical College (16)
	Krzysztof Bury, MD, PhD			
	Piotr Pruszczyk, MD, PhD	Andrzej Łabyk, MD	Warszawa	Department of Internal Medicine and Cardiology, Infant Jesus Teaching Hospital, Medical
	Marek Roik, MD, PhD	Agnieszka Szramowska, MD		
		Olga Zdończyk, MD		

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
				University of Warsaw (15)
	Krystyna Łoboz-Grudzień, MD, PhD			
	Leszek Sokalski, MD, PhD	Joanna Jaroch, MD, PhD	Wrocław	T.Marciniak Hospital (11)
	Barbara Brzezińska, MD, PhD			
	Maciej Lesiak, Professor, MD			Szpital Kliniczny
	Magdalena Łanocha, MD		Poznan	Przemienienia Pańskiego (10)
	Krzysztof W. Reczuch, MD	Adam Kolodziej, MD	Wroclaw	Military Hospital / Medical University (4)
	Zbigniew Kalarus, MD			Medical University of Silesia, School of Medicine with the Division of Dentistry, Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center for Heart Diseases (3)
	Andrzej Swiatkowski, MD			
	Mariola Szulik, MD		Zabrze	
	Wlodzimierz J. Musial, MD	Marta Marcinkiewicz-Siemion, MD	Bialystok	University Hospital in Bialystok (1)
Russia (303)				
Country Coordinator				
Olga Bockeria, MD, PhD				
	Leo Bockeria, MD, PhD	Olga Bockeria, MD, PhD	Moscow	National Medical Research Center for Cardiovascuar Surgery (113)
	Karen Petrosyan, MD, PhD	Zalina Kudzoeva, MD		
	Tatiana Trifonova, MD	Nodira Aripova, MD		
	Alexander M. Chernyavskiy, MD, PhD	Ivan A. Naryshkin, MD	Novosibirsk	E.Meshalkin National Medical Research Center of the Ministry of Health of the Russian Federation (101)
	Evgeniy I. Kretov, MD	Alena Kuleshova, MD		
	Igor O. Grazhdankin, MD	Dastan Malaev, MD		
	Leonid L. Bershtein, MD, PhD			
	Sergey A. Sayganov, MD, PhD	Irina Subbotina	Saint Petersburg	North-Western State Medical University (50)
	Anastasia M. Kuzmina-Krutetskaya, MD	Victoria Gumerova		
	Elizaveta V. Zbyshevskaya, MD, PhD			
	Nana O. Katamadze, MD, PhD			

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Elena A. Demchenko, MD, PhD Pavel S. Kozlov, MD Vikentiy Y. Kozulin, MD Ekaterina I. Lubinskaya, MD	Olga B. Nikolaeva, MD	Saint Petersburg	Federal Almazov North-West Medical Research Centre (39)
*Spain (286) Country Leader Jose Luis Lopez-Sendon, MD, PhD Country Coordinator Almudena Castro, MD				
	Jose Lopez-Sendon, MD, PhD Almudena Castro, MD Elena Refoyo Salicio, MD Gabriela Guzman, MD Gabriel Galeote, MD Silvia Valbuena, MD	Virginia Fernández-Figares, Pharm	Madrid	Hospital La Paz. IdiPaz (118)
	Jesús Peteiro, MD, PhD María Dolores Martínez-Ruíz, MD Ruth Pérez-Fernández, MD	Moisés Blanco-Calvo, PhD		Complejo Hospitalario Universitario A Coruña (CHUAC) Sergas, Department of Cardiology. INIBIC
	José J Cuenca-Castillo, MD Xacobe Flores-Ríos, MD Óscar Prada-Delgado, MD Gonzalo BargeCaballero, MD Jose Ramon Gonzalez Juanatey, MD, PhD Miguel Souto Bayarri, MD, PhD	Encarnación Alonso-Álvarez, BSc Paula García-González, BSc	A Coruna	A Coruña. CIBER-CV. Universidad de A Coruña, Spain (112)
	Virginia Pubull Nuñez, MD Raymundo Ocaranza Sanchez, MD, PhD Belen Cid Alvarez, MD Carlos Peña Gil, MD, PhD Amparo Martinez Monzonis, MD Alessandro Sionis, MD	Jose Seijas Amigo, Pharm	Santiago de Compostela	Hospital Clinico Universitario de Santiago (17)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Montserrat Vila Perales, MD			
	Josep Maria Padró, MD			
	Antonio Serra Peñaranda, MD			
	Joan García Picart, MD	Ana Fernández Martínez, RN	Barcelona	Hospital de la Santa Creu i Sant Pau (11)
	Antonino Ginel Iglesias, MD			
	Xavier Garcia-Moll Marimon, MD			
	Guillem Pons Lladó, MD			
	Francesc Carreras Costa, MD			
	Vicente Miro, MD			
	Jose L Diez, MD	Begoña Igual, MD	Valencia	Hospital Universitario y Politecnico La Fe (10)
	Pilar Calvillo, MD			
	F. Marin Ortuño, MD, PhD			
	M. Valdés Chávarri, MD, PhD	M. Quintana Giner, MD	Murcia	HUVA, Hospital Clínico Universitario Virgen De La Arrixaca (8)
	A. Tello Montolliu, MD, PhD	A.I. Romero Aniorte, MD		
	E. Pinar Bermudez, MD, PhD	JM. Rivera Caravaca, MD		
	G. De La Morena, MD, PhD			
		Olga Cañavate		
	Montserrat Gracida Blancas, MD	Sonia Guerrero Silvia Riera Jose Enrique Castillo	Barcelona	Hospital De Bellvitge (4)
	Jose Enrique Castillo Luena, MD	Luena Maria Lasala	Zaragoza	Hospital Universitario Miguel Servet (4)
	Francisco Fernandez-Aviles, MD	Maria Lorenzo Olga Sobrino Alexandra Vazquez	Madrid	Hospital General Universitario Gregorio Maranon (2)
China (246)				
Country Leader				
Lixin Jiang, MD, PhD				
		Haojian Dong		
	Jiyan Chen, MD	Peiyu He Chunli Xia	Guangzhou	Guangdong General Hospital (102)
		Junqing Yang Qi Zhong		
	Yongjian Wu, MD, PhD	Yanmeng Tian, MD Dongze Li	Beijing	Chinese Academy of Medical Sciences, Fuwai Hospital (17)
	Yitong Ma, MD	Xiaomei Li	Urumqi	First Affiliated Hospital of Xinjiang

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Yining Yang, MD	Xiang Ma Zixiang Yu Qian Zhao Chunguang Li		Medical University (15)
	Zheng Ji, MD	Lei Zhang Yu Zhao Bolin Zhu	Tangshan	Tangshan Gongren Hospital (15)
	Xinchun Yang, MD	Mulei Chen Hongjie Chi Yang Wang Jing Zhang	Beijing	Beijing Chao-yang Hospital, Capital Medical University (12)
	Wenhua Lin, MD	Rui Jing Jingjing Liu Qiang Zhou, MD Chang Xu, MD	Tianjing	TEDA International Cardiovascular Hospital (12)
	Hesong Zeng, MD	Zhuxi Li, MD Junhua Li, MD Luyang Xiong, MD Dan Gao	Wuhan	Tongji Medical College (11)
	Xin Fu, MD	Dengke Jiang Ran Leng Xutong Wang Qianqian Yuan Lili Zhang Ziliang Bai Jianhua Li Jie Qi	Zhengzhou	The First Affiliated Hospital of Zhengzhou University (11)
	Bin Yang, MD	Fei Wang Haitao Wang Bin Yang Zhou Yue Zhulin Zhang Yumei Dong	Taiyuan	Shanxi Cardiovascular Hospital (10)
	Songtao Wang, MD	Jiajia Mao Bin Zhang	Qingdao	Qingdao Fuwai Hospital (8)
	Gong Cheng, MD	Xiuhong Li Xiaowei Yao Nier Zhong Ning Zhou	Xian	Shanxi Provincial People's Hospital (6)
	Yulan Zhao, MD	Yaping Huang, MS Panpan Zhou, MS	Zhengzhou	The Second Affiliated Hospital of Zhengzhou University (6)
	Xuehua Fang, MD	Wei Su	Beijing	Liangxiang Hospital, Beijing Fangshan District (6)
	Qiutang Zeng, MD	Yu Kunwu Yudong Peng Xin Su	Wuhan	Wuhan Union Hospital, Tongji Medical College, Huazhong Science and Tech University (3)
	Xi Su, MD	Chen Wang Yunhai Zhao	Wuhan	Wuhan Asia Heart Hospital (3)
	Qingxian Li, MD	Yaming Geng Yanfu Wang Jing-yao Fan, MD Si-ting Feng, MD,PhD	Jining	Affiliated Hospital of Jining Medical University (3)
	Shao-ping Nie, MD, PhD	Xiao Wang, MD,PhD Yan Yan, MD,PhD	Beijing	Beijing Anzhen Hospital (2)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
		Hui-min Zhang, MD,PhD		
	Qin Yu, MD	Lingping Chi Fang Liu	Dalian	Affiliated Zhongshan Hospital of Dalian University (2)
	Jian'an Wang, MD	Han Chen Jun Jiang Huajun Li Jian'an Wang Yechen Han, MM Lihong Xu, RN	Hangzhou	The Second Affiliated Hospital Zhejiang University School of Medicine (1)
	Shuyang Zhang, MD, PhD	Zhenyu Liu	Beijing	Peking Union Medical College Hospital (1)
	Zhenyu Liu, MD	Gang Chen Rongrong Hu		
*Italy (139)				
Country Leader				
Aldo P. Maggioni, MD				
	Gian Piero Perna, MD Marco Marini, MD	Francesca Pietrucci, PhD	Ancona	Cardiology and CCU - Ospedali Riuniti Ancona (54)
	Gabriele Gabrielli, MD Stefano Provasoli, MD Edoardo Verna, MD	Anna Di Donato	Varese	Ospedale di Circolo e Fondazione Macchi (23)
	Lorenzo Monti, MD Barbara Nardi, MD		Rozzano	Humanitas Research Hospital, Rozzano (MI) (17)
	Antonio Di Chiara, MD	Francesca Pezzetta, MD	Tolmezzo	Azienda Servizi Sanitaria n.3 Alto Friuli-Collinare-Medio Friuli (9)
	Andrea Mortara, MD Marcello Galvani, MD	Valentina Casali, MD	Monza	Policlinico di Monza, Monza MB (8) Ospedale "G.B. Morgagni – L. Pierantoni" Forli (AUSL della Romagna) (8)
	Filippo Ottani, MD	Chiara Attanasio	Forli	
		Gianpiero Leone, MD		
	Marco Sicuro, MD	Francesco Pisano, MD Cristina Bare, BSc	Aosta	Ospedale Regionale Umberto Parini (5)
	Paolo Calabro, MD			AORN Dei Colli "V. Monaldi" UOC Cardiologia Università della Campania "L.Vanvitelli" (4)
	Tiziana Formisano, MD	Fabio Fimiani	Napoli	
	Giuseppe Tarantini, MD	Alberto Barioli, MD		
	Umberto Cucchini, MD Anto Luigi Andres, MD	Federica Ramani	Padua	University of Padua-Cardiology Clinic (3)
	Emanuela Racca, MD	Fabrizio Rolfo, MD Cecilia Goletto	Cuneo	Azienda Ospedaliera S. Croce e Carle (3)
	Carlo Briguori, MD	Francesca De Micco	Naples	Clinica Mediterranea (2)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Roberto Amati, MD	Stefano Di Marco, MD		UO Cardiologia Ospedale SS Cosma e Damiano (2)
	William Vergoni, MD	Martina Tricoli	Pescia	
	Aldo Russo, MD Raffaele Fanelli, MD	Massimo Villella, MD	San Giovanni Rotondo	IRCCS “Casa Sollievo della Sofferenza” (1)
*Singapore (61)				
Country Leader				
Harvey D. White, DSc				
Country Coordinator				
Caroline Alsweiler				
	Kian-Keong Poh, MD Ping Chai, MD			
	Joshua P. Loh, MD Edgar L. Tay, MD			
	Kristine Teoh, MD Lynette L. Teo, MD	Sik-Yin V Tan, BSc Winnie C Sia, BSc	Singapore	National University Heart Center Singapore (33)
	Ching-Ching Ong, MD Raymond C. Wong, MD Poay-Huan Loh, MD Theodoras Kofidis, MD David Foo, MBBS	Audrey W Leong, BSc		
	Jason Loh Kwok Kong, MD Ching Min Er, MD	Li Hai Yan, RN	Singapore	Tan Tock Seng Hospital (22)
	Fahim Haider Jafary, MD			
	Terrance Chua, MD	Nasrul Ismail Min Tun Kyaw Deborah Yip	Singapore	National Heart Centre Singapore (6)
Germany (54)				
Country Leader				
Rolf Doerr, MD				
	Rolf Doerr, MD			
	Juergen Stumpf, MD	Dorit Grahl		
	Klaus Matschke, MD, PhD	Franziska Guenther	Dresden	Praxisklinik Herz und Gefaesse (29)
	Gregor Simonis, MD, PhD Clemens T. Kadalie, MD	Kerstin Bonin		
	Udo Sechtem, MD Peter Ong, MD	Ina Wenzelburger Susanne Gruensfelder, RN	Stuttgart	Robert-Bosch-Krankenhaus (22)
	P. Christian Schulze, MD, PhD		Jena	University Hospital Jena (2)
	Bjoern Goebel, MD			
	Karsten Lenk, MD			
	Georg Nickenig, MD	Jan-Malte Sinning, MD	Bonn	Universitatsklinikum Bonn (1)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
		Marcel Weber, MD Nikos Werner, MD		
Austria (50)				
Country Leaders				
Irene Marthe Lang, MD Kurt Huber, MD				
	Herwig Schuchlenz, MD Stefan Weikl, MD	Gudrun Steinmaurer	Graz	LKH Graz West Austria (35)
	Irene Marthe Lang, MD	Max-Paul Winter, MD	Vienna	Medical University of Vienna, Department of Cardiology (8)
	Kurt Huber, MD	Tijana, Andric, MD Maximilian, Tscharre, MD		
	Gabriele, Jakl-Kotauschek, MD	Claudia, Wegmayr, MSc Bernhard, Jäger, MD Florian, Egger, MD	Vienna	Wilhelminen Hospital Vienna (7)
Hungary (49)				
Country Leader				
Matyas Keltai, MD, PhD, DSc				
		Judit Sebo, MD		
	Andras Vertes, MD	Zoltan Davidovits, MD	Budapest	Eszszk- Szent Istvan Hospital (20)
	Albert Varga, MD, PhD	Laszlone Matics Gergely Ágoston, MD	Szeged	University of Szeged (12)
	Geza Fontos, MD	Gabor Dekany, MD	Budapest	George Gottsegen National Institute of Cardiology (9)
	Bela Merkely, MD, PhD, DSc	Andrea Bartykowszki, MD Pal Maurovich-Horvat, MD, PhD, MPH	Budapest	Heart and Vascular Center, Semmelweis University (8)
Serbia (47)	Gabor Kerecsen, MD	Agnes Jakal	Budapest	Military Hospital, Budapest (1)
	Sasa Hinic, MD,		BSc	
Jelena Djokic, MD	Belgrade			
	Marija Zdravkovic, MD, PhD Vladan Mudrenovic, MD Bogdan Crnokrak, MD			University Hospital Center Bezanijska Kosa (13)
	Branko D. Beleslin, MD, PhD Nikola N. Boskovic, MD Marija T. Petrovic, MD	Ana D. Djordjevic-Dikic, MD, PhD Vojislav L. Giga, MD, PhD	Belgrade	Faculty of Medicine, University of Belgrade; Cardiology Clinic, Clinical Center of Serbia (10)
	Milan R. Dobric, MD	Jelena J. Stepanovic, MD, PhD		
	Zeljko Z. Markovic, MD, PhD Ana S. Mladenovic, MD, PhD			

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
		Lazar Velicki, MD		Institute of Cardiovascular Diseases Vojvodina, Sremska Kamenica, Serbia and Faculty of Medicine, University of Novi Sad (9)
	Nada Cemerlic-Adjic, MD	Ljiljana Pupic	Sremska Kamenica	
	Goran Davidović, MD, PhD Rada Vučić, MD	Stefan M. Simović, MD	Kragujevac	Clinical Center Kragujevac (7)
	Milica Nikola Dekleva, MD PhD	Miroslav Stevo Martinovic, MD Gordana Stevanovic	Belgrade	University Clinical Hospital Zvezdara (6)
	Goran Stankovic, MD	Milan Dobric	Belgrade	Clinical Center of Serbia (1)
	Svetlana Apostolovic, MD	Sonja Salinger Martinovic Dragana Stanojevic	Nis	Clinic for Cardiovascular Diseases, Clinical Center Nis (1)
Mexico (46)	Jorge Escobedo, MD Rubén Baleón-Espinosa, MD Arturo S Campos-Santaolalla, MD Elihú Durán-Cortés, MD			
	José M Flores-Palacios, MD Andrés García-Rincón, MD Moisés Jiménez-Santos, MD		Joaquín	V Peñafiel, MD
Ramon de Jesús-Pérez, RN		Benito Juarez Instituto Mexicano del	Seguro Social (35)	
	José A Ortega-Ramírez, MD Aquiles Valdespino-Estrada, MD			
	Erick Alexánderson Rosas, MD	María Fernanda Canales Brassetti, MD Diego Adrián Vences Anaya, MD María Pérez García Isabel Estela Carvajal Juarez, MD Magdalena Madero Rovalo, MC Erick Donato Morales Rodríguez, MD	Mexico City	Instituto Nacional de Cardiología “Ignacio Chávez” (11)
Australia (45)				
Country Leaders				
Joseph B. Selvanayagam, MBBS (Hons), DPhil				
Jamie Rankin, MBBS *(past)*				
Country Coordinator				
Deirdre Murphy				
	Joseph B. Selvanayagam, MBBS (Hons), DPhil	Sau Lee, PhD Prince Thomas, RN Melissa D Chaplin, RN	Adelaide	Flinders Medical Centre (30)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Majo X. Joseph, MBBS			
	Suku T. Thambar, MBBS	Stephanie C Boer, B Biotechnology (Honours)	New Lambton Heights	John Hunter Hospital (8)
	John F. Beltrame, MD	Jeanette K. Stansborough, RN Marilyn Black, RN Michelle M. Bonner, B. Nursing	Woodville	The Queen Elizabeth Hospital (5)
	Graham S. Hillis, PhD	Kim F. Ireland, RN Clare Venn-Edmonds, RN	South Perth	Royal Perth Hospital (2)
France (42)				
Country Leader				
Philippe-Gabriel Steg, MD				
Country Coordinators				
Helene Abergel				
Jean-Michel Juliard				
	Christophe Thuaire, MD Téodora Dutoiu, MD	Corine Thobois, RN Emilie Tachot, RN Christophe Laure, RN Christel Vassaliere, RN	Chartres	C.H. Louis Pasteur (21)
	Philippe Gabriel Steg, MD Jean-Michel Juliard, MD	Helene Abergel, MSc Axelle Fuentes, MSc	Paris	Bichat Hospital (9)
	Michel S. Slama, MD	Ludivine Eliahou, MD Olivier Dubourg, MD	Clamart Cedex	Antoine-Beclere Hospital (5)
	Rami El Mahmoud, MD	Pierre Michaud, MD	Boulogne	Ambroise Pare Hospital (2)
	Eric Nicollet, MD	Sarah Hadjih	Corbeil-Essonnes Cedex	Centre Hospitalier Sud Francilien (2)
	Pascal Goube, MD	Patricia Brito		
	Gilles Barone-Rochette, MD	Gilles Barone-Rochette	Grenoble	Grenoble University Hospital (2)
	Alain Furber, MD Loïc Bière, MD	Charles Cornet, MD, PhD Jeremy Rautureau, MD, PhD	Angers Cedex 9	Centre Hospitalier Universitaire d'Angers (1)
Lithuania (39)		Agne Juceviciene, MD		
		Irma Kalibataite-Rutkauskiene, MD Laura Keinaite		
	Aleksandras Laucevicius, MD Jelena Celutkiene, MD	Monika Laukyte Gelmina Mikolaitiene Akvile Smigelskaite, MD Ilona Tamasauskiene, MD Agne Urboniene, MD	Vilnius	Vilnius University Hospital Santariskes Clinic (39)
*Netherlands (37)				
	Elvin Kedhi MD, PhD			

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	Jorik Timmer, MD Rik Hermanides, MD	Ilse Bouwhuis		Eliza Kaplan, MD Robert K. Riezebos,
Lia Nijmeijer		Zwolle Isala Klinieken (25)		
	MD, PhD Pouneh Samadi, MD	Jeannette, J. M. Schoep, RN	Cardio Research Amsterdam	Hartcentrum OLVG (11)
	Elise van Dongen, MD Sander R. Niehe, MD Harry Suryapranata, MD	Elisabeth, M. Janzen, RN		
	Stijn van Vugt, MD, PhD	Sandra Ahoud	Nijmegen	Radboudumc (1)
Portugal (33)				
	Ruben Ramos, MD			
	Duarte Cacela, MD			
	Ana Santana, MD			
	Antonio Fiarresga, MD			
	Lidia Sousa, MD			
	Hugo Marques, MD			
	Lino Patricio, MD	Mafalda Selas		
	Luis Bernanrdes, MD	Filipa Silva	Lisbon	Hospital de Santa Marta (25)
	Pedro Rio, MD	Cláudia Freixo		
	Ramiro Carvalho, MD			
	Rui Ferreira, MD			
	Tiago Silva, MD			
	Ines Rodrigues, MD			
	Pedro Modas, MD			
	Guilherme Portugal, MD			
	Jose Fragata, MD			
	Fausto J. Pinto, PhD	Inês Zimbarra Cabrita, PhD		
	Miguel Nobre Menezes, MD	Andreia Rocha, MSc		
	Guilhermina Cantinho Lopes, MD	Francisca Patuleia Figueiras, PhD		
	Ana Gomes Almeida, PhD	Andreia Coelho, BSc	Lisbon	Santa Maria University Hospital, Cardiology Department, CHLN (6)
	Pedro Canas Silva, MD	Marta Capinha		
	Angelo Nobre, MD	Maria Inês Caetano		
	Ana Rita Francisco, MD	Susana Silva		
	Nuno Ferreira, MD			
	Ricardo L. Lopes, MD		Vila Nova de Gaia	Centro Hospitalar de Vila Nova de Gaia/ Espinho, EPE (2)
Argentina (29)				

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
Country Leader				
Rafael Diaz, MD *(past)*				
	Luis Guzman, MD	Veronica Tinnirello	Cordoba	Instituto Medico DAMIC (11)
	Julio César Figal, MD			
	Oscar Méndiz, MD Claudia Cortés, MD	Matías Nicolás Mungo	Ciudad Autonoma de Buenos Aires	Fundación Favaloro (10)
	Roberto René Favaloro, MD			
	Carlos Alvarez, MD	Marina Garcia	Bahia Blanca	Hospital Italiano Regional del Sur Bahia Blanca (3)
	Javier Courtis, MD Gabriela Zeballos, MD	Valeria Godoy	Cordoba	Clinica Romagosa and Clinica De La Familia (2)
	Lilia Schiavi, MD	Maria Victoria Actis	Cordoba	Clinica Del Prado (2)
	Mariano Rubio, MD	Graciela Scaro, MD	Cordoba	Clínica Privada Vélez Sarsfield (1)
*New Zealand (28)				
Country Leader				
Harvey D. White, DSc				
Country Coordinator				
Caroline Alsweiler				
	Gerard Patrick Devlin, MD	Liz Low, RN		
	Raewyn Fisher, MD	Jayne Scales, RN Kirsty Abercrombie, RN	Hamilton	Waikato Hospital (22)
	Ralph Alan Huston Stewart, MB,ChB, MD Harvey D. White, DSc Jocelyne Benatar, MD	Leah Howell, RN Cathrine Patten, RN	Auckland	Auckland City Hospital (6)
*Macedonia (28)				
	Sasko Kedev, MD, PhD Irena Peovska Mitevska, MD, PhD Elizabeta Srbinovska Kostovska, MD, PhD Hristo Pejkov, MD, PhD		Skopje	University Clinic of Cardiology (28)
*Sweden (23)				
Country Leader				
Claes Held, MD, PhD				
	Claes Held, MD, PhD Kai Eggers, MD, PHhD Gunnar Frostfelt, MD, PhD Nina Johnston, MD,	Christina Björklund, RN Maria Andreasson, RN Marie Essermark, RN	Uppsala	Uppsala University (18)

Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
	PhD Maciej Olsowka, MD Axel Åkerblom, MD, PhD Inga Soveri, MD, PhD			
	Johannes Aspberg, MD	Liselotte Persson	Stockholm	Karolinska Institutet at Danderyd Hospital (5)
Israel (15)				
Country Leaders				
Rafael Beyar, MD, MD, DSc, MPH				
Tali Sharir, MD				
Country Coordinator				
Eugenia Nikolsky, MD				
	Tali Sharir, MD Dan Elian, MD	Or Harel, MA	Tel-Aviv	Assuta Medical Centers (9)
	Arthur Kerner, MD Samia Massalha, MD	Margalit Bentzvi Ludmila Helmer	Haifa	Rambam Medical Center (6)
Japan (14)				
Country Leader				
Shun Kohsaka, MD				
	Keiichi Fukuda, MD, PhD	Ikuko Ueda, PhD	Shinjuku-ku	Keio University (7)
	Shun Kohsaka, MD	Jun Fujita, MD		
	Satoshi Yasuda, MD, PhD Kanae Hirase, RN	Akemi Furukawa, RN Toshiyuki Nagai, MD, PhD Fumiyuki Otsuka, MD, PhD	Suita-shi	National Cerebral and Cardiovascular Center (4)
	Shigeyuki Nishimura, MD	Shintaro Nakano	Hidaka	Saitama Medical University (3)
*Belgium (7)				
Country Leader				
Frans Van de Werf, MD, PhD				
Country Coordinator				
Kaatje Goetschalckx, MD				
	Kaatje Goetschalckx, MD Frans Van de Werf, PhD, MD Kathleen Claes, PhD, MD	Valerie Robesyn	Leuven	University Hospital Leuven (7)
*Taiwan (7)				
Country Leader				
Harvey D. White, DSc				
Country Coordinator				
Caroline Alsweiler				
	Chung-Lieh Hung, MD			
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Country (No.Randomizations)	Investigator(s)	Study Coordinator(s)	City & State (if applicable)	Institution (No. Randomizations)
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*Countries participated in Economics Quality of Life (EQoL) Questionnaires

**This site received one participant in transfer that was randomized at another site

Abbreviations

CAD	coronary artery disease
CCTA	computed coronary tomographic angiography
ECG	electrocardiography
ETT	exercise tolerance test
ISCHEMIA	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
LAD	left anterior descending coronary artery
LCX	left circumflex coronary artery
LMD	left main coronary artery disease with ≥50% diameter stenosis
	SPECT = single photon emission computed tomography

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CLINICAL PERSPECTIVES

Competency in Medical Knowledge:

Among patients with moderate or severe ischemia on stress testing, the likelihood of left main coronary artery disease (LMD) is 8%, but the predictive value of clinical assessment and stress testing is limited, and anatomic imaging is necessary for accurate identification of LMD.

Translational Outlook:

Subgroups of patients with LMD in prior trials comparing revascularization to medical therapy have been small in size and predated effective preventive medical therapy. Future trials may consider inclusion of patients with LMD.

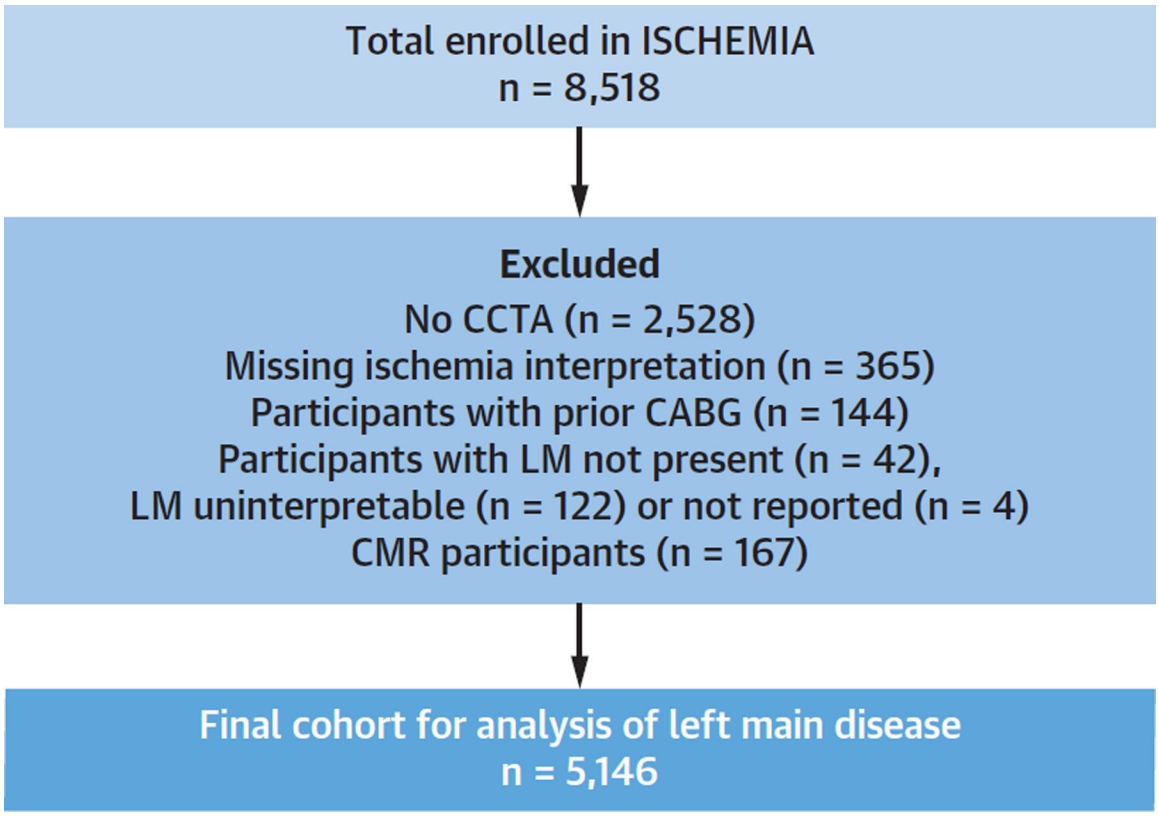


Figure 1. Study Flow Diagram

This analysis included participants enrolled in ISCHEMIA and either excluded from randomization or randomized in the trial. Those without a coronary CT angiogram (CCTA) were excluded, as were participants with missing data for ischemia or left main stenosis. Those with prior coronary artery bypass grafting (CABG) were excluded because the left main is often bypassed. Participants enrolled after stress cardiac magnetic resonance imaging (CMR) were excluded due to inadequate sample size to permit detailed analysis.

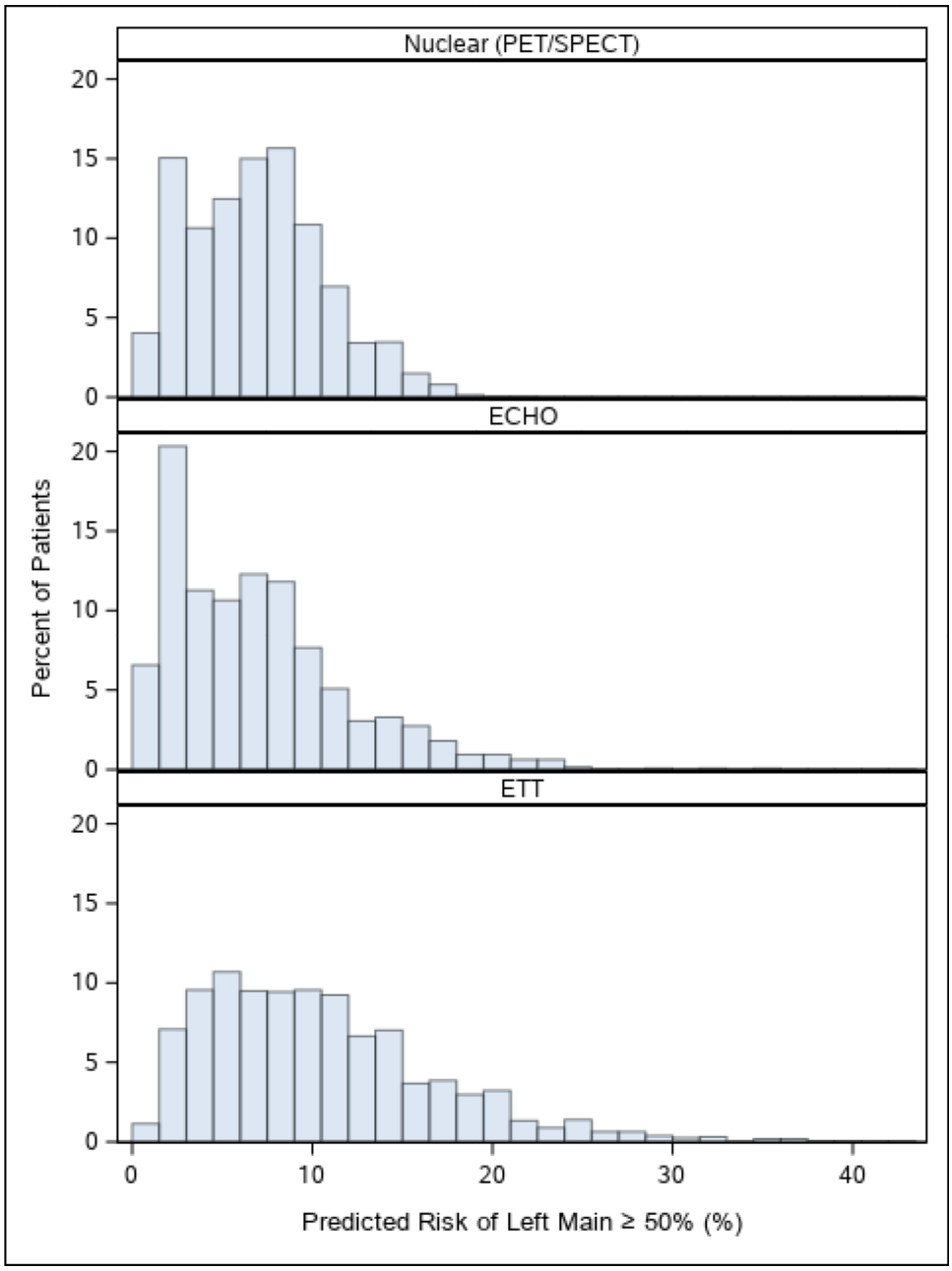
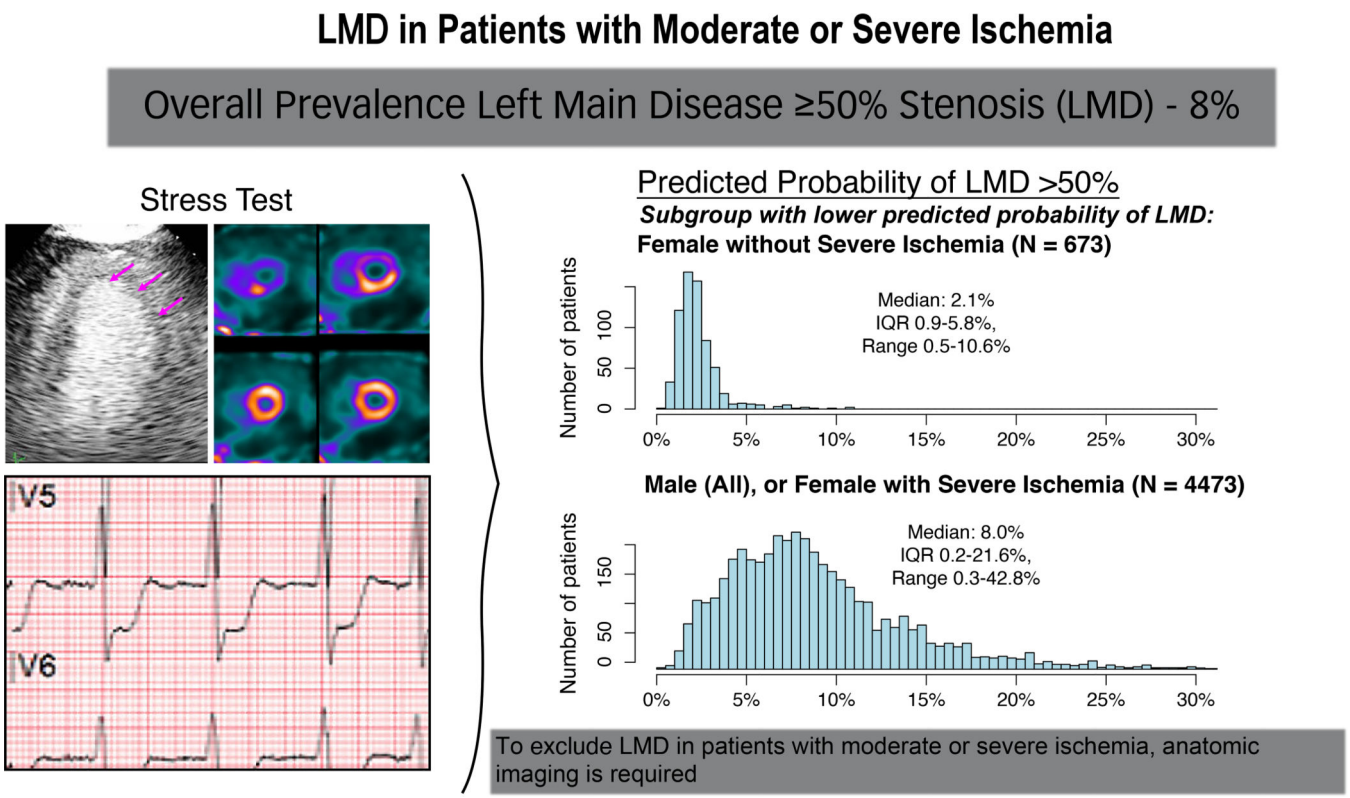


Figure 2. Distribution of the predicted risk estimates of left main disease (LMD)

The sample was stratified by qualifying stress test modality, whether nuclear, echocardiography (echo) or exercise tolerance testing (ETT). The predicted risk of significant LMD, defined as ≥50% on coronary CT angiography, ranged from less than 2% through over 30%. The proportion of participants with each level of predicted risk is shown.



Central Illustration. LMD in Patients with Moderate or Severe Ischemia

Enrolled participants in ISCHEMIA had moderate or severe ischemia on a stress test (e.g., stress echocardiography, upper left, stress nuclear, upper right of stress test panel, or exercise tolerance testing, bottom left). Those with LMD on coronary computed tomography angiography (CCTA) after enrollment were excluded from randomization.

Top right histogram, distribution of predicted probability of LMD among females without severe ischemia.Half of the patients in this subgroup had predicted probability of LMD >2.1%.

Histogram, bottom right, distribution of predicted probability of LMD among males with any degree of ischemia, or among females with severe ischemia.”

TABLE 1.

Baseline Clinical Characteristics of the Study Population with and without LMD

Characteristic	Overall N= 5146	Left main stenosis ≥ 50% N=414	No Left main stenosis ≥ 50% N=4732	P-Value
Demographics				
Age at Enrollment	63.4 (56.6 – 69.7)	64.6 (59.1 – 70.5)	63.3 (56.4 – 69.7)	<.001
Male	3816 (74.2%)	367 (88.6%)	3449 (72.9%)	<.001
Race/Ethnicity				0.008
Non-Hispanic White	2464/4769 (51.7%)	189/384 (49.2%)	2275/4385 (51.9%)	
Non-Hispanic Asian	1310/4769 (27.5%)	130/384 (33.9%)	1180/4385 (26.9%)	
Other	995/4769 (20.9%)	65/384 (16.9%)	930/4385 (21.2%)	
Cardiovascular Risk Factors				
Hypertension	3472/5120 (67.8%)	268/412 (65.0%)	3204/4708 (68.1%)	0.210
Diabetes	1888 (36.7%)	146 (35.3%)	1742 (36.8%)	0.531
Cigarette Smoking				0.693
Never Smoked	2365/5017 (47.1%)	187/380 (49.2%)	2178/4637 (47.0%)	
Former Smoker	2021/5017 (40.3%)	148/380 (38.9%)	1873/4637 (40.4%)	
Current Smoker	631/5017 (12.6%)	45/380 (11.8%)	586/4637 (12.6%)	
Cardiovascular Disease History				
Prior MI	684/5106 (13.4%)	36/400 (9.0%)	648/4706 (13.8%)	0.007
Baseline Labs				
eGFR (ml/min)	86 (73 – 101)	83 (73 – 99)	86 (73 – 101)	0.511
Imaging and Stress Test				
Modality				<.001
Nuclear SPECT/PET	2286 (44.4%)	158(38.2%)	2128 (45.0%)	
SE	1279 (24.9%)	89 (21.5%)	1190 (25.0%)	
ETT	1581(30.7%)	167 (40.3%)	1414 (29.9%)	
Number of ischemic segments on SE	4 (3 – 5)	4 (3 – 6)	4 (3 – 5)	0.008
Number of infarcted segments on SE	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.311
Summed difference score on SPECT	8 (7 – 11)	9 (7 – 12)	8 (7 – 11)	<.001
Summed stress score on SPECT	9 (7 – 14)	11 (8 – 15)	9 (7 – 14)	0.007
TID (Transient ischemic dilation in the LV) on SPECT	309/2286 (13.5%)	26/158 (16.5%)	283/2128 (13.3%)	0.263
TID (Transient ischemic dilation in the LV) on SE	349/1279 (27.3%)	38/89 (42.7%)	311/1190 (26.1%)	<.001
Maximum ST Depression in Any Lead on ETT, mm	2.5 (2.0 – 3.1)	2.7 (2.2 – 3.3)	2.4 (2.0 – 3.1)	0.001
Peak METs on ETT				<.001
< 7	579/1167 (49.6%)	48/68 (70.6%)	531/1099 (48.3%)	
≥ 7	588/1167 (50.4%)	20/68 (29.4%)	568/1099 (51.7%)	

Characteristic	Overall N= 5146	Left main stenosis ≥ 50% N=414	No Left main stenosis ≥ 50% N=4732	P-Value
Severe or moderate anterior ischemia on SPECT	683/2285 (29.9%)	58/158 (36.7%)	625/2127 (29.4%)	0.052
Severe or moderate anterior ischemia on SE	422/1277 (33.0%)	40/89 (44.9%)	382/1188 (32.2%)	0.013
LAD + LCX ischemia on SPECT	201/2286 (8.8%)	16/158 (10.1%)	185/2128 (8.7%)	0.539
LAD + LCX ischemia on SE	211/5146 (4.1%)	22/89 (24.7%)	189/1190 (15.9%)	0.03
Coronary Anatomy on CCTA				
Number of Diseased Vessels with ≥70% stenosis				<.001
0	1016/5146 (19.7)	15/414 (3.6)	1001/4732 (21.2)	
1	1048/5146 (20.4)	49/414 (11.8)	999/4732 (21.1)	
2	776/5146 (15.1)	97/414 (23.4)	679/4732 (14.3)	
3	551/5146 (10.7)	113/414 (27.3)	438/4732 (9.3)	
Non-evaluable	1755/5146 (34.1)	140/414 (33.8)	1615/4732 (34.1)	
Multi-vessel Disease with ≥70% stenosis				<.001
No	2511/5146 (48.8)	86/414 (20.8)	2425/4732 (51.2)	
Yes	1633/5146 (31.7)	256/414 (61.8)	1377/4732 (29.1)	
Not evaluable	1002/5146 (19.5)	72/414 (17.4)	930/4732 (19.7)	

Continuous variables are presented as medians (Q1, Q3) and categorical variables are presented as counts (column percentages). The number of diseased vessels was not evaluable if pre-determined key segments were not interpretable for stenosis severity.

TABLE 2 -

RESULTS FROM CLINICAL LOGISTIC MODEL FOR LMD

	Left main stenosis ≥ 50%		
Variable	**OR**	**95% CI**	**P-value**
Age at Enrolment, years[1]			<.001
65 versus 55	1.42	1.21 – 1.66	
75 versus 55	1.56	1.21 – 2.01	
Female Sex	0.32	0.24 – 0.44	<.001
Race/Ethnicity			0.028
Non-Hispanic White	ref		
Non-Hispanic Asian	1.34	1.04 – 1.73	
Other	0.90	0.67 – 1.2	
Hypertension	0.93	0.74 – 1.18	0.560
Diabetes	0.88	0.71 – 1.1	0.268
Cigarette Smoking			0.219
Never Smoked	ref		
Former Smoker	0.81	0.64 – 1.03	
Current Smoker	0.92	0.65 – 1.3	
Prior MI	0.61	0.42 – 0.88	0.008
eGFR (ml/min)[1]			0.908
60 versus 120	1.05	0.76 – 1.44	
90 versus 120	0.98	0.77 – 1.24	

[1]Modeled as a restricted cubic spline

C-index for Left main stenosis ≥ 50%: 0.643

TABLE 3

RESULTS FROM STRESS TEST MODEL FOR LMD ADJUSTING FOR CLINICAL FACTORS

	Left main stenosis ≥ 50%		
Clinical Variables	**OR**	**95% CI**	**P-value**
Age at Enrolment, years [1]			<.001
65 versus 55	1.40	1.19 – 1.65	
75 versus 55	1.56	1.21 – 2.01	
Female Sex among nuclear modality	0.26	0.14 – 0.48	<.001
Race/Ethnicity			0.489
Non-Hispanic White	ref		
Non-Hispanic Asian	1.01	0.74 – 1.37	
Other	0.84	0.62 – 1.14	
Hypertension	0.95	0.75 – 1.2	0.681
Diabetes	0.87	0.70 – 1.09	0.217
Cigarette Smoking			0.36
Never Smoked	ref		
Former Smoker	0.84	0.66 – 1.07	
Current Smoker	0.97	0.67 – 1.35	
Prior MI	0.61	0.42 – 0.88	0.009
eGFR (ml/min) [1]			0.977
60 versus 120	1.03	0.74 – 1.43	
90 versus 120	1.00	0.78 – 1.27	
Stress Test Variables			
Number of ischemic segments on stress echo, per 1 segment increase	1.10	0.96 – 1.25	0.158
Number of infarcted segments on stress echo, per 1 segment increase	1.08	0.94 – 1.25	0.268
Summed difference score on nuclear ≥ 10	1.49	0.95 – 2.33	0.080
Summed stress score on nuclear	1.00	0.96 – 1.04	0.977
TID (Transient ischemic dilation in the LV) on nuclear	1.01	0.63 – 1.62	0.965
TID (Transient ischemic dilation in the LV) on stress echo	1.63	1 – 2.66	0.049
Maximum ST Depression in Any Lead on ETT, per 1 mm increase	1.28	1.08 – 1.52	0.004
Peak exercise METs on ETT [3]			<.001
Peak exercise METs up to 5	0.82	0.58 – 1.17	
Peak exercise METs above 5	0.74	0.63 – 0.86	
Severe or Moderate Anterior Ischemia on nuclear	1.32	0.91 – 1.92	0.141
Severe or Moderate Anterior Ischemia on stress echo	1.04	0.58 – 1.84	0.904
LAD + LCX ischemia on nuclear	1.32	0.76 – 2.32	0.327
LAD + LCX ischemia on stress echo	1.24	0.69 – 2.22	0.475

[1]Modeled as a restricted cubic spline.

[2]Note: There is a sex by modality interaction term in model. The odds ratios for modality by sex are not presented in this table due to the modality specific covariates.

The sex by modality interaction p-value in LM>= 50% model is: 0.15

[3]Modeled as a linear spline.

Cindex for Left main stenosis ≥ 50%: 0.684

Joint test for Imaging and Stress Test variables is: <.001

ETT = exercise tolerance testing (non-imaging); METs = metabolic equivalents achieved during stress testing

TABLE 4

SUBGROUPS WITH AN AVERAGE MODEL-PREDICTED PROBABILITY OF LMD THAT IS ≤ 2.5% (COMBINED COHORT)

Subgroup definition	N	Mean Predicted Probability (Bootstrapped 95% confidence interval)
Female; No, Mild or Moderate Ischemia	673	0.023 (0.019–0.024)
Female; Mild or Moderate Ischemia	577	0.023 (0.019–0.024)
Female; Mild or Moderate Ischemia; Age ≤ 75	501	0.022 (0.018–0.023)
Female; Mild or Moderate Ischemia; Age > 55	480	0.024 (0.020–0.025)
Female; Moderate Ischemia	444	0.024 (0.020–0.025)
Female; Moderate Ischemia; Age > 55	376	0.025 (0020–0.026)

The following variables were used to define subgroups: Sex, age (categorized as ≤55, ≤65, and ≤75), prior MI and degree of ischemia (none, none/mild, none/mild/moderate). Only subgroups including at least 350 participants were considered.

TABLE 5

SUBGROUPS WITH AN AVERAGE MODEL-PREDICTED PROBABILITY OF LMD THAT IS ≤ 2.5% DEFINED USING MODALITY SPECIFIC VARIABLES

Subgroup definition	N	Mean Predicted Probability (Bootstrapped 95% confidence interval)
Female; Nuclear	508	0.024 (0.018–0.026)
Female; Stress Echo	446	0.025 (0.019–0.028)
Female; Nuclear; Summed difference score <10	389	0.021 (0.016–0.023)
Female; Stress Echo; Number of ischemic segments ≤5	361	0.021 (0.016–0.024)

The following variables were used to define subgroups: Sex, age (categorized as ≤55, ≤65, and ≤75), prior MI, imaging modality (Nuclear, Stress Echo, and ETT). Modality specific variables included: Summed difference score on Nuclear≥ 10; Severe or Moderate Anterior Ischemia on Nuclear; Number of ischemic segments (categorized as ≤3, ≤5) on Stress Echo; TID (Transient ischemic dilation in the LV) on Stress Echo; Maximum ST Depression in Any Lead on ETT (categorized as ≤2, ≤3). Only subgroups including at least 350 participants were considered.