Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bangalore S, Maron DJ, O'Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. N Engl J Med 2020;382:1608-18. DOI: 10.1056/NEJMoa1915925

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Table of Contents

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	Asim N. Cheema, MD, PhD Akshay Bagai, MD, MHS Ron Wald, MDCM, MPH (N) Shaun Goodman, MD, MSc John Joseph Graham, MRCP, MB ChB, BSc Mark Peterson, MD, FRCSC, PhD Chi-Ming Chow, MD, CM, MSc Beth Abramson, MD, MSc	Khrystyna Kushniriuk, HBSc, MD Mohammed Hussain Olugbenga Bello	Toronto, ON	St. Michael's Hospital (3)
	Graham Wong, MD Kenneth Gin, MD Christopher Fordyce, MD	Jackie Chow, BSN Andrew Starovoytov, MD Naomi Uchida, BSN Ngaire Meadows	Vancouver, BC	Vancouver General Hospital (2)
	Ariel Diaz, MD Philippe Rheault, MD Alejandro Gisbert, MD Alain Raymond, MD Yanek Pépin-Dubois, MD Miguel Barrero, MD Carl-Éric Gagné, MD Mark Garand, MD Ricardo Costa, MD Catherine Lemay, MD	Isabelle Roy, RN Patricia Alarie, RN Linda Arcand, RN Estelle Montpetit	Trois-Rivieres, QC	Centre Hospitalier de Regional Trois-Rivieres (1)

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	Philippe Généreux, MD Jean Diodati, MD François Madore, MD (N)	Chantale Mercure, RN	Montréal, QC	Centre Intégré Universitaire De Santé et de Services Sociaux du Nord de l'île de Montréal /Hôpital du Scaré-Cœur de Montréal (1)
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	David Foo, MBBS Jason Loh Kwok Kong, MD Ching Min Er, MD Fahim Haider Jafary, MD Tracy Tan, MD (N)	Li Hai Yan, RN	Singapore	Tan Tock Seng Hospital (2)

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	Whady Hueb, MD Eduardo Gomes Lima, MD Paulo Cury Rezende, MD Expedito Eustáquio Ribeiro Silva, MD Alexandre Ciappina Hueb, MD	Myrthes Emy Takiuti, RN	Sao Paulo	Heart Institute (InCor) University of São Paulo (6)
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	Alexandre Schaan de Quadros, MD Renato Abdala Karam Kalil, MD José Luiz da Costa Vieira, MD Gabriel Grossmann , MD Pedro Píccaro de Oliveira, MD Leonardo Bridi, MD Simone Savaris, MD Renato George Eick, MD (N)	Aline Peixoto Deiro Alice Manica Muller Maria Antonieta Pereira de Moraes Bruna Maria Ascoli Sílvia Zottis Poletti	Porto Alegre	Instituto de Cardiologia de Porto Alegre (1)
	Paola Emanuela Poggio Smanio, MD, PhD Leda Lotaif, MD, PhD (N)	Leonardo Pizzol Caetano, PhD	São Paulo	Instituto Dante Pazzanese de Cardiologia (1)
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	Pedro Farto e Abreu, MD Sérgio Bravo Baptista, MD, PhD Miguel Borges Santos, MD Patricia Carrilho, MD (N)	Maura Carina Nédio, BSc	Amadora	Hospital Professor Doutor Fernando Fonseca, EPE (1)
	Fausto J. Pinto, PhD Miguel Nobre Menezes, MD Guilhermina Cantinho Lopes, MD Ana Gomes Almeida, PhD Pedro Canas Silva, MD Angelo Nobre, MD Ana Rita Francisco, MD Jose Lopes, MD (N)	Inês Zimbarra Cabrita, PhD Andreia Rocha, MSc Francisca Patuleia Figueiras, PhD Andreia Coelho, BSc Marta Capinha Maria Inês Caetano Susana Silva	Lisbon	Santa Maria University Hospital, Cardiology Department, CHLN (1)
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	Rafael Selgas, MD (N)			
	Jesús Peteiro, MD, PhD María Dolores Martínez-Ruíz, MD Ruth Pérez-Fernández, MD José J Cuenca-Castillo, MD Xacobe Flores-Ríos, MD Óscar Prada-Delgado, MD Gonzalo Barge-Caballero, MD Miguel Perez Fontan, MD (N)	Moisés Blanco-Calvo, PhD Encarnación Alonso-Álvarez, BSc Paula García-González, BSc	A Coruna	Complexo Hospitalario Universitario A Coruña (CHUAC) Sergas, Department of Cardiology. INIBIC A Coruña. CIBER-CV. Universidad de A Coruña, Spain (2)
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	Julio César Figal, MD Oscar Méndiz, MD Claudia Cortés, MD Roberto René Favaloro, MD Pablo Raffaele, MD (N)	Matías Nicolás Mungo	Ciudad Autonoma de Buenos Aires	Fundación Favaloro (1)
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	Christophe Thuaire, MD Téodora Dutoiu, MD Catherine Albert, MD (N) Bougrida Hammouche, MD (N)	Corine Thobois, RN Emilie Tachot, RN Christophe Laure, RN Christel Vassaliere, RN	Chartres	C.H. Louis Pasteur (2)
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	Dwayne S. G. Conway, MD	Judith Wright Donna Exley	Wakefield	Pinderfields Hospital (1)
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Australia (4) Lead Country Cardiologist Joseph B. Selvanayagam, MBBS (Hons), Dphil Lead Country Cardiologist Magid Fahim, MBChB, FRACP				

	Joseph B. Selvanayagam, MBBS(Hons), DPhil	Sau Lee, PhD	Adelaide	Flinders Medical Centre and College of Medicine and Public Health (4)
	Majo X. Joseph, MBBS Jonathan M Gleadle, BM Dphil (N)	Prince Thomas, RN		
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	Irene Marthe Lang, MD	Max-Paul Winter, MD	Vienna	Medical University of Vienna, Department of Cardiology (1)
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	Christiaan Vrints, MD	Nathalie Brosens	Edegem	Universitair Ziekenhuis Antwerpen (1)
	Bharati Shivalkar, MD Amaryllis Van Craenenbroeck, MD (N)			
Israel (4)				
	Yaron Arbel, MD	Daniela Puzhevsky	Tel Aviv	Tel Aviv Sourasky Medical Center (4)
	Doron Schwartz, MD (N) Orit Kliuk, MD	Miri Revivo		
Egypt (3)				
	Magdy Abdelhamid, MD Ahmed Kamal, MsC Hossam Mahrous, MD Mohamed Adel , MsC Hussien El Fishawy, MD (N)	Ahmed Talaat, MD	Cairo	Cairo University (3)
United Arab Emirates (2)				
	Wael A. Almahmeed, MD Mohamed Hassan, MD (N) Seema Nour, MD Abdallah M. Abdallah, MD Salamah Alfalahi, MD	Virendra Misra, MD	Abu Dhabi	Sheikh Khalifa Medical City (2)

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	Rolf Doerr, MD	Karin Ploetze, PhD	Dresden	Praxisklinik Herz und Gefaesse (1)
	Gregor Simonis, MD, PhD Juergen Stumpf, MD Clemens T. Kadalie, MD Klaus Matschke, MD, PhD Doreen Reimann, MD (N)	Franziska Guenther Kerstin Bonin Kerstin Mikes, RN Katharina Knaut		
Macedonia (1)				
	Sasko Kedev, MD, PhD Irena Peovska Mitevska, MD, PhD Elizabeta Srbinovska Kostovska, MD, PhD Hristo Pejkov, MD, PhD Zvezdana Petronijevic, MD (N) Liljana Tozija, MD (N)		Skopje	University Clinic of Cardiology (1)
Netherlands (1)				
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	Elise van Dongen, MD	Elisabeth, M. Janzen, RN		
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** (N) = Nephrologist*

III. Supplementary Methods

Required Quality Metrics for Participating Sites

Sites qualifying (criteria below) and participating in ISCHEMIA were considered for ISCHEMIA-CKD (majority of sites). In addition, sites with the potential to enroll advanced CKD participants were considered for the trial even if they did not participate in ISCHEMIA (minority of sites- 15 such sites randomized at least 1 participant). Identification of a lead nephrologist was encouraged for every site participating in ISCHEMIA-CKD.

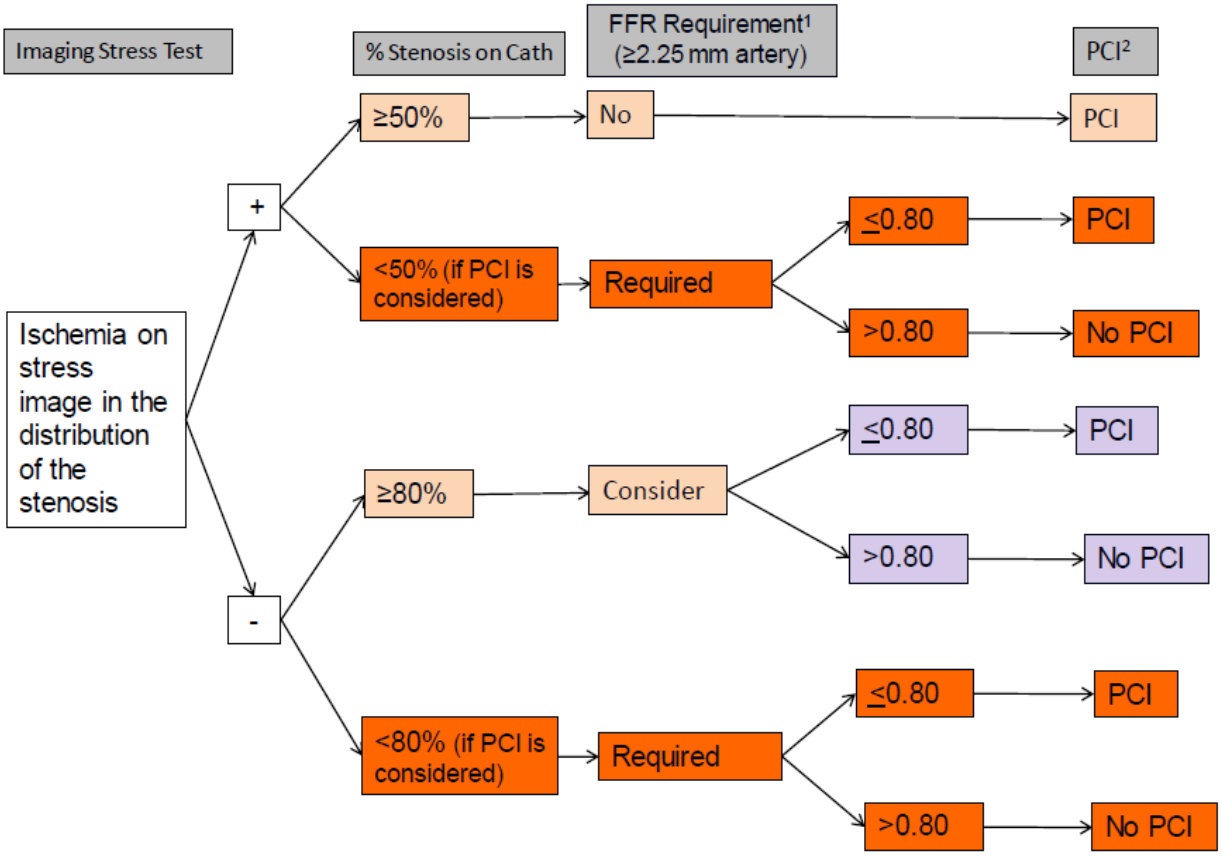
1. PCI site and operator requirements are as follows:
    a. PCI Site Criteria
        i. Must be willing to establish an ISCHEMIA-CKD trial HEART KIDNEY TEAM of cardiovascular interventionalists, cardiologist, cardiovascular surgeons and nephrologist that can evaluate randomized patients on an ongoing basis in a collaborative, multidisciplinary fashion
        ii. Average number of annual PCI cases over the last 3 years for the primary PCI location ≥400/year
        iii. Excluding cases with total occlusion and STEMI:
            1. Average procedural success rate over the last 3 years >95%:
            2. Average rate of emergency CABG over the last 3 years <0.6%:
            3. Average rate of in-hospital mortality over the last 3 years <1.5%
    b. PCI Operator Criteria
        i. Average number of annual PCI cases for the operator over the last 3 years ≥75cases/year. If the volume is <75 per year, total number of lifetime PCI cases must be >1500 cases:
4. CABG Site and Operator requirements are as follows:
    a. CABG Site Criteria
        i. Average annual total procedures with CABG over the last 3 years ≥125/year
        ii. Average annual cardiac surgical procedures (open heart) over the last 3 years ≥300/year
        iii. AND [either 1, 2 or 3]
            1. Non-risk adjusted in-hospital mortality for all isolated CABG procedures over the last 3 years ≤3.0%
            2. Non-risk adjusted in-hospital mortality for isolated elective CABG procedures over the last 3 years ≤2.0%
            3. (For US Sites participating in STS Registry): Risk adjusted operative mortality for isolated CABG procedures over the last 3 years ≤2.7%
    b. CABG Operator Criteria:
        i. Average number of annual total procedures with CABG for the surgeon over the last 3 years ≥75 cases/year
        ii. Lifetime total procedures with CABG ≥750 cases

Sites that qualified for participation in the EXCEL trial[1] qualified for participation in ISCHEMIA. [[1]Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Disease. N Engl J Med 2017;376:1089.]

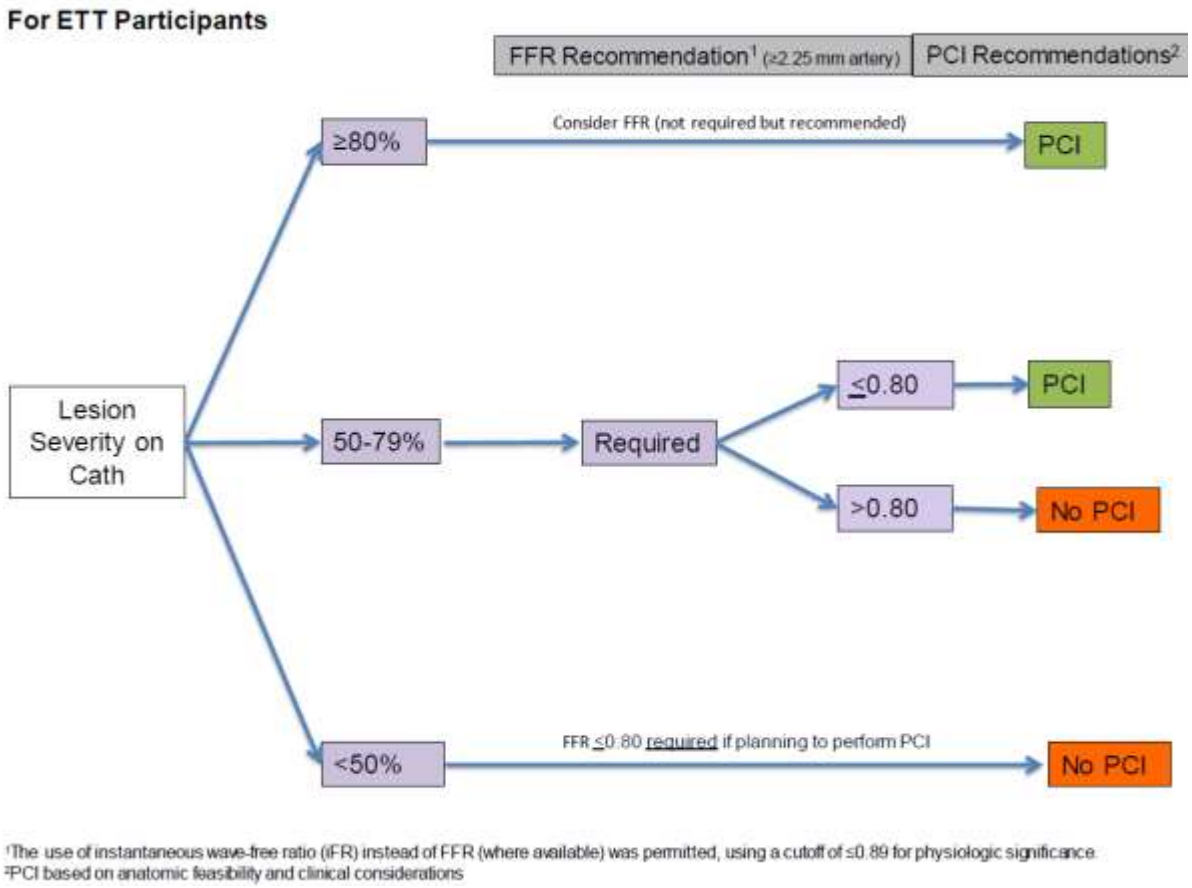
Guidelines for Revascularization Therapy

The guidelines for revascularization therapy were similar to that of ISCHEMIA. Revascularization therapy will be performed based on findings from the diagnostic catheterization as well as other relevant clinical information. The goal is revascularization of all ischemic myocardial segments (detected by non-invasive imaging or by fractional flow reserve (FFR) testing in the catheterization laboratory). The choice of revascularization strategy will be based on anatomy and contemporaneous guideline recommendations, determined by investigators at the enrolling sites. It is recommended that the study Heart-Kidney Team (interventional cardiologist, cardiac surgeon, cardiologist and nephrologist) discuss each case (as applicable) after diagnostic angiography to reach a consensus as to the best revascularization technique.

Fractional Flow Reserve Use Algorithm



[1]The use of instantaneous wave-free ratio (iFR) instead of FFR (where available) was permitted, using a cutoff of ≤0.89 for physiologic significance.
[2]PCI based on anatomic feasibility and clinical considerations



[1]The use of instantaneous wave-free ratio (iFR) instead of FFR (where available) was permitted, using a cutoff of ≤0.89 for physiologic significance.
[2]PCI based on anatomic feasibility and clinical considerations

Strategies to minimize contrast induced acute kidney injury after cardiac catheterization/PCI

- Pre-, intra- and post-procedure hydration
  - Protocol used in the POSEIDON trial:
    - Initiate 3mL/kg/h of normal saline (NaCl 0.9%) IV, for at least 1 hour prior to angiography
    - Measure LVEDP prior to contrast administration
    - Adapt infusion rate based on LVEDP measurement as follows:
      - 5 mL/kg/hr for LVEDP < 13 mm Hg
      - 3 mL/kg/hr for LVEDP of 13 mm Hg to 18 mm Hg
      - 1.5 mL/kg/hr for LVEDP > 18 mm Hg
    - Continue fluid administration for 4 hours post procedure
  - Simplified protocol based on LVEF (expert opinion):
    - Participants with preserved EF
      - IV 0.9% NS at 1 cc/kg/hour for 12 hours pre- and post-procedure
  - Participants with EF<40%

        - IV 0.45% NS at cc/cc replacement (urine output should be match to maintain euvolemic state) for 12 hours pre- and post-procedure
    - Pre-procedure high dose statins
    - Avoid nephrotoxic agents for at least 48 hours prior
    - Use iso- or low-osmolar contrast agents
    - Limit contrast used: Ultra-low/Zero volume contrast techniques (IVUS guided PCI)
        - Use small diameter catheters (i.e., 5–6 French) without side-holes
        - All contrast injections require simultaneous cine angiogram, i.e., ‘‘no dye without the cine’s eye.’’
        - Limit the volume of contrast injected from the catheter to 1–2 cm^3 per injection using a 3-cm^3 syringe.
        - During PCI, prior to exchange of devices such as balloon catheters, remove contrast from the guide catheter by back bleeding contrast out of the ‘‘Y’’ connector.
        - If available, display previous angiographic images (including angiography from past procedures) alongside active fluoroscopy screen as a reference to use as guidance during guide wire, balloon, stent and ultrasound passage.
        - Absolutely no contrast ‘‘puffing’’/test injections during the procedure.
        - Use IVUS liberally for pre-PCI assessment of the lesion, selection of therapeutic modalities, and post-PCI result assessment.
        - Avoid ventriculography
        - Use of biplane if available
    - Consider ischemia-guided revascularization
    - Consider staged PCI for complex multivessel disease

IV= intravenous; IVUS= intravascular ultrasound; LVEDP= left ventricular end diastolic pressure; LVEF= left ventricular ejection fraction; PCI= percutaneous coronary intervention

Strategies to minimize acute kidney injury after CABG

Consider delay of surgery ≥7 days from time of cardiac catheterization

Use of off pump CABG may be reasonable

Renally dose all medications

In patients undergoing on pump CABG, maintain perioperative hematocrit > 19% and mean arterial pressure > 60 mmHg

CABG= coronary artery bypass graft surgery

Guidelines for Medical Therapy

Medical therapy for participants in the ISCHEMIA-CKD will consist of intensive, comprehensive secondary prevention with lifestyle and pharmacologic intervention applied equally to both treatment groups. The minimum goals of medical therapy will be those recommended by the American College of Cardiology (ACC), American Heart Association (AHA), the European Society of Cardiology (ESC) for secondary prevention and angina management, the National Kidney Foundation and the UK renal association.

There are challenges as the evidence on which the guidelines are based for those with advanced chronic kidney disease (CKD) and especially those on dialysis is weak at best, as most randomized trials exclude these high-risk subsets. Consequently, most of the national and international guidelines base their recommendations for secondary prevention on cohorts without CKD. These are the existing standards and will be used in the ISCHEMIA-CKD trial with some modification, as outlined below.

General Considerations:

The medical management of stable ischemic heart disease (SIHD) patients with advanced CKD, including patients on dialysis, should follow that of the general population. In particular, patients should receive aspirin (ASA), beta-blockers, nitroglycerin, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), statins, and calcium-channel blockers (CCB) as indicated.

- Dose adjustments are required for medications that are renally excreted or dialyzed.
- In patients with difficult-to-control hypertension, the dialyzability of antihypertensive medications should be considered.
- Patients on dual antiplatelet therapy should be monitored more carefully for increased risk of bleeding.
- Diagnosis, evaluation, prevention and treatment (including diet and medications) of CKD-mineral and bone disorders should be based on local practice and in accordance with national and international guidelines.
- Evaluation and treatment of anemia associated with CKD should be based on local practice and in accordance with national and international guidelines.

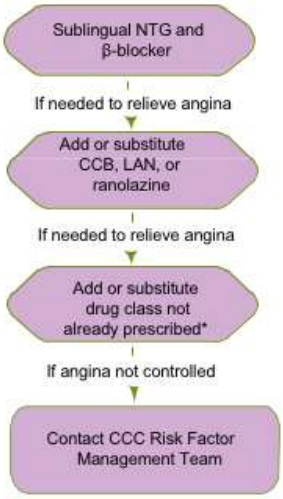
Goals of Medical Therapy

Risk Factor	Goals
Behavioral	
Smoking	Smoking cessation
Physical activity	$\geq$30 minutes of moderate intensity $\geq$5 times/week
Saturated fat	<7% calories

Physiological		
Blood pressure	<130/80 mm Hg[1] Significantly lower BP (e.g., <110 mm Hg systolic) should be avoided	
LDL cholesterol	LDL-C <70 mg/dl (1.8 mmol/L)	
Body Mass Index (kg/m^2)	Initial BMI 25-27.5 >27.5	Weight Loss Goal BMI <25 10% relative weight loss
Diabetes	HbA1c <8%	
Pharmacological agents[2]	**Indications**	
Aspirin	75-162 mg daily	
Statin	Pre-dialysis: Maximum tolerated dose of high-intensity statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) Dialysis: Maximum tolerated dose of moderate- or high-intensity statin (atorvastatin 20-80 mg or rosuvastatin 10-40 mg)	
ACEi/ARB	All participants (as tolerated)	
Beta blocker	Use for history of MI or LVEF <40%	
P2Y12 receptor antagonist	Use for participants with contraindication to aspirin; In combination with aspirin for participants who receive PCI (duration depends on BMS vs. DES); post-MI/ACS for 1 year	
Ezetimibe	Use for participants unable to reach LDL-C goal on maximally tolerated statin dose	

[1]This risk factor goal was changed in April 2018. Prior goal was <140/90 mm Hg in participants without proteinuria and for participants on dialysis, and a goal of <130/80 mm Hg in participants with proteinuria (>300mg/day).
[2]Dose adjustments are required for medications that are renally excreted or dialyzed
BMI = body mass index; HbA1c = hemoglobin A1c; MI = myocardial infarction; ACEi/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; BMS = bare metal stent; DES = drug-eluting stent; ACS = acute coronary syndrome; LDL-C = low-density lipoprotein cholesterol.

ANGINA THERAPY

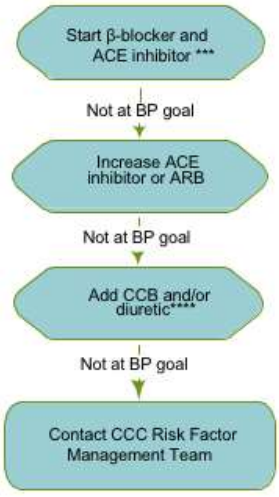


*Consider (not in order of preference): ivabradine, nicorandil, perhexiline, trimetazidine, where approved. LAN=long-acting nitrate

LIPID LOWERING THERAPY
Goal: LDLC <70mg/dL (1.8 mmol/L)

**Where available

HYPERTENSION THERAPY
Goal: Systolic BP <130 mmHg



***Or ARB if appropriate. Monitor serum potassium closely in participants not on dialysis

****Loop diuretic preferred

Definitions of Clinical Outcomes

Death

All deaths will be adjudicated and classified as cardiovascular, non- cardiovascular or undetermined. Cardiovascular deaths are defined as all deaths excluding those for which the principal and underlying cause is solely non-cardiovascular. Any death for which a cardiovascular contributing cause is suspected will also be considered a cardiovascular death.

Myocardial Infarction

Two versions of MI will be adjudicated in ISCHEMIA-CKD: a primary definition and secondary definition. Each definition includes a hierarchy of markers and threshold values as well as a set of rules for diagnosing MI when one or more key elements of the medical record are missing.

The Primary Definition is based upon the Universal Definition of MI, but relies upon site- reported MI decision limits for troponin (which may or may not be the same as the manufacturer 99%URL), and has selected unique marker criteria for MI after PCI or CABG (Type 4a, 5).

The Secondary Definition is also based upon the Universal Definition of Myocardial Infarction, but specifically uses the 99%URL from the assay manufacturer's package insert (which may or may not be the site's MI decision limit) and uses the same supporting criteria (eg. angiographic and ECG) as the UMI definition.

All MI events will be classified based on the Universal MI classification system as follows:

- Type 1: Spontaneous MI
- Type 2: Secondary MI
- Type 3: Sudden Death MI
- Type 4a: MI related to PCI
- Type 4b: MI related to stent thrombosis
- Type 4c: MI related to stent restenosis
- Type 5: MI related to CABG
- Silent MI

Spontaneous MI (Types 1, 2, 4b, 4c)

Diagnosis of spontaneous MI will be satisfied by a clinical setting consistent with acute myocardial ischemia and any one or more of the following criteria:

Marker elevation, as outlined below and at least 1 of the following:

- Symptoms of ischemia, usually lasting > 20 minutes in duration
- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus, stent thrombosis (4b) or high- grade in-stent restenosis (≥50%) (4c)

Marker data not available and at least 2 of the following:

- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test

- Angiographic evidence of intracoronary thrombus.

Autopsy evidence of a fresh myocardial infarction as stand-alone criterion

Spontaneous MI Marker Criteria
Troponin, including high-sensitivity troponin, is the preferred biomarker and takes precedence over CK-MB for both definitions.

Primary Definition: Preferentially uses a troponin threshold value reported as MI Decision Limit or the Upper Limit of Normal (ULN). Marker elevation is defined as troponin > ULN/MI decision limit. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK > 2 x ULN will qualify.

Secondary Definition: Preferentially uses a troponin threshold reported by the manufacturer, namely, the manufacturer 99th percentile. Marker elevation is defined as troponin > 99th percentile. If the troponin 99th percentile is not reported, then troponin > ULN will qualify. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK > 2 x ULN will qualify.

Spontaneous MI ECG Criteria
ECG criterion is considered to be met if any of the following:

ST elevation: New ST elevation at the J-point in two contiguous leads with the cutpoints:
≥ 0.2 mV in men >age 40 and ≥ 0.25mV in men <40 years or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads, or new LBBB.

Any new Q-wave in leads V2–V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 or Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4–V6; II, III, and aVF) or R-wave ≥ 0.04 seconds in V1–V2 and R/S ≥ 1 with a concordant positive T- wave in the absence of a conduction defect.

ST depression and/or T-wave changes, new horizontal or down-sloping ST depression
≥ 0.05 mV in two contiguous leads; and/or T-wave inversion ≥ 0.1 mV in two contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitationand pacemakers.

Silent MI
This event includes evidence of new silent Q-wave MI detected during routine protocol or clinically obtained ECG follow-up. Silent MI events will be classified as a type 1 MI.

Sudden death MI (Type 3)
MI events in which a presentation consistent with infarction is present but the patient dies before the biomarkers are drawn or within the first few hours of the event before the biomarkers become positive. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

PCI-Related MI (Type 4a)
Primary Definition

CK-MB is the preferred biomarker and takes precedence over troponin. For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CK- MB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6 h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

- Post- procedure angiographic TIMI 0/1 flow in a major coronary artery or a side branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.
- New ECG changes (ST segment elevation or depression >0.1mV in 2 contiguous leads), new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.

NOTE: A type 4a MI will be diagnosed with a rise in CK-MB to >10-fold the ULN (or when CK-MB is unavailable, a rise in troponin to >70 times the MI Decision Limit/ULN) as a stand-alone criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre-PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Secondary Definition

Elevation of troponin values >5 X 99th percentile URL within 48 hours post-PCIin patients with normal baseline troponin values pre-PCI AND a rise of troponin values >20% if the baseline values are elevated pre-PCI and are stable or falling. If the troponin 99th percentile is not available, the MI Decision Limit / ULN may be used. If troponins are not available, CKMB elevation >5 X ULN will be used.

In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

- Symptoms suggestive of myocardial ischemia (≥20 min)
- New ischemic ST changes or new pathological Q waves. (see “ECG Criteria” above) Note the UMI definition uses ≥0.05 mV of STD whereas the ISCHEMIA definition uses ≥ 0.1mV for PCI related ECG criteria
- Angiographic evidence of a flow limiting complication, such as loss of patency of a side branch, persistent slow-flow or no re-flow, embolization, or Type C dissection (NHLBI classification) or greater in the target vessel.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

NOTE: A type 4a MI will be diagnosed with a rise in troponin to >70 times the 99th percentile URL (or, when troponin is unavailable, a rise in CK-MB to >10 times the ULN) as a stand-alone criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre- PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

CABG-Related MI (Type 5)

Primary Definition

CK-MB is the preferred serum biomarker and takes precedence over cardiac troponin. For subjects with normal baseline biomarker level pre-CABG, peri-CABG MI requires a rise in CK-MB to >10-fold the ULN (or a rise in troponin to >70 times MI Decision Limit/ULN when CK-MB is unavailable) within 48 hrs post-CABG. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

- A new substantial wall motion abnormality by cardiac imaging (CEC assessed), except new septal and apical abnormalities. The CEC will have latitude in determining whether a new wall motion abnormality is "substantial" in the context of the clinical event.
- New pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB is present on post CABG ECG obtained day 3 post CABG, or hospital discharge, whichever comes earlier in the absence of any intervening coronary event between the time of the CABG procedure and the ECG showing changes.

NOTE: A type 5 MI will be diagnosed with a rise in CK-MB to >15-fold the ULN (or when CK-MB is unavailable a rise in troponin to >100 times the MI Decision Limit/ULN) as a stand-alone criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Secondary Definition

Elevation of troponin values >10 X 99th percentile URL within 48 hrs post-CABG in patients with normal baseline troponin values (≤ 99th percentile URL). If the troponin 99th percentile is not available, the ULN may be used. If troponins are not available, CKMB elevation >10 X ULN will be used. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

- New pathologic Q waves or new LBBB
- Angiographic evidence of new graft or new native coronary artery occlusion.
- Imaging evidence of new loss of viable myocardium.

NOTE: A type 5 MI will be diagnosed with a rise in troponin to >100 times the 99th percentile URL (or when troponin is unavailable a rise in CK-MB to >15 times the ULN) as a stand-alone criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Complicated MI and Large MI

Complicated MI: Prognostically important MIs may also be identified as those with complications such as hemodynamic instability, cardiogenic shock, drop in EF >10% from baseline, electrical instability with life-threatening VT or VF, or heart failure complicating MI. Complicated myocardial infarctions may typically require ICU care, invasive support (eg. intubation, IABP, PA catheters) and intravenous medications (eg. inotropes or antiarrhythmics.) CEC adjudicators will identify complicated MIs based upon the information available to them in the eCRF and source documents.

- Hemodynamic instability: requiring fluids, inotropic or vasopressor support to maintain end-organ perfusion. May progress to shock if also accompanied by end-organ underperfusion.
- Shock: Compromise of end-organ perfusion due to hemodynamic instability and sustained hypotension. Often manifested by hypotension, increased creatinine, shock liver, and decreased mentation.
- Life-threatening VT or VF: Requiring antiarrhythmics or defibrillation to return sinus rhythm. Transient runs of VT (eg. during reperfusion) are not associated with hemodynamic instability are not usually considered life-threatening.
- Decreased EF ≥ 10%: EF assessment during the event which indicates a drop from prior assessments (eg. EF 30% from previous EF 55%)
- HF in the setting of an MI is defined on the basis of the physician's decision to treat HF with an intravenous (IV) diuretic, IV inotropic agent or IV vasodilator and at least 1 of the following:
  - Presence of pulmonary edema or pulmonary vascular congestion on chest radiograph believed to be of cardiac cause.
  - Rales greater than 1/3 up the lung fields believed to be due to HF.
  - Pulmonary Capillary Wedge Pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) greater than 18 mmHg.
  - Dyspnea, with documented paO2 less than 80 mmHg on room air or O2 saturation less than 90% on room air, without significant lung disease

Large MI: The size of MI will be assessed by examining peak levels of cardiac biomarkers as a continuous function.

Hospitalization for Unstable Angina

Prolonged ischemic symptoms at rest (usually ≥10 minutes in duration), or accelerating pattern of chest pain that occurs with a lower activity threshold (CCS class III or IV) considered to be myocardial ischemia upon final diagnosis resulting in an unscheduled visit to a healthcare facility resulting in an overnight stay generally within 24 hours of the most recent symptoms, cardiac biomarkers not meeting MI criteria, and at least one of the following:

- New or worsening ST or T wave changes on resting ECG* (core laboratory assessed)
- Angiographic evidence of a ruptured/ulcerated plaque, or thrombus in an epicardial coronary artery believed to be responsible for the ischemic symptoms/signs (core laboratory assessed).

*ECG Criteria:
ST segment shifts and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads, or new ST segment elevation ≥0.1mV in 2 contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitation and pacemakers.

Resuscitated Cardiac Arrest

Resuscitated cardiac arrest is defined as successful resuscitation for documented cardiac arrest out-of-hospital (or ER) in a patient subsequently admitted to hospital, and then discharged. A patient who is successfully resuscitated but dies before hospital discharge of complications related to the cardiac arrest (e.g., anoxic encephalopathy, septic shock), will be classified as a coronary heart disease death. An uncomplicated procedure-related cardiac arrest with prompt

resuscitation and without adverse sequelae will not be counted as an event. Events that meet the MI criteria will be categorized as MI.

Hospitalization for Heart Failure

While patients may have multiple simultaneous disease processes, for the end point event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary process. Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that result in at least a 24 hour stay (or a date change if the time of admission/discharge is not available).

AND

b. Clinical symptoms of heart failure, including at least one of the following: New or worsening
   - Dyspnea
   - Orthopnea
   - Paroxysmal nocturnal dyspnea
   - increasing fatigue/worsening exercise tolerance

AND

c. Physical signs of heart failure, including at least two of the following:
   1. Edema (> 2+ lower extremity)
   2. Pulmonary rales (pulmonary edema not occurring as the consequence of an arrhythmia in the absence of worsening heart failure. If pulmonary edema complicates acute MI event should be coded as MI)
   3. Jugular venous distension
   4. Tachypnea (respiratory rate > 20 breaths/minute)
   5. Rapid weight gain
   6. S3 gallop
   7. Increasing abdominal distension or ascites
   8. Hepatojugular reflux
   9. Radiological evidence of worsening heart failure
   10. A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg and/or a cardiac output < 2.2 L/min/m2

NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)> 500 or Pro-NT BNP > 2500) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity).

AND

d. Need for additional/increased therapy

Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least one of the following:

1. Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure
2. Initiation of intravenous diuretic, inotrope, or vasodilator therapy
3. Uptitration of intravenous therapy, if already on therapy
4. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

AND

e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms are identified.

Stroke

Stroke is defined as the rapid onset of a new neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (eg. trauma, tumor, or infection). 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.

Classification:

Transient Ischemic Attack

A Transient Ischemic Attack is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an ischemia of central nervous system tissue which resolves within 24 hrs and without neuroimaging evidence of acute infarction.

Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Signs/ symptoms $\geq$ 24 hrs regardless of neuroimaging findings:

Ischemic stroke can be defined clinically- by persistence of signs and symptoms $\geq$ 24 hrs, usually supported by evidence of infarction on neuroimaging (CT or MRI) although very early neuroimaging (usually with CT) may not demonstrate the infarction.

Signs/ symptoms < 24 hrs with neuroimaging evidence of infarction:

Ischemic stroke can be defined by neuroimaging- where neuroimaging (usually MRI diffusion weighted or flair images) confirms the presence of acute infarction even if signs/ symptoms resolve within 24 hrs.

Patients admitted for an acute stroke treated with thrombolysis or interventions that have no residual neurologic symptoms after treatment will be classified as an ischemic stroke.

Ischemic Stroke with Symptomatic Hemorrhagic Conversion

Hemorrhagic conversion may be a consequence of ischemic stroke and may be symptomatic, resulting in neurologic deterioration, or asymptomatic. Symptomatic Hemorrhagic Conversion is defined neuroimaging evidence of hemorrhage within the area of infarction associated with clinical

deterioration (eg. increase in NIHSS of ≥ 4 points) or death, symptoms to hemorrhage related mass effect, or symptoms out of proportion to what would be expected from the ischemic stroke or cerebral edema alone. When an Ischemic Stroke with Symptomatic Hemorrhagic Conversion is identified, the date and time of stroke onset will refer to the first onset of the Ischemic Stroke and will not be counted as two events.

Hemorrhagic Stroke
Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined- or Uncertain type- of Stroke
Undetermined stroke is defined as a stroke with insufficient information to allow categorization as Ischemic Stroke or Hemorrhagic Stroke. If possible, speculate on the stroke subtype and note in Comments. This is not to signify an indeterminate event where there is insufficient evidence to suspect a stroke had occurred.

Sample Size and Power Calculations

ISCHEMIA-CKD was originally designed to randomize approximately 1,000 participants. The sample size was estimated to provide 80-95% power to detect a 15% to 19% relative reduction in the primary composite Outcome assuming the 4-year cumulative rate of the primary composite Outcome is 50-70% in participants randomized to the conservative strategy. The projected event rate for the primary composite Outcome in the conservative strategy participants was based on multiple observational studies although none enrolled precisely the cohort under consideration. The sample size was revised to 650 participants (range 500-700) due to slow recruitment. The final sample size of 777 participants provided approximately 80% power to detect a 22% to 24% relative reduction in the primary outcome assuming an aggregate 4-year rate of 41% to 48% and accrual of 240 to 270 primary outcome events.

IV. Supplementary Tables

Table S1. ISCHEMIA and ISCHEMIA-CKD: Differences in Trial Design

Parameter	ISCHEMIA	ISCHEMIA-CKD
Inclusion Criteria	eGFR ≥30	eGFR <30 or on dialysis
Coronary CT Angiography required prior to randomization	Yes (in those with eGFR >60)	No
Core lab review of stress test	Yes	No
Primary Outcome	Cardiovascular death, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest	Death or myocardial infarction
Invasive Strategy guidelines	Recommendation for coronary angiography, revascularization, FFR use and heart team	Similar to ISCHEMIA + recommendation to minimize risk of acute kidney injury and involvement of heart-kidney team
Conservative Strategy guidelines	Algorithm for angina, hypertension and LDL-C management (high intensity statins)	Similar to ISCHEMIA + moderate or high intensity statins in those on dialysis; renal dosing of medications
PACE lifestyle counseling	Full PACE counseling	The recommendations provided in the PACE guidelines on fluid and fruit intake may not apply to CKD participants especially if they are on dialysis. CKD participants should follow the recommendation of their nephrologist.
Quality of Life (QOL) and Economics	Brief QoL and full QoL collected Medical billing data collected	Only brief QoL collected Medical billing data not collected for ISCHEMIA CKD participants
First participant randomized	August 7, 2012	May 12, 2014

Table S2. Industry Support

MEDICATIONS AND DEVICES PROVIDED BY INDUSTRY		
Company Name	**Product**	**Country**
Abbott, Abbott Vascular	XIENCE Everolimus Eluting Coronary Stent System	ALL
Abbott (previously St. Jude Medical)	PressureWire™ Certus and PressureWire™ Aeris; RadiAnalyzer™ Xpress Measurement System	Argentina; Australia; Austria; Belgium; Brazil; Canada; China; Egypt; France; Hungary; India; Israel; Lithuania; Malaysia; Netherlands; New Zealand; Poland; Russia; Saudi Arabia; Serbia; Singapore; South Africa; Spain; Taiwan; Thailand; UK; United Arab Emirates; USA
Arbor Pharmaceuticals	Nitrolingual® Pumpspray (nitroglycerin lingual spray)	Canada *(distributor Pohl Boskamp);* USA
	Edarbi® (azilsartan medoxomil)	USA
	Edarbyclor® (azilsartan medoxomil/chlorthalidone)	USA
AstraZeneca	Crestor® (rosuvastatin calcium) Brilinta® (ticagrelor)	Brazil; Canada; China; Mexico;Singapore;USA
Espero Pharmaceuticals	GoNitro™ (nitroglycerin) sublingual powder	USA
Medtronic	Resolute Integrity DES	ALL
Merck & Co.	Zetia® (ezetimibe) Vytorin® (ezetimibe and simvastatin)	Argentina; Brazil; USA
Omron	Pedometers	ALL
Philips (previously Volcano Corporation)	Prime Wire Prestige PLUS Imaging Consoles	Austria, Belgium, Canada, France, Germany, Italy, Japan, Netherlands, Poland, Portugal, South Africa, Spain, Sweden, UK, USA
Sunovion Pharmaceuticals	Niaspan® (extended-release niacin)	Canada

Table S3. Ischemia Eligibility Criteria by Stress Test Modality

Stress Test Modality	Diagnostic Criteria for Moderate or Severe Ischemia
Nuclear perfusion via SPECT or PET	≥10% myocardium ischemic[1]
Echocardiography	≥3/16 segments with stress-induced severe hypokinesis or akinesis
Cardiac Magnetic Resonance	Perfusion: ≥12% myocardium ischemic, and/or Wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis
Exercise Test without Imaging (criteria 1-3 must all be met)	1. Absence of resting ST-segment depression ≥1.0 mm or confounders that render exercise ECG non-interpretable (LBBB, LVH with repolarization, pacemaker, etc.) 2. As compared to the baseline tracing, additional exercise-induced horizontal or downsloping ST-segment depression ≥1.5 mm in 2 leads *or* ≥2.0 mm in any lead; ST-segment elevation ≥1mm in a non-infarct territory. Both the J-point and the ST-segment at 80 msec need to meet criteria. When the HR is >130/min, the ST-segment at 60 msec. may be used if the segment at 80 msec. cannot be determined. 3. Either of the following: a. Workload at which ST-segment criteria are met is not to exceed completion of stage 2 of a standard Bruce protocol or 7 METs if a non-Bruce protocol is used *or* b. ST segment criteria are met at <75% of the maximum predicted HR

Table S4. Inclusion and Exclusion Criteria

Inclusion Criteria	• At least moderate ischemia on an exercise or pharmacologic stress test • End-stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2 • Willingness to comply with all aspects of the protocol, including adherence to the assigned strategy, medical therapy and follow-up visits • Willingness to give written informed consent • Age ≥ 21 years
Exclusion Criteria	• Left ventricular ejection fraction < 35% • History of unprotected left main stenosis ≥50% on prior coronary computed tomography angiography (CCTA) or prior cardiac catheterization (if available) • Finding of "no obstructive coronary artery disease " (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months • Coronary anatomy unsuitable for either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) • Unacceptable level of angina despite maximal medical therapy • Very dissatisfied with medical management of angina • History of noncompliance with medical therapy • Acute coronary syndrome within the previous 2 months • PCI within the previous 12 months • Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time • History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause • NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months • Non-ischemic dilated or hypertrophic cardiomyopathy • Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial

- Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast
- Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery)
- Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity
- Pregnancy
- High likelihood of significant unprotected left main stenosis, in the judgment of the patient's physician
- Enrollment in a competing trial that involves a non-approved cardiac drug or device
- Inability to comply with the protocol
- Body weight or size exceeding the limit for cardiac catheterization at the site
- Canadian Cardiovascular Society Class III angina of recent onset, OR angina of any class with a rapidly progressive or accelerating pattern
- Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina
- High risk of bleeding which would contraindicate the use of dual antiplatelet therapy
- Cardiac transplant recipient
- Prior CABG, unless CABG was performed more than 12 months ago, and coronary anatomy has been demonstrated to be suitable for PCI or repeat CABG to accomplish complete revascularization of ischemic areas

Table S5. Baseline and On-Trial Physiologic Measurements, Risk Factors, and Medications by Treatment Group

Variables	Baseline Total (N=777)	Last Visit Total (N=777)	Baseline INV (N=388)	Baseline CON (N=389)	Last Visit INV (N=388)	Last Visit CON (N=389)
Systolic BP <140 mm Hg	55.3% (429/776)	68.6% (450/656)	54.3% (210/387)	56.3% (219/389)	67.5% (214/317)	69.6% (236/339)
LDL cholesterol <70 mg/dl	34.9% (254/727)	49.4% (298/603)	35.1% (126/359)	34.8% (128/368)	49.1% (144/293)	49.7% (154/310)
Not smoking	89.2% (693/777)	92.1% (580/630)	88.1% (342/388)	90.2% (351/389)	90.6% (278/307)	93.5% (302/323)
Medications						
Aspirin or aspirin alternative	83.2% (616/740)	87.4% (548/627)	84.2% (314/373)	82.3% (302/367)	87.7% (265/302)	87.1% (283/325)
Clopidogrel	22.6% (175/776)	26.4% (175/664)	23.0% (89/387)	22.1% (86/389)	29.1% (94/323)	23.8% (81/341)
Anticoagulant	10.4% (79/763)	10.3% (68/661)	9.5% (36/379)	11.2% (43/384)	11.2% (36/322)	9.4% (32/339)
Antiplatelet or anticoagulant	100% (652/652)	100% (585/585)	100% (328/328)	100% (324/324)	100% (286/286)	100% (299/299)
Statin	81.1% (629/776)	85.2% (566/664)	81.7% (316/387)	80.5% (313/389)	87.0% (281/323)	83.6% (285/341)
High-intensity statin	32.4% (203/626)	43.2% (259/600)	35.0% (110/314)	29.8% (93/312)	45.6% (136/298)	40.7% (123/302)
Ezetimibe	3.5% (27/776)	18.4% (122/664)	4.1% (16/387)	2.8% (11/389)	19.5% (63/323)	17.3% (59/341)
ACE inhibitor / ARB	47.7% (370/776)	42.6% (283/664)	47.5% (184/387)	47.8% (186/389)	41.8% (135/323)	43.4% (148/341)
Adherence to Medications[1]	64.1% (479/747)	73.1% (469/642)	63.2% (234/370)	65.0% (245/377)	71.7% (226/315)	74.3% (243/327)

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blockers; BP= blood pressure; CON= conservative; INV= invasive; LDL= low density lipoprotein. Aspirin alternative denotes P2Y12 inhibitor. Antiplatelet denotes aspirin or P2Y12 inhibitor. [1]Based on Morisky-Green-Levine medication adherence survey (Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical Care 1986;24:67-74). A summary binary variable was created by coding those who responded strongly agree, agree, don't know, or refuse to any of the 4 questions in the survey as nonadherent; otherwise, patients were coded as adherent.

Table S6. Coronary Angiography and Revascularization in the Invasive Strategy

Parameter	Invasive (N=388)
Angiographic Characteristics	
Number of Native Vessels With ≥50% Stenosis (QCA)	
0	26.5% (82/310)
1	22.3% (69/310)
2	28.1% (87/310)
3	23.2% (72/310)
Specific Native Vessels With ≥ 50% Stenosis (QCA)	
Left main	2.5% (8/326)
Left Anterior Descending	57.2% (183/320)
Proximal Left Anterior Descending	21.2% (69/326)
Left Circumflex	44.4% (143/322)
Right Coronary Artery	45.4% (142/313)
FFR use	19.3% (62/321)
Revascularization Characteristics	
PCI	84.7% (161/190)
Stent use	91.9% (148/161)
DES use	100% (146/146)
Second Generation DES	97.9% (143/146)
First Generation DES	2.1% (3/146)
Stent not deliverable	4.3% (7/161)
Balloon angioplasty only	3.1% (5/161)
CABG	15.3% (29/190)
IMA use	86.2% (25/29)
Reasons for No Coronary Angiography (site-reported)	64 (16.5%)
Intercurrent Illness	21.9% (14/64)
Participant Died	9.4% (6/64)
Patient Preference	37.5% (24/64)
Physician Preference	9.4% (6/64)
Other	14.1% (9/64)
Missing or Unknown	7.8% (5/64)
Reasons for No Revascularization During Follow-up (site-reported)	
Medical Therapy Only	95.5% (128/134)
No Obstructive Coronary Artery Disease	75.4% (101/134)
Anatomy Not Suitable for Any Mode of Revascularization	14.2% (19/134)
Patient Preference	3.0% (4/134)
Other	3.0% (4/134)
Intent to Perform PCI / CABG / Hybrid	3.7% (5/134)
Unknown	0.7% (1/134)

CABG=coronary artery bypass graft surgery; DES=drug eluting stent; FFR=fractional flow reserve; IMA= internal mammary graft; IMA=internal mammary artery; PCI=percutaneous coronary intervention; QCA= quantitative coronary angiography.

Table S7. Outcomes based on Secondary Definition of Myocardial Infarction

Outcome	Number of Subjects with Event		3-year Cumulative Incidence Rates		Hazard Ratio Invasive vs. Conservative (95% CI)	
	Invasive	Conservative	Invasive	Conservative	Unadjusted	Adjusted
All-cause Death or myocardial infarction	134	133	38.7% (32.9%, 44.5%)	37.6% (32.0%, 43.3%)	1.07 (0.85, 1.37)	1.10 (0.86, 1.40)
All-cause Death, myocardial infarction, Hospitalization for Unstable Angina or Heart Failure, or Resuscitated Cardiac Arrest	142	142	40.6% (34.7%, 46.4%)	40.6% (34.8%, 46.3%)	1.07 (0.85, 1.35)	1.09 (0.87, 1.38)
All-cause Death, myocardial infarction, or stroke	143	135	41.5% (35.5%, 47.4%)	37.9% (32.2%, 43.5%)	1.16 (0.91, 1.46)	1.19 (0.94, 1.50)
Myocardial infarction	67	60	20.4% (15.9%, 25.4%)	16.9% (13.0%, 21.3%)	1.19 (0.84, 1.69)	1.19 (0.84, 1.69)
Procedural myocardial infarction	28	11	7.3% (5.0%, 10.2%)	3.1% (1.6%, 5.4%)	2.69 (1.34, 5.39)	2.87 (1.42, 5.79)
Non procedural myocardial infarction	37	52	12.7% (8.8%, 17.3%)	14.2% (10.6%, 18.3%)	0.73 (0.48, 1.12)	0.72 (0.47, 1.09)

Table S8. Rate of Revascularization in ACS trials of Invasive vs. Conservative which Randomized Participants Prior to Defining Coronary Anatomy

Trial	% Revascularization in Invasive Arm
RITA-3	44%
VANQUISH	44%
After Eighty	50%
Italian Elderly ACS	56%
OASIS 5	58%
MATE	58%
TACTICS TIMI 18	60%
FRISC II	77%
ICTUS	76%

ACS= acute coronary syndrome.

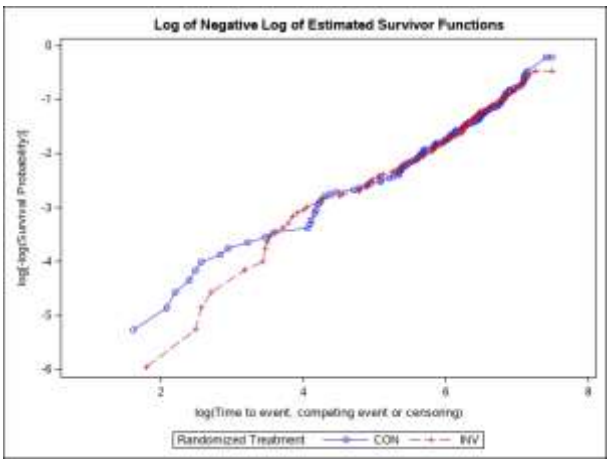
V. Supplementary Figures

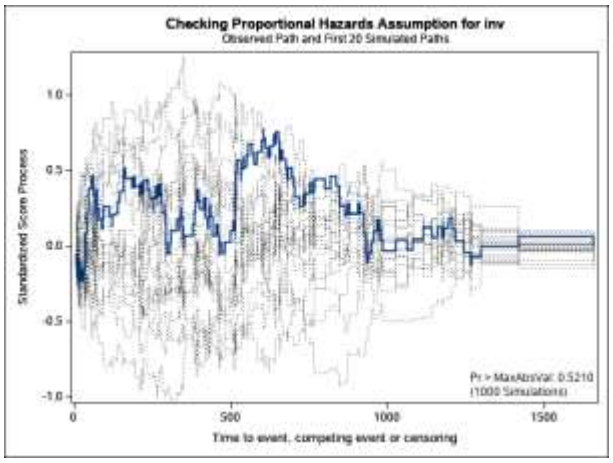
Figure S1. Assessment of Proportional Hazards Assumption for Treatment Effect

Results of tests for log(time) by treatment interactions by Outcome

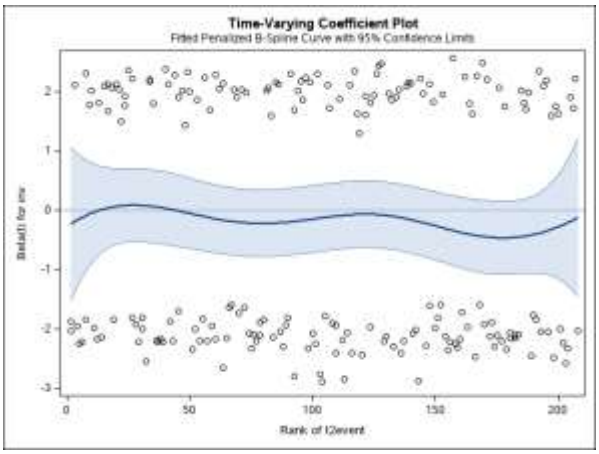
Outcome	P-Value
Death or MI	0.598
All-cause death / MI / UA / HF / RCA	0.379
All-cause death	0.661
Primary MI	0.748
Hospitalization for Unstable Angina	0.999
Hospitalization for Heart Failure	0.917

Primary Outcome (Death or MI)



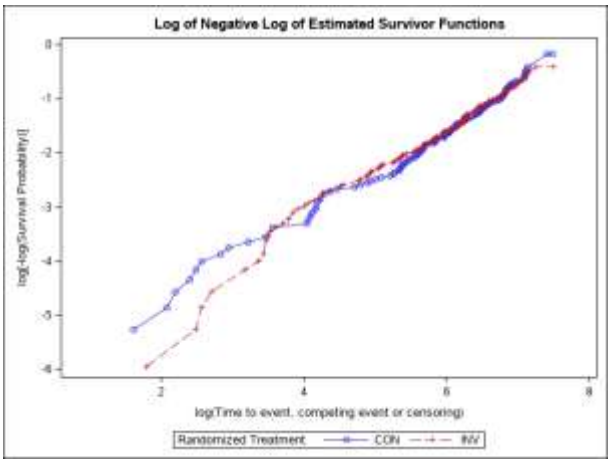


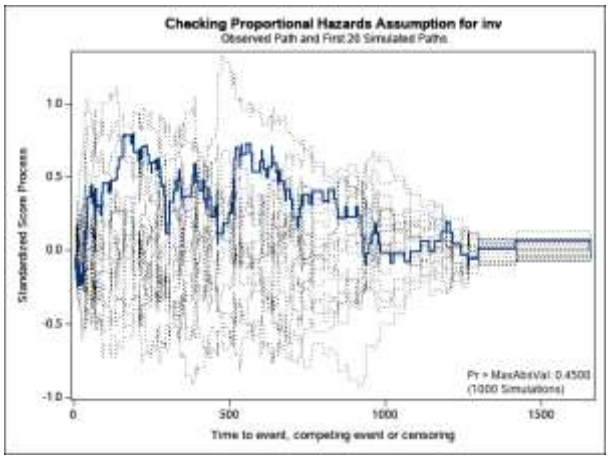
Plot of simulated empirical score processes under proportional hazards (dotted lines) and observed empirical score process (solid line). The probability that the maximum score under proportional hazards is greater than the observed maximum score is shown in the lower right corner of the plot. This can be interpreted as a p-value testing for whether the proportional hazards assumption is violated.



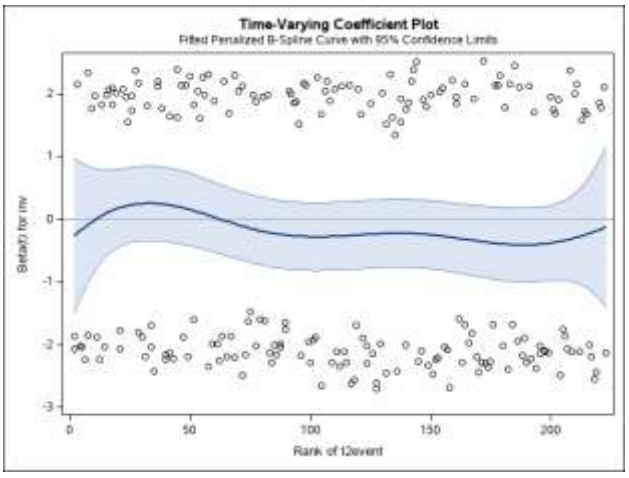
Plot of weighted Schoenfeld residuals by the ordered rank of times when events occurred. The weighted Schoenfeld residuals are plotted as small circles. A penalized B-Spline curve with its 95% Confidence Limits for the weighted Schoenfeld residuals is fit. The further the overall slope of the spline is from being a horizontal line, the more evidence against the proportional hazards assumption.

Major Secondary Outcome



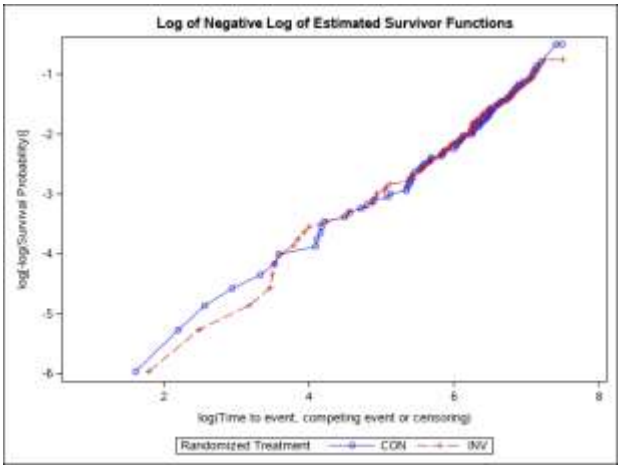


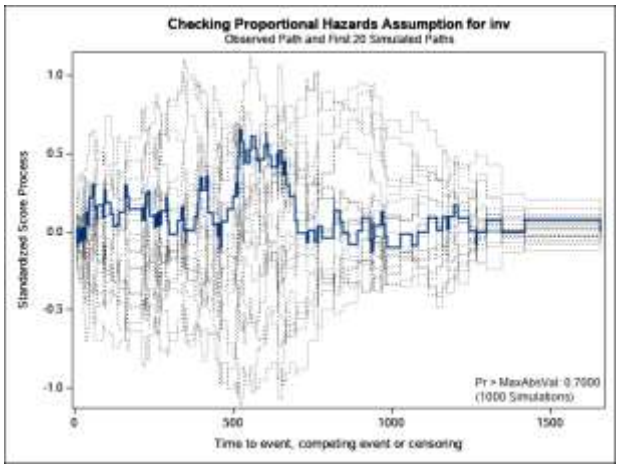
Plot of simulated empirical score processes under proportional hazards (dotted lines) and observed empirical score process (solid line). The probability that the maximum score under proportional hazards is greater than the observed maximum score is shown in the lower right corner of the plot. This can be interpreted as a p-value testing for whether the proportional hazards assumption is violated.



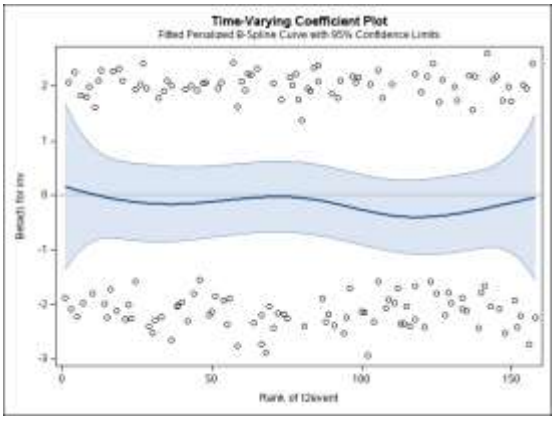
Plot of weighted Schoenfeld residuals by the ordered rank of times when events occurred. The weighted Schoenfeld residuals are plotted as small circles. A penalized B-Spline curve with its 95% Confidence Limits for the weighted Schoenfeld residuals is fit. The further the overall slope of the spline is from being a horizontal line, the more evidence against the proportional hazards assumption.

Outcome: All-cause Death



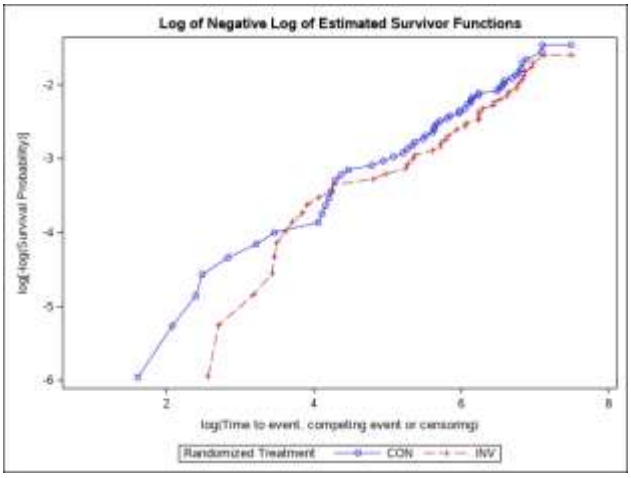


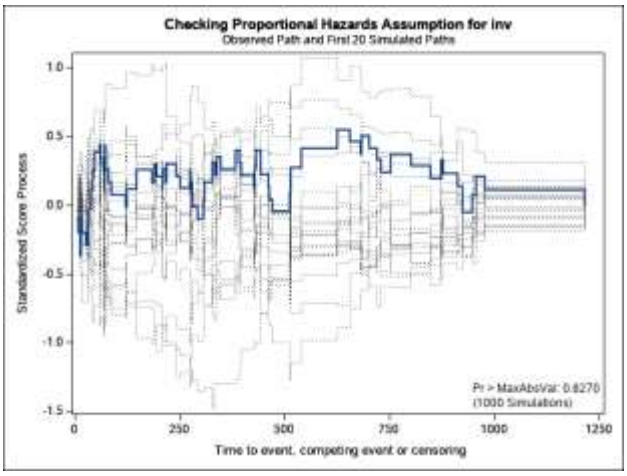
Plot of simulated empirical score processes under proportional hazards (dotted lines) and observed empirical score process (solid line). The probability that the maximum score under proportional hazards is greater than the observed maximum score is shown in the lower right corner of the plot. This can be interpreted as a p-value testing for whether the proportional hazards assumption is violated.



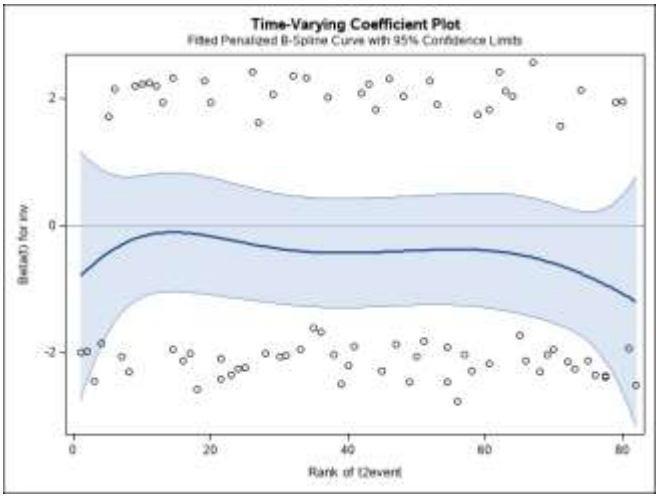
Plot of weighted Schoenfeld residuals by the ordered rank of times when events occurred. The weighted Schoenfeld residuals are plotted as small circles. A penalized B-Spline curve with its 95% Confidence Limits for the weighted Schoenfeld residuals is fit. The further the overall slope of the spline is from being a horizontal line, the more evidence against the proportional hazards assumption.

Outcome: Myocardial Infarction



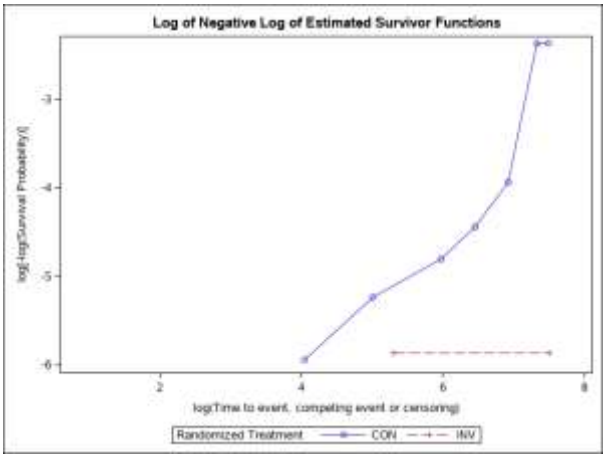


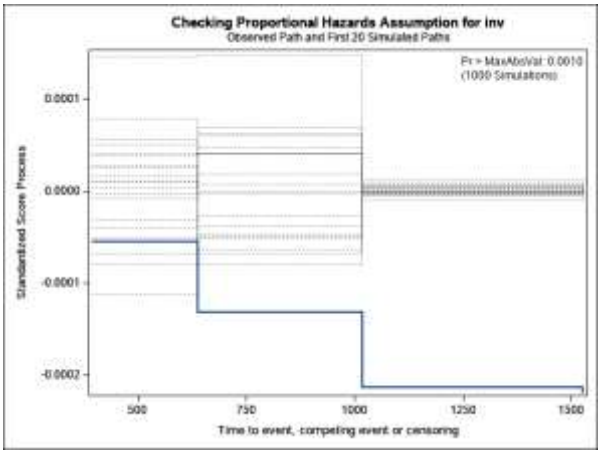
Plot of simulated empirical score processes under proportional hazards (dotted lines) and observed empirical score process (solid line). The probability that the maximum score under proportional hazards is greater than the observed maximum score is shown in the lower right corner of the plot. This can be interpreted as a p-value testing for whether the proportional hazards assumption is violated.



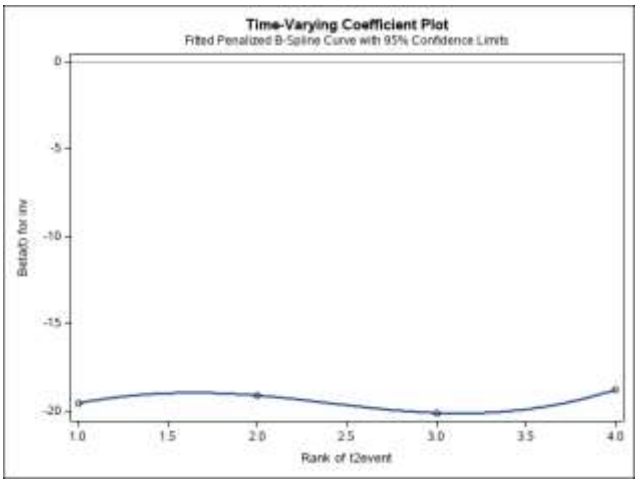
Plot of weighted Schoenfeld residuals by the ordered rank of times when events occurred. The weighted Schoenfeld residuals are plotted as small circles. A penalized B-Spline curve with its 95% Confidence Limits for the weighted Schoenfeld residuals is fit. The further the overall slope of the spline is from being a horizontal line, the more evidence against the proportional hazards assumption.

Outcome: Hospitalization for Unstable Angina



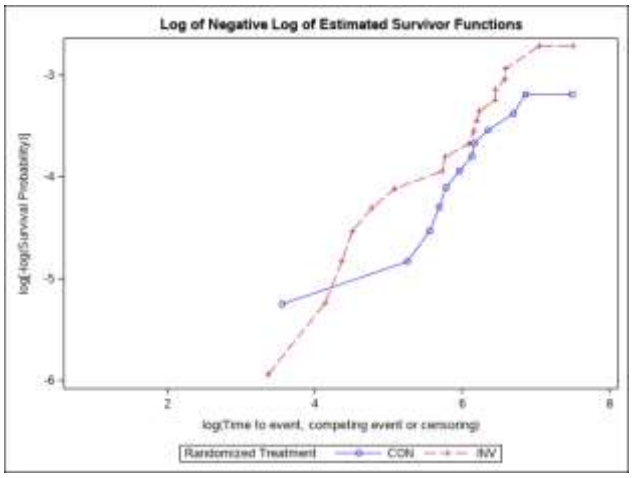


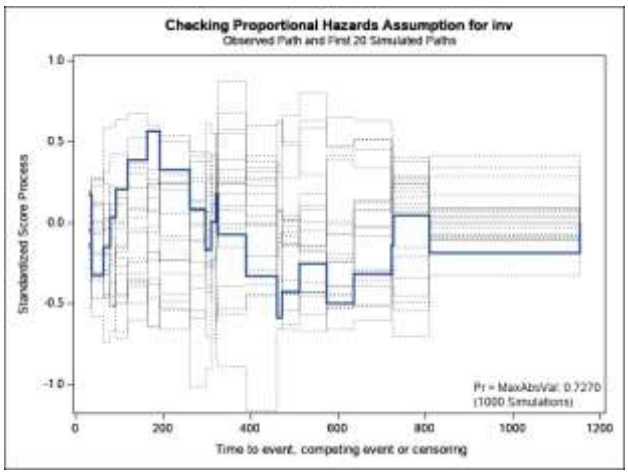
Plot of simulated empirical score processes under proportional hazards (dotted lines) and observed empirical score process (solid line). The probability that the maximum score under proportional hazards is greater than the observed maximum score is shown in the upper right corner of the plot. This can be interpreted as a p-value testing for whether the proportional hazards assumption is violated.



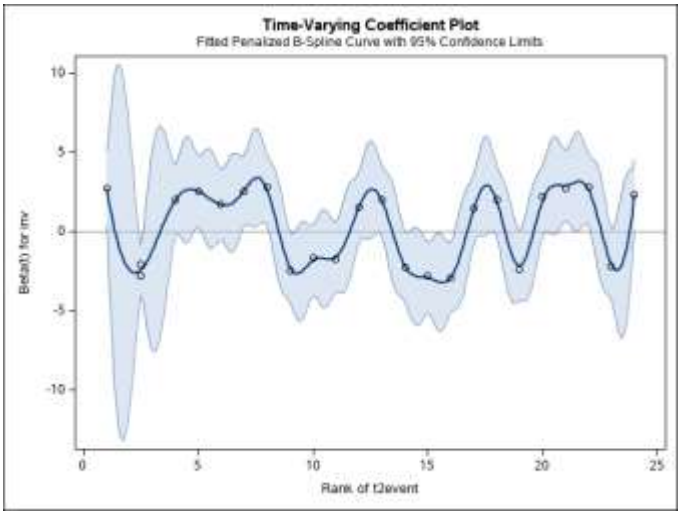
Plot of weighted Schoenfeld residuals by the ordered rank of times when events occurred. The weighted Schoenfeld residuals are plotted as small circles. A penalized B-Spline curve with its 95% Confidence Limits for the weighted Schoenfeld residuals is fit. The further the overall slope of the spline is from being a horizontal line, the more evidence against the proportional hazards assumption.

Outcome: Hospitalization for Heart Failure





Plot of simulated empirical score processes under proportional hazards (dotted lines) and observed empirical score process (solid line). The probability that the maximum score under proportional hazards is greater than the observed maximum score is shown in the lower right corner of the plot. This can be interpreted as a p-value testing for whether the proportional hazards assumption is violated.



Plot of weighted Schoenfeld residuals by the ordered rank of times when events occurred. The weighted Schoenfeld residuals are plotted as small circles. A penalized B-Spline curve with its 95% Confidence Limits for the weighted Schoenfeld residuals is fit. The further the overall slope of the spline is from being a horizontal line, the more evidence against the proportional hazards assumption.

Figure S2. Participant Flow

Proportion of patients in the conservative strategy who underwent coronary angiography or revascularization prior to an outcome event were 77 (19.8%) and 43 (11.0%) respectively.

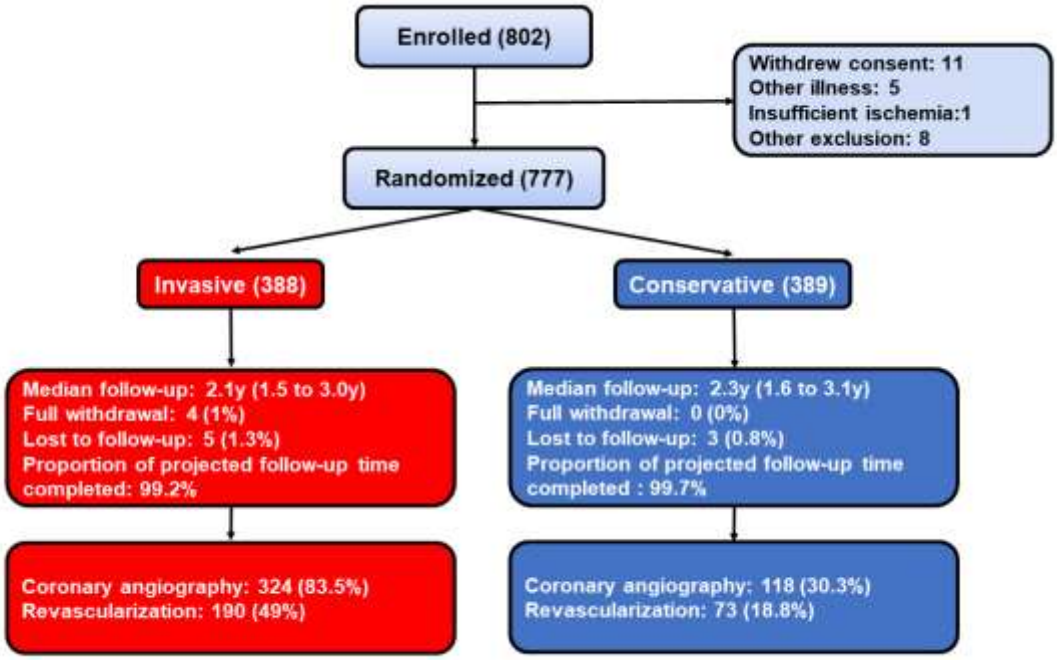
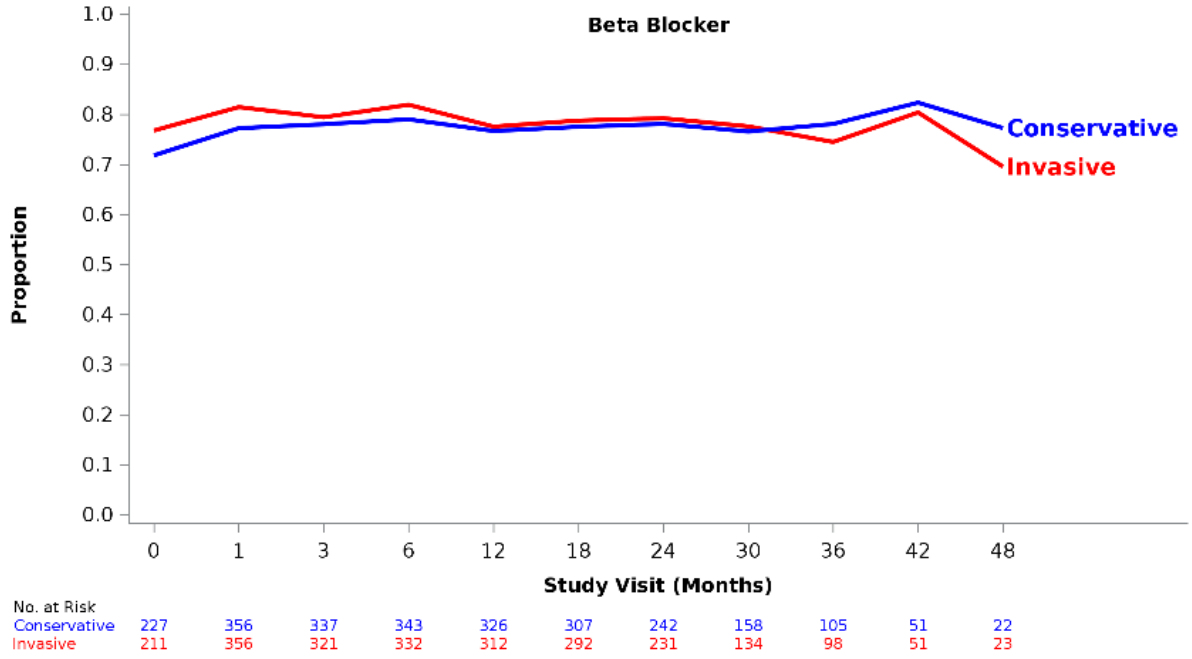
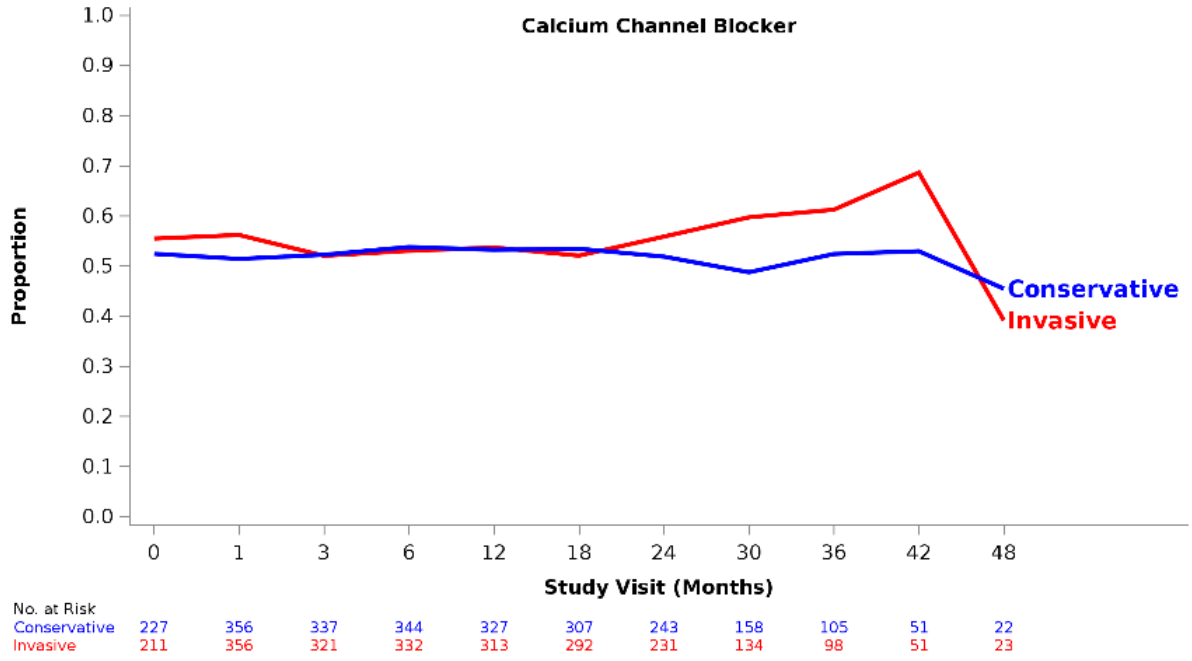
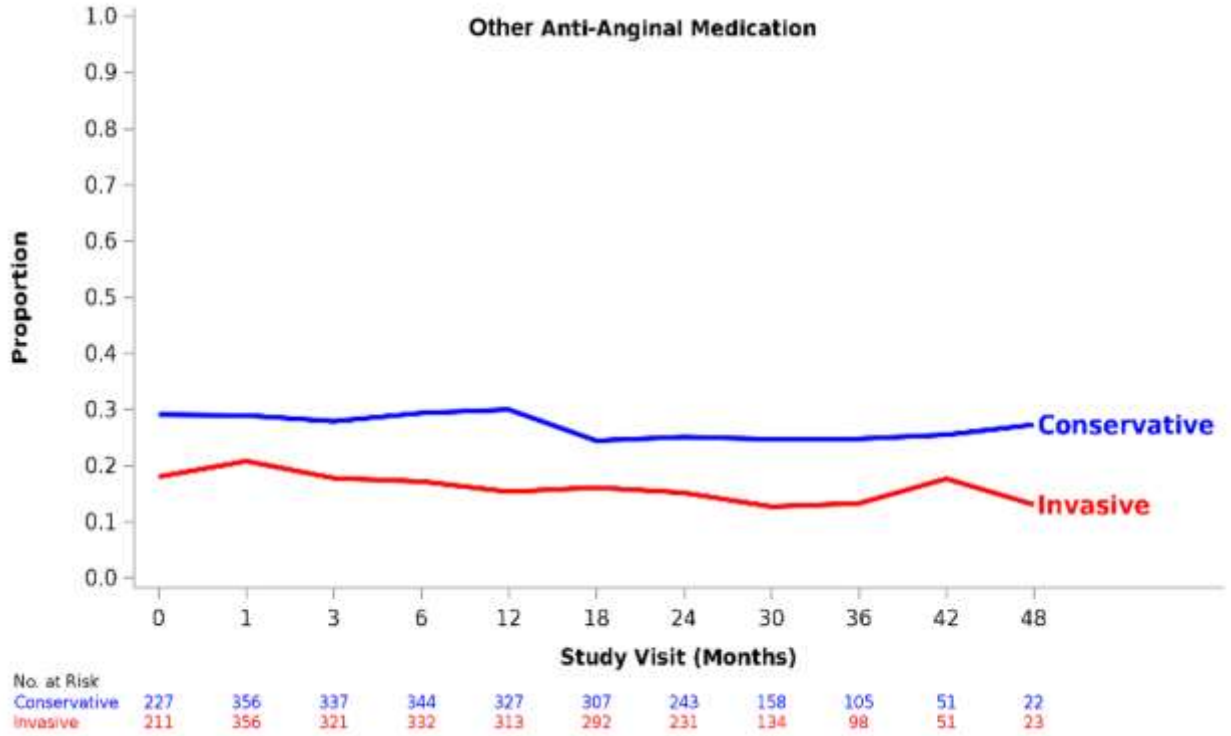


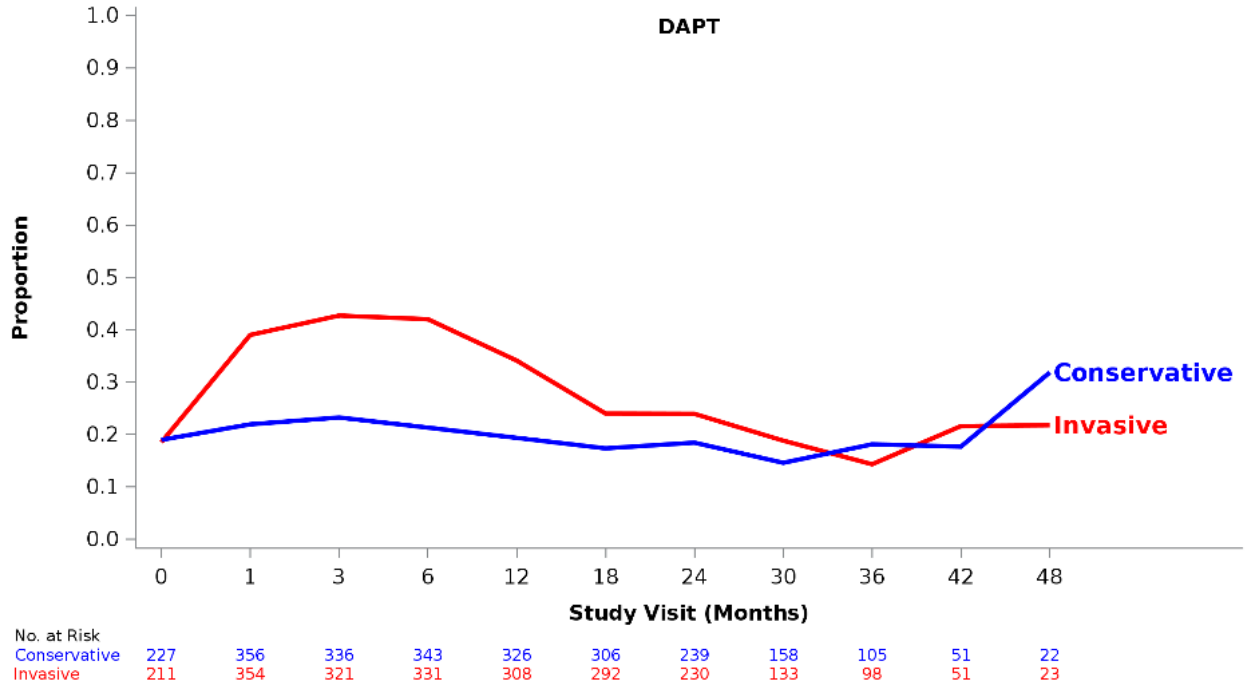
Figure S3. Select Medications Use over Time by Treatment Group

CCBs= calcium channel blockers; DAPT= dual antiplatelet therapy

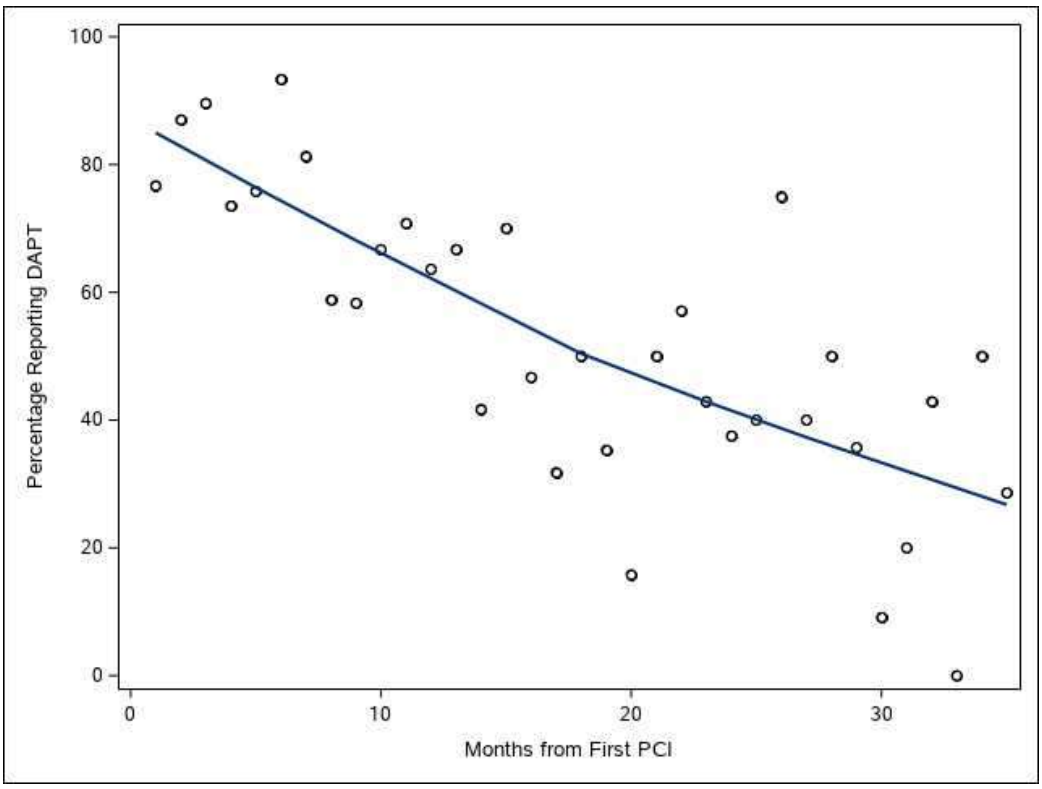





Other Anti-Anginal Medication
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Conservative
Invasive
0
1
3
6
12
18
24
30
36
42
48
Study Visit (Months)
No. at Risk
Conservative 227 356 337 344 327 307 243 158 105 51 22
Invasive 211 356 321 332 313 292 231 134 98 51 23


DAPT
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Conservative
Invasive
0
1
3
6
12
18
24
30
36
42
48
Study Visit (Months)
No. at Risk
Conservative 227 356 336 343 326 306 239 158 105 51 22
Invasive 211 354 321 331 308 292 230 133 98 51 23

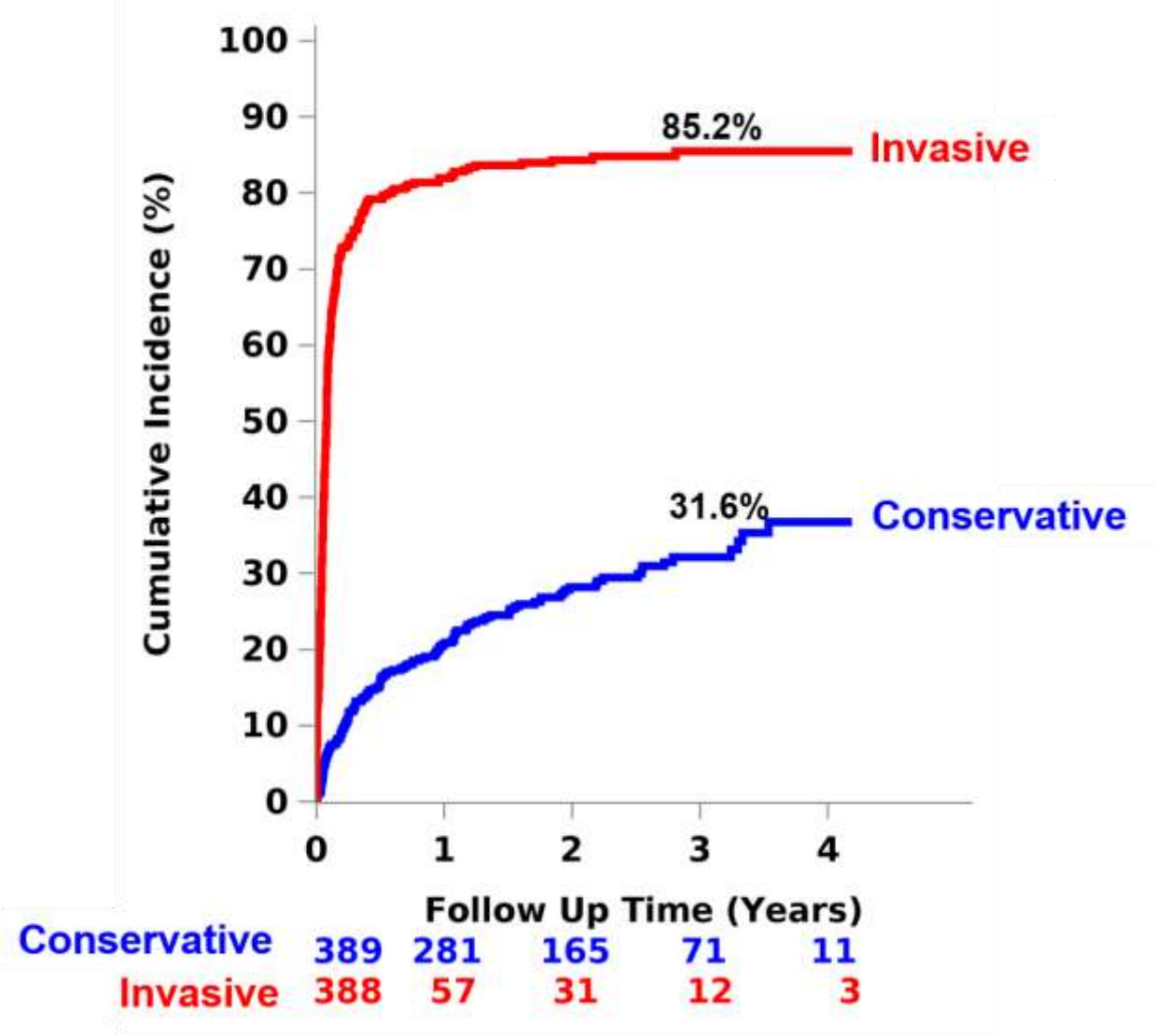
DAPT use in patients who underwent PCI in the Invasive group



Due to timing of visits when current medication use was collected and varying DAPT duration, it does not reflect 100% DAPT use which we believe was universal. Collection of information at follow-up visits may have occurred after completion of prescribed course of DAPT.

Figure S4. Cumulative Incidence Plot of First Cardiac Catheterization and First Revascularization by Treatment Group

S4a. Coronary Angiography



S4b. Revascularization

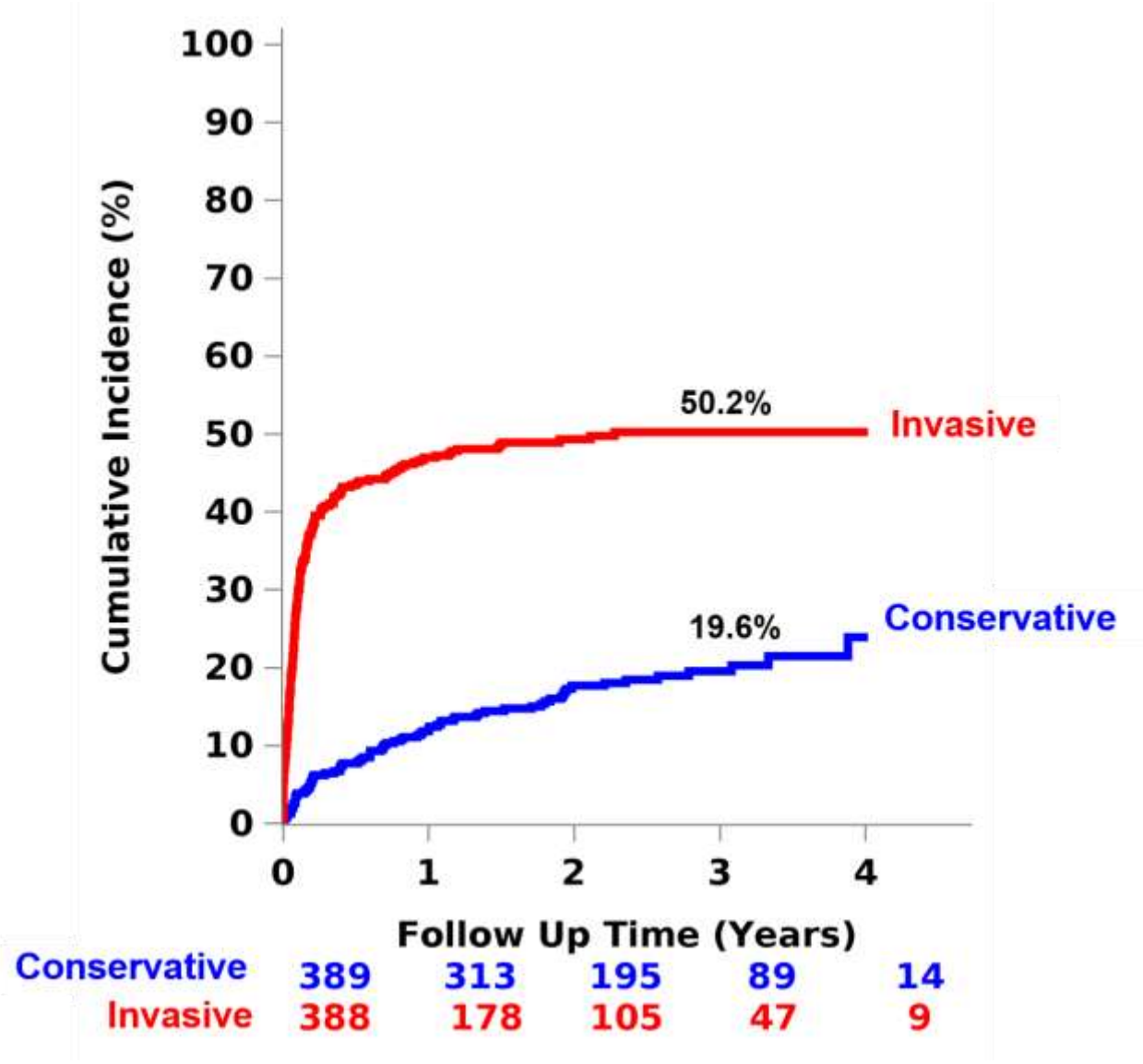


Figure S5. Reasons for Coronary Angiography and Revascularization at 3 Years in the Conservative Group

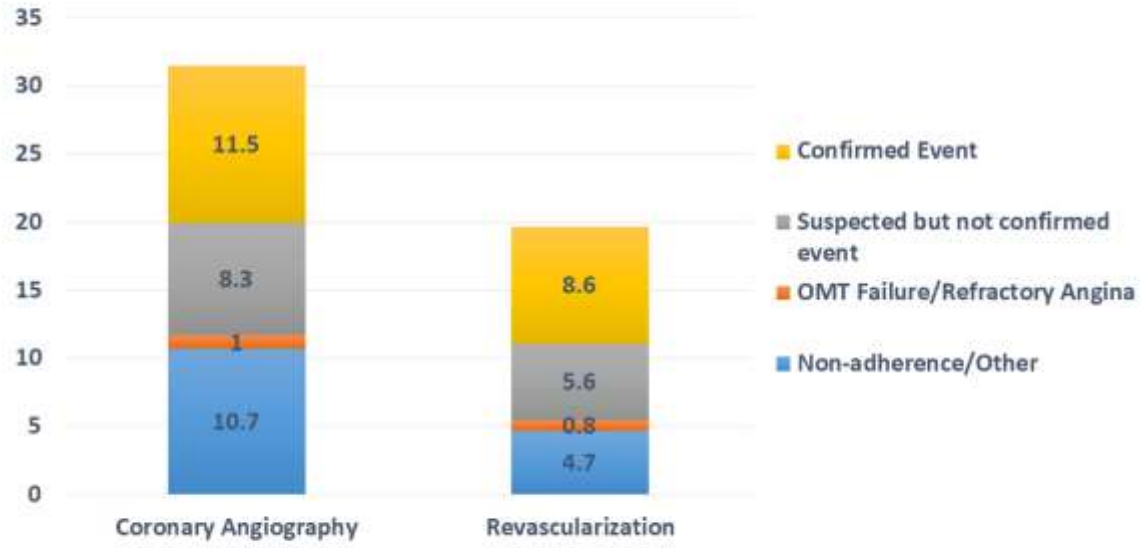
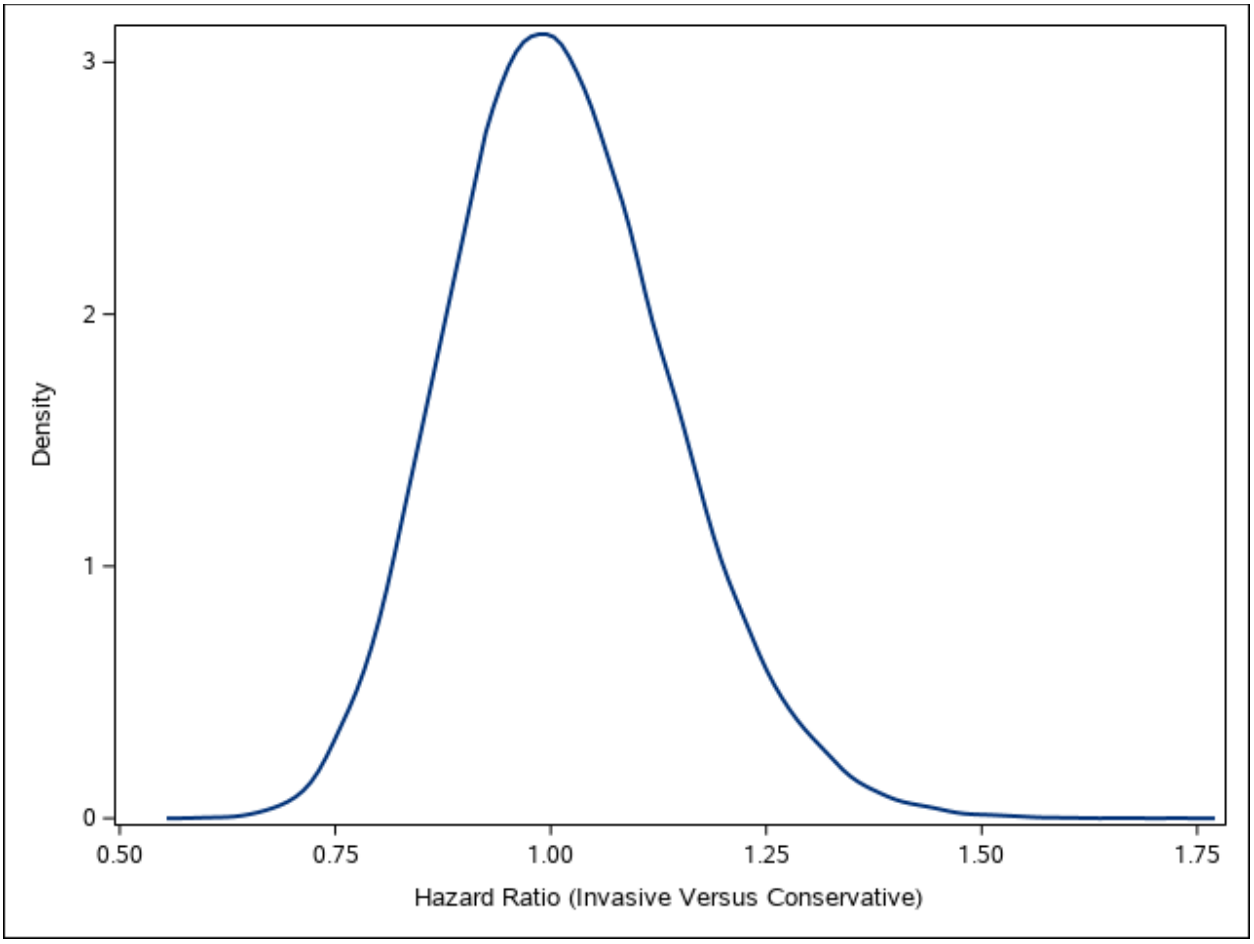


Figure S6. Posterior distribution for the Bayesian analysis for the primary outcome



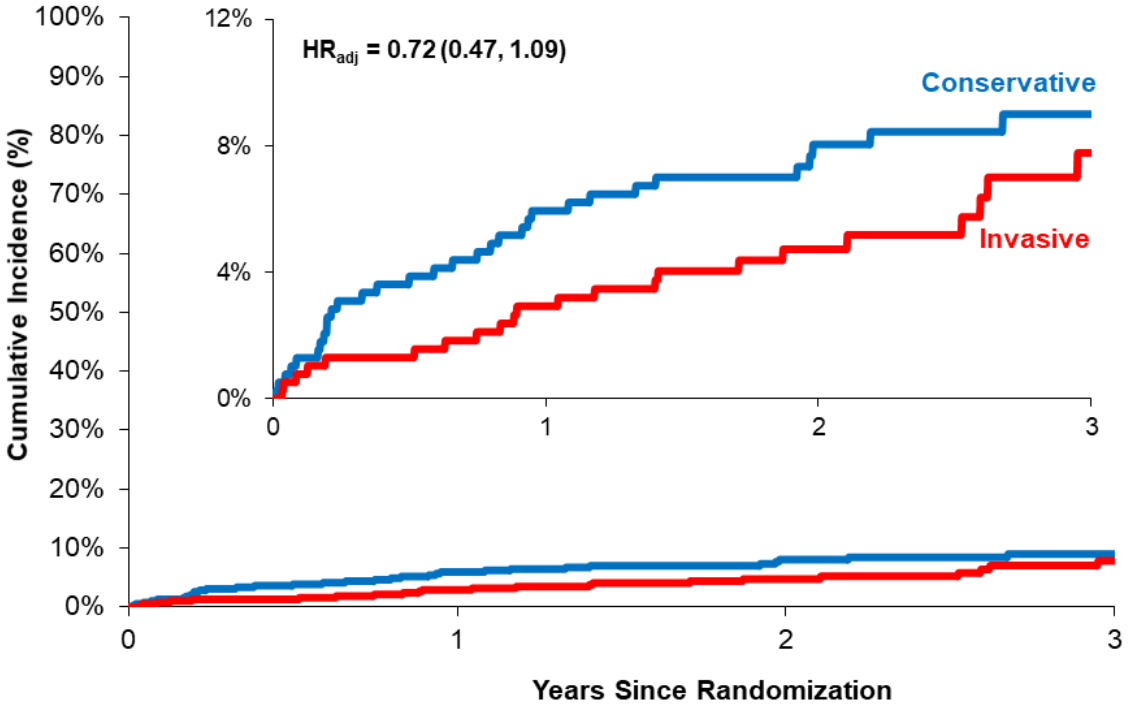
Interpretation: The post-trial probability that the true adjusted hazard ratio is between two number, say a and b, is proportional to the area under the curve between a and b on the x-axis.

References:

- Kalbfleisch JD. Non-parametric Bayesian analysis of survival time data. Journal of the Royal Statistical Society: Series B. 1978 Jan;40(2):214-21.
- Sinha D, Ibrahim JG, Chen MH. A Bayesian justification of Cox's partial likelihood. Biometrika. 2003 Sep 1;90(3):629-41.

Figure S7. Cumulative Incidence Plot of Non Procedural MI and Procedural MI

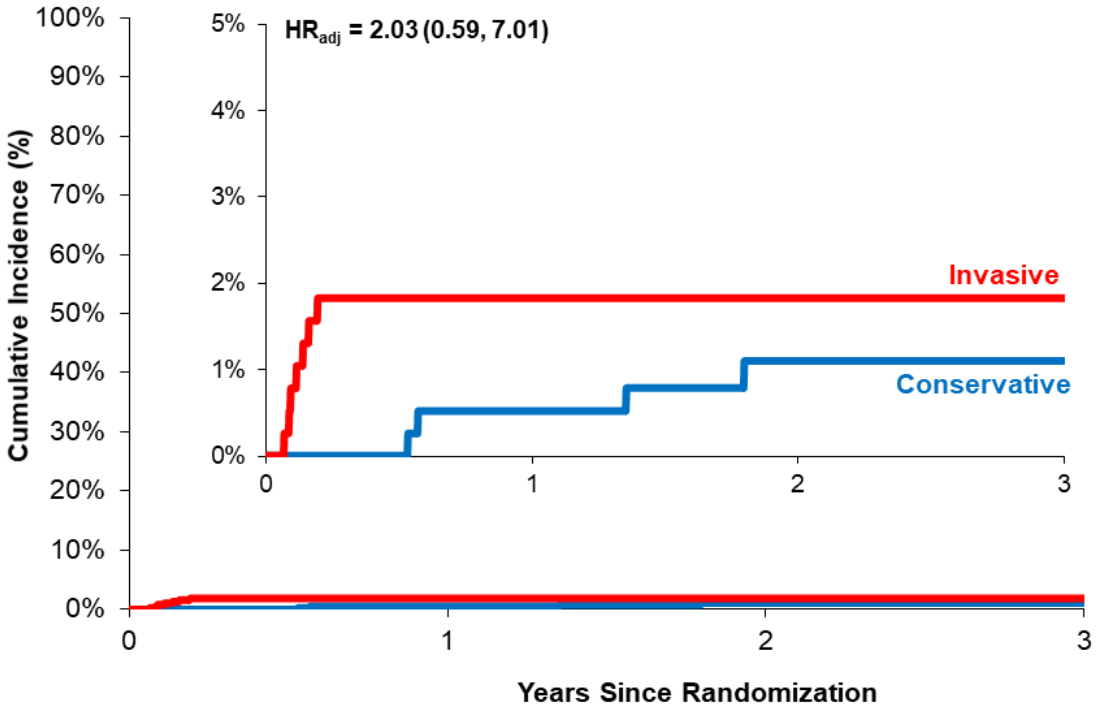
S7a. Non Procedural MI



No. at Risk

Conservative	389	332	213	94
Invasive	388	322	191	81

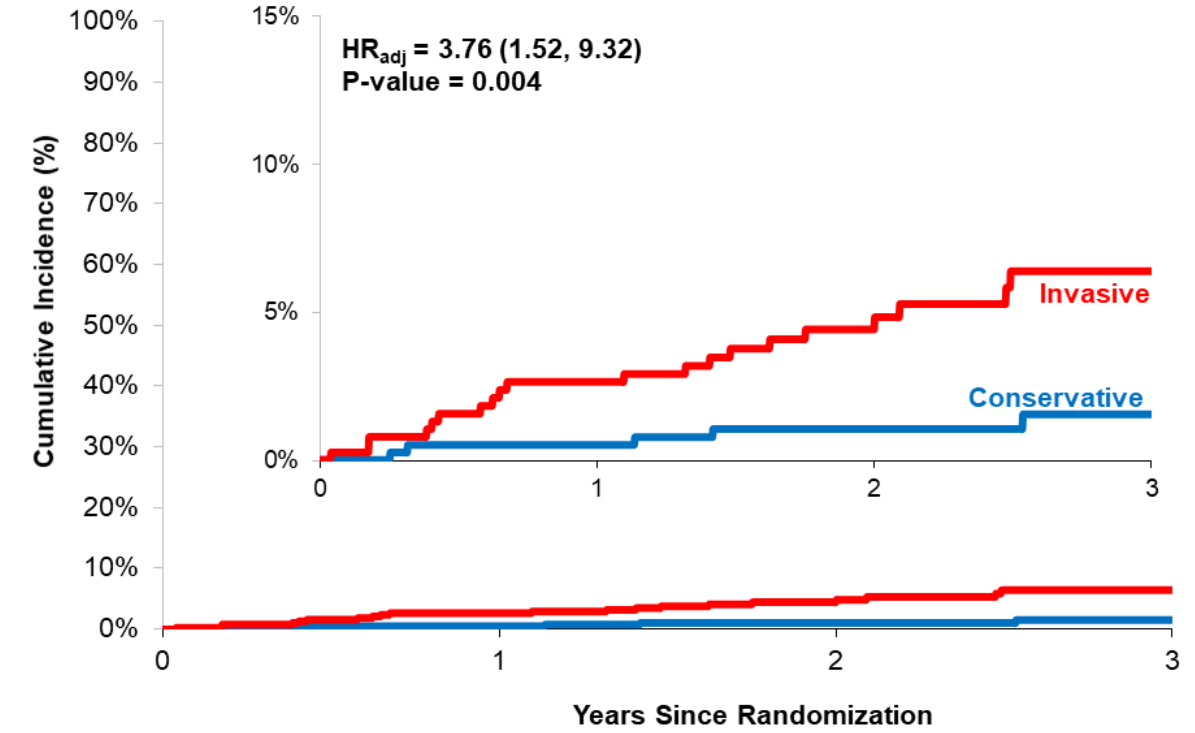
S7b. Procedural MI



No. at Risk

Conservative	389	349	230	107
Invasive	388	333	203	90

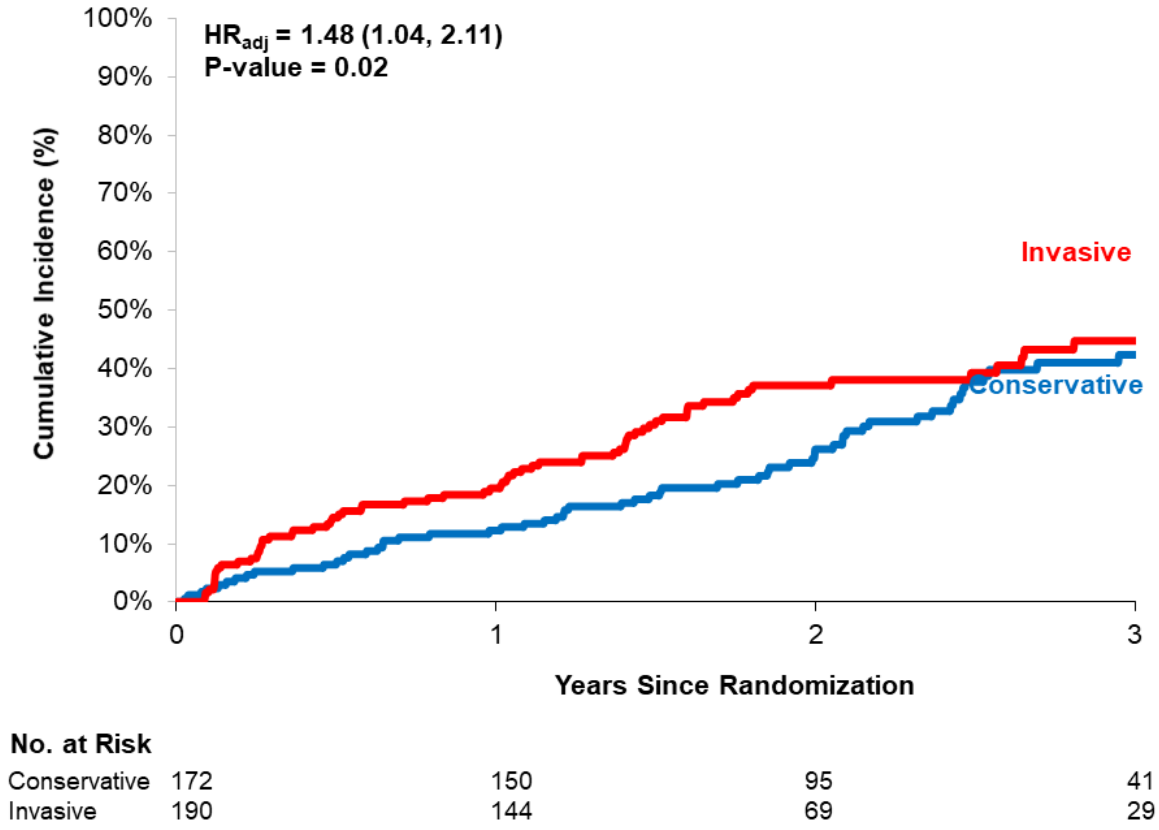
Figure S8. Cumulative Incidence Plot of Stroke



No. at Risk

Conservative	389	351	230	108
Invasive	388	330	198	85

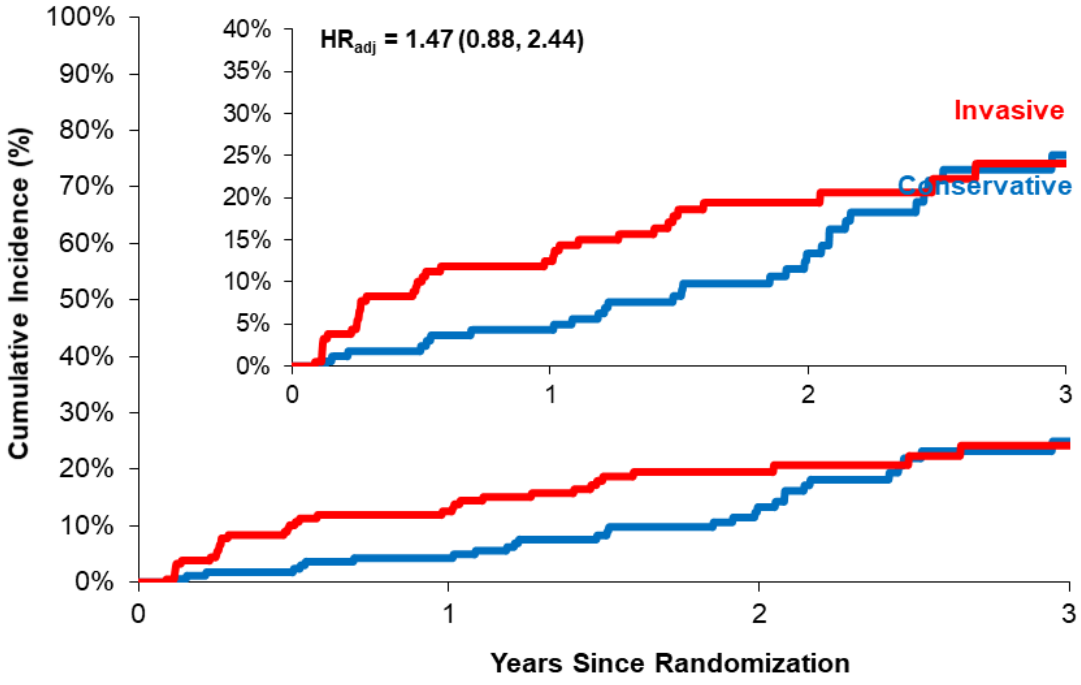
Figure S9. Cumulative Incidence Plot of Death or Initiation of Dialysis (in those not on dialysis at baseline)



No. at Risk

Conservative	172	150	95	41
Invasive	190	144	69	29

Figure S10. Cumulative Incidence Plot of New Dialysis



No. at Risk				
Conservative	172	147	91	40
Invasive	190	138	67	27

Figure S11. Heterogeneity of Treatment Effect Analyses for the Major Secondary Outcome

There were no significant interactions between the subgroups and randomization arm except for site-determined ischemia eligibility (P = 0.02).

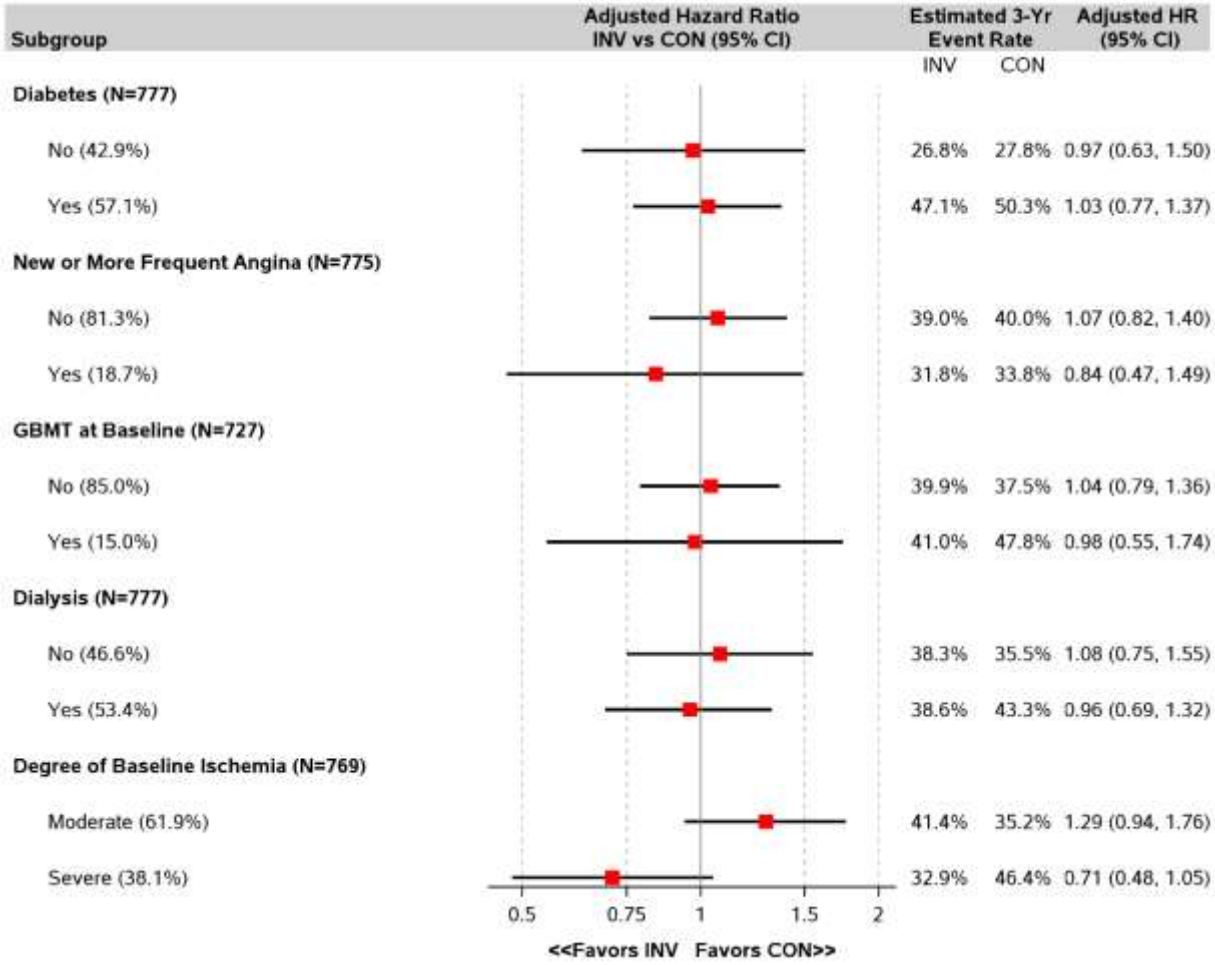


Figure S12. Heterogeneity of Treatment Effect for the Primary Outcome as a Function of Baseline Ejection Fraction

The reference treatment group is the Conservative group. The range of values displayed on X-axis represent the 1st and 99th percentile of the observed distribution.

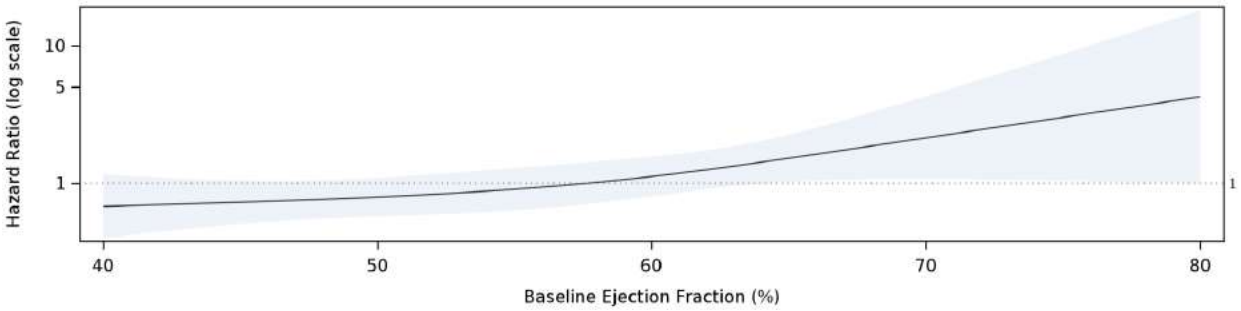


Figure S13. Heterogeneity of Treatment Effect for the Primary Outcome as a Function of Baseline eGFR

The reference treatment group is the Conservative group. The range of values displayed on X-axis represent the 1st and 99th percentile of the observed distribution.