Appendix : Myocardial Infarction Ascertainment and Definition

The BARI 2D protocol required that each patient have a 12-lead ECG at baseline, before the initial revascularization procedure, post procedure generally before hospital discharge, 3 months after randomization, and annually thereafter. Additional ECGs were required in patients who underwent subsequent coronary revascularization procedures (before and after the procedure) and in cases of suspected ischemic events.

All ECGs were interpreted at the Saint Louis University Central ECG and Myocardial Infarction Classification Laboratory. With the use of the Minnesota code criteria, each ECG was coded independently by trained central laboratory staff blinded to the patient's clinical history and treatment assignment. Serial comparison of sequential tracings was performed with the use of a modified Novacode system to identify patients with new ECG changes in the Minnesota Code[36, 37]. The modified Novacode adjusts for nonsignificant Minnesota Code Q-wave changes that result from minimal biological or technical procedural variations in the QRS waveform.

Acute coronary syndrome events requiring hospitalization were classified as Q-wave MI, non–Q-wave MI, unstable angina with new ECG changes, or none of the above. The MI criteria used were modified from the universal MI definition in that a two fold elevation of abnormal biomarker profile above the upper limits of normal was used rather than the 99th percentile. This modification enhances specificity but reduces sensitivity. When cardiac troponin and CKMB were simultaneously acquired, cardiac troponin took precedence over CKMB in establishing the diagnosis. Myocardial infarction was confirmed if abnormal cardiac biomarkers occurred and there was evidence of angina or angina equivalent symptoms, or ECG or imaging evidence of new myocardial ischemia. Cardiac biomarkers were not routinely collected after coronary revascularization. When

they were collected, a 3 fold elevation in CKMB following a PCI procedure and a 10 fold increase in CKMB following coronary bypass surgery were used as the cut-points to define abnormality.

Q-wave MI required the development of new pathologic Q waves as defined above or the new occurrence of a left bundle branch block in addition to abnormal biomarkers. Silent Q-wave MI was recorded when new pathologic Q waves were detected during a regularly scheduled follow-up ECG and were counted as a new Q wave MI, as were the presence of new pathologic Q waves following a coronary revascularization procedure. A non Q-wave MI met the MI criteria minus new pathologic Q waves. Unstable angina was defined by the presence of angina or angina equivalent symptoms accompanied by hospitalization and new ECG changes.

Table 1 Appendix: Baseline Characteristics of BARI 2D Patients by Randomized Treatment Groups and Intended Method of Revascularization Strata

		Randomized Treatment Groups				Revascularization Strata	
Characteristic	BARI 2D Patients N=2368	Prompt Revasc N=1176	Intensive Medical N=1192	Insulin Sensitization N=1183	Insulin Provision N=1185	PCI Intended Stratum N=1605	CABG Intended Stratum N=763
Age at study entry, mean, SD	62.4, 8.9	62.3, 8.8	62.4, 9.0	62.3 9.2	62.5, 8.7	62.0, 9.1	63.2, 8.4,
Male, %	70.4	70.4	70.3	70.1	70.6	67.8	75.8
Race/Ethnicity, %							
White non-Hispanic	65.9	65.1	66.6	66.0	65.7	63.6	70.6
Black non-Hispanic	16.8	17.3	16.3	16.7	17.0	19.8	10.5
Hispanic	12.5	12.8	12.3	12.1	13.0	11.7	14.3
Asian non-Hispanic / Other	4.8	4.8	4.8	5.2	4.3	4.9	4.6
Region of world, %							
USA	63.3	63.2	63.4	63.1	63.5	73.7	41.4
Canada	14.9	14.9	14.9	15.0	14.9	13.6	17.6
Brazil	15.0	15.1	14.9	15.0	15.0	7.9	30.0
Mexico	3.6	3.6	3.6	3.6	3.6	2.1	6.8
Czech Republic/Austria	3.2	3.2	3.1	3.3	3.0	2.7	4.2
HbA1c, % mean, SD	7.7, 1.6	7.6,1.6	7.7,1.6	7.6,1.6	7.7, 1.6	7.6, 1.6	7.7, 1.7
Duration of diabetes, years mean, SD	10.4, 8.7	10.2,8.5	10.7,8.8	10.1, 8.4	10.8, 8.9	10.4, 8.8	10.5, 8.4
Currently taking insulin, %	27.9	27.1	28.7	27.4	28.3	30.5	22.4
History of myocardial infarction, %	32.0	31.7	32.4	32.6	31.5	30.1	36.0
History of congestive heart failure, %	6.6	7.1	6.2	6.7	6.6	7.7	4.5
Cerebrovascular accident TIA, %	9.8	9.5	10.0	9.9	9.6	10.5	8.2
Peripheral artery disease, %	23.7	23.7	23.7	23.9	23.5	23.9	23.5
Angina category (within 6 weeks),%*							
Stable Angina 1, 2	42.5	40.8	44.2	42.8	42.3	41.3	45.0
Stable Angina 3, 4	8.6	10.2	7.1	8.6	8.6	7.9	10.1
Unstable Angina	9.5	11.3	7.7	9.7	9.4	10.7	7.0
Angina equivalents and no angina	21.4	21.5	21.3	20.8	22.0	22.3	19.6
No angina nor angina equivalents	17.9	16.1	19.7	18.1	17.8	17.7	18.4
Prior revascularization, %	23.6	22.9	24.2	23.1	24.1	28.6	13.0
Triple Vessel Disease, %	30.7	31.0	30.4	30.7	30.7	20.3	52.4
Proximal LAD Disease, %	13.2	13.2	13.3	12.1	14.4	10.3	19.4
LV Ejection Fraction < 50%, %	17.5	17.4	17.5	18.4	16.6	17.5	17.5

* Angina category comparison between Prompt Revasc / Intense Medical group, p=0.0003

Table 2 Appendix: Event Counts and Percent of Patients with Events by Randomized Treatment and Intended Revascularization Strata

	Prompt Revasc	Intensive Medical	Insulin Sensitization	Insulin Provision	Rev-IS	Med-IS	Rev-IP	Med-IP
All Patients	N=1176	N=1192	N=1183	N=1185	N=584	N=599	N=592	N=593
Death	155(13.2%)	161(13.5%)	156(13.2%)	160(13.5%)	75(12.8%)	81(13.5%)	80(13.5%)	80(13.5%)
MI	118(10.0%)	138(11.6%)	118(10.0%)	138(11.7%)	51(8.7%)	67(11.2%)	67(11.3%)	71(12.0%)
Stroke	30 (2.6%)	33 (2.8%)	27(2.3%)	36 (3.0%)	13(2.2%)	14(2.3%)	17(2.9%)	19(3.2%)
Death/MI/Stroke	266(22.6%)	283(23.7%)	261(22.1%)	288(24.3%)	121(20.7%)	140(23.4%)	145(24.5%)	143(24.1%)
PCI Stratum	N=798	N=807	N=804	N=801	N=396	N=408	N=402	N=399
Death	102(12.8%)	96(11.9%)	101(12.6%)	97(12.1%)	49(12.4%)	48(11.8%)	53(13.2%)	48(12.0%)
MI	90(11.3%)	82(10.2%)	81 (10.1%)	91(11.4%)	42(10.6%)	39(9.6%)	48(11.9%)	43(10.8%)
Stroke	23(2.9%)	23(2.9%)	19(2.4%)	27 (3.4%)	9 (2.3%)	10(2.5%)	14(3.5%)	13(3.3%)
Death/MI/Stroke	187(23.4%)	168(20.8%)	169(21.0%)	186(23.2%)	88(22.2%)	81(19.9%)	99(24.6%)	87(21.8%)
CABG Stratum	N=378	N=385	N=379	N=384	N=188	N=191	N=190	N=194
Death	53(14.0%)	65(16.9%)	59(15.6%)	59(15.4%)	26(13.8%)	33(17.3%)	27(14.2%)	32(16.5%)
MI	28(7.4%)	56(14.6%)	37(9.8%)	47(12.2%)	9(4.8%)	28(14.7%)	19(10.0%)	28(14.4%)
Stroke	7(1.9%)	10(2.6%)	8(2.1%)	9(2.3%)	4(2.1%)	4(2.1%)	3(1.6%)	6(3.1%)
Death/MI/Stroke	79(20.9%)	115(29.9%)	92(24.3%)	102(26.6%)	33(17.6%)	59(30.9%)	46(24.2%)	56(28.9%)

Appendix S Figure Legends

Figure S1:

The Consort chart depicting the number of patients randomly assigned to each of the four mutually exclusive treatment groups. For the 3 year and the 5 year follow-up clinic visit, patients are categorized as having completed the appropriate visit or according to the reason that the visit was not completed.

Figure S2:

The estimated percent of patients who underwent revascularization in the prompt revascularization (Panel A solid line) and the intensive medical (Panel A dashed line) randomized treatment groups over five years of follow-up. The percent of active patients receiving any IS drug (blue bars) and any IP drug (red bars) at the baseline, 1, 3, and 5 year visits for the Insulin Sensitization (Panel B) and the Insulin Provision (Panel C) randomized treatment groups. For each group and time, the mean HbA1c is presented below the bars.

Figure S1 Appendix

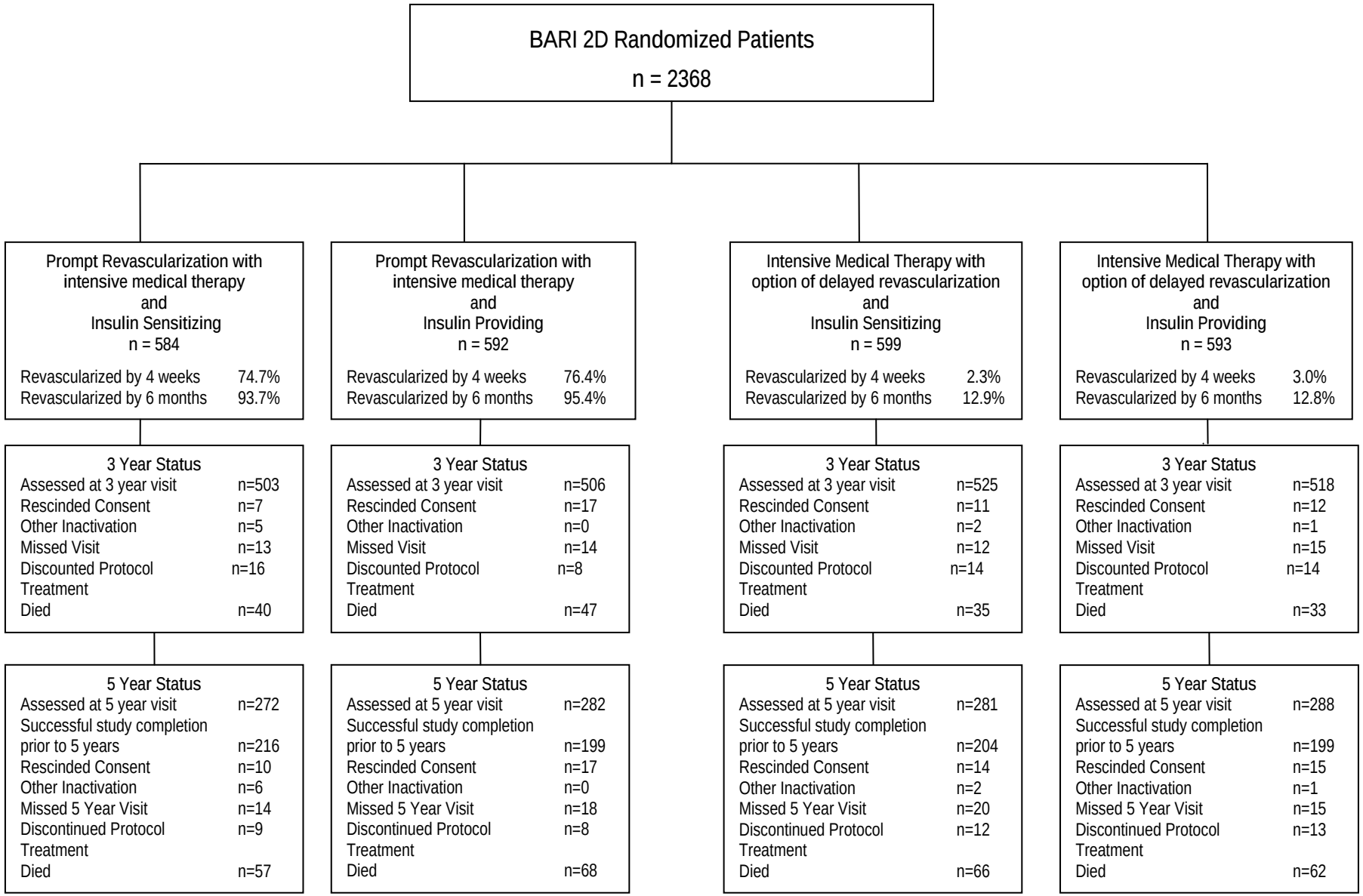
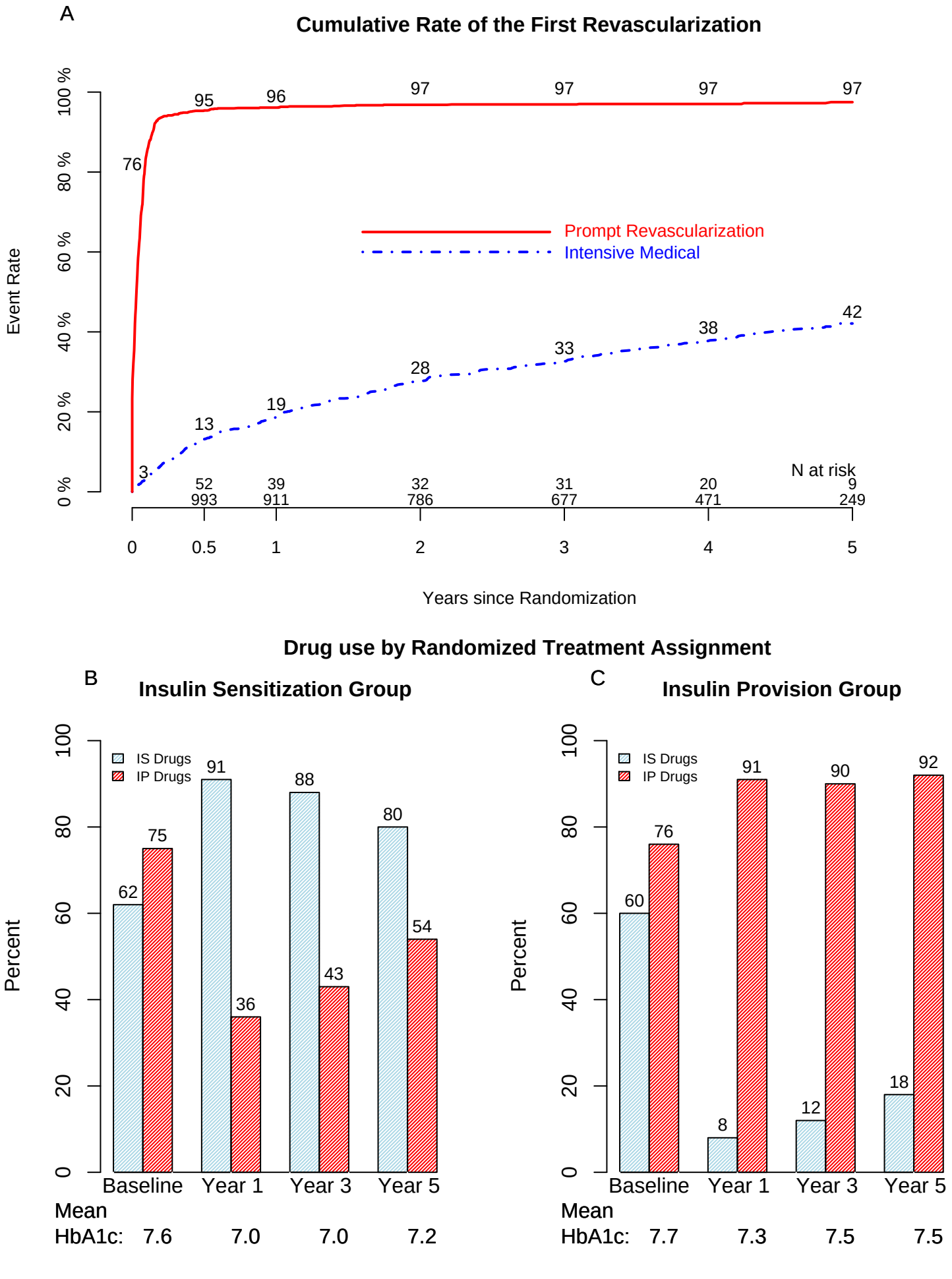


Figure 2 Appendix



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Gabriel Habib, MD, MS; Diabetology: Marco Marcelli, MD *(Investigators)* Issam Mikati, MD *(Coordinators)* Emilia Cordero, NP, Gina Caldwell, LVN ***New York Hospital Queens /Lang Research Center, Queens, NY (Clinical Site):*** *(Principal Investigators)* Cardiology: David Schechter, MD; Diabetology: Daniel Lorber, MD; Nephrology: Phyllis August, MD, MPH *(Coordinators)* Maisie Brown, RN, MSN, Patricia Depree, PhD, ANP, CDE ***Wilhelminen Hospital, Vienna, Austria (Clinical Site):*** *(Principal Investigators)* Cardiology: Kurt Huber, MD; Diabetology: Ursula Hanusch-Enserer, MD *(Investigators)* Nelly Jordanova, MD *(Coordinators)* Dilek Cilesiz, MD, Birgit Vogel, MD ***St. Joseph Mercy Hospital/Michigan Heart and Vascular Institute and the Ann Arbor Endocrinology and Diabetes, P.C., Ann Arbor, MI (Clinical Site):*** *(Principal Investigators)* Cardiology: Ben McCallister Jr., MD; Diabetology: Michael Kleerekoper, MD, Kelly Mandagere, MD, Robert Urbanic, MD *(Investigators)* James Bengston, MD, MPH, Bobby K. Kong, MD, Andrew Pruitt, MD, Jeffrey Sanfield, MD *(Coordinators)* Carol Carulli, RN, Ruth Churley-Strom, MSN ***The Ohio State University Medical Center, Columbus, OH (Clinical Site):*** *(Principal Investigators)* Cardiology: Raymond Magorien, MD; Diabetology: Kwame Osei, MD (Coordinators) Cecilia Casey Boyer, RN, MS, CDE ***Mayo Clinic-Scottsdale, Scottsdale, AZ (Clinical Site):*** *(Principal Investigators)* Cardiology: Richard Lee, MD; Diabetology: Pasquale Palumbo, MD *(Coordinator)* Joyce Wisbey, RN ***Angiographic Core Laboratory, Stanford University, Stanford, CA:*** *(Principal Investigator)* Edwin Alderman, MD *(Staff)* Fumiaki Ikeno, MD, Anne Schwarzkopf† ***Biochemistry Core Laboratory, University of Minnesota, Minneapolis, MN:*** *(Principal Investigator)* Michael Steffes, MD, PhD *(Staff)* Maren Nowicki, CLS, Jean Bucksa, CLS ***ECG Core Laboratory, Saint Louis University, St. Louis, MO (U01 HL061746):*** *(Principal Investigator)* Bernard Chaitman, MD *(Staff)* Jane Eckstein, RN, Karen Stocke, BS, MBA ***Economics Core Laboratory, Stanford University, Stanford, CA (U01 HL061748):*** (Principal Investigator) Mark A. Hlatky, MD *(Staff)* Derek B.

Boothroyd, PhD, Kathryn A. Melsop, MS ***Fibrinolysis Core Laboratory, University of Vermont, Burlington, VT (U01 HL063804):*** *(Principal Investigator)* Burton E. Sobel, MD *(Staff)* Michaelanne Rowen, RN, CCRC, Dagnija Neimane, BS ***Nuclear Cardiology Core Laboratory, University of Alabama at Birmingham, Birmingham, AL (Astellas Pharma US, Inc.):*** *(Principal Investigator)* Ami E. Iskandrian, MD *(Staff)* Mary Beth Schaaf, RN, BSN ***Diabetes Management Center, Case Western Reserve University, Cleveland, OH:*** *(Director)* Saul Genuth, MD *(Staff)* Theresa Bongarno, BS, ***Hypertension Management Center, Lahey Clinic Medical Center, Burlington, MA:*** *(Co-Director)* Richard Nesto, MD ***Hypertension Management Center, New York Hospital Queens, Queens, NY:*** *(Co-Director)* Phyllis August, MD, MPH *(Staff)* Karen Hultberg, MS ***Lifestyle Intervention Management Center, Johns Hopkins Bayview Medical Center, Baltimore, MD:*** *(Co-Director)* Sheldon H. Gottlieb, MD ***Lifestyle Intervention Management Center, St. Luke's/Roosevelt Hospital Center, New York, NY:*** *(Co-Director)* Jeanine Albu, MD *(Staff)* Helene Rosenhouse-Romeo, RD, CDE ***Lipid Management Center, University of Pittsburgh, Pittsburgh, PA:*** *(Director)* Trevor J. Orchard, MBBCh, MMedSci *(Staff)* Georgia Pambianco, MPH, Manuel Lombardero, MS ***Safety Officer, North Canton, OH:*** Michael Mock, MD **Operations Committee:** *(Chair)* Robert L. Frye, MD*(Members)* Maria Mori Brooks, PhD, Patrice Desvigne-Nickens, MD, Abby Ershow, ScD, Saul Genuth, MD, Suzanne Goldberg, RN, MSN, David Gordon, MD, PhD, Regina Hardison, MS, Teresa L. Z. Jones, MD, Sheryl Kelsey, PhD, Richard Nesto, MD, Trevor Orchard, MBBCh, MMedSci, Dina Paltoo, PhD, MPH, Yves Rosenberg, MD, MPH **Morbidity and Mortality Classification Committee (MMCC):** *(Chair)* Thomas Ryan, MD *(Co-Chair)* Harold Lebovitz, MD *(Members)* Robert Brown, MD, Gottlieb Friesinger, MD, Edward Horton, MD, Jay Mason, MD, Renu Virmani, MD, Lawrence Wechsler, MD **Data and Safety Monitoring Board (DSMB):** *(Chair)* C. Noel Bairey-Merz, MD *(former Chair)* J. Ward Kennedy, MD† *(Executive Secretary)* David

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