Supplemental Material

Data S1.

Supplemental Statistical Methods - Multiple Imputation of Baseline Covariates Used in Cox Modeling

Introduction

The purpose of this document is to document the methodological details for imputing missing data for the baseline covariates used in the Cox models in the ISCHEMIA trial.

Methods

The statistical techniques used for multiple imputation include chained equations and predictive mean matching (PMM). PMM using chained equations does not require too many assumptions and the imputations do not change much when those assumptions are violated[1]. PMM first involves fitting an ordinary linear model on an outcome variable using all covariates of interest. Predictions of the outcome variable can be determined based on the model where continuous covariates are expanded into restricted cubic splines that usually have 3 knots. For a given covariate, PMM then replaces a missing value with an observed value whose predicted value is very close to the predicted value for the missing value. PMM does not assume a conditional distribution form for the covariate being imputed.

The particular algorithm used to implement PMM uses Van Buuren's Type 1 matching[39] which incorporates uncertainty in matching an observed value to a missing value. This method does not find observed values using an exact match on predicted values, but instead uses weighted multinomial sampling of potential observed observations. The weight function that is used for the weighted multinomial sampling is Tukey's bicube function which gives heavy preference to observed values that are closest to the missing value's predicted value. The algorithm uses the bootstrap method to obtain the right amount of uncertainty instead of a Bayesian sampling approach that samples from the posterior distribution of imputation model parameters.

For the model that is used for multiple imputation, the outcome variable must be a study specific outcome variable when using baseline variables in the imputation model. This is done to avoid the situation where the final regression coefficients are biased towards zero. We include all event or censoring times and the corresponding indicators simultaneously when conducting the multiple imputation.

The multiple imputation algorithm used for ISCHEMIA makes 100 imputations for each missing value. The result is 100 sets of complete datasets of which values are averaged within each participant to get the final imputed covariates to be used in Cox proportional hazards regression modeling.

Table S1. Baseline Characteristics of Women and Men by Treatment Group.

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value
Demographics						
Age at Randomization (yrs.)			0.288			<.001
N	606	1982		562	2029	
Median (Q1, Q3)	65 (59, 71)	64 (58, 70)		65 (59, 72)	64 (57, 70)	
Race			0.322			0.009
American Indian or Alaskan Native	2/602 (0.3%)	6/1,967 (0.3%)		1/552 (0.2%)	4/2,008 (0.2%)	
Asian	159/602 (26.4%)	588/1,967 (29.9%)		123/552 (22.3%)	615/2,008 (30.6%)	
Native Hawaiian or Other Pacific Islander	1/602 (0.2%)	4/1,967 (0.2%)		1/552 (0.2%)	6/2,008 (0.3%)	
Black or African American	30/602 (5.0%)	66/1,967 (3.4%)		27/552 (4.9%)	81/2,008 (4.0%)	
White	409/602 (67.9%)	1,297/1,967 (65.9%)		399/552 (72.3%)	1,298/2,008 (64.6%)	
Multiple Races Reported	1/602 (0.2%)	6/1,967 (0.3%)		1/552 (0.2%)	4/2,008 (0.2%)	
Ethnicity			0.980			0.043
Hispanic or Latino	88/567 (15.5%)	284/1,835 (15.5%)		100/524 (19.1%)	291/1,889 (15.4%)	
Not Hispanic or Latino	479/567 (84.5%)	1,551/1,835 (84.5%)		424/524 (80.9%)	1,598/1,889 (84.6%)	
Clinical History						
Hypertension	460/604 (76.2%)	1,434/1,975 (72.6%)	0.084	462/560 (82.5%)	1,433/2,022 (70.9%)	<.001
Diabetes	280/606 (46.2%)	791/1,982 (39.9%)	0.006	242/562 (43.1%)	851/2,029 (41.9%)	0.635
Diabetes Treatment			<.001			0.015
Insulin Treated	86/272 (31.6%)	153/774 (19.8%)		73/238 (30.7%)	180/833 (21.6%)	
Non-Insulin Diabetes Medication	153/272 (56.3%)	524/774 (67.7%)		137/238 (57.6%)	541/833 (64.9%)	
None/Diet Controlled	33/272 (12.1%)	97/774 (12.5%)		28/238 (11.8%)	112/833 (13.4%)	
Prior MI	95/604 (15.7%)	400/1,976 (20.2%)	0.014	89/561 (15.9%)	407/2,021 (20.1%)	0.023
Cigarette Smoking			<.001			<.001
Never Smoked	396/606 (65.3%)	723/1,981 (36.5%)		360/561 (64.2%)	729/2,026 (36.0%)	
Former Smoker	152/606 (25.1%)	997/1,981 (50.3%)		149/561 (26.6%)	1,028/2,026 (50.7%)	
Current Smoker	58/606 (9.6%)	261/1,981 (13.2%)		52/561 (9.3%)	269/2,026 (13.3%)	
Family History of Premature Coronary Heart Disease	150/524 (28.6%)	428/1,704 (25.1%)	0.109	147/492 (29.9%)	445/1,770 (25.1%)	0.034
Prior PCI	104/605 (17.2%)	447/1,981 (22.6%)	0.005	85/562 (15.1%)	414/2,027 (20.4%)	0.005
Years from Most Recent PCI to Randomization			0.103			0.017
N	90	390		76	364	
Median (Q1, Q3)	4 (2, 7)	5 (2, 8)		3 (2, 5)	4 (2, 8)	
Prior CABG	15/606 (2.5%)	95/1,982 (4.8%)	0.013	17/562 (3.0%)	76/2,029 (3.7%)	0.416
Years from Most Recent CABG to Randomization			<.001			0.742

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value
N	11	72		16	59	
Median (Q1, Q3)	5 (2, 6)	9 (5, 15)		7 (3, 15)	10 (5, 16)	
Prior MI or Prior PCI or Prior CABG	154/603 (25.5%)	648/1,977 (32.8%)	<.001	135/562 (24.0%)	633/2,020 (31.3%)	<.001
Atrial Fibrillation/Atrial Flutter	27/606 (4.5%)	101/1,981 (5.1%)	0.523	19/560 (3.4%)	74/2,026 (3.7%)	0.770
Non-cardiac Vascular and Comorbidity History						
Prior Cerebrovascular Disease*	41/604 (6.8%)	160/1,978 (8.1%)	0.296	48/562 (8.5%)	128/2,021 (6.3%)	0.066
Prior Stroke	19/606 (3.1%)	64/1,981 (3.2%)	0.907	21/562 (3.7%)	47/2,029 (2.3%)	0.062
Stroke Type			0.184			0.877
Hemorrhagic	1/19 (5.3%)	0/64 (0.0%)		1/21 (4.8%)	1/47 (2.1%)	
Ischemic	16/19 (84.2%)	59/64 (92.2%)		16/21 (76.2%)	37/47 (78.7%)	
Not known	2/19 (10.5%)	5/64 (7.8%)		4/21 (19.0%)	9/47 (19.1%)	
Residual Disability from Stroke	5/14 (35.7%)	19/57 (33.3%)	1.000	4/17 (23.5%)	12/38 (31.6%)	0.750
Prior Carotid Artery Surgery or Stent	17/605 (2.8%)	61/1,981 (3.1%)	0.735	23/562 (4.1%)	62/2,024 (3.1%)	0.226
Prior Transient Ischemia Attack (TIA)	15/605 (2.5%)	57/1,975 (2.9%)	0.595	7/562 (1.2%)	35/2,023 (1.7%)	0.422
Prior Peripheral Vascular Disease (PVD)	26/605 (4.3%)	90/1,980 (4.5%)	0.797	17/560 (3.0%)	71/2,023 (3.5%)	0.584
Prior Surgery or Percutaneous Procedure for PAD	8/24 (33.3%)	45/88 (51.1%)	0.122	6/16 (37.5%)	38/67 (56.7%)	0.166
Qualifying Stress Test Core Lab Interpretation						
Ischemia Severity by Imaging Modality						
Stress Imaging Overall	476/606 (78.5%)	1,473/1,982 (74.3%)	0.035	448/562 (79.7%)	1,512/2,029 (74.5%)	0.011
Severity			0.068			0.038
Severe	194/475 (40.8%)	654/1,466 (44.6%)		189/444 (42.6%)	709/1,506 (47.1%)	
Moderate	201/475 (42.3%)	617/1,466 (42.1%)		185/444 (41.7%)	598/1,506 (39.7%)	
Mild	50/475 (10.5%)	113/1,466 (7.7%)		36/444 (8.1%)	119/1,506 (7.9%)	
None	30/475 (6.3%)	82/1,466 (5.6%)		34/444 (7.7%)	80/1,506 (5.3%)	
Exercise Tolerance Test (ETT)	130/606 (21.5%)	509/1,982 (25.7%)	0.005	114/562 (20.3%)	517/2,029 (25.5%)	0.002
Severity			0.837			0.065
Severe	102/120 (85.0%)	432/494 (87.4%)		87/106 (82.1%)	430/494 (87.0%)	
Moderate	13/120 (10.8%)	42/494 (8.5%)		9/106 (8.5%)	37/494 (7.5%)	
Mild	4/120 (3.3%)	9/494 (1.8%)		4/106 (3.8%)	17/494 (3.4%)	
None	1/120 (0.8%)	11/494 (2.2%)		6/106 (5.7%)	10/494 (2.0%)	
Nuclear	288/606 (47.5%)	988/1,982 (49.8%)	0.005	270/562 (48.0%)	1,021/2,029 (50.3%)	0.002
Severity			<.001			0.026
Severe	79/287 (27.5%)	395/982 (40.2%)		87/268 (32.5%)	407/1,018 (40.0%)	
Moderate	146/287 (50.9%)	450/982 (45.8%)		137/268 (51.1%)	470/1,018 (46.2%)	
Mild	35/287 (12.2%)	74/982 (7.5%)		22/268 (8.2%)	83/1,018 (8.2%)	
None	27/287 (9.4%)	63/982 (6.4%)		22/268 (8.2%)	58/1,018 (5.7%)	

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value
Echocardiogram	148/606 (24.4%)	400/1,982 (20.2%)	0.005	143/562 (25.4%)	394/2,029 (19.4%)	0.002
Severity			0.171			0.168
Severe	87/148 (58.8%)	218/399 (54.6%)		78/141 (55.3%)	243/391 (62.1%)	
Moderate	47/148 (31.8%)	131/399 (32.8%)		41/141 (29.1%)	97/391 (24.8%)	
Mild	12/148 (8.1%)	32/399 (8.0%)		12/141 (8.5%)	32/391 (8.2%)	
None	2/148 (1.4%)	18/399 (4.5%)		10/141 (7.1%)	19/391 (4.9%)	
CMR	40/606 (6.6%)	85/1,982 (4.3%)	0.005	35/562 (6.2%)	97/2,029 (4.8%)	0.002
Severity			0.144			0.951
Severe	28/40 (70.0%)	41/85 (48.2%)		24/35 (68.6%)	59/97 (60.8%)	
Moderate	8/40 (20.0%)	36/85 (42.4%)		7/35 (20.0%)	31/97 (32.0%)	
Mild	3/40 (7.5%)	7/85 (8.2%)		2/35 (5.7%)	4/97 (4.1%)	
None	1/40 (2.5%)	1/85 (1.2%)		2/35 (5.7%)	3/97 (3.1%)	
Baseline ECG Findings[†]						
Q-waves: Meets UMI Criteria in 2 Leads[‡]	51/570 (8.9%)	219/1,823 (12.0%)	0.043	43/519 (8.3%)	241/1,862 (12.9%)	0.004
ST Segment Depression ≥0.5mm	63/580 (10.9%)	169/1,899 (8.9%)	0.155	83/526 (15.8%)	202/1,927 (10.5%)	<.001
ST Segment Depression ≥1mm	10/580 (1.7%)	36/1,899 (1.9%)	0.789	10/526 (1.9%)	31/1,927 (1.6%)	0.643
T Wave Inversion ≥1mm	54/579 (9.3%)	144/1,901 (7.6%)	0.173	44/527 (8.3%)	160/1,926 (8.3%)	0.975
T Wave Inversion ≥3mm	5/579 (0.9%)	30/1,901 (1.6%)	0.202	4/527 (0.8%)	19/1,926 (1.0%)	0.801
Left Ventricular Hypertrophy	46/564 (8.2%)	123/1,781 (6.9%)	0.317	47/510 (9.2%)	148/1,821 (8.1%)	0.433
Left Bundle Branch Block (LBBB)	13/598 (2.2%)	23/1,965 (1.2%)	0.068	16/553 (2.9%)	34/1,998 (1.7%)	0.074
Right Bundle Branch Block (RBBB)	13/598 (2.2%)	120/1,965 (6.1%)	<.001	17/553 (3.1%)	109/1,998 (5.5%)	0.022
Non-specific IVCD	2/598 (0.3%)	20/1,965 (1.0%)	0.113	5/553 (0.9%)	21/1,998 (1.1%)	0.761
Paced Rhythm	3/598 (0.5%)	20/1,965 (1.0%)	0.241	5/553 (0.9%)	20/1,998 (1.0%)	0.838
Atrial Fibrillation/Flutter	8/598 (1.3%)	37/1,965 (1.9%)	0.374	8/553 (1.4%)	29/1,998 (1.5%)	0.993
QTc >460 msec	19/386 (4.9%)	33/1,250 (2.6%)	0.025	21/354 (5.9%)	30/1,308 (2.3%)	<.001
CCTA Findings						
Any Obstructive Disease ≥50% Stenosis	407/407 (100.0%)	1,517/1,519 (99.9%)	1.000	380/381 (99.7%)	1,528/1,529 (99.9%)	0.359
Multi-vessel Disease ≥50% Stenosis	245/342 (71.6%)	1,091/1,360 (80.2%)	<.001	234/322 (72.7%)	1,109/1,366 (81.2%)	<.001
Vessels ≥50% Stenosis			<.001			0.005
0	0/291 (0.0%)	2/1,199 (0.2%)		1/277 (0.4%)	1/1,219 (0.1%)	
1	96/291 (33.0%)	264/1,199 (22.0%)		82/277 (29.6%)	255/1,219 (20.9%)	

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value
2	93/291 (32.0%)	341/1,199 (28.4%)		91/277 (32.9%)	413/1,219 (33.9%)	
≥3	102/291 (35.1%)	592/1,199 (49.4%)		103/277 (37.2%)	550/1,219 (45.1%)	
Specific Native Vessels ≥50% Stenosis						
Left Main	2/411 (0.5%)	19/1,515 (1.3%)	0.282	2/387 (0.5%)	17/1,532 (1.1%)	0.397
Left Anterior Descending (LAD)	326/389 (83.8%)	1,265/1,448 (87.4%)	0.132	324/366 (88.5%)	1,275/1,474 (86.5%)	0.275
Proximal LAD	166/405 (41.0%)	699/1,465 (47.7%)	0.016	182/378 (48.1%)	702/1,491 (47.1%)	0.711
Left Circumflex	200/349 (57.3%)	984/1,400 (70.3%)	<.001	207/344 (60.2%)	963/1,402 (68.7%)	0.011
Right Coronary Artery	228/345 (66.1%)	950/1,339 (70.9%)	0.073	186/322 (57.8%)	947/1,353 (70.0%)	<.001
Any Obstructive Disease ≥70% Stenosis	311/354 (87.9%)	1,306/1,408 (92.8%)	0.003	299/337 (88.7%)	1,283/1,401 (91.6%)	0.100
Multi-vessel Disease ≥70% Stenosis	117/307 (38.1%)	647/1,207 (53.6%)	<.001	119/289 (41.2%)	646/1,244 (51.9%)	<.001
Vessels ≥70% Stenosis			<.001			0.021
0	43/248 (17.3%)	102/1,026 (9.9%)		38/238 (16.0%)	118/1,047 (11.3%)	
1	120/248 (48.4%)	398/1,026 (38.8%)		105/238 (44.1%)	404/1,047 (38.6%)	
2	51/248 (20.6%)	297/1,026 (28.9%)		62/238 (26.1%)	321/1,047 (30.7%)	
≥3	34/248 (13.7%)	229/1,026 (22.3%)		33/238 (13.9%)	204/1,047 (19.5%)	
Specific Native Vessels ≥70% Stenosis						
Left Main	1/411 (0.2%)	6/1,515 (0.4%)	1.000	0/387 (0.0%)	5/1,532 (0.3%)	0.590
Left Anterior Descending (LAD)	199/356 (55.9%)	871/1,351 (64.5%)	0.005	200/330 (60.6%)	858/1,385 (61.9%)	0.264
Proximal LAD	70/405 (17.3%)	326/1,460 (22.3%)	0.028	72/378 (19.0%)	339/1,487 (22.8%)	0.116
Left Circumflex	126/329 (38.3%)	653/1,328 (49.2%)	0.002	135/326 (41.4%)	630/1,333 (47.3%)	0.164
Right Coronary Artery	137/320 (42.8%)	657/1,245 (52.8%)	0.006	116/305 (38.0%)	643/1,265 (50.8%)	<.001
Modified Duke Prognostic Index			<.001			0.010
No Vessel (LAD, LCx, RCA) with at least Moderate (≥50%) Stenosis	0/247 (0.0%)	2/1,023 (0.2%)		1/235 (0.4%)	1/1,043 (0.1%)	
1 Vessel with at least Moderate (≥50%) Stenosis	25/247 (10.1%)	66/1,023 (6.5%)		27/235 (11.5%)	61/1,043 (5.8%)	
2 Vessels with at least Moderate (≥50%) Stenosis or 1 Severe (≥70%) Stenosis	95/247 (38.5%)	271/1,023 (26.5%)		78/235 (33.2%)	306/1,043 (29.3%)	
3 Vessels with at least Moderate (≥50%) Stenosis or 2 Severe (≥70%) Stenosis or Proximal LAD with Severe (≥70%) Stenosis	84/247 (34.0%)	361/1,023 (35.3%)		79/235 (33.6%)	383/1,043 (36.7%)	
3 Vessels with Severe (≥70%) Stenosis or 2 Severe (≥70%) Stenosis Including Proximal LAD	41/247 (16.6%)	304/1,023 (29.7%)		48/235 (20.4%)	275/1,043 (26.4%)	
Left Main ≥50% Stenosis	2/247 (0.8%)	19/1,023 (1.9%)		2/235 (0.9%)	17/1,043 (1.6%)	
Angina & Heart Failure History						
Baseline Seattle Angina Questionnaire Angina Frequency Scale			<.001			<.001
N	550	1764		530	1803	
Median (Q1, Q3)	80 (70, 100)	90 (70, 100)		80 (70, 100)	90 (70, 100)	
Baseline Seattle Angina Questionnaire Angina Frequency Scale			<.001			<.001
Daily Angina (0-30)	17/550 (3.1%)	44/1,764 (2.5%)		16/530 (3.0%)	38/1,803 (2.1%)	

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value
Weekly Angina (31-60)	112/550 (20.4%)	329/1,764 (18.7%)		109/530 (20.6%)	279/1,803 (15.5%)	
Monthly Angina (61-99)	274/550 (49.8%)	744/1,764 (42.2%)		255/530 (48.1%)	784/1,803 (43.5%)	
No Angina in Past Month (100)	147/550 (26.7%)	647/1,764 (36.7%)		150/530 (28.3%)	702/1,803 (38.9%)	
Baseline Seattle Angina Questionnaire Summary Score			<.001			<.001
N	551	1765		530	1804	
Median (Q1, Q3)	71 (55, 85)	77 (63, 89)		73 (56, 84)	79 (65, 92)	
Participant Has Ever Had Angina	553/606 (91.3%)	1,776/1,982 (89.6%)	0.237	515/562 (91.6%)	1,797/2,029 (88.6%)	0.038
Angina Over the Past Month			<.001			<.001
None	96/606 (15.8%)	408/1,980 (20.6%)		93/562 (16.5%)	438/2,029 (21.6%)	
CCS Angina Class I	144/606 (23.8%)	526/1,980 (26.6%)		139/562 (24.7%)	580/2,029 (28.6%)	
CCS Angina Class II	320/606 (52.8%)	961/1,980 (48.5%)		290/562 (51.6%)	951/2,029 (46.9%)	
CCS Angina Class III	46/606 (7.6%)	84/1,980 (4.2%)		40/562 (7.1%)	60/2,029 (3.0%)	
CCS Angina Class IV	0/606 (0.0%)	1/1,980 (0.1%)		0/562 (0.0%)	0/2,029 (0.0%)	
New Onset of Angina Over the Past 3 Months	92/574 (16.0%)	323/1,878 (17.2%)	0.513	90/529 (17.0%)	350/1,937 (18.1%)	0.574
Angina Began or Became More Frequent Over the Past 3 Months	165/552 (29.9%)	515/1,773 (29.0%)	0.703	164/512 (32.0%)	511/1,791 (28.5%)	0.125
Prior Heart Failure	33/606 (5.4%)	79/1,982 (4.0%)	0.122	28/562 (5.0%)	66/2,029 (3.3%)	0.052
Ejection Fraction[§]			<.001			<.001
N	544	1775		509	1809	
Median (Q1, Q3)	63 (60, 68)	60 (55, 64)		62 (57, 68)	60 (55, 64)	
Heart Failure Over the Past Month			<.001			<.001
None	346/606 (57.1%)	1,238/1,982 (62.5%)		324/562 (57.7%)	1,255/2,029 (61.9%)	
NYHA Class I	101/606 (16.7%)	398/1,982 (20.1%)		77/562 (13.7%)	423/2,029 (20.8%)	
NYHA Class II	159/606 (26.2%)	346/1,982 (17.5%)		161/562 (28.6%)	351/2,029 (17.3%)	
NYHA Class III	0/606 (0.0%)	0/1,982 (0.0%)		0/562 (0.0%)	0/2,029 (0.0%)	
NYHA Class IV	0/606 (0.0%)	0/1,982 (0.0%)		0/562 (0.0%)	0/2,029 (0.0%)	
Vital Signs						
Heart Rate (bpm)			0.012			<.001
N	603	1966		559	2018	
Median (Q1, Q3)	68 (61, 75)	67 (60, 76)		68 (61, 76)	66 (60, 74)	
Systolic Blood Pressure (mmHg)			0.402			0.009
N	604	1968		560	2018	
Median (Q1, Q3)	130 (120, 144)	130 (120, 142)		131 (120, 146)	130 (120, 141)	
Diastolic Blood Pressure (mmHg)			<.001			0.039
N	604	1968		560	2018	
Median (Q1, Q3)	75 (70, 80)	78 (70, 82)		76 (70, 80)	78 (70, 81)	

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value
Body Mass Index (kg/m^2)			0.245			<.001
N	601	1963		559	2001	
Median (Q1, Q3)	28 (25, 32)	28 (25, 31)		29 (25, 33)	28 (25, 31)	
Lab Values						
Lipid Panel						
Total Cholesterol (mg/dL)			<.001			<.001
N	589	1933		554	1998	
Median (Q1, Q3)	167 (143, 205)	150 (128, 182)		166 (141, 202)	151 (127, 180)	
Triglycerides (mg/dL)			0.876			0.028
N	580	1902		545	1957	
Median (Q1, Q3)	124 (96, 170)	124 (89, 181)		129 (97, 182)	124 (90, 174)	
HDL Cholesterol (mg/dL)			<.001			<.001
N	587	1916		547	1973	
Median (Q1, Q3)	47 (40, 58)	41 (35, 49)		48 (42, 58)	41 (35, 49)	
LDL Cholesterol (mg/dL)			<.001			<.001
N	574	1890		542	1934	
Median (Q1, Q3)	90 (69, 123)	81 (62, 107)		91 (69, 120)	81 (62, 106)	
HbA1c for Diabetics (%)			0.057			0.003
N	253	738		225	785	
Median (Q1, Q3)	7 (7, 9)	7 (7, 8)		8 (7, 9)	7 (7, 8)	
Complete Blood Counts						
Hemoglobin (g/dL)			<.001			<.001
N	577	1889		530	1891	
Median (Q1, Q3)	13 (12, 14)	14 (13, 15)		13 (12, 14)	14 (13, 15)	
Platelets (10^9/L)			<.001			<.001
N	568	1866		521	1867	
Median (Q1, Q3)	249 (206, 295)	213 (177, 249)		247 (210, 294)	214 (178, 253)	
WBC (10^9/L)			0.239			0.672
N	572	1863		522	1874	
Median (Q1, Q3)	7 (6, 9)	7 (6, 9)		7 (6, 9)	7 (6, 9)	
Chemistry Panel						
Enrollment Creatinine (mg/dL)			<.001			<.001
N	606	1982		562	2029	
Median (Q1, Q3)	1 (1, 1)	1 (1, 1)		1 (1, 1)	1 (1, 1)	
Estimated GFR from Enrollment (mL/min)			<.001			<.001
N	606	1982		562	2029	
Median (Q1, Q3)	77 (63, 92)	83 (69, 98)		76 (60, 92)	82 (70, 98)	

Characteristic	Invasive Strategy Group			Conservative Strategy Group		
	Women (N=606)	Men (N=1,982)	P-value	Women (N=562)	Men (N=2,029)	P-value

*Prior carotid artery surgery or stent, prior stroke, or prior TIA.

†Baseline ECG results are only reported on those ECGs with interpretable tracings as determined by the core lab.

‡Meets universal definition of MI in 2 leads in at least 1 territory (anterior, inferior, or lateral).

§Site-reported value, if available. If not available, then core-lab entered value.

Table S2. Use of CABG in Women and Men in the Invasive Strategy Group within the ISCHEMIA Trial.

Characteristic	Overall (N=2,588)	Women (N=606)	Men (N=1,982)	P-value
Overall among Participants undergoing Revascularization in Invasive Strategy	530/2,054 (25.8%)	93/445 (20.9%)	437/1,609 (27.2%)	0.008
Duke Score=6*	113/282 (40.1%)	10/33 (30.3%)	103/249 (41.4%)	0.223
3-Vessel CAD ≥50% by Angio	366/843 (43.4%)	58/149 (38.9%)	308/694 (44.4%)	0.223
3-Vessel CAD ≥70% by Angio	167/340 (49.1%)	24/54 (44.4%)	143/286 (50.0%)	0.454

*3 vessels with severe (≥70%) stenosis or 2 severe (≥70%) stenosis including proximal LAD.

Table S3. Medical Therapy for Randomized Participants at End of Study by Sex in Participants Who Underwent CCTA.

Medical Therapy Goal	All Participants (N=3,913)	Women (N=816)	Men (N=3,097)	P-value
On Guideline-Directed Medical Therapy				
Not Smoking	3,298/3,667 (89.9%)	703/769 (91.4%)	2,595/2,898 (89.5%)	0.125
Systolic Blood Pressure < 140 mmHg	2,898/3,763 (77.0%)	577/782 (73.8%)	2,321/2,981 (77.9%)	0.016
LDL-C < 70 mg/dL	2,226/3,706 (60.1%)	388/773 (50.2%)	1,838/2,933 (62.7%)	<.001
On Aspirin or Aspirin Alternative	3,553/3,671 (96.8%)	727/762 (95.4%)	2,826/2,909 (97.1%)	0.015
On High-Intensity Statin Therapy	2,466/3,785 (65.2%)	492/787 (62.5%)	1,974/2,998 (65.8%)	0.081
On ACE Inhibitor/ARB*	2,261/3,020 (74.9%)	484/659 (73.4%)	1,777/2,361 (75.3%)	0.341
On Beta-Blocker*	557/664 (83.9%)	96/110 (87.3%)	461/554 (83.2%)	0.290
Number of Goals Met†				<.001
0	3/3,601 (0.1%)	1/754 (0.1%)	2/2,847 (0.1%)	
1	77/3,601 (2.1%)	20/754 (2.7%)	57/2,847 (2.0%)	
2	500/3,601 (13.9%)	137/754 (18.2%)	363/2,847 (12.8%)	
3	1,498/3,601 (41.6%)	338/754 (44.8%)	1,160/2,847 (40.7%)	
4	1,523/3,601 (42.3%)	258/754 (34.2%)	1,265/2,847 (44.4%)	
High Level of Medical Therapy Optimization‡	1,523/3,601 (42.3%)	258/754 (34.2%)	1,265/2,847 (44.4%)	<.001
On Aspirin or Aspirin Alternative/Other Anti-platelet Among All Participants	3,669/3,787 (96.9%)	753/788 (95.6%)	2,916/2,999 (97.2%)	0.016
LDL-C < 70 mg/dL and on a Statin	2,199/3,698 (59.5%)	382/769 (49.7%)	1,817/2,929 (62.0%)	<.001
On ACE Inhibitor/ARB Among All Participants	2,606/3,786 (68.8%)	539/788 (68.4%)	2,067/2,998 (68.9%)	0.769
On Statin	3,595/3,787 (94.9%)	734/788 (93.1%)	2,861/2,999 (95.4%)	0.010
On Anti-anginal Medications§	3,420/3,788 (90.3%)	712/788 (90.4%)	2,708/3,000 (90.3%)	0.940
Number of Anti-anginal Medications§				0.007
1	1,748/3,420 (51.1%)	331/712 (46.5%)	1,417/2,708 (52.3%)	
2	1,213/3,420 (35.5%)	266/712 (37.4%)	947/2,708 (35.0%)	
3	365/3,420 (10.7%)	95/712 (13.3%)	270/2,708 (10.0%)	
4	82/3,420 (2.4%)	15/712 (2.1%)	67/2,708 (2.5%)	
5	12/3,420 (0.4%)	5/712 (0.7%)	7/2,708 (0.3%)	
HbA1c < 8%	2,460/2,908 (84.6%)	474/593 (79.9%)	1,986/2,315 (85.8%)	<.001
Adherent to Medications Based on Morisky-Green-Levine Assessment	3,022/3,705 (81.6%)	619/776 (79.8%)	2,403/2,929 (82.0%)	0.146

Medical Therapy Goal	All Participants (N=3,913)	Women (N=816)	Men (N=3,097)	P-value

*Participants who are not indicated for ACE Inhibitor/ARBs or Beta-Blockers are counted as having missing data for the individual goals.
†The following OMT goals contribute to the Number of Goals Met: not smoking, systolic blood pressure < 140 mm/Hg, LDL-C < 70 mg/dL and on any statin, and on
aspirin or other antiplatelet or anticoagulant contribute to this count. Number of Goals Met is missing if any of the individual goals are mi ssing.
‡High Level of Medical Therapy Optimization is defined as a participant meeting all of the following goals: not smoking, systolic blood pressure < 140 mm/Hg, LDL-C < 70 mg/dL and on any statin, and on aspirin or other antiplatelet or anticoagulant. High level of medical therapy optimization is missing if any of the individual goals are missing.
§Includes Beta Blocker, Calcium Channel Blocker, Long-acting Nitrate, Ranolazine, Trimetazadine, Ivabradine, Nicorandil and other anti-anginal medications marked as "Unknown".
||For each individual GDMT goal, the last visit is defined as the latest visit (at least 12 months after randomization) where the goal is evaluable. If the latest visit where the
goal is evaluable is less than 12 months after randomization then the individual OMT goal is missing.
#A total of 3,913 randomized participants had a CCTA performed (96.7% were protocol CCTA and 3.3% were non-protocol CCTA).
Abbreviations defined: GDMT – guideline-directed medical therapy; LDL-C - low-density lipoprotein cholesterol; ACE - Angiotensin-converting enzyme; ARB - angiotensin-receptor blocker; HbA1c - Hemoglobin A1C

Table S4. Medical Therapy for Randomized Participants at End of Study by Sex* in the Subgroup of Invasive Strategy Group Participants Who Underwent Cardiac Catheterization and had at least One Diseased Vessel ≥50% Stenosis**.

Medical Therapy Goal	All Participants (N=2,177)	Women (N=479)	Men (N=1,698)	P-value
Specific Goals				
Not Smoking	1,851/2,045 (90.5%)	408/446 (91.5%)	1,443/1,599 (90.2%)	0.431
Systolic Blood Pressure < 140 mmHg	1,625/2,098 (77.5%)	344/458 (75.1%)	1,281/1,640 (78.1%)	0.174
LDL-C < 70 mg/dL	1,245/2,065 (60.3%)	241/454 (53.1%)	1,004/1,611 (62.3%)	<.001
On Aspirin or Aspirin Alternative	1,995/2,039 (97.8%)	427/440 (97.0%)	1,568/1,599 (98.1%)	0.194
On High-Intensity Statin	1,379/2,109 (65.4%)	293/461 (63.6%)	1,086/1,648 (65.9%)	0.350
On ACE Inhibitor/ARB*	1,303/1,755 (74.2%)	299/404 (74.0%)	1,004/1,351 (74.3%)	0.902
On Beta-Blocker*	371/431 (86.1%)	70/79 (88.6%)	301/352 (85.5%)	0.472
Number of Goals Met†				0.004
0	0/2,006 (0.0%)	0/440 (0.0%)	0/1,566 (0.0%)	
1	32/2,006 (1.6%)	7/440 (1.6%)	25/1,566 (1.6%)	
2	282/2,006 (14.1%)	76/440 (17.3%)	206/1,566 (13.2%)	
3	831/2,006 (41.4%)	200/440 (45.5%)	631/1,566 (40.3%)	
4	861/2,006 (42.9%)	157/440 (35.7%)	704/1,566 (45.0%)	
High Level of Medical Therapy Optimization‡	861/2,006 (42.9%)	157/440 (35.7%)	704/1,566 (45.0%)	<.001
On Aspirin or Aspirin Alternative/Other Anti-platelet Among All Participants	2,065/2,109 (97.9%)	448/461 (97.2%)	1,617/1,648 (98.1%)	0.212
LDL-C < 70 mg/dL and on a Statin	1,224/2,064 (59.3%)	234/453 (51.7%)	990/1,611 (61.5%)	<.001
On ACE Inhibitor/ARB Among All Participants	1,484/2,109 (70.4%)	334/461 (72.5%)	1,150/1,648 (69.8%)	0.267
On Statin	2,026/2,110 (96.0%)	429/461 (93.1%)	1,597/1,649 (96.8%)	<.001
On Anti-anginal Medications§	1,897/2,110 (89.9%)	417/461 (90.5%)	1,480/1,649 (89.8%)	0.657
Number of Anti-anginal Medications§				0.031
1	1,089/1,897 (57.4%)	222/417 (53.2%)	867/1,480 (58.6%)	
2	641/1,897 (33.8%)	154/417 (36.9%)	487/1,480 (32.9%)	
3	145/1,897 (7.6%)	39/417 (9.4%)	106/1,480 (7.2%)	
4	20/1,897 (1.1%)	1/417 (0.2%)	19/1,480 (1.3%)	
5	2/1,897 (0.1%)	1/417 (0.2%)	1/1,480 (0.1%)	
HbA1c < 8%	1,340/1,618 (82.8%)	280/359 (78.0%)	1,060/1,259 (84.2%)	0.006

Medical Therapy Goal	All Participants (N=2,177)	Women (N=479)	Men (N=1,698)	P-value
Adherent to Medications Based on Morisky-Green-Levine Assessment	1,722/2,069 (83.2%)	366/452 (81.0%)	1,356/1,617 (83.9%)	0.147

*Participants who are not indicated for ACE Inhibitor/ARBs or Beta-Blockers are counted as having missing data for the individual goals.
†The following OMT goals contribute to the Number of Goals Met: not smoking, systolic blood pressure < 140 mm/Hg, LDL-C < 70 mg/dL and on any statin, and on
aspirin or other antiplatelet or anticoagulant contribute to this count. Number of Goals Met is missing if any of the individual goals are mi ssing.
‡High Level of Medical Therapy Optimization is defined as a participant meeting all of the following goals: not smoking, systolic blood pressure < 140 mm/Hg, LDL-C < 70 mg/dL and on any statin, and on aspirin or other antiplatelet or anticoagulant. High level of medical therapy optimization is missing if any of the individual goals are missing.
§Includes Beta Blocker, Calcium Channel Blocker, Long-acting Nitrate, Ranolazine, Trimetazadine, Ivabradine, Nicorandil and other anti-anginal medications marked as "Unknown".
||For each individual GDMT goal, the last visit is defined as the latest visit (at least 12 months after randomization) where the goal is evaluable. If the latest visit where the
goal is evaluable is less than 12 months after randomization then the individual OMT goal is missing.
#A total of 3,913 randomized participants had a CCTA performed (96.7% were protocol CCTA and 3.3% were non-protocol CCTA).
Abbreviations defined: GDMT – guideline-directed medical therapy; LDL-C - low-density lipoprotein cholesterol; ACE - Angiotensin-converting enzyme; ARB - angiotensin-receptor blocker; HbA1c - Hemoglobin A1C

Table S5. Interaction between Sex and CAD Severity on Coronary Computed Tomography Angiography and MI.

	Number of Diseased Vessels ≥50%		Number of Diseased Vessels ≥70%	
Event	**HR (95% CI)***	**Interaction P-value**	**HR (95% CI)***	**Interaction P-value**
MI		0.018		0.052
			Zero: 0.21 (0.03, 1.61)	
	One: 0.36 (0.13, 1.04)		One: 0.74 (0.39, 1.38)	
	Two: 0.44 (0.19, 1.03)		Two: 0.56 (0.22, 1.41)	
	Three: 1.25 (0.82, 1.92)		Three: 1.77 (0.93, 3.37)	
Non-procedural MI		0.028		0.022
			Zero: 0.29 (0.04, 2.26)	
	One: 0.64 (0.22, 1.88)		One: 1.20 (0.62, 2.32)	
	Two: 0.65 (0.27, 1.52)		Two: 0.63 (0.22, 1.78)	
	Three: 1.96 (1.21, 3.17)		Three: 3.06 (1.51, 6.22)	

*Hazard ratios compare women vs. men at each level of number of diseased vessels by CCTA. Nonprocedural MI excludes type 4a and 5.

†Note: Sex-by-CAD-severity interactions were not significant for the primary outcome (50%: p=0.188, 70%: p=0.210), CV death or MI (50%: p=0.065, 70%: p=0.086) and all-cause mortality (50%: p=0.186, 70%: p=0.397). Zero vessel disease based on a 50% stenosis threshold was not evaluated due to low sample size, N=4.

‡Sex-by-CAD-Severity interactions were not significant for the primary outcome (p=0.342), CV death or MI (p=0.141) or all-cause mortality (p=0.339). Zero vessel disease based on a 50% stenosis threshold was not evaluated due to low sample size, N=4.

Abbreviations: MI = myocardial infarction, HR= hazard ratio

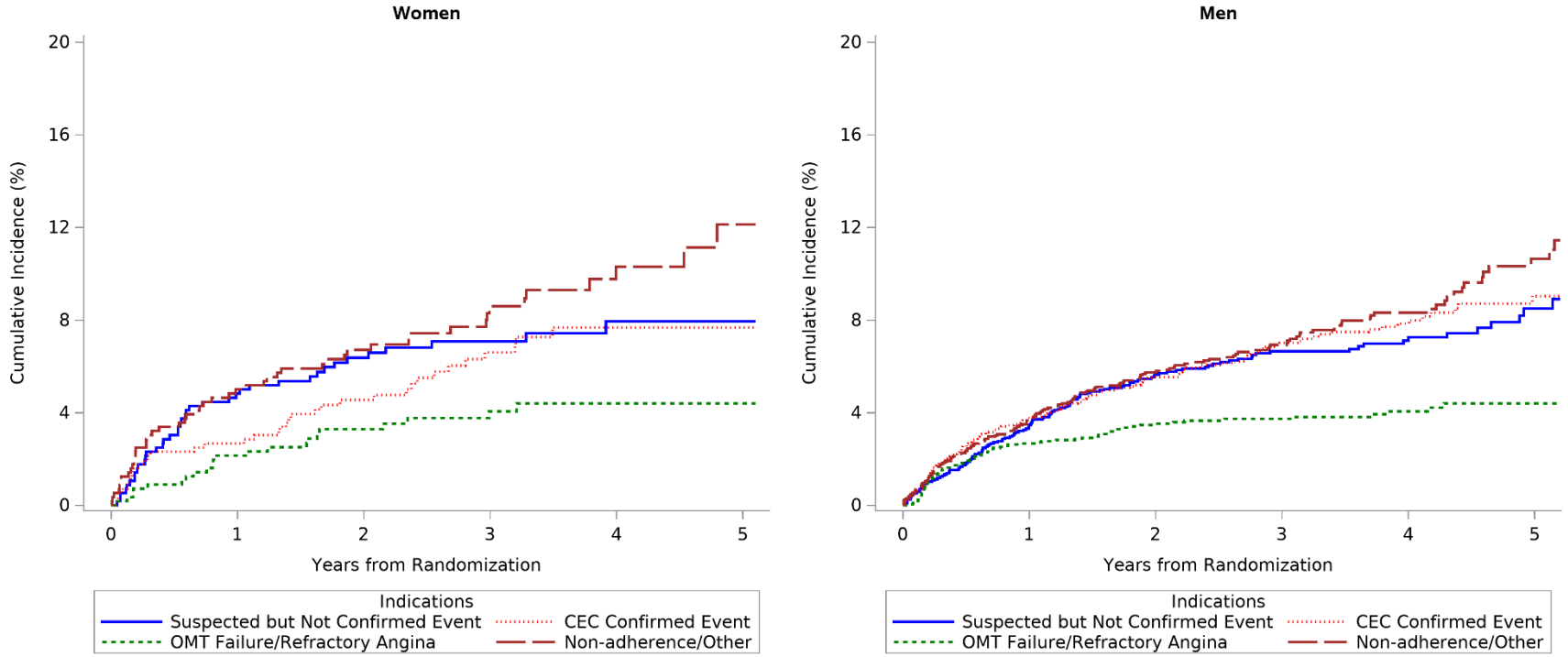
Table S6. Estimated Treatment Hazard Ratios (INV vs. CON) by Sex for Clinical Outcomes.

Event	Women Adjusted HR (95% CI)*	Men Adjusted HR (95% CI)*	Interaction P-value
Cardiovascular Death, MI, Hospitalization for Unstable Angina or Heart Failure, Resuscitated Cardiac Arrest	1.05 (0.76, 1.45)	0.89 (0.75, 1.06)	0.378
Cardiovascular Death or MI	0.93 (0.66, 1.31)	0.89 (0.74, 1.07)	0.819
All-cause Death	1.29 (0.82, 2.03)	0.98 (0.75, 1.28)	0.313
Cardiovascular Death	1.11 (0.66, 1.85)	0.79 (0.57, 1.10)	0.278
MI	0.93 (0.61, 1.40)	0.92 (0.75, 1.13)	0.970
Non-procedural MI (Type 1, 2, 4b, 4c)	0.88 (0.56, 1.39)	0.61 (0.48, 0.79)	0.176
Procedural MI (Type 4a, 5)	2.53 (0.67, 9.55)	3.04 (1.85, 4.99)	0.801
Stroke	2.80 (1.09, 7.19)	0.93 (0.56, 1.54)	0.044
Hospitalization for Heart Failure	2.46 (1.04, 5.78)	2.14 (1.20, 3.82)	0.794

*Hazard ratios compare INV vs. CON. Models are adjusted for age at randomization, diabetes, left ventricular ejection fraction, and eGFR. Continuous variables are modeled as restricted cubic splines with knots at the 10^{th}, 50^{th}, and 90^{th} percentiles of each variables empirical distribution. MI was defined according to the primary trial definition.

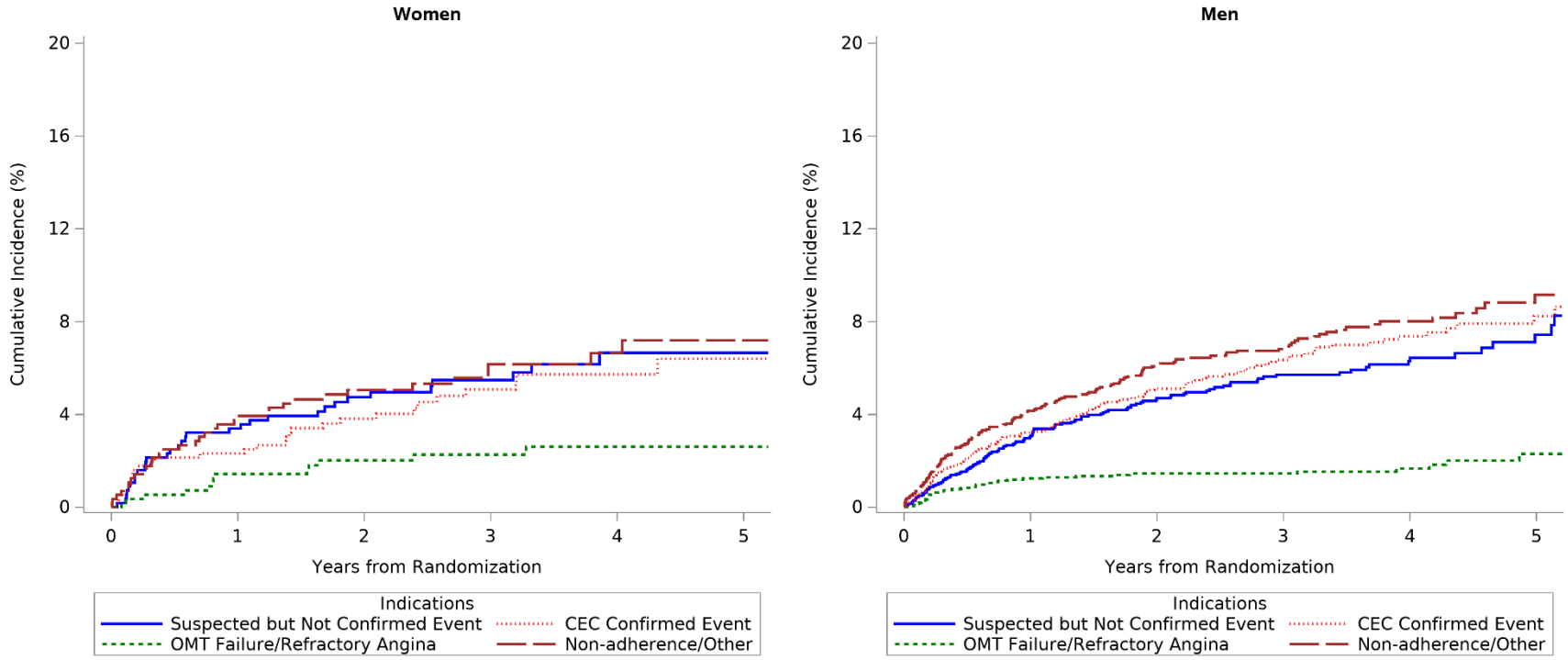
Abbreviations: INV = invasive group, CON = conservative group, HR = hazard ratio, CI = confidence interval, MI = myocardial infarction

Figure S1. Unadjusted Cumulative Incidence Plot of Catheterization for Participants Randomized to the CON Treatment Arm by Indication for Procedure.



CON = conservative group, CEC = clinical events adjudication committee, OMT = optimal medical therapy

Figure S2. Unadjusted Cumulative Incidence Plot of Revascularization for Participants Randomized to the CON Treatment Arm by Indication for Procedure.



CON = conservative group, CEC = clinical events adjudication committee, OMT = optimal medical therapy