Randomized Trial Of Hybrid Coronary Revascularization Versus Percutaneous Coronary Intervention
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RANDOMIZED TRIAL OF HYBRID CORONARY REVASCULARIZATION VERSUS PERCUTANEOUS CORONARY INTERVENTION

Trial Protocol

Sponsored By NHLBI

Data Coordinating Center
InCHOIR
Mount Sinai School of Medicine
New York

Version 2.1

CONFIDENTIAL

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TABLE OF CHANGES

Rev.	Section	Change	Reason	Page
2.0	Abstract /Study Design and throughout	Delete mention of CathPCI registry	Not using CathPCI registry	7, 13
2.0	Abstract /Study Design and throughout	Change "extracted directly" to "partially extracted"	Clarification, CathPCI registry will not be used, most but not all sites will use STS	7, 13
2.0	Abstract /Study Design	Wording added, "When allowed by local IRB/REBs…"	Canadian IRBs may require Canadian sites perform all follow up calls	7, 13
2.0	Abstract, Rx arms	"sternal sparing, off-pump" added to hybrid arm	Definition clarification	7
2.0	Abstract, Endpoints	The word "repeat' has been removed from "…unplanned repeat revascularization"	Definition clarification	7,14
2.0	Abstract, Endpoints	"post-procedure" added after "Measured at 30 days"	Specify time point	7, 14
2.0	Abstract, Endpoints	"and non-cardiovascular" added to secondary endpoint	Secondary endpoints include all-cause mortality	7, 14, 25
2.0	Inclusion criteria	#3) Delete "multivessel" before coronary revascularization	Clarification	8, 15
2.0	Inclusion criteria	Note added under coronary revascularization criterion	Clarification	8, 15
2.0	Exclusion criteria	#4) Delete the word "territories" after LAD	Clarification	9, 15
2.0	Exclusion criteria	Added exclusion of bare metal stents use in past year	Protocol update	9, 15
2.0	Exclusion criteria	Deleted mention of bare metal stents	Protocol update	9, 15
2.0	Exclusion criteria	Update sentence on pregnancy exclusion	Clarification	9, 16
2.0	Data Collection Schedule	Change 30 day visit window to +/- 7 days	Protocol update	10
2.0	Data Collection Schedule	Remove NYHA 30 day visit	Protocol update	10
2.0	Data Collection Schedule	Delete "X" where CathPCI registry was indicated	Not using CathPCI registry	10
2.0	Randomization table	"minimally invasive" added throughout	For trial, hybrid must be off-pump minimally invasive procedure	18
2.0	Randomization	Wording updated to describe specific vessels to be treated	Clarification	18
2.0	Hybrid Coronary Revascularization	Deleted non-sternal sparing from definition of minimally invasive approach. Wording updated to indicate only off-pump, sternal sparing procedures to be planned.	Protocol update	19
2.0	Hybrid Coronary Revascularization	Sentence added to indicate that planned open sternotomy is not permitted but conversion is acceptable for patient safety	Protocol update	20
2.0	Hybrid Coronary Revascularization	Sentence added to define LIMA-LAD anastomosis during TECAB	Clarification	21
2.0	Treatment Interventions	Revised reference vessel diameter measurement from 2.0 mm to 2.25 mm	To align with available delivery systems	21
2.0	Additional HCR Considerations	Added two paragraphs regarding possible open sternotomy protocol violation	Clarification	21
2.0	Unplanned Revascularization	Wording changed/added to define ischemia-driven unplanned revascularization	Update and clarify definition	24
2.0	Secondary Endpoints	Words "post procedure" added after "*MACCE* (defined above) at 30 days"	Specify time point	25
2.0	Secondary Endpoints	Ischemia-driven repeat revascularization paragraph deleted. Ischemia-driven revascularization (adjudicated)" bullet point added.	This was described in previous section	25
2.0	Unexpected Adverse Device Effects	Section added after endpoints	Defines what to do in the event of serious adverse events and unexpected adverse device effects	27
2.0	Clinical Centers, Investigators, Site Initiation and throughout	"PIPEDA" and "REBs" added where HIPAA and IRB are mentioned	Include Canadian privacy law and ethics board	28, 29
2.0	Data Collection	Sentence added regarding collection of STS data	Sites not using STS registry will be required to collect and submit data	30, 33,34
2.0	Data Collection	"Pre-Implant" deleted from heading Screening /Pre-Implant Data Collection	"Pre-Implant" not needed	30
2.0	Data Collection	Pre-Screening Failure Form changed to Screening Registration Form	More accurate description of form	30
2.0	Data Collection	"race' added to description of data collected	Clarification	30
2.0	Data Collection	Planned Revascularization changed to Revascularization Plan	Clarification	31
2.0	Data Collection	Revascularization plan updated and Note added to define	Clarification	31
2.0	Data Collection	Sentence deleted regarding Quality of Life data collection	Protocol update	32

2.0	Data Collection	Deleted first, middle, and last initial collected for Demographics	Protocol update	32
2.0	Treatment Intervention	Wording changed to reflect that medication data during and within 24 hours after the revascularization procedure will be collected by the sites	Protocol update	33
2.0	Laboratory Assessment	Subheading added to note that lab value will be extracted from STS database after index coronary revascularization	Protocol update	33
2.0	PCI Procedure	Reworded to exclude mention of CathPCI registry and to state data that will be collected by site coordinators	Protocol update, CathPCI registry will not be used	33
2.0	Hospitalization and MACCE Events	Reworded to describe limited information that will be collected from the STS registry	Clarification	33,34
2.0	Post-Intervention Site Activities	Follow-up window changed from two weeks to one week; phrase added: …following all procedures "that occur within 90 days of the first revascularization procedure."	Protocol update	34
2.0	Medications	Phrase "since the date of index hospital discharge" deleted from regarding medication use collection	Protocol update	34
2.0	NYHA	Section deleted. NYHA will be captured only at baseline	Protocol update	34
2.0	Quality of life	Sentence regarding QOL checklist deleted	Protocol update	34
2.0	Long-term Patient-Reported MACCE & QoL	Wording added to reflect that site coordinators will conduct telephone follow ups in the event that local IRB/REBs will not allow centralized DCC follow up and to make clear that follow up window is plus or minus one month.	Canadian REBs may only allow site coordinators to conduct telephone follow ups.	35
2.0	Long-term Patient-Reported MACCE & QoL	Missed Visit - event driven section deleted.	Data will be captured on an event driven form instead of a missed visit form	35
2.0	Patient Retention Strategies	DCC nurse "or local site coordinator" added regarding building relationships with participants; phrase regarding giving gifts and cards to patients deleted	Canadian REBs may only allow site coordinators to conduct telephone follow ups. Cards and gifts will not be sent to participants due to budgetary constraints	38
2.0	Analytical Plan	Individual components of MACCE changed to delete "all cause unplanned and repeat revascularizations" and to include "ischemia-driven revascularizations, cardiovascular and non cardiovascular mortality, re-hospitalization (all-cause and cardiovascular), health status and …"	Protocol update	38
2.0	Cardiovascular Events	The words "and bleeding" deleted from sub heading. Wording changed to clarify MACCE components	Protocol update	40
2.0	Data Coordinating Center (DCC)	The following has been added:" The DCC holds the study-specific IDE with the FDA and will be responsible for reporting UADEs to the FDA according to 21CFR812.150. In addition, the DCC will be responsible for submitting the required progress reports to the FDA."	Protocol update	42
2.0	Abstract /Study Design and throughout	Delete mention of CathPCI registry	Not using CathPCI registry	7, 13
2.1	Title page and footer	Revised to Version 2.1, July 2017	Protocol update to reflect administrative changes	All pages
2.1	Abstract	Added "Selected" to Exclusion Criteria	Correction	9
2.1	Study Population	Added as criterion 16, "Allergy or hypersensitivity to any of the study drugs or devices used in the trial" and renumbered	Correction	16
2.1	Treatment Interventions	In the subsection, Percutaneous Interventions (HCR Group & PCI-only Group) revised to state, "Only commercially available metallic drug-eluting stents may be used in this protocol. Because the use of DES in PCI on patients with left main disease or with three-vessel disease, both of which are off-label uses for DES, is considered investigational, this trial will be conducted under an Investigational Device Exemption (IDE)."	Correction	21
2.1	Investigators	Added "As stated in the Investigator agreement form, they will conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA." Also added FDA to parties that may review source documentation.	Correction	29

DEFINITIONS, ACRONYMS & ABBREVIATIONS

AE	Adverse event
BMS	Bare metal stent
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCSC	Canadian Cardiovascular Society Classification
CEC	Clinical Events Committee
CK MB	Creatine kinase- myocardial band
CFR	Code of Federal Regulations
DCC	Data Coordinating Center
DES	Drug eluting stent
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
EuroQOL	European Quality of Life Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCR	Hybrid coronary revascularization
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LAD	Left anterior descending (coronary artery)
LBBB	Left bundle branch block
LIMA	Left internal mammary artery
LM	Left main (coronary artery)
MACCE	Major adverse cardiac and cerebrovascular events
MI	Myocardial infarction
NHLBI	National Heart, Lung and Blood Institute
PCI	Percutaneous coronary intervention
PIPEDA	Personal Information Protection and Electronic Documents Act
RBC	Red blood cells
REB	Research Ethics Board
SAE	Serious adverse event
SF-12	Short Form 12 Health Survey
STS	Society of Thoracic Surgeons
SVG	Saphenous vein graft
UADE	Unanticipated Adverse Device Effect
UB	Uniform Billing
UHC	University HealthSystem Consortium
ULN	Upper limit of normal
URL	Upper reference limit

ABSTRACT

Objectives	To evaluate the effectiveness and safety of hybrid coronary revascularization (HCR) compared to multi–vessel percutaneous cardiac intervention (PCI) with metallic drug-eluting stents (DES) in patients with multi-vessel coronary artery disease (CAD) involving the Left Anterior Descending (LAD) and/or Left Main (LM) arteries. The primary objective of this trial is to determine whether hybrid coronary revascularization is associated with a reduction in Major Adverse Coronary and Cerebrovascular Events (MACCE) compared to PCI with DES.
Study Design	Prospective, randomized, multi-center, comparative effectiveness trial; patients randomized with equal allocation (1:1). Baseline and peri-procedural data collection will be partially extracted from the Society of Thoracic Surgeons (STS) Data Registry. Limited additional data will be collected to assess coronary anatomy, pharmacology specific to the procedure, device usage, etc. When allowed by local IRB/REBs, follow-up data collection, with the exception of data collection at post-intervention clinical visits, will be collected centrally via phone follow-up by the Hybrid Trial Data Coordinating Center (DCC), and will focus on patient-reported MACCE and QOL, supplemented by limited supporting documentation to verify MACCE events, and cost data collected from the University Health Consortium (UHC) and directly from hospitals for non-UHC members. All MACCE events will be adjudicated by a Clinical Events Committee (CEC). The estimated enrollment period is 24 months and all patients (n = 2354) will be followed for 5 years following randomization.
Target Population	Patients with multi-vessel CAD involving the LAD distribution with a clinical indication for revascularization *and* eligible for both HCR and multi-vessel PCI with DES.
Rx arms	o HCR with sternal-sparing, off-pump Left Internal Mammary Artery (LIMA) to LAD + PCI with metallic drug eluting stents (DES) of non-LAD vessels o Multi-vessel PCI with metallic DES, including the LAD and or LM.
Sample Size	2354 patients; assuming an estimated event rate of approximately 25% in the PCI group at 5 years; 0.05 type I error (2-sided) and assuming: (a) minimum follow-up of 5 years, (b) 80% power, (c) drop-in and drop-out rates of approximately 0.5% and 2% respectively, annually, and (d) 15% loss to follow-up by end of the study, 530 events will need to be observed (or 2354 patients) to detect a relative decrease in MACCE of ≥ 20% in the HCR compared to the PCI group. Estimates of loss to follow-up, and cross-over rates are conservative and justify fixing the power at 80%.
Duration	Accrual over 2 years; accrual will terminate when 530 events have occurred or 2354 patients are randomized, whichever comes first. All patients will be followed for 5-years.
1° Endpoints	The occurrence of MACCE defined as all-cause mortality, myocardial infarction (MI), stroke, or unplanned revascularization over 5-year follow-up after randomization or at the time when 530 events have accrued.

2° Endpoints	Measured at 30 days post procedure, 12, 24, 36, 48, 60 months, unless otherwise specified:
	Cardiovascular Events
	o MACCE at each data collection time point
	o Individual components of MACCE
	  o All-cause mortality
	  o Unplanned revascularization
	  o Stroke
	  o Myocardial infarction (MI)
	o Ischemia-driven revascularization
	o Cardiovascular and non-cardiovascular mortality
	Hospitalizations
	o Re-hospitalization (all-cause and cardiovascular)

	Health Status o Angina Score (Canadian Cardiovascular Society Classification [CCSC]) o Quality of Life (SF-12 and EuroQOL) *Cost-effectiveness* o Costs
Selected Inclusion Criteria	o Signed informed consent, release of medical information, and HIPAA documents (US sites) o Age ≥ 18 years o Clinical indication for coronary revascularization o Coronary anatomy requiring revascularization as follows[1]: - Multivessel CAD involving the LAD (proximal or mid) *and/or* LM (ostial, mid-shaft or distal) *with* at least 1 other epicardial coronary artery requiring treatment (LCX or RCA), OR - Single vessel disease involving the LAD and a major diagonal, with both requiring independent revascularization with at least one stent if randomized to HCR and stents for both the LAD and diagonal if randomized to multivessel PCI Note: If the patient qualifies based <u>only</u> on a LM lesion, then there must be involvement of the distal bifurcation (Medina 1,1,1) intended for treatment with a 2-stent approach (separate stents into the LAD and LCX) if randomized to PCI. However, if the patient <u>also has</u> non-LM disease in the RCA and/or non-ostial LAD and/or non-ostial LCX that requires separate treatment, any LM lesion is a valid criterion for enrollment, whether LM ostial, shaft or distal bifurcation disease, and any strategy of treating the LM may be employed, including not treating the ostial LCX, a provisional approach or a planned 2-stent strategy as appropriate. Similarly, if the patient qualifies based <u>only</u> on LAD-Dg disease, whether a bifurcation lesion or separate lesions in the LAD and Dg, without RCA or LCX disease, then both the LAD and Dg must be true lesions intended for stents (planned 2-stent approach). However, if the patient has LAD-Dg disease <u>and</u> a lesion in the RCA or LCX that also requires treatment, the LAD-Dg disease can then be treated in any fashion (2-stents, a provisional approach, or the Dg not even dilated if it is small), according to operator preference o Suitable candidate for both PCI with metallic DES and HCR as determined by clinical assessment and angiogram review by an interventional cardiologist and a cardiac surgeon at the site o Ability to tolerate and no plans to interrupt dual anti-platelet therapy for ≥ 6 months if presentation with stable CAD, or ≥ 12 months if presentation with biomarker positive acute coronary syndrome (ACS)

Selected Exclusion Criteria	o Previous cardiac surgery of any kind, including CABG o Previous thoracic surgery involving the left pleural space o Previous LM or LAD stent (a) with evidence of in-stent restenosis *or* (b) within 1 cm of a qualifying lesion o Previous PCI of the LM and/or LAD within 12 months prior to randomization o PCI with bare metal stent (BMS) within 12 months prior to randomization o Any complication or unsuccessful revascularization with PCI within 30 days prior to randomization Note: A patient may be considered eligible for enrollment if PCI with DES in non-LM and non-LAD territories was performed within 30 days prior to randomization, as long as revascularization was successful and uncomplicated, or has been performed any time more than 30 days prior even if unsuccessful or complicated. o Planned treatment with bioresorbable vascular scaffold(s) after randomization o Total occlusion (TIMI 0 or 1 flow) of the LM, LAD or LCX. o Cardiogenic shock at time of screening o STEMI within 72 hours prior to randomization o Need for concomitant vascular or other cardiac surgery during the index hospitalization (including, but not limited to, valve surgery, aortic resection, left ventricular aneurysmectomy, or carotid endarterectomy or stenting) o Indication for chronic oral anticoagulation therapy at the time of randomization o Extra-cardiac illness that is expected to limit survival to less than 5 years o Therapy with an investigational drug, device or biologic within 1 year prior to randomization, or plan to enroll patient in additional investigational study during participation in this trial o Unable to give informed consent or potential for noncompliance with the study protocol in the judgment of the investigator o Pregnant at time of screening or unwilling to use effective birth control measures while dual antiplatelet therapy is required

[1] Enrollment is based on the initial coronary anatomy. If PCI was already performed enrollment is still possible if the initial angiogram demonstrated anatomy that qualified under these criteria.

DATA COLLECTION SCHEDULE

	Screening & Randomization		Surg/PCI Procedure	Hosp D/C	30 (±7) Days Post Interv	6 (±1) Mo	12 (±1) Mo	18 (±1) Mo	24 (±1) Mo	30 (±1) Mo	36 (±1) Mo	42 (±1) Mo	48 (±1) Mo	54 (±1) Mo	60 (±1) Mo	Event Driven
Description	*Clinical Site*	*Registry Data**														
Informed Consent	X															
Angiogram	X	X														
Eligibility	X															
Demographics	X	X														
Medical History	X	X														
Medications	X		X	X	X	C	C	C	C	C	C	C	C	C	C	C
Laboratory Assessment	X	X														
Randomization	X															
PCI Procedure Data	X		X													
Surgical Procedure Data	X		X													X
Hospitalization																C
CCSC Angina Class	X				X	C	C	C	C	C	C	C	C	C	C	C
NYHA	X															
QoL (SF-12 & EuroQoL)	X				X		C		C		C		C		C	
MACCE					X	C	C	C	C	C	C	C	C	C	C	X[1]/C
Cost Data				X			X		X		X		X		X	
Study Completion/ Early Termination																X[1]/C
End of Study/Inv. Statement																X/C

X= Site coordinator activity; X= STS registry data or site coordinator; X = University HealthSystem Consortium/Uniform Bill-forms; C = DCC phone follow-up (when allowed by local IRB/REBs)

* For sites participating in the STS registry

[1]If ≤ 30 days post-index intervention (STS data terminates thereafter); thereafter, collected by DCC phone follow-up

OBJECTIVES

The overall objective of this trial is to evaluate the *effectiveness* and *safety* of Hybrid Coronary Revascularization (HCR) compared to multi–vessel percutaneous coronary intervention (PCI) with metallic drug-eluting stents (DES) in patients with multi-vessel coronary artery disease involving the Left Main and/or Left Anterior Descending arteries.

The ***primary objective*** of the trial is to determine whether hybrid coronary revascularization is associated with a reduction in Major Adverse Cardiac and Cerebrovascular Events [MACCE] compared to PCI with DES.

The ***secondary objectives*** are to determine the impact of HCR compared to PCI on health status and quality of life.

BACKGROUND AND SIGNIFICANCE

Importance of the Study

The increasing prevalence of coronary artery disease (CAD), advances in coronary artery bypass grafting (CABG), PCI, and concomitant medical therapy, and the costs of revascularization have resulted in rising interest regarding the appropriate indications and alternatives for coronary revascularization. The 2009 ACCF/SCAI/STS/AATS/ AHA/ASNC Appropriateness Criteria for Coronary Revascularization document that for patients with 3-vessel disease requiring revascularization, CABG is rated as appropriate while revascularization by PCI is rated as uncertain. [1] Moreover, the recent SYNTAX trial demonstrated that CABG was superior to PCI with first generation drug eluting stents (DES) for patients with 3- vessel disease and/or left main coronary artery (LM) disease.[2] However, the SYNTAX trial results were driven by the repeat revascularization component of the primary composite endpoint (lower for CABG), and divergence with the outcomes of the stroke component (higher for CABG) has led to differences in interpretation of the overall results.

These differences in interpretation, coupled with strong patient preferences for the lower level of invasiveness, a potentially lower stroke risk, and faster recovery have driven the widespread adoption of PCI. At the same time, CABG has been shown to provide improved long-term durability, superior long term symptom relief, fewer repeat interventions and higher rates of survival.[2-4] Integrating the positive features of both PCI and CABG has been the fundamental rationale of “hybrid” coronary revascularization.

Hybrid coronary revascularization is the intended combination of CABG and PCI. The HCR strategy combines grafting of the left anterior descending artery (LAD) coronary artery using the left internal mammary artery (LIMA) and PCI of non-left anterior descending coronary artery (LAD) coronary stenoses. Essentially, stents are substituted for saphenous vein grafts (SVG) for non-LAD lesions, and the surgical LIMA to LAD bypass is performed, ideally through a limited access, minimally traumatic approach. The rationale for choosing HCR over PCI or CABG alone stems from a number of observations:

(1) The LAD is the most important of the three coronary branches, supplying 50% to 60% of the ventricular mass and twice the mass of the circumflex or right coronary distributions;

(2) The LIMA has been shown to be more effective than PCI with respect to event-free survival, relief of angina, and long term patency;[4,5]
(3) The LIMA to LAD bypass graft contributes the vast majority of the survival advantage provided by CABG and the value of additional arterial grafts to non-LAD targets is limited and difficult to demonstrate;[6-9]
(4) The early restenosis rate of non-LAD vessels after PCI with drug eluting stents (DES) may not be significantly different from the early occlusion rate of saphenous vein grafts.[10,11]

Perrault and colleagues[12] found the 3-month occlusion rates of saphenous vein grafts to be between 14.8% and 15.6%. Similar results were found by Yun and colleagues[13] with vein graft occlusion rates between 17.6% and 21.7% at 6 months.

Unfortunately, the published data to date on HCR must be considered limited and hypothesis generating. Over a ten-year period, the collective published work constitutes only 500 patients in twelve small series (See Table 1)[14-22] Nonetheless, the data from these uncontrolled studies suggest that HCR (1) can potentially provide a higher degree of durability, symptom relief and survival relative to three-vessel stenting by virtue of incorporating a LIMA to LAD graft as part of the overall therapy, (2) afford a stroke rate comparable to PCI and lower than standard CABG by not manipulating the ascending aorta, and (3) offer a very low infection rate, transfusion rate and recovery time, by minimizing chest wall trauma and completely avoiding a median sternotomy. To date, no randomized trial comparing HCR to either CABG or PCI has been performed. Preliminary observational data suggest that HCR has the potential to disseminate widely and become the third major interventional alternative for patients with multi-vessel CAD. Without sound data from a clinical trial, there will be insufficient evidence to guide dissemination of this potentially important procedure for a major patient population.

Table 1. Contemporary HCR Results

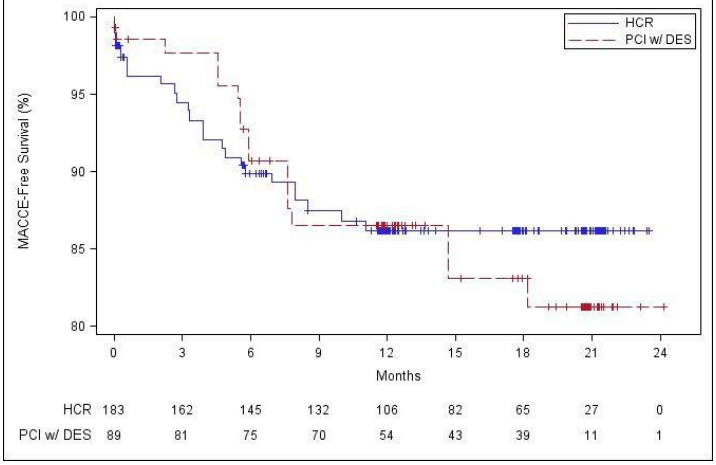
Author	Year	Patients	Surgical Procedure	LIMA patency (%)	Mortality (%)	Target Vessel Revasc (%)	Event-free Survival (%)
Bonatti[14]	2008	5	TECAB	100	0	0	100
Holzhey[15]	2008	107	MIDCAB	99	1.9	4.2	86
		10	TECAB				
Kiaii[16]	2008	58	Robotic-assist	93	0	10.3	NR
Reicher[17]	2008	13	MIDCAB	93	0	7	86
Vassiliades[18]	2009	91	EndoACAB	100	0	5.5	NR
Zhao[19]	2009	112	Sternotomy	100	2.6	6	88
Gao[20]	2009	10	Robotic-assist	100	NR	NR	NR
Srivastava[21]	2010	50	TECAB	98.2	0	NR	NR
Bonatti[22]	2012	226	TECAB	-	1.3	16.9	75

In short, clinicians, payers, and patients are interested in the specific benefits of revascularization alternatives. HCR as a scientifically validated approach would have a major healthcare impact. The ability to deliver a new therapy for CAD that provides durability, but without the obligatory trauma and prolonged recovery time characteristic of conventional CABG would be a major advance in the field of cardiovascular medicine. Candidates in whom HCR would be particularly advantageous would be several subgroups of CAD patients that are increasing in numbers: the elderly, patients with a high predicted risk of mortality and/or morbidity for CABG, deconditioned patients or patients with significant disabilities and patients in whom treatment durability is important, but a significantly invasive approach is not an option. Moreover, HCR is likely to bridge the divide in treatment philosophies and approaches that exist between

cardiologists and cardiac surgeons. Collaboration rather than competition between these specialties will ultimately benefit patients, hospitals, payers and healthcare providers.

The National Heart, Lung, and Blood Institute (NHLBI)-funded Hybrid Observational Study (RC1 HL100951-01, Principal Investigators, J. Puskas, D. Ascheim) was the first multicenter prospective cohort study of practice patterns and outcomes of patients undergoing HCR, and informed the design of this trial. The 200 HCR and 98 HCR-eligible, multi-vessel PCI with DES patients enrolled at 11 U.S. sites in the Hybrid Observational Study, demonstrated similar risk-adjusted MACCE rates over the first 12 months following intervention, with rates diverging over approximately 18 months of total follow up (see Figure 1).[23] The study further confirmed that there is strong concordance between cardiac surgeons and interventional cardiologists regarding anatomic eligibility for HCR, with disagreement in only 3.0% of cases.[24] Such consensus supports the feasibility of conducting a much needed comparative effectiveness trial of this emerging new coronary revascularization paradigm.

Figure 1: Risk-Adjusted MACCE-free Survival



Thus, the NHLBI-funded Hybrid Observational Study demonstrated that equipoise exists between the two coronary revascularization paradigms; however, a rigorously designed randomized clinical trial is now needed to provide sufficient evidence to guide clinical decision making for this important patient population.

STUDY DESIGN

This trial is a prospective, multi-center randomized comparative effectiveness trial of HCR compared to multi-vessel PCI with metallic DES in patients with multi-vessel CAD involving the LAD or LM territories. The trial is designed as a "large, simple" trial, and some baseline, procedure-related and short-term outcomes data collection will be extracted from existing registry data from the Society of Thoracic Surgeons [STS] Data Registry. By incorporating existing clinical data collected by sites for reporting to STS registry, the design greatly reduces trial-specific data collection at the sites participating in STS. When allowed by local Institutional Review Boards (IRBs) or Research Ethics Boards (REBs), follow-up data collection, with the exception of data collection at post-intervention clinical visits, will be collected centrally via phone follow-up by the Hybrid Trial Data Coordinating Center (DCC). All follow-up data collection will focus on patient-reported MACCE events and QOL, and will be supplemented by limited supporting documentation to verify MACCE events. All MACCE events will be adjudicated by a Clinical Events Committee (CEC). Health care costs will be collected

electronically through Uniform Billing (UB) medical claim forms and the University HealthSystem Consortium (UHC) operational database system. This design decreases (1) duplication of effort, (2) the burden on participating patients and sites, and (3) the cost of conducting the trial, while maintaining the rigor of traditional RCTs. The estimated enrollment period is 24 months (n = 2354), and all patients will be followed for a minimum of 5 years following randomization.

ENDPOINTS

Primary Endpoint

The primary endpoint of this trial is MACCE over 5 years following randomization. For the purpose of this trial, the components of MACCE include (1) all-cause mortality, (2) myocardial infarction, (3) stroke, and (4) unplanned revascularization. The primary objective of this trial is to determine whether hybrid coronary revascularization is associated with a reduction in MACCE compared to PCI with metallic DES.

Secondary Endpoints

The secondary endpoints of the trial (measured at 30 days post procedure, 12, 24, 36, 48, and 60 months, unless otherwise specified) include:

Cardiovascular Events

- MACCE at 30 days post procedure, and 12, 24, 36, 48 months
- Individual components of MACCE: All-cause mortality, myocardial infarction, stroke, unplanned revascularization
- Ischemia-driven revascularization
- Cardiovascular and non-cardiovascular mortality

Hospitalizations

- Re-hospitalization (all-cause and cardiovascular)

Health Status

- Angina Score (Canadian Cardiovascular Society Classification [CCSC])
- Quality of Life (QoL) (Short Form 12 Health Survey [SF-12}, European Quality of Life Scale [EuroQoL])

Cost-effectiveness

- Costs
- Quality-adjusted life expectancy

STUDY POPULATION

The patient population for this trial consists of adult patients with multi-vessel coronary artery disease involving the Left Main (LM) and/or Left Anterior Descending (LAD) arteries, and a clinical indication for revascularization, who are candidates for both HCR *and* PCI with metallic DES.

Eligibility Criteria

All patients who meet all inclusion criteria and no exclusion criteria will be eligible for the trial

regardless of gender, race, or ethnicity.

Inclusion Criteria

1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation (US sites)
2. Age ≥ 18 years
3. Clinical indication for coronary revascularization
4. Coronary anatomy requiring revascularization as follows[2]
   - Multivessel CAD involving the LAD (proximal or mid) *and/or* LM (ostial, mid-shaft or distal) *with* at least 1 other epicardial coronary artery requiring treatment (LCX or RCA), OR
   - Single vessel disease involving the LAD and a major diagonal, with both requiring independent revascularization with at least one stent if randomized to HCR and stents for both the LAD and diagonal if randomized to multivessel PCI

     Note: If the patient qualifies based only on a LM lesion, then there must be involvement of the distal bifurcation (Medina 1,1,1) intended for treatment with a 2-stent approach (separate stents into the LAD and LCX) if randomized to PCI. However, if the patient also has non-LM disease in the RCA and/or non-ostial LAD and/or non-ostial LCX that requires separate treatment, any LM lesion is a valid criterion for enrollment, whether LM ostial, shaft or distal bifurcation disease, and any strategy of treating the LM may be employed, including not treating the ostial LCX, a provisional approach or a planned 2-stent strategy as appropriate. Similarly, if the patient qualifies based only on LAD-Dg disease, whether a bifurcation lesion or separate lesions in the LAD and Dg, without RCA or LCX disease, then both the LAD and Dg must be true lesions intended for stents (planned 2-stent approach). However, if the patient has LAD-Dg disease and a lesion in the RCA or LCX that also requires treatment, the LAD-Dg disease can then be treated in any fashion (2-stents, a provisional approach, or the Dg not even dilated if it is small), according to operator preference
5. Suitable candidate for both PCI with metallic DES and HCR as determined by clinical assessment and angiogram review by an interventional cardiologist and a cardiac surgeon at the enrolling clinical site
6. Ability to tolerate and no plans to interrupt dual anti-platelet therapy for ≥ 6 months if presentation with stable CAD, or ≥ 12 months if presentation with biomarker positive acute coronary syndrome (ACS)
7. Willing to comply with all protocol required follow-up

Exclusion Criteria

1. Previous cardiac surgery of any kind, including CABG
2. Previous thoracic surgery involving the left pleural space
3. Previous LM or LAD stent (a) with evidence of in-stent restenosis *or* (b) within 1 cm of a qualifying lesion
4. Previous PCI of the LM and/or LAD within 12 months prior to randomization
5. PCI with bare metal stent (BMS) within 12 months prior to randomization
6. Any complication or unsuccessful revascularization with PCI within 30 days prior to randomization.

   Note: A patient may be considered eligible for enrollment if PCI with DES in non-

LM and non-LAD territory was performed within 30 days prior to randomization, as long as revascularization was successful and uncomplicated, or has been performed any time more than 30 days prior even if unsuccessful or complicated

7. Planned treatment with bioresorbable vascular scaffold(s) after randomization
8. Total occlusion (TIMI 0 or 1 flow) of the LM, LAD or LCX.
9. Cardiogenic shock at time of screening
10. STEMI within 72 hours prior to randomization
11. Need for concomitant vascular or other cardiac surgery during the index hospitalization (including, but not limited to, valve surgery, aortic resection, left ventricular aneurysmectomy, and carotid endarterectomy or stenting)
12. Indication for chronic oral anticoagulation therapy at the time of randomization
13. Any prior lung resection
14. ESRD on dialysis
15. Patients who could not be switched from prasugrel or ticagrelor to clopidogrel, should that be needed prior to a CABG, during reverse HCR
16. Extra-cardiac illness that is expected to limit survival to less than 5 years
17. Allergy or hypersensitivity to any of the study drugs or devices used in the trial
18. Therapy with an investigational drug, device or biologic within 1 year prior to randomization, or plan to enroll patient in additional investigational study during participation in this trial
19. Unable to give informed consent or potential for noncompliance with the study protocol in the judgment of the investigator
20. Pregnant at time of screening or unwilling to use effective birth control measures while dual antiplatelet therapy is required.

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(2) Enrollment is based on the initial coronary anatomy. If PCI was already performed enrollment is still possible if the initial angiogram demonstrated anatomy that qualified under these criteria.

Recruitment Strategies

The Hybrid Observational Study previously described, demonstrated that 44% of the 6,669 patients who underwent diagnostic cardiac catheterization over the course of the study had normal or non-obstructive CAD, and that among patients with obstructive CAD, 55% had multi-vessel disease, 24% had at least three vessel disease, and 12% had significant left main disease. Surgeons and interventional cardiologists exhibited a high degree of concordance in decisions regarding anatomic eligibility for HCR (LIMA to LAD combined with PCI of at least one additional vessel). Of the 3,715 patients with any obstructive CAD, 12% were deemed anatomically eligible for HCR; in only 3% of patients did the surgeon and cardiologist disagree regarding anatomic eligibility.

We plan to enroll 2354 patients in the Hybrid Coronary Revascularization Trial through active screening and recruitment by the multidisciplinary Heart Teams at the clinical sites. The strategies used to successfully enroll this trial will build on the momentum achieved over the last several years in the formation of Heart Teams at participating hospitals, consisting of interventional cardiologists and surgeons who work collaboratively to provide unified treatment recommendations for patients with complex CAD and valvular heart disease. The strategies will include: frequent presentations by the site Principal Investigators regarding the trial in weekly interventional cardiology and cardiac surgery conferences, as well as the combined multi-

disciplinary conferences; review of consecutive patients with multi-vessel disease by the site participating Heart Teams prior to recommending treatment options; regular Grand Rounds presentations at clinical sites as well as referring hospitals, mailings to referring physicians of the study hospitals, symposia and health care events targeted towards this population; as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified goals, and additional interventions directed by the Clinical Coordinating Center (CCC) to increase enrollment, will be implemented as needed. The Pre-Screening Failure Form will identify numbers of patients screened and reasons for non-enrollment in the study.

Inclusion of Women and Minorities

The inclusion of women and minorities in clinical trials is critical for scientific, ethical, social reasons, and for the generalizability of trial results. The Hybrid Trial investigators are strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity, and intend to recruit at least 30% women and 25% minorities. The following measures will be employed to ensure adequate representation of these groups: (1) documentation of the number of women and minorities screened and enrolled via screening/exclusion logs; (2) monitoring of such logs from each clinical center on a regular basis; and (3) if necessary, the development and implementation of additional outreach programs designed to recruit adequate numbers of women or minorities.

TREATMENT ASSIGNMENTS

All patients enrolled in this trial will undergo coronary artery revascularization. Patients will be randomly assigned to the following treatment groups:

Hybrid Coronary Revascularization (HCR Group)
LIMA to LAD + PCI with metallic DES of non-LAD vessel(s)

Multi-vessel PCI (PCI-only Group)
Multi-vessel PCI with metallic DES, including the LAD and or LM

RANDOMIZATION

Qualifying angiogram type	Time from the 3-vessel qualifying angiogram until randomization	Time from randomization to 1st procedure	Sequence options if randomized to HCR	Sequence options if randomized to multi-vessel PCI	If staged: Time from first revascularization intervention after randomization until final planned revascularization intervention
3-vessel angiogram only (PCI not performed)	Anytime within 90 days	≤14 days after randomization	1. Off-pump minimally invasive CABG first followed by staged PCI (recommended) 2. PCI first followed by staged Off-pump minimally invasive CABG 3. Concomitant Off-pump minimally invasive CABG and PCI (same calendar day)	1. Single procedure multi-vessel PCI 2. Staged PCI procedures	No longer than 90 days (≤60 days recommended)
3-vessel angiogram followed by PCI of a non-LM or non-LAD lesion in the same or subsequent procedure within 90 days prior to randomization	Anytime within 90 days	≤14 days post randomization	1. If only untreated LM or LAD lesion remains: Off-pump minimally invasive CABG 2. If non-LM or non-LAD lesion(s) remain: Same 3 options as above	1. If only untreated LM or LAD lesion remains: single PCI procedure 2. If non-LM or non-LAD lesion(s) remain: Same 2 options as above	No longer than 90 days (≤60 days recommended)

Patients will be randomly assigned (1:1) to HCR or multi-vessel PCI. The randomization procedure will be performed after patient eligibility is confirmed.

For patients identified in the setting of a qualifying 3-vessel diagnostic angiogram without a PCI performed during or subsequent to the diagnostic angiogram*,* randomization must occur within 90 days following the qualifying angiogram. The first study revascularization intervention is recommended to be performed within 72 hours post randomization and must be performed within 14 days following randomization (see above Table for possible procedure options).

For patients identified in the setting of a 3-vessel qualifying diagnostic angiogram and successful PCI of a non-LM or non-LAD vessels in the same or subsequent procedure*,* randomization into the trial must occur within 90 days following the initial qualifying angiogram. The first "study" intervention must be performed within 14 days following randomization (see above Table for possible procedure options).

Randomization will be stratified by center, PCI of non-LM or non-LAD vessels within the prior 90 days, and type of vessels treated (1) LAD and Diagonal only; 2) LAD (or Left Main) and LCX or RCA; 3) LAD (or Left Main) and both LCX and RCA). The randomization scheme will be in random blocks of 4 and 6 within each stratum to maintain balance.

Randomization will be generated centrally and performed through a Web-based data collection system that automates the delivery of the randomization codes. The treatment assignment will be

sent to the site coordinator electronically, in a secure fashion, and electronic verification of the treatment assignment will be required before proceeding with the treatment intervention. From that point on, primary efficacy will be analyzed by intention-to-treat; that is, the patients will be grouped by their assignment at randomization whether or not they actually received the treatment to which they were assigned.

MASKING

Neither patients nor investigators will be blinded to treatment assignment due to the nature of treatment interventions. Clinical and CCC investigators will, however, be blinded to all data from other clinical sites, except serious unexpected adverse events (SAEs) for IRB/REB reporting purposes. The DCC Research Nurse will be blinded to treatment assignment during follow-up telephone calls and will be blinded to aggregate outcomes data. MACCE events will be adjudicated by the independent CEC and trial oversight will be provided by an independent Data & Safety Monitoring Board (DSMB).

TREATMENT INTERVENTIONS

By design, patients in the HCR group will undergo planned staged procedures, and patients in the PCI group may or may not undergo planned staged procedures. The treatment strategy for staged procedure will be collected at the time of the first index procedure. Regardless of treatment assignment (HCR or PCI group), the revascularization strategy for staged procedures must be completed (in all cases) within *90 days* after the first revascularization intervention after randomization, with ≤60 days recommended. Unplanned ischemia-driven procedures at any time, and all procedures performed >90 days after the first post-randomization revascularization intervention will be considered endpoint events.

To minimize ascertainment bias in the identification of peri-procedural MI, baseline cardiac biomarkers (CK-MB and/or Troponin T or I) and an electrocardiogram (ECG) must be performed in all patients prior to CABG and PCI. For patients with stable CAD, the baseline biomarkers may be sent at the time of the first procedure, before revascularization. An ECG must be repeated once within 24 hours after each revascularization procedure, and the biomarkers must be repeated at least twice within 24 hours after each procedure (at 12 ± 4 hours and at 24 ± 4 hours, or at discharge if sooner than 24 hours).

Hybrid Coronary Revascularization

HCR is defined, for the purposes of this trial, as a planned off-pump, minimally invasive (sternal-sparing) isolated LIMA-LAD revascularization, combined with percutaneous revascularization of at least one non-LAD target. The revascularization targets and procedural timing strategy to be utilized should be outlined prior to the initial revascularization procedure. Three possible timing strategies may be used: surgery followed by PCI on separate calendar days, PCI followed by surgery on separate calendar days, or concomitant (simultaneous) PCI and surgery (defined as: a. PCI followed by CAGB in the same room on the same day, or b. CABG followed by PCI in the same room on the same day, or c. PCI followed by CABG in different rooms on the same day, or d. CABG followed by PCI in different rooms on the same day). The specific strategy adopted will be collected and categorized. The complete revascularization strategy, if staged, must be completed within *90 days* of the first revascularization intervention (≤ 60 days preferred).

Note: Whenever PCI is performed after the LIMA-LAD revascularization, LIMA angiography must be performed prior to the PCI to assess the graft and distal anastomosis. Please see the Procedural Treatment Guidance Document for further recommendations as to when and how to intervene if the distal anastomosis appears abnormal and/or antegrade flow is reduced.

In most surgical specialties, minimally invasive surgery refers to the access the operator takes to the surgical field. Minimally invasive cardiac surgery, however, aims to ameliorate two potentially invasive surgical components: the cardiopulmonary bypass machine and the sternotomy incision. For the purpose of this trial, acceptable minimally invasive approaches to LIMA-LAD revascularization are sternal sparing off-pump procedures.

Listed below are definitions of the beating heart, sternal sparing minimally invasive operations that are acceptable for patients enrolled in this trial and randomly assigned to the HCR group. The selection of the HCR strategy below remains at the discretion of the surgical investigator. The chosen approach will be documented and reported for each patient in the trial.

Surgical Interventions

Off-Pump CABG
An off-pump CABG will be defined as an isolated LIMA-LAD revascularization performed on the beating heart without the use of cardiopulmonary bypass. Additional bypass grafts to other targets (including the diagonal) are not allowed in this study as part of an HCR procedure. For the trial, the planned minimally invasive approach to the LIMA – LAD revascularization must be a **sternal sparing off-pump procedure.** Planned open sternotomy will not be allowed in this study. However, after randomization, conversion of a planned sternal-sparing procedure to an open sternotomy procedure is acceptable if required to safely and successfully complete the revascularization procedure. Such conversions will be tracked.

The planned sternal-sparing, off-pump LIMA-LAD revascularization may be performed by Mid-CAB, Robotic- Assisted CAB, or TECAB as described below

1. Minimally Invasive Direct Coronary Artery Bypass (Mid-CAB)
A mid-CAB will be defined as any operation in which LIMA mobilization is undertaken in an open fashion through a limited anterior or lateral thoracotomy incision. The anastomosis will be performed by hand on the beating heart.

2. Robotic-Assisted Coronary Artery Bypass
A robotic mid-CAB or endo-ACAB will be defined as a procedure in which the LIMA is mobilized with the use of robotics through a port access approach. Both directed non-rib spreading and small rib spreading thoracotomies can be used for surgical access to the LAD. The anastomosis will be performed by hand on the beating heart. *Planned surgery performed with cardiopulmonary support will not be allowed in this study.*

3. Beating Heart Totally Endoscopic Coronary Artery Bypass Graft (TECAB)
Beating heart TECAB will proceed in a fashion similar to robotically assisted CABG in terms of vessel identification and LIMA takedown. Target mobilization,

LAD arteriotomy and anastomosis will be performed endoscopically with the robot. The LIMA-LAD anastomosis will be constructed by robotic/endoscopic techniques on the beating heart, utilizing sutures, U-clips or facilitated anastomotic connectors, according to surgeon preference. *Planned beating heart endoscopic operations on cardiopulmonary bypass as well as planned arrested heart TECAB are not allowed in this study.*

Additional HCR Considerations

Anastomotic Patency

Whenever possible, anastomotic patency should be confirmed with intra-operative transit time Doppler flow prior to closure. The data derived from the Doppler graft assessment will be documented and reported for all patients in whom Doppler assessment is performed; the printout of each patient's data will be provided to the DCC for analysis and correlation with angiographic findings. These data points will include the graft flow (ml/min), the pulsatility index, the diastolic fraction and the presence/absence of backwards flow.

If open sternotomy is required after an unsuccessful or complicated minimally invasive approach, only a LIMA to LAD should be performed; PCI, as per protocol, should be done in non-LAD territories. Unplanned sternotomy is not a protocol violation if required to safely and successfully complete the revascularization procedure. Bypassing a non-LAD vessel, however, is a protocol violation **unless** there is evidence of ongoing ischemia in the non-LAD territories, in which case bypass of the ischemic vessels will not be considered a protocol violation.

Percutaneous Interventions (HCR Group & PCI-only Group)

Only commercially available metallic drug-eluting stents may be used in this protocol. Because the use of DES on patients with left main disease or with three-vessel disease, both of which are off-label uses for DES, is considered investigational, this trial will be conducted under an Investigational Device Exemption (IDE). PCI should be performed using standard techniques at the discretion of the operator. In general PCI should be performed of lesions in vessels with visually estimated reference vessel diameter ≥2.25 mm with evidence of a) plaque rupture or thrombosis, or b) with an angiographic diameter stenosis ≥80%, or c) with evidence of ischemia on either non-invasive testing or by fractional flow reserve ≤0.80 or iFR ≤0.90. Which of these criteria are met will be categorized. The specific adjunctive devices used (e.g. atherectomy, cutting/scoring balloons, or aspiration) and techniques (e.g. 1- vs. 2-stent and technique for treatment of bifurcation lesions) will be collected. Bioresorbable vascular scaffolds may not be used in this study.

Procedures may be staged at the discretion of the operator, but the intention to stage procedures must be specified within 24 hours after completion of the first procedure, should ideally be completed within 60 days of the first procedure, and in all cases must be completed within 90 of the first procedure after randomization.

For patients randomized to HCR, if off-pump CAB is performed first, prior to the staged PCI procedure a diagnostic angiogram of the LIMA-LAD graft must be performed, irrespective of the

surgical approach chosen for HCR. Please see the Anticoagulation Guidance Document for further recommendations as to when and how to intervene if the distal anastomosis appears abnormal and/or antegrade flow is reduced.

Optimal Medical Management
All patients should be managed according to guideline-directed medical therapy (GDMT) by clinicians at each clinical site according to generally accepted societal recommendations. Details of GDMT are included in the MOP. Information will be collected about adherence to GDMT.

DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoint
The primary endpoint for this trial is a composite of MACCE over 5 years following randomization.

All MACCE events will be adjudicated by an independent CEC. For the purpose of this trial **MACCE** is defined as a non-weighted composite score comprised of the following components:

- *All-cause mortality*
  Death from any cause

- *Stroke*
  Stroke (ischemic or hemorrhagic) is defined as the rapid onset of a new neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection) that i) persists beyond 24 hours, or ii) less than 24 hours if: a) associated with infarction or hemorrhage on an imaging study, or b) treated with pharmacologic or mechanical intervention, or c) results in death. Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies. In most cases a vascular neurologist or stroke specialist will determine whether a stroke has occurred. Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.

- *Myocardial Infarction*

  A. Non-Procedure Related Myocardial Infarction[3]
  The Third Universal Definition of Myocardial Infarction will be used to define Non-Procedure Related Myocardial Infarction. This definition applies to an event occurring >48 hours after any revascularization procedure as follows:
  Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) of the assay together with evidence of myocardial ischemia with at least one of the following:
    - Symptoms of ischemia;
    - ECG changes indicative of new ischemia (new ST-T changes or

new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

In the absence of knowledge of the URL, the local laboratory upper limit of normal (ULN) may be substituted.

Note: Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to spontaneous MI.

B. Peri-PCI and Peri-CABG Myocardial Infarction[4]

The SCA&I definition of a clinically relevant peri-procedural myocardial infarction (MI) will be used for this definition. CK-MB is the preferred biomarker for post revascularization assessment of myonecrosis, but cardiac troponin I or T may be used as described below. A baseline pre-procedure value should be measured in all patients, and 2 additional biomarker measurements must be measured post procedure at 12±4 hours and 24±4 hours post- procedure. If any measurement is elevated, serial measures should be repeated until the peak is reached and the levels are returning toward baseline. This definition applies to an event occurring ≤48 hours after any revascularization procedure as follows:

a. In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cardiac troponin (cTn) I or T level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q- waves in ≥2 contiguous leads or new persistent LBBB. If baseline CK-MB or cTn is unavailable in a patient with stable CAD, they will be assumed to be normal.
b. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute
c. increment equal to those levels recommended above from the most recent pre- procedure level.
d. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling, or in the patients with ACS without a baseline CK-MB or cTn measure: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above *plus* new ST-segment elevation or depression *plus* signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

[3]Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*. 2007;116:0-0.

[4] Moussa ID, Klein LW, Shah B, et al. Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization: An Expert Consensus Document From the Society for Cardiovascular

Note: Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by new ST-segment elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to peri-procedural MI.

- *Unplanned Revascularization (adjudicated)*
  (a) An unplanned revascularization procedure is defined as any PCI or CABG procedure performed that is an entirely new procedure due to ischemia not included in the pre-specified revascularization strategy, or (b) was included in the pre-specified revascularization strategy as a planned staged procedure, but was performed >90 days after the first revascularization procedure after randomization, or (c) that is a repeat intervention of a previously performed study-related revascularization. Determination as to whether the revascularization procedure involves an original target vessel and lesion or a new (non-target) vessel and lesion will be made by the CEC whenever possible.

Ischemia-driven Unplanned Revascularization
Ischemia-driven *unplanned* revascularization procedures will be assessed. All *unplanned* revascularization procedures will be reviewed and adjudicated by the CEC to determine if they are ischemia-driven. Revascularization will be considered ischemia-driven if the diameter stenosis of the revascularized coronary segment is ≥50% or new thrombus and/or ulceration is present, and if any of the following criteria for ischemia are met: i) A positive functional study corresponding to the area served by the target lesion; or ii) Ischemic ECG changes at rest in a distribution consistent with the target vessel; or iii) Typical ischemic symptoms referable to the target lesion; or iv) IVUS of the target lesion with a minimal lumen area (MLA) of ≤4 mm^2 for non-left main lesions or ≤6 mm^2 for left main lesions; or v) FFR of the target lesion ≤0.80 or iFR of the target lesion <0.90 . A target lesion revascularization for a diameter stenosis less than 50% might also be considered ischemia-driven by the CEC if there was a markedly positive functional study or ECG changes corresponding to the area served by the target lesion.

Planned staged procedures which are declared within 24 hours of the first revascularization procedure or post randomization and are performed within 90 days of the first post- randomization revascularization procedure will not be considered an unplanned revascularization. Staged procedures performed >90 days after the first post-randomization revascularization procedure, even if originally pre-specified, will be considered an endpoint unplanned revascularization. Intervention on the LIMA, LIMA-LAD distal anastomosis or LAD triggered by routine LIMA angiography prior to a planned staged PCI will not be considered an unplanned revascularization. However, if anterior ischemia occurs after CABG necessitating LIMA angiography prior to the planned staged PCI with subsequent intervention on the LIMA, LIMA- LAD distal anastomosis or LAD, this event will be adjudicated as an unplanned revascularization.

Secondary Endpoints

The secondary endpoints for the trial (each measured at 30 days post procedure, 12, 24, 36, 48, and 60 months, unless otherwise specified) of the trial include:

Cardiovascular Events (adjudicated)

- *MACCE* (defined above) at 30 days post procedure, and 12, 24, 36, 48 months
- *Individual components of MACCE* (*adjudicated*, as defined above):
  - All-cause mortality
  - Stroke
  - Myocardial infarction
  - Unplanned revascularization

- Ischemia-driven revascularization *(adjudicated)*

- *Cardiovascular and Non-cardiovascular Mortality (adjudicated)*
  Cardiovascular mortality, as adjudicated by the CEC, will be assessed. Cardiovascular death includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, stroke, other cardiovascular causes, or bleeding. Non- cardiovascular death is defined as any death with known cause not of cardiovascular causes. Any deaths in which the cause is unknown or undetermined will be considered cardiovascular.

- *Stent thrombosis (adjudicated)*
  Stent thrombosis will be adjudicated according to the Academic Research Consortium scale.[25] Stent thrombosis will be considered to be present if criteria for definite or probable stent thrombosis are met. According to its timing, stent thrombosis will be further classified as acute <24 hours), subacute (24 hours – 30 days), early (≤30 days), late (>30 days – 1 year), or very late (>1 year).

- *Symptomatic graft stenosis or occlusion (adjudicated)*
  Symptomatic graft stenosis or occlusion requires angiographic confirmation of a DS ≥50%, and the presence of at least one of the following criteria: i) A positive functional study corresponding to the area served by the target lesion; or ii) Ischemic ECG changes at rest in a distribution consistent with the target vessel; or iii) Typical ischemic symptoms referable to the target lesion; or iv) IVUS of the target lesion with a minimal lumen area (MLA) of ≤4 mm^2; or v) FFR of the target lesion ≤0.80 or iFR of the target lesion ≤0.90.
  Intervention on the LIMA, LIMA-LAD distal anastomosis or LAD triggered by routine LIMA angiography prior to a staged PCI will also be considered to meet the criteria for symptomatic graft stenosis or occlusion.
  The adjudicated rates of symptomatic graft stenosis or occlusion of the LIMA to the LAD in the HCR arm will be compared to the rate of angiographic definite stent thrombosis of LAD stents in the PCI arm.

Hospitalizations (non-adjudicated)

- Re-hospitalization will be assessed and classified as all-cause or cardiovascular (further subdivided as due to cardiac arrest, acute MI, heart failure or cardiogenic shock, other cardiovascular causes, or bleeding).

Bleeding (non-adjudicated)

- Site assessed bleeding complications will be reported using the Bleeding Academic Research Consortium (BARC) Scale[26]:
  - **Type 0:** no bleeding
  - **Type 1:** bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
  - **Type 2:** any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation (this does not apply to routine evaluation of chest tube drainage).
  - **Type 3**
    - **Type 3a**
      - Overt bleeding plus hemoglobin drop of 3 to 5 g/dL (corrected for transfusion: 1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin or 3% hct), OR
      - Any transfusion with overt bleeding
    - **Type 3b**
      - Overt bleeding plus hemoglobin drop 5 g/dL (corrected for transfusion: 1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin or 3% hct), OR
      - Cardiac tamponade, OR
      - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), OR
      - Bleeding requiring intravenous vasoactive agents outside routine care
    - **Type 3c**
      - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), OR
      - Subcategories confirmed by autopsy or imaging or lumbar puncture, OR
      - Intraocular bleed compromising vision
  - **Type 4: CABG-related bleeding**
      - Perioperative intracranial bleeding within 48 h, OR
      - Reoperation after closure of sternotomy for the purpose of controlling bleeding, OR
      - Transfusion of 5 U whole blood or packed red blood cells within a 48-hr period (excluding cell saver products), OR
      - Chest tube output 2L within a 24-h period
  - **Type 5: fatal bleeding**
    - **Type 5a**
      - Probable fatal bleeding; no autopsy or imaging confirmation but

clinically suspicious

- **Type 5b**
  - Definite fatal

- Transfusion of blood products (number of units of whole blood, pRBCs, fresh frozen plasma, platelets, cryoprecipitate and other, excluding auto-transfused blood) will be recorded. Relationships between anti-platelet medication regimens and transfusion requirement will be analyzed.
- Total chest tube drainage will also be reported for HCR patients at 48 hours postop or prior to chest tube removal, whichever is earlier.

Health Status

- *Angina class*
  Health status will be assessed by *angina class* measured by the Canadian Cardiovascular Society Classification (CCSC). The CCSC guidelines are detailed in Appendix I.

- *Quality of Life*
  The change in quality of life (QOL) from baseline will be measured, using the Short Form-12 (SF-12) general health status index and EuroQol 5-D (EuroQoL) which measures health state preference from the individual and societal perspective. The SF-12 instrument examines 8 quality of life dimensions (physical activity, social activity, role/physical, body pain, general mental health, role/emotional, vitality and general health perception). The EuroQoL 5-D is a standardized instrument for measuring health-related quality of life. This questionnaire provides a simple descriptive profile that consists of 5 dimensions. The 5 domains are anxiety/depression, pain/discomfort, usual activities, self-care, and mobility. The instrument also has a self-assessment of health status.

- *Cost-effectiveness*
  Cost-effectiveness will be evaluated using a microsimulation model, which will predict the accrued health care costs and quality-adjusted life expectancy for each subject at the end of the trial follow-up period and in addition over a lifetime horizon.

For this trial, the SF-12 is available in English, Spanish and French, and the EuroQol is available in English and French. Inability to read and complete these instruments in the available languages does not preclude a patient from enrollment in the trial (a family member may assist in completing the QOL questionnaires). Copies of these instruments can be found in Appendix II.

UNANTICIPATED ADVERSE DEVICE EFFECTS

Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects
All unanticipated adverse device effects (UADEs) must be reported to the DCC and the clinical center's IRB/REB within 24 hours of knowledge of the event.

The DCC will notify the NHLBI program officer of any UADEs via e-mail within 24 hours of receipt of the event. The program officer will report these events to the DSMB chair within 72 hours of notification.

DCC Reporting to FDA

The DCC will report UADEs to FDA according to Code of Federal Regulations 21CFR812.150 for this Investigational Device Exemption (IDE) trial.

CLINICAL CENTERS

The study will be conducted in between 50 and 125 U.S. and non-U.S. clinical sites with extensive experience in minimally invasive surgical coronary revascularization and multi-vessel PCI, as well as expertise in hybrid revascularization. The sites will be selected by the multi-disciplinary Hybrid Trial Steering Committee with particular focus on procedural expertise and evidence of a functioning multi-disciplinary heart team. An average recruitment of 98 patients monthly (2 patients/month/site) is anticipated.

Each clinical center will be required to obtain IRB/REB approval for the initial protocol and informed consent document and any subsequent revisions in a timely fashion, to recruit patients, to collect data and enter it accurately into the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP) and HIPAA or Personal Information Protection and Electronic Documents Act (PIPEDA) regulations. In addition, centers will be required to provide the DCC the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents to study monitors, to respond promptly to DCC inquiries, and, to participate in analyses and reporting of study results.

Site Approval

The following documents are required for all sites approved to participate in the trial:

- Clinical Study Agreement with the CTSN DCC: InCHOIR, Department of Health Policy, Icahn School of Medicine at Mount Sinai
- Signed Conflict of Interest Statements
- Signed and dated CVs for all staff on Delegation of Authority Log
- Completed Delegation of Authority Log
- HIPAA/PIPEDA and Human Subjects/GCP training documentation (as required by local institutional guidelines) for all staff on Delegation of Authority Log
- Current licenses for all staff on Delegation of Authority Log
- IRB/REB roster
- IRB/REB approval for protocol, informed consent document, HIPAA authorization (US sites)
- NIH Stroke Scale Training Certification for appropriate staff
- Laboratory Normal Ranges
- Certification forms for Surgeons and Interventional Cardiologists
- Signed Document Approval Form for protocol
- Study-specific training documents

INVESTIGATORS

All surgeons, cardiologists, coordinators and other investigators involved in the trial must complete the Investigator Contact Form with their hospital affiliation, address, contact numbers (phone, fax, cell, pager), and email address. All investigators must send their CV,

Clinical Study Agreement/Conflict of Interest Statement, Good Clinical Practice Certificate and HIPAA or PIPEDA certification to the DCC. As stated in the Investigator agreement form, they will conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA.

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in minimally invasive coronary revascularization and interventional cardiologists with expertise in multi-vessel PCI, as well as experience with HCR. To qualify, the surgical and interventional cardiology investigators must have demonstrated proficiency in HCR procedures and be approved by the Hybrid Trial Site Selection Committee. Surgical and interventional cardiology qualifications for all participating investigators will be collected on the Certification Form and faxed to the DCC prior to accreditation. The clinical site Surgical and Interventional Co-Principal Investigators will be responsible for overseeing the ongoing performance of the other participating surgical and cardiology investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol the electronic data capture system.

Good Clinical Practices (GCP) Certificate

All investigators and coordinators who are involved in care of study patients, and/or research data collection must provide certification that they have successfully completed their local institutional GCP course.

Conflict of Interest

A conflict of interest statement will be collected from all study investigators to ensure that no investigator may exert undue influence that may bias the trial. Any conflict of interest identified will be reviewed by the NIH and managed in compliance with 21 CFR 54 and 42 CFR 50(f). Conflict of interest statements will be updated as changes occur and no less than annually.

Patient Confidentiality

Confidentiality of all patient records will be maintained according to HIPAA or PIPEDA guidelines. Study Investigators, site IRBs/REBs, the DCC (InCHOIR), the CEC, the FDA and the NHLBI may review source documentation for enrolled patients as necessary, but all unique patient and hospital identifiers will be removed prior to review. If the results of this study are published, the data will be presented in aggregate, with all patient identifiers removed.

HIPAA or PIPEDA Certification

All investigators and coordinators must provide documentation that they have successfully completed the institutional requirements to ensure patient rights, privacy and security under HIPAA or PIPEDA.

SITE INITIATION

IRB/REB approval and the clinical study agreement between the clinical site and the DCC must be signed and executed prior to the site initiation. Additionally, applicable CVs and other regulatory documentation must be on file with the DCC prior to site initiation. A representative from the DCC will conduct a site initiation teleconference prior to enrollment of the first patient. The surgeon(s), interventional cardiologist(s), and study coordinator will be required to attend the initiation.

DATA COLLECTION

For clinical sites participating in the STS registry, data collection will be done using the STS registry dataset. For clinical sites that are not part of the STS registry, and for patients randomized to PCI, data collection will be done at the site.

Screening Data Collection

Screening Registration Form

Prior to informed consent

Prior to approaching a patient to begin the informed consent process, the study personnel will review data on prospective patients to determine eligibility for inclusion in the trial. All pre-screened patients (patients who are not consented) who are not enrolled are recorded in the Screening Registration form in the EDC. The data collected is HIPAA compliant and does not include patient identifiers but does include screening quarter, screening year, age, gender, race and reason not eligible or not enrolled.

Informed Consent

Prior to screening data collection and all protocol defined procedures

The site co-principal investigators are responsible for ensuring that the informed consent process is conducted and documented appropriately by trained study staff. A signed informed consent form, which has been approved by the DCC and the individual IRB/REB s, is required. The consent form must incorporate HIPAA (US sites only) clinical research authorization and Release of Medical Information that authorizes both transfer of specified STS Registry data to the DCC, release of medical records and release of billing information from all hospitalizations and outpatient services to the trial investigators, monitors, sponsor (NIH) and the DCC. The consent form will also permit analysis of all angiographic films at a central angiographic core laboratory. The investigators or a designated individual, will provide a thorough explanation of the objectives, patient responsibilities, risks and benefits of the study, and will fully address all concerns raised by the patient and/or family. After all issues have been adequately resolved, and the investigator has confirmed that the patient has been fully consented, the patient will be asked to sign the informed consent. The consent process must be documented in the medical chart, and a signed copy of the consent must be given to the patient.

For the purpose of primary analysis, patients meeting the eligibility criteria are considered enrolled in the study at time of randomization.

Anatomic Eligibility

Prior to proceeding with the following trial-specific activities, the coronary angiogram will be reviewed by both an interventional cardiologist and a cardiothoracic surgeon to establish consensus that the patient is an appropriate candidate for hybrid revascularization as well as

multi-vessel PCI with metallic DES. The clinical inclusion and exclusion criteria will be documented on the Eligibility Form (see below).

Once consensus regarding eligibility for HCR and multi-vessel PCI with DES is established, the following activities should be undertaken.

Screening & Baseline Site Activities

Eligibility Evaluation
Prior to randomization
This checklist of inclusion and exclusion criteria will be completed and signed by the investigator to verify that the patient meets all eligibility requirements for this trial.

Randomization Procedure
A DCC representative will be available to discuss any questions regarding patient eligibility. Once the site investigator has confirmed that the patient meets all eligibility criteria for participation in the trial, and has completed the eligibility forms in the EDC, randomization will be performed electronically.

Randomization
Must be completed
(a) within 90 days of the 3-vessel qualifying angiogram for patients identified in the setting of a diagnostic angiogram, or
(b) within 90 days following the qualifying 3-vessel angiogram for patients also undergoing a PCI of a non-LAD and non-LM vessel prior to randomization. (See table under Randomization Section)

The first study intervention is recommended to be performed within 72 hours post randomization and must be performed within 14 days following randomization. Randomization to the treatment assignment will be generated by the EDC system once the checklist of inclusion and exclusion criteria has been completed and verified and the planned revascularization strategy form has been completed. For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated.

Revascularization Plan
Prior to randomization
The surgical and percutaneous revascularization plan will be described for both HCR and PCI-only revascularization *prior to randomization.* This plan may be revised within 24 hours of the first procedure after randomization to reflect procedural complications, should they occur. Any revascularization procedures deviating from the final revascularization plan in place 24 hours after the first procedure will be considered unplanned revascularization procedures.
Note: Any revascularization procedure that is done during a planned revascularization procedure will NOT be considered an unplanned procedure. E.g.: planned minimally invasive LIMA-LAD procedure becomes complicated by inferior ischemia requiring conversion to an open procedure and RCA bypass; or planned PCI after minimally invasive

LIMA-LAD procedure demonstrated LIMA-LAD graft occlusion requiring PCI; or planned PCI of the LCX results in a LM dissection requiring a LM stent. However, CABG complications that result in separate **unplanned** PCI or CABG procedures, and PCI complications that result in separate **unplanned** PCI or CABG procedures, will be considered unplanned procedures and endpoint events.

Angina Class - Canadian Cardiovascular Society Classification (CCSC)

Following determination of eligibility and within 14 days prior to randomization

The presence of angina will be assessed, and when present, classified according to the CCSC scale and documented on this form. CCSC classification scheme is detailed in Appendix I.

NYHA Class

Following determination of eligibility and within 14 days prior to randomization

The presence of heart failure will be assessed, and when present, classified according to the NYHA scale. NYHA classification will be determined by investigative center personnel and documented on the "New York Heart Association Classification" form. The NYHA classification scheme is detailed in Appendix III.

Quality of Life

Following determination of eligibility and within 14 days prior to randomization

The SF 12 and EuroQol (Appendix II) questionnaires will be completed by the patient to assess quality of life.

Pre-intervention Existing STS Registry Data Extraction (collected by sites if not participating in STS or for patients randomized to PCI group)

Angiogram

Data partially extracted from the STS Registry database

Data regarding the coronary anatomy, including the number of lesions, degree of coronary obstruction and SYNTAX score will be extracted from the STS registry database.

Demographics

For all patients screened, the date of birth, race, ethnicity, sex, and insurance will be captured.

Medical History

Data partially extracted from the STS Registry database

Information pertaining to the medical history, with particular focus on cardiovascular history, will be extracted from the STS registry database. The data collection includes, but is not limited to previous myocardial infarction and coronary revascularization, AICD and pacemaker therapy, stroke and other comorbidities such as diabetes, dialysis and peripheral vascular disease. Information regarding the current cardiac condition is also captured, including symptoms and severity of cardiac disease and the patient's current height and weight.

Laboratory Assessment

Data partially extracted from the STS Registry database

Data regarding the following laboratory values prior to index coronary revascularization will

be extracted from the clinical registry databases:

- CK MB (creatine kinase- myocardial band) and/or Troponin I or T (ng/mL)
- Hematocrit *(%)*
- Creatinine *(mg/dl)*

Treatment Intervention
The assigned study coronary revascularization intervention (or first revascularization intervention, for staged procedures) are *recommended to be performed within 72 hours post randomization, and must be performed within 14 days following randomization.* (See Randomization section)

Procedural and Peri-Procedural STS Registry Data Extraction (collected by sites if not participating in STS or for patients randomized to PCI group)

The following will be collected for all hospitalizations required to complete the original planned revascularization strategy, if staged.

Medications
Data regarding medication use within 24 hours prior to, during the revascularization procedure or within 24 hours after the procedure, including antiplatelet and antithrombin agents, beta blocker, and ACE inhibitors, ARBs, aldosterone antagonists, and statins, will be collected at the sites. This data will be collected whenever possible for all subsequent revascularization procedures.

Laboratory Assessment
Data partially extracted from the STS Registry database
Data regarding the following laboratory values after the index coronary revascularization will be extracted from the clinical registry databases:

- CK MB and/or Troponin I or T (ng/mL)

PCI Procedure

Data regarding the index PCI procedure(s) will be provided by the site coordinators. Information to be collected includes, but is not limited to, the status of the procedure (e.g., elective, urgent, emergency, salvage), indications for the procedure, the percutaneous intervention(s) performed, and intra and post-procedural events.

Index Surgical Procedure
Data partially extracted from the STS registry database; HCR Group ONLY. Additional data to be supplied by cardiac surgical investigator
Data regarding the surgical intervention for the HCR procedure will be extracted from the STS dataset, including but not limited to the status of the procedure (e.g., elective, urgent, emergent, and emergent salvage), details regarding the anesthesia and intra-operative interventions, bypass pump use, conduit and harvest technique, anastomoses, concomitant procedures, and intra-operative blood use and complications if applicable. Modest additional

data will be provided by the surgical investigator, including surgical technique such as MIDCAB, EndoCAB or TECAB.

Hospitalization & MACCE Events
Limited information about the index revascularization procedure(s) and hospitalization will be extracted from the STS registry dataset including length of stay, transfusion requirements, repeat procedures, and discharge disposition when possible. Information regarding MACCE events that occur during study-procedure related hospitalizations will also be extracted from the STS registry when possible. Limited source documentation pertaining to the MACCE event will be collected and uploaded into the EDC as detailed in the trial Manual of Procedures (MOP).

Index Hospital Costs
Data extracted from UHC database and UB forms for all hospitalizations required to complete the original planned revascularization strategy (if staged)

Medical costs are defined as hospital costs and physician fees incurred during the index revascularization procedure(s) and hospitalization. Cost data will be extracted from the UHC operational database system for member sites, and from UB medical claims forms for sites without UHC membership. Dates of charges and revenue codes will be used to match the cost data with data on study-procedure related hospitalization from the STS registry. UB medical claims will be converted to costs using the same methodology as used by UHC to estimate costs including center-specific ratios of cost to charges. These ratios will be based on the annual Medicare costs reports submitted annually by participating study sites to Medicare. Physician fees will be based on collected length of stay data and the Medicare fee schedule. Physician fees for HCR and PCI procedures will include those for the primary surgeon, surgical assistant, and anesthesiologist. Non procedure-related physician fees regarding the index hospitalization(s) will be based on collected length of stay data and the Medicare fee schedule. The patient-specific cost data downloaded from the UHC operational database system and electronic UB data will be de-identified and coded with the unique study ID, and subsequently transferred by the participating clinical site to the DCC via a secure FTP website.

Post-Intervention Site Activities

Follow-up must be performed at 30 (±7) days following all procedures (index and staged) that occur within 90 days of the first study revascularization procedure.. However, if a staged procedure occurs <45 days after the first procedure, it will not be considered a protocol violation if a 30-day follow-up visit was not performed after the first procedure.

Medications
This form captures medication use, including antiplatelet and anticoagulant agents, beta blocker, and ACE inhibitors, ARBs, aldosterone antagonists and statins.

Angina Class - Canadian Cardiovascular Society Classification (CCSC)
The presence of angina will be assessed, and when present, classified according to the CCSC

scale and documented on this form. CCSC classification scheme is detailed in Appendix I.

Quality of Life
The SF-12 and EuroQol (Appendix II) questionnaires will be completed by the patient to assess quality of life.

MACCE and Other Cardiovascular and Bleeding Events
Information regarding MACCE, other cardiovascular and bleeding events will be recorded. Limited source documentation pertaining to the MACCE event will be collected and uploaded into the EDC as detailed in the trial Manual of Procedures (MOP).

Long-term Patient-Reported MACCE & QoL

MACCE and Other Cardiovascular and Bleeding Events
Follow-up must be performed at 6 (±1)*, 12* (±1)*, 18* (±1)*, 24* (±1)*, 30* (±1)*, 36* (±1)*, 42*(±1)*, 48* (±1)*, 54* (±1)*, and 60* (±1) *months post-randomization***,** *via centralized DCC telephone follow-up (when allowed by local IRB/REBs)*
Follow-up MACCE and other cardiovascular and bleeding event assessments will be conducted via telephone contact with patients by the DCC research nurse. Site coordinators will conduct follow-up via telephone at sites where the IRB/REB does not approve of centralized DCC follow-up. Vital status and the occurrence of any MACCE and other cardiovascular and bleeding event events since the last follow-up will be ascertained. Information regarding MACCE and other cardiovascular and bleeding event events will be recorded by the DCC research nurse or local site coordinator. In addition, limited source documentation pertaining to the MACCE and selected other cardiovascular events will be collected by the site coordinator and uploaded into the EDC for review by the Clinical Events Committee.

For patients who have completed their planned revascularization procedure(s) as documented on the Planned Revascularization form, including planned staged procedures, any subsequent PCI or CABG performed will be considered an unplanned revascularization, and treated as a MACCE event. As noted in the Definition and Measurement of Endpoints section, this excludes an additional planned staged revascularization if it is declared by the end of the prior planned study intervention procedure.

Medications
At 6 (±1)*, 12* (±1)*, 18* (±1)*, 24* (±1)*, 30* (±1)*, 36* (±1)*, 42*(±1)*, 48* (±1)*, 54* (±1)*, and 60* (±1) *months post-randomization***,** *via centralized DCC telephone follow-up (when allowed by local IRB/REBs)*

Patient reported medication use since the last follow-up, specifically, antiplatelet and anticoagulant agents, beta blocker, ACE inhibitors, ARB, aldosterone antagonists and statin use will be recorded by the DCC research nurse or local site coordinator.

Angina Class - Canadian Cardiovascular Society Classification (CCSC)
At 6 (±1)*, 12* (±1)*, 18* (±1)*, 24* (±1)*, 30* (±1)*, 36* (±1)*, 42*(±1)*, 48* (±1)*, 54* (±1)*, and 60* (±1) *months post-randomization***,** *via centralized DCC telephone follow-up (when allowed by local*

IRB/REBs)

The presence of angina will be assessed by the DCC research nurse, and when present, classified according to the CCSC scale and documented on this form. CCSC classification scheme is detailed in Appendix I.

Quality of Life

At 12 (±1)*, 24* (±1)*, 36*(±1)*, 48* (±1)*, and 60* (±1) *months post-randomization***,** *via centralized DCC telephone follow- up (when allowed by local IRB/REBs)*

The SF-12 and EuroQoL will be administered annually, either by phone from the DCC research nurse or site coordinator, or via electronic patient portals, including electronic QoL surveys that can be utilized for all patients with computer, tablet or smart phone capability. The electronic forms will also be accessible for patient reporting via a password protected portal on the HCR Trial website.

Costs

Collected at 12 (±1)*, 24* (±1)*, 36* (±1)*, 48* (±1)*, and 60* (±1) *months post-randomization, via electronic transfer from UHC database and UB forms*

Medical costs were defined as hospital costs, physician fees, outpatient procedure costs, the cost of prescription drugs, and the cost of rehabilitation incurred after the index hospitalization. Medical claims associated with any hospital stay and outpatient service in participating sites are collected annually. Cost data will be extracted from the UHC operational database system for member sites, and from UB medical claims forms for sites without UHC membership. UB medical claims will be converted to costs using the same methodology as used by UHC to estimate costs using center-specific ratios of cost to charges. These ratios will be based on the annual Medicare costs reports submitted by participating study sites to Medicare. Multivariable imputation algorithms will be used to impute costs for patient-reported out of network hospital stays. Physician fees will be based on collected MACCE and length of stay data and the Medicare fee schedule. Resource use associated with prescribed medication and the rehabilitation of myocardial infarction and stroke will be estimated based on patient-reported information and will be converted into dollars using reimbursements from Centers for Medicare and Medicaid Services costing reports

Event Driven Data Collection

Major Adverse Cardiac and Cerebrovascular Events (MACCE) and Other Cardiovascular and Bleeding Events (when allowed by local IRB/REBs)

Patient reported via electronic patient portal or phone call to DCC (when allowed by local IRB/REBs)

Patients will be encouraged to report interim MACCE and other cardiovascular and bleeding events between the annual phone follow-ups. Follow-up MACCE and other cardiovascular and bleeding event reporting will be conducted either via telephone contact to the DCC research nurse or the site coordinator, or via one of the electronic patient portals (e.g., electronic QoL surveys for all patients with computer, tablet or smart phone capability. The electronic forms will also be accessible for patient reporting via a password protected portal on the HCR Trial website).

Information regarding MACCE and other cardiovascular and bleeding events reported via telephone will be recorded by the DCC research nurse or site coordinator. In addition, limited source documentation pertaining to the MACCE and other selected cardiovascular events will be collected by the site coordinator.

End of Study

Study Completion/Early Termination
Event Driven
This form records the date and reason for study completion or early termination.

Investigator Statement
At the end of study after electronic case report form (eCRF) data completion and review
After a complete review of the eCRFs and patient summaries, the investigator will sign this form to attest to the accuracy and completeness of the data collected.

DATA MANAGEMENT

In order to capture the highest quality data, we will use a web-based system with electronic validation. In addition, we will cross-validate the data for complex errors. Ongoing review of data collection by the DCC will ensure that the quality and completeness of the data will be reflective of the state of the art in clinical trials.

Electronic Data Capture

All study data will be entered in the EDC system. Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on individuals' roles and responsibilities. The EDC application provides hierarchical user permission data entry, viewing, and reporting options. For optimum security, the system operates Secure Socket Layer 128-bit encryption protocol over Virtual Private Networks. This application is designed to be in full compliance with the International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's CFR21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials," and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

EDC supports efficient data collection and management and facilitates rapid data closure. A strong advantage of web-based design is that the DCC has immediate and ongoing access to the data from all clinical centers so that queries can be generated and distributed to the sites in real-time, the frequency of missing data can be reduced by two mechanisms, the coordinators will receive a list of queries generated by the study monitors upon logging into the system, and any data required during a visit is immediately evident through the system and can be collected before closure of the visit window. The EDC will be a vital part of the centralized monitoring planned for this study.

Monitoring

The DCC will employ a risk-based approach to monitoring for this study. This will be accomplished via centralized or remote monitoring of data via the EDC with a focus on safety,

study endpoints, data completion and data outliers. Clinical centers will provide source documentation to the DCC for remote monitoring via upload to the EDC or remote access to electronic medical records. The DCC will also centrally monitor study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event/ Investigational Device Exemption (IDE) Safety Report Log periodically to ensure that the sites are adhering to the study protocol and procedures. The DCC will generate performance metrics to analyze site characteristics such as recruitment rates and timeliness of data entry. This will allow the DCC to identify trends across sites and to address low-performing sites appropriately. The monitors will also conduct a review of the regulatory documents for the study.

Through the combination of centralized monitoring, the EDC system, instantaneous electronic validation, and visual cross-validation by the DCC to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

Patient Retention Strategies
The DCC nurse or local site coordinator will build relationships with each participant, beginning immediately after discharge from the index hospitalization, to maximize data completion and participant retention. Tools to enhance the patient/DCC relationship will include 24 hour phone access for study questions and clinical referrals, quarterly newsletters (electronic and paper based).

ANALYTICAL PLAN

The primary objective of this trial is to determine whether hybrid coronary revascularization (HCR) is associated with a reduction in MACCE defined as all-cause mortality, myocardial infarction (MI), stroke, or unplanned revascularization over a minimum of 5 years follow-up after randomization, compared to PCI with metallic DES. Secondary outcomes of this study will include MACCE at each data collection time point, individual components of MACCE, ischemia-driven revascularizations, cardiovascular and non-cardiovascular mortality, Re-hospitalization (all-cause and cardiovascular) health status, and the comparative cost-effectiveness of HCR vs. PCI.

Power and Sample Size
Sample size for this study was determined based on the following operating characteristics: (a) two sided type I error fixed at 0.05, (b) 80% power, (c) minimum follow-up of 5 years, 2-year enrollment period with uniform enrollment (d) 5-year MACCE rate in the PCI group of approximately 25%, (e) expected 5-year MACCE relative rate reduction in the HCR group of ≥ 20%, (f) drop-in (HCR to PCI) and drop-out (PCI to HCR) rates of approximately 0.5% and 2% respectively, and (g) loss to follow-up by the end of the study of 15%.Under the above assumptions it is estimated that 530 events (or 2354 patients) will be required to detect a relative decrease in MACCE of ≥ 20% in the HCR compared to the PCI group. This is a reasonable improvement based on estimates from recent studies.[25-28]

Interim Monitoring Guidelines
The objectives of interim monitoring are to (1) monitor for safety, (2) track participant accrual rates, and (3) monitor the primary and secondary outcomes for early evidence of efficacy, harm or futility. To accomplish this, summaries of data quality, accrual, adherence, distribution of

baseline factors, safety, study endpoints and other analyses as requested will be prepared for review by the DSMB. A single interim analysis and one final analysis are planned for this trial, for a total of two analyses. The interim analysis will be conducted when 0.5 fraction of the total number of events have been observed. This interim analysis will evaluate the composite rate of adjudicated death, stroke or MI (excluding unplanned repeat revascularization), as the endpoint is being conducted for safety, rather than efficacy, purposes. We will use an alpha-spending O'Brien-Fleming sequential procedure as a guideline for decision-making. At the interim analysis the value of the test statistic will be compared with the alpha spending function critical value. The p-values for the interim monitoring analysis and the final analysis are, 0.0031, and 0.05, respectively.

Stopping Rule

We do not anticipate stopping the trial for evidence of early efficacy or futility at the time of the interim analysis. The collection of 5-year follow-up information on all patients enrolled in the trial is necessary to provide a comprehensive overview of the relative safety and effectiveness of the two randomized strategies.

A decision to stop the trial for safety reasons will be based on the result of the interim analysis as well as other supporting evidence that either arm of the trial poses unacceptable risk to patients. Should the data suggest that the composite rate of death, stroke or MI is significantly higher in one group than the other at the interim analysis (with a p-value of ≤ 0.0031), additional analyses and sub-group analyses will be conducted to supplement this information including investigation of site effects, adherence to the guideline-directed medical therapy, and other ad-hoc pertinent analyses as discussed and agreed upon with the DSMB.

Analysis Plan

The primary analysis will be an intent-to-treat analysis that will include all randomized participants regardless of treatment actually received or follow-up schedule. All hypothesis testing will be conducted using two sided tests at $\alpha = 0.05$.

Univariate Analysis

All outcome measures will be described in a univariate analysis. For continuous variables means and standard deviations will be calculated. For discrete and dichotomous variables, contingency tables will be used.

Analysis of Primary Endpoint

The primary endpoint of this study will be MACCE defined as all-cause mortality, myocardial infarction (MI), stroke, or unplanned revascularization over a minimum of 5 years of follow-up after randomization. Overall time to first event will be estimated using Kaplan-Meier curves. Survival time will be defined as the time (in months) between randomization and the occurrence of MACCE. To compare the HCR arm with the PCI arm we will use a stratified log-rank statistic using the stratification variables from the randomization procedure. A Cox proportional hazards model with treatment and stratification factors as covariates will be used for the multivariate analysis of the time to first MACCE. The assumption of proportionality will be tested prior to fitting the model. If the proportional hazards assumption is not met, the extended Cox model will be used. Hazard ratios and their 95% confidence intervals will be computed. Survival will be included in the analysis as censored if they are alive and free of

MACCE at the end of the study. Although we do not anticipate interactions between treatment and stratification factors, formal tests for interactions will be assessed using proportional hazards models.

Analysis of Secondary End-points
Secondary outcomes of the study will be analyzed as follows:

Cardiovascular Events
Secondary cardiovascular events include MACCE at each data collection time point; individual components of MACCE (all-cause mortality, stroke, myocardial infarction, unplanned revascularization,); cardiovascular and non-cardiovascular mortality, ischemia-driven revascularization, and other cardiovascular events.

MACCE at each time point, individual components of MACCE, cardiovascular and non-cardiovascular mortality, , ischemia-driven revascularization other cardiovascular endpoints such as stent thrombosis and symptomatic graft stenosis or occlusion, and bleeding events will be analyzed using the stratified log-rank statistic in the manner of the primary outcome. Unplanned revascularization, stroke, MI, and cardiovascular mortality may not occur because death from any cause precedes the event, thus it is possible that censoring patients from all-cause mortality may lead to biased estimates when analyzing time to first event of these outcomes. As a sensitivity analysis, competing risks analysis using the methods of Gray[29] and Fine and Gray[30] will be used to calculate cause-specific cumulative incidence. Gray and Fine's test will be compared with the log-rank test for the treatment group effect, and the cumulative incidence curve will be compared to the Kaplan-Meier curve.

For unplanned and ischemia-driven revascularizations, a Poisson regression model will be used to assess differences in the rate of revascularization between groups. Time to death will be described by Kaplan-Meier curves and differences between randomization groups assessed via the stratified log-rank test. Mortality analyses will be conducted for both cardiovascular and non-cardiovascular mortality.

Hospitalizations
All cause and cardiovascular re-admissions will be recorded. A Poisson regression model will be used to compare the rate of readmission between groups for any cause, and specifically for cardiovascular hospitalizations.

Health Status
Health status will be measured by Angina Score (Canadian Cardiovascular Society Classification [CCSC]) and by QoL surveys (SF-12 and EuroQOL). The distribution of CCSC angina class will be presented for each randomization arm and compared using a chi-squared test at each time point. Quality of life will be measured using the SF-12 and EuroQol. Quality of life will be analyzed longitudinally using mixed effects models. [31, 32, 33] Log-transformations will be used, if necessary to normalize the variables or stabilize the variance. These models will be used to predict outcome given treatment group and time. The interaction between treatment and time will be used to determine the difference between the two arms over time.

Cost-effectiveness

A cost-effectiveness analysis will be performed from an overall healthcare system perspective. Costs associated with hospitalizations and outpatient services will be estimated from collected medical claim data using center-specific ratios of cost to charges. Multivariable imputation algorithms will be used to impute costs for patient-reported out of network MACCE related hospitalizations. Community-based health state preferences will be estimated from the trial's EuroQOL data using an algorithm developed for the U.S. general population.[34]

We will subsequently develop an individual-level decision model, which will predict and extrapolate the overall survival, quality of life, and costs per trial participant as a function of randomization and MACCE. With the decision model we will compare the two scenarios: HCR vs. PCI by rerunning the randomized trial "in silico". In this re-simulated trial, each of the 2354 patients will be virtually exposed to both scenarios. Subsequently, each patient's life course according to an intention-to-treat principle is modeled by microsimulation while individualizing event rates, quality of life and costs.

For the base case analysis, we will use the trial duration as time horizon and in addition an extended lifetime horizon. The modeled future costs and quality-adjusted life years (QALYs) will be discounted at the annual rate of 3% and averaged for the two scenarios. To take into account patient heterogeneity and parameter uncertainty, the decision model's equations for event rates, quality of life, and costs will be regenerated in bootstrap datasets, each with the same size of 2354 patients. Using the decision models' output of each bootstrap (probabilistic cost-effectiveness analysis), we will construct incremental cost effectiveness (ICE) scatterplots. Second, we will calculate average net health benefits for HCR and PCI. The net health benefit is defined as the difference between the health effect in QALY associated with the chosen intervention and the minimum health effect that society would demand in return for the investment: QALY – QALY/cost-effectiveness threshold .[35] Recently recommended cost-effectiveness thresholds of $50,000, $100,000, and $200,000 per QALY will be considered.[36] In addition, 95% confidence intervals will be calculated for the difference in mean QALYs, costs and net health benefits by comparing the two scenarios across bootstraps. Deterministic sensitivity analyses will be performed to explore the robustness of the findings, including variations in discount rates, different time horizons, and changes in costs, survival and QoL due to increased use and experience.

Missing Data
For participants who are lost to follow-up we will use all the information available up to the time of loss to follow-up. If the data are missing at random (MAR), that is, the probability of being missing depends only on observed values, then likelihood-based methods such as mixed-effects models will be used for analysis without bias.[37] If the fraction of missing data is small we expect that even non-ignorability will have a negligible effect on the final estimates. If the extent of missingness is large compared to the effect size, we will use the multiple imputation procedure proposed by Rubin and Little.[38, 39]

Safety Analysis
The DSMB will receive regular reports on MACCE and the individual components of MACCE, as well as other cardiovascular and bleeding events for all participants in the trial. As part of the

safety analysis, mortality data will also be provided. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual components of MACCE for HCR versus PCI will be computed.

ORGANIZATION OF THE STUDY

This section describes the overall study organization. The study is conducted in at least 50 clinical sites selected by the Hybrid Trial Steering Committee. The following committees and institutions will be involved in the administration of the study.

Clinical Events Committee (CEC)

The charge of the CEC is to review source documents and to adjudicate all MACCE events according to their pre-specified definitions. The individuals who will serve on the committee will be appointed by the DCC, and will be independent of the DCC, CCC, clinical centers and the investigators. The committee will consist of, at least, a cardiothoracic surgeon with HCR experience, an interventional cardiologist, and a neurologist. The CEC will meet via teleconference, and when possible, Skype, every 6 months or as needed to adjudicate outcomes data for each subject enrolled.

Data and Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its subjects, an independent DSMB will monitor results during the study. The board consists of physicians, biostatisticians, and ethicists, who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC, CCC, or the clinical sites, and will be appointed by the NHLBI. The DSMB will act in a senior advisory capacity to the DCC, CCC, Steering Committee, and the NHLBI regarding data and safety matters throughout the duration of the study. These data include adverse events (e.g., MACCE) and mortality. They will communicate their findings directly with the DCC and the NHLBI. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

Data Coordinating Center (DCC)

A university-based DCC (InCHOIR) will collaborate with the CCC, Steering Committee, and clinical investigators to finalize and revise the study protocol as necessary, and bears responsibility for monitoring interim data, and analyzing the study's results in conjunction with the CCC, Steering Committee, investigators and the sponsor. The DCC will coordinate and monitor the trial, and will administrate the DSMB. The DCC holds the study-specific IDE with the FDA and will be responsible for reporting UADEs to the FDA according to 21CFR812.150. In addition, the DCC will be responsible for submitting the required progress reports to the FDA.

Clinical Coordinating Center (CCC)

The clinical coordination for the Hybrid Trial will be directed by a CCC, co-chaired by an interventional cardiologist (Gregg W. Stone) and cardiac surgeon (John Puskas). The CCC will collaborate with the DCC, Steering committee and clinical investigators to optimize the close collaboration between the interventional cardiologists and surgeons within the clinical site Heart Teams. The charge of the CCC will be to (1) maximize enrollment, (2) monitor the appropriateness of enrollment, (3) mentor site investigators, and (4) facilitate communication

between site investigators and the DCC, (5) interpreting and disseminating the study results in collaboration with the DCC, Steering Committee and clinical investigators. The CCC will oversee the medical and surgical management committees with site investigators, and monitor respective surgical and medical literature and other knowledge sources to assure state-of-the-art patient management standards are integrated into the protocol.

Steering Committee

The Steering Committee will provide the overall scientific direction for the Hybrid Trial. The committee will consist of the surgical and interventional cardiology Principal Investigators from the two highest enrolling centers, representatives of the DCC and CCC, and the NHLBI project officer. The responsibilities of the Steering Committee are to: (a) maintain contact with study investigators to ensure high quality data collection; (b) approve and implement major protocol changes in response to advice from the DSMB; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the study.

NIH

This trial is funded by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI has appointed an independent DSMB to provide oversight of this trial. NHLBI program officials will serve as members of the Steering Committee.

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APPENDIX I: Canadian Cardiovascular Society Classification

Overview:
The Canadian Cardiovascular Society Classification of angina pectoris separates patients with anginal symptoms into groups based on the severity of their symptoms. The classification uses the extent of limitation on daily activities and the kind of physical activity which precipitates the anginal episode.

Clinical Findings	Features	Grade
No limitation of ordinary activity	Ordinary physical activity (such as walking or climbing stairs) does not cause angina. Angina may occur with strenuous rapid or prolonged exertion at work or recreation.	I
Slight limitation of ordinary activity	Angina may occur with • Walking or climbing stairs rapidly; • Walking uphill; • Walking or stair climbing after meals or in the cold in the wind or under emotional stress, or only during the few hours after awakening. • Walking more than 2 blocks on the level at a normal pace and in normal conditions • Climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions	II
Marked limitation of ordinary physical activity	Angina may occur after • Walking 1-2 blocks on the level or • Climbing 1 flight of stairs in normal conditions at a normal pace	III
Unable to carry on any physical activity without discomfort	Angina may be present at rest.	IV

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Appendix II: Quality of Life Measures

SHORT FORM – 12 (SF-12 version 2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

EURO QoL 5-D QUESTIONNAIRE

Check one box for each of the following six health dimensions.

Mobility	
I have no problems in walking about	1.
I have some problems in walking about	2.
I am confined to bed	3.
Self-Care	
I have no problems with self-care	1.
I have some problems washing or dressing myself	2.
I am unable to wash or dress myself	3.
Usual Activities (*e.g. work, study, housework, family or leisure activities*)	
I have no problems with performing my usual activities	4.
I have some problems with performing my usual activities	5.
I am unable to perform my usual activities	6.
Pain/Discomfort	
I have no pain or discomfort	7.
I have moderate pain or discomfort	8.
I have extreme pain or discomfort	9.
Anxiety/Depression	
I am not anxious or depressed	10.
I am moderately anxious or depressed	11.
I am extremely anxious or depressed	12.
Compared with my general level of health over the past 12 months, my health state today is:	
Better	13.
Much the same	14.
Worse	15.

To help people say how good or bad a health state is we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Best imaginable health state

Your own health state today

Worst imaginable health state

Appendix III: New York Heart Association (NYHA) Classification

Class	Patient Symptoms
Class I (Asymptomatic)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.