Supplement Table 1. Definitions for Causes of Death

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3. Cause of Death: To record the primary cause of death. Record only one answer. Classify cause of death as one of the following:

3.1 Cardiac: Death originating from heart malfunction. Examples include cardiogenic shock, MI and primary cardiac arrest.

Cardiac cause of death: Specific definition provided below (check all that apply):

Sudden cardiac death (SCD): Death that occurs instantaneously or within 60 minutes after the onset of cardiac symptoms. Classification as sudden cardiac death will be made on the basis of time from onset of cardiac symptoms until death, regardless of subsequent pathologic findings. Patients who are resuscitated from cardiac arrest but die within 60 minutes after arrest will be classified as sudden death.

Probable sudden cardiac death: Death that is a consequence of SCD. For example, if the patient is resuscitated from SCD and survives 60 minutes or more, but does not recover function and dies. This would be classified as probable SCD. Also, an unwitnessed death where evidence clearly indicates SCD, could also be classified as probable SCD.

Definite myocardial infarction (MI): Death when the patient had an infarction with documentation that patient met the criteria for confirmed Q-wave or non-Q-wave MI.

Probable MI: Check if there was evidence highly suggestive of necrosis, but no physical documentation (no testing was performed or testing was incomplete).

Congestive heart failure: Verification by a physician's statement in the medical record is required. In general, CHF is clinically manifested by one or more features including: dyspnea on exertion (shortness of breath on exertion), bilateral pedal edema, fatigue, orthopnea (sleeping on two or more pillows to facilitate breathing), paroxysmal nocturnal dyspnea (shortness of breath that awakens the patient from sleep). Other findings supporting the clinical manifestations include but are not restricted to: presence of S3 gallop by auscultation, elevated jugular venous pressure >8 cm H_20 by physical exam or radiographic evidence of pulmonary congestion.

Cardiac procedure: Death within 30 days or within the same hospitalization of a cardiac procedure such as PCI, CABG, or diagnostic angiogram, when death can be reasonably attributed to the procedure (i.e. death would not have been likely to occur had the procedure not been performed).

Cardiogenic shock: Defined as a systolic blood pressure < 80 mmHg, which either persists for more than one hour or requires specific treatment for at least one hour. In general, shock is associated with a low urine output, decreased mental acuity or coma, and compensatory

vasoconstriction (decrease in blood vessel caliber). Hypotension without these associated manifestations of low cardiac output will NOT be considered shock.

Unwitnessed: Death which occurs more than 60 minutes after last observation of patient.

Other: A death for which there is evidence of a primary cardiac cause but has not been or cannot be classified as any of the above. Specify if this is the case.

3.2 Stroke: Stroke is defined as the rapid onset of persistent neurologic deficit attributed to an obstruction or rupture of the brain arterial system. The deficit is not known to be secondary to brain trauma, tumor, infection or other cause. The deficit must last more than 24 hours unless death supervenes or there is demonstrable lesion on CT or MRI compatible with an acute stroke.

Type of stroke (check one):

Cerebral infarction (CI): The acute onset (minutes to hours) of a focal neurological deficit persisting for longer than 24 hours, with or without CT or MRI documentation, and due to altered circulation to a limited region of the cerebral hemispheres, brainstem or cerebellum. CT or MRI will not show evidence of an intracerebral hemorrhage. Hemorrhagic infarction found on CT or MRI will be classified as infarction. Infarction of the retina, cochlea or labyrinth will be excluded.

Intracerebral hemorrhage (ICH): The acute onset of a focal neurological deficit associated with some or all of the following: headache, vomiting, altered level of consciousness, signs of meningeal irritation or blood stained cerebrospinal fluid. CT or MRI or autopsy will demonstrate a parenchymal hemorrhage. The rupture of either an arteriovenous malformation (AVM) or aneurysm resulting in a parenchymal hemorrhage which is noted associated with hemorrhage in the subarachnoid space will be classified as an ICH. Traumatic ICH will be excluded. ICH into an area of brain affected by another disease process such as tumor (primary or secondary) or encephalitis will be excluded.

Primary subarachnoid hemorrhage (SAH): The abrupt onset of headache, with or without altered consciousness, with signs of meningeal irritation. A focal neurological deficit may develop acutely or with a delay of hours or days after the other criteria were known to have been present. CT or MRI will show blood in the subarachnoid space. If performed, cerebrospinal fluid examination will show increased red blood cell count or xanthochromia. The imaging studies may show an intraparenchymal hemorrhage which occurred either at or after the onset of the primary subarachnoid hemorrhage. Parenchyma hemorrhage that extends into the subarachnoid space will be classified as an Intracerebral hemorrhage. SAH due to trauma will be excluded.

Indeterminant cerebrovascular event (stroke of uncertain type): Clinical evidence of a stroke but insufficient information to establish a pathologic diagnosis.

3.3 Non-cardiovascular – atherosclerotic disease other than stroke: Death related to atherosclerotic vascular disease other than stroke but clearly not to cardiac death. Examples include aneurysm and atherosclerotic renal failure.

3.4 **Non-cardiovascular – medical**: Death clearly not related to cardiac disease or atherosclerotic vascular disease, although heart disease may be present. This category includes neoplasm, liver disease and septic shock.

3.**5 Non-cardiovascular – related to surgery or procedure**: Patient died as a direct result of a complication occurring during or within 24 hours after an elective procedure. An example of such elective procedures would be surgery for hernia repair and GI bleeding post procedure.

3.6 Diabetes complication other than cardiovascular disease: Disease complication cause of death (check all that apply):

Hypoglycemia: (1.) Sudden death within 30 minutes of a known blood glucose < 40 mg/dL. (2.) Death resulting from MVA, drowning, fall, injury, accident within 30 minutes of a known blood glucose < 50 mg/dL.

Diabetic ketoacidosis (DKA): Death from metabolic cause within 24 hours of documented DKA defined by absolute insulin deficiency with hyperglycemia (glucose level >300 mg/dL) with increased lipolysis, increased ketone production (ketone levels positive at 1:4 dilution of serum or greater OR beta hydroxybutyrate > 2 mmol/L), and acidosis (pH<7.30 or HCO3 <15 mEq/L).

Hyperosmolar hyperglycemic nonketotic coma: Death within 48 or 72 hours of documented blood glucose >600 mg/dL and no other cause (e.g. MI, pancreatitis, sepsis, etc.)

Other: If diabetes cause of death is other than one of the above categories, specify cause of death.

Specify: Self-explanatory.

3.7 Diabetes-related renal failure: Death with BUN >100, serum creatinine >5.0, serum potassium >6.0, urine protein >300 mg/DL or on dialysis with nephropathy or biopsy proven glomerulosclerosis, or no evidence of renal disease other than diabetic nephropathy.

3.**8 Diabetes-related amputation**: Non-traumatic amputation required for gangrene, foot ulcer and intractable infection leading to death.

3.**9 Accident and trauma**: Refers to violent death due to accident, such as automobile accident, drowning, or gunshot wound.

3.**10 Suicide**: Patient deliberately brings about own death.

3.11 **<u>Unknown</u>**: If primary cause cannot be determined, record “unknown.”

Supplement Table 2. Five Year Kaplan-Meier Estimates for Non-Procedural MI Events, According to Type of Myocardial Infarction (Q-wave and non-Q-wave), and Cardiac Cath or Non-Procedural Myocardial Infarction, According to Initial Treatment Strategy, and According to PCI and CABG Stratum

		Non-Procedural MI			
		Documented			
5 year KM estimate (n)	N	Q-wave	Non-Q	All Non-procedural MI (includes Fatal)	Cardiac Death or Nonprocedural MI
All Patients	2368				
Prompt Coronary Revascularization	1176	2.5% (25)	5.5% (61)	8.8% (96)	13.4% (149)
Intensive Medical Therapy	1192	2.9% (32)	9.0% (92)	13.3% (138)	15.8% (167)
Nominal P-Value		0.41	0.017*	0.009*	0.40
PCI Stratum	1605				
Prompt Coronary Revascularization	798	2.3% (17)	6.6% (51)	9.4% (72)	13.3% (105)
Intensive Medical Therapy	807	2.6% (18)	8.0% (54)	11.4% (79)	13.2% (93)
Nominal P-Value		0.93	0.87	0.69	0.29
CABG Stratum	763				
Prompt Coronary Revascularization	378	3.0% (8)	2.9% (10)	7.6% (24)	13.7% (44)
Intensive Medical Therapy	385	3.6% (14)	11.2% (38)	17.1% (59)	21.4% (74)
Nominal P-Value		0.23	<0.001**	0.0001**	0.006*
Insulin Provision Therapy	1185	2.1% (22)	8.2% (89)	11.4% (122)	15.0% (164)
Insulin Sensitization Therapy	1183	3.3% (35)	6.3% (64)	10.7% (112)	14.2% (152)
Nominal P-value		0.08	0.03*	0.47	0.45

†Cause of Death determined by independent Mortality and Morbidity committee; ††Includes documented MI's from the Core ECG lab and/or Fatal MI's as determined by death classification

*significant at nominal level

** significant after Bonferroni adjustment for multiple tests done in the table

Supplement Table 3. Hazard Ratio of Death or Cardiac Death by Post Randomization Non-procedural MI Status

	Number of Deaths†		HR of Death† (95% CI)	Nominal p-value for equality between HR	Number of Cardiac Deaths†		HR of Cardiac Death* (95% CI)	Nominal p-value for equality between HR
	Rev	IMT	Rev/IMT		Rev	IMT	Rev/IMT	
All Patients (n = 2368)								
MI	30	45	0.96 (0.61- 1.53)	0.48	19	35	0.78 (0.44 –1.36)	0.013*
No MI	107	93	1.17 (0.89– 1.54)		52	27	1.96* (1.23 – 3.12)	
PCI Stratum (n = 1605)								
MI	19	26	0.66 (0.37 – 1.20)	0.04*	11	19	0.54 (0.26 – 1.15)	0.003*
No MI	72	54	1.37 (0.97 – 1.96)		33	14	2.41* (1.28- 4.50)	
CABG Stratum (n = 763)								
MI	11	19	2.1 (1.01– 4.52)	0.05	8	16	1.50 (0.63 – 3.54)	0.97
No MI	35	39	0.88 (0.56 – 1.39)		19	13	1.47 (0.72 – 2.97	
	IP	IS	IP/IS		IP	IS	IP/IS	
All Patients (n = 2368)								
MI	41	34	0.98 (0.62-1.55)	0.93	28	26	0.88 (0.52 – 1.51)	0.56
No MI	100	100	1.01 (0.76 – 1.33)		41	38	1.09 (0.70-1.69)	

†censored at last known MI follow-up
*significant at nominal level

CABG = coronary artery bypass grafting; IP/IS = insulin provision/insulin sensitization; MI = myocardial infarction; PCI = percutaneous coronary intervention; Rev/Med = revascularization/medicine