

SUPPLEMENTARY DATA

Supplementary Table 1. Adjudication definitions of mortality

Cause of death	Definition
<p>Cardiovascular</p> <p>Sudden cardiac death</p>	<p>This refers to death that occurs unexpectedly in a previously stable patient and will include the following deaths:</p> <ul style="list-style-type: none"> i. Witnessed and instantaneous without new or worsening symptoms and also in the absence of progressive circulatory failure, the latter lasting for 60 minutes or more. ii. Witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious. iii. Witnessed and attributed to an identified arrhythmia (e.g. captured on an ECG recording or witnessed on a monitor by either a medic or paramedic). iv. Patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including myocardial infarction, and who die within 24 hours or without gaining consciousness; similar patients who die during an attempted resuscitation. v. Unwitnessed death in the absence of pre-existing progressive circulatory failure or other causes of death (information regarding the patient’s clinical status within the week preceding death should be present or the “presumed CV death” classification should be used)
<p>Myocardial infarction death</p>	<p>Death occurring up to 7 days after a documented acute myocardial infarction (verified either by the diagnostic criteria outlined above for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus) and where there is no conclusive evidence of another cause of death.</p> <p>NOTE: If death occurs before biochemical confirmation of myocardial necrosis can be obtained, the CECC will adjudicate based on clinical presentation and ECG evidence. Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause (see definition for death due to other cardiovascular cause, below).</p>
<p>Congestive heart failure</p>	<p>Death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death:</p> <p>Any of the following:</p> <ul style="list-style-type: none"> i. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure. ii. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration.

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	<p>iii. Confinement to bed but only if this is due entirely to heart failure symptoms.</p> <p>iv. Pulmonary oedema sufficient to cause tachypnoea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.</p> <p>v. Cardiogenic shock (defined as hypotension resulting in failure to maintain normal renal or cerebral function for > 60 minutes prior to death) not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.</p> <p>This category will include sudden death occurring during an admission for worsening heart failure.</p>
Stroke	Death occurring within 30 days of a confirmed stroke
Other cardiovascular cause	Death must be due to a fully documented cardiovascular cause not included above (e.g. ruptured aortic aneurysm, pulmonary embolism, or cardiovascular intervention).
Presumed cardiovascular death	All deaths not attributed to the above categories of cardiovascular death and not attributed to a non-cardiovascular cause.
Death from unknown cause	A case will be classified as “unknown” if the circumstances of death are totally unknown and assessment of a cardiovascular or non-cardiovascular cause is not possible. All unknown deaths will be considered to be cardiovascular deaths.
Non-cardiovascular cause of death	A death will be considered non-cardiovascular only if an unequivocal and documented non-cardiovascular cause can be established. This category includes deaths related to non-cardiovascular procedures.

Supplementary Table 2. Baseline demographics by death status

Characteristic	Survivors (N=13587)	Cardiovascular Death (N=530)	Non-Cardiovascular Death (N=338)	Unknown Cause (N=216)	P-value
Demographics					
Age, years	65 (59, 71)	68 (62, 75)	70 (65, 76)	70 (62, 76)	<0.001
Female	4018 (29.6%)	140 (26.4%)	80 (23.7%)	59 (27.3%)	0.042
Race groups					<0.001
White	9221 (67.9%)	343 (64.7%)	252 (74.6%)	141 (65.3%)	
Black	423 (3.1%)	12 (2.3%)	6 (1.8%)	6 (2.8%)	
Asian	3058 (22.5%)	114 (21.5%)	47 (13.9%)	46 (21.3%)	
Other	885 (6.5%)	61 (11.5%)	33 (9.8%)	23 (10.6%)	
Not Hispanic or Latino	11944 (87.9%)	457 (86.2%)	285 (84.3%)	187 (86.6%)	0.143
Hispanic or Latino	1643 (12.1%)	73 (13.8%)	53 (15.7%)	29 (13.4%)	0.143
Region					<0.001
Latin America	1336 (9.8%)	68 (12.8%)	46 (13.6%)	21 (9.7%)	
Asia Pacific/Other	4267 (31.4%)	160 (30.2%)	76 (22.5%)	62 (28.7%)	
Western Europe	1938 (14.3%)	55 (10.4%)	61 (18.0%)	22 (10.2%)	
Eastern Europe	3638 (26.8%)	173 (32.6%)	80 (23.7%)	74 (34.3%)	
North America	2408 (17.7%)	74 (14.0%)	75 (22.2%)	37 (17.1%)	

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Characteristic	Survivors (N=13587)	Cardiovascular Death (N=530)	Non-Cardiovascular Death (N=338)	Unknown Cause (N=216)	P-value
Medical History and Baseline Labs					
Duration of diabetes, years	10.0 (5.0, 16.0)	11.0 (6.0, 17.0)	12.0 (6.0, 20.0)	11.0 (6.0, 18.5)	<0.001
Qualifying HbA1c %	7.2 (6.8, 7.6)	7.3 (6.8, 7.7)	7.2 (6.9, 7.6)	7.3 (6.8, 7.8)	0.140
Qualifying HbA1c (mmol/mol)	55 (51, 60)	56 (51, 61)	55 (52, 60)	56 (51, 61)	-
Baseline HbA1c %	7.2 (6.8, 7.7)	7.3 (6.8, 7.8)	7.2 (6.8, 7.7)	7.3 (6.8, 7.8)	0.024
Baseline HbA1c (mmol/mol)	55 (51, 61)	56 (51, 62)	55 (51, 61)	56 (51, 62)	-
Qualifying HbA1c categories					0.063
<7%	4453 (33.8%)	169 (32.4%)	105 (31.8%)	73 (34.3%)	
7–7.5%	4088 (31.0%)	138 (26.4%)	104 (31.5%)	56 (26.3%)	
≥7.5%	4626 (35.1%)	215 (41.2%)	121 (36.7%)	84 (39.4%)	
eGFR, mL/min/1.73 m ²	73.0 (60.0, 88.0)	65.0 (54.0, 83.0)	64.6 (53.0, 80.0)	65.0 (54.8, 82.0)	<0.001
Log of eGFR, mL/min/1.73 m ²	4.3 (4.1 4.5)	4.2 (4.0 4.4)	4.2 (4.0 4.4)	4.2 (4.0 4.4)	<0.001
Serum creatinine, mg/dL	0.98 (0.82, 1.13)	1.06 (0.88, 1.26)	1.06 (0.90, 1.30)	1.05 (0.85, 1.24)	<0.001
Log of creatinine, mg/dL	-0.02 (-0.20 0.12)	0.06 (-0.13 0.23)	0.06 (-0.11 0.26)	0.05 (-0.16 0.22)	<0.001
History of vascular disease	13515 (99.5%)	525 (99.1%)	336 (99.4%)	214 (99.1%)	0.319
History of CAD	10054 (74.0%)	406 (76.6%)	253 (74.9%)	150 (69.4%)	0.229
Cerebrovascular disease	3274 (24.1%)	161 (30.4%)	87 (25.7%)	66 (30.6%)	0.001
Peripheral artery disease	2219 (16.3%)	91 (17.2%)	77 (22.8%)	46 (21.3%)	0.003
Prior myocardial infarction	5739 (42.2%)	270 (50.9%)	149 (44.1%)	97 (44.9%)	<0.001
Prior CABG	3376 (24.8%)	147 (27.7%)	93 (27.5%)	48 (22.2%)	0.223
Prior congestive heart failure	2295 (16.9%)	187 (35.3%)	95 (28.1%)	66 (30.6%)	<0.001
History of hypertension	11675 (85.9%)	472 (89.1%)	307 (90.8%)	194 (89.8%)	0.005
NYHA classification at baseline					<0.001
I	477 (20.8%)	32 (17.1%)	18 (18.9%)	8 (12.1%)	
II	1159 (50.5%)	83 (44.4%)	41 (43.2%)	29 (43.9%)	
III	301 (13.1%)	37 (19.8%)	12 (12.6%)	10 (15.2%)	
IV	6 (0.3%)	3 (1.6%)	0 (0.0%)	4 (6.1%)	
Not available	352 (15.3%)	32 (17.1%)	24 (25.3%)	15 (22.7%)	
Systolic BP, mmHg	134 (124, 145)	132 (121, 147)	134 (125, 147)	135 (123, 145)	0.947
Diastolic BP, mmHg	79 (70, 84)	79 (70, 84)	75 (68, 82)	78 (70, 85)	<0.001
Baseline weight, kg	83 (72, 97)	82 (69, 96)	83 (70, 94)	78 (66, 93)	0.001
Baseline BMI, kg/m ²	29.6 (26.3, 33.3)	29.0 (25.5, 33.2)	29.0 (25.8, 32.8)	28.4 (25.8, 32.5)	<0.001
Smoking history					0.047
Never	6634 (48.8%)	269 (50.8%)	136 (40.2%)	110 (50.9%)	
Current	1550 (11.4%)	65 (12.3%)	42 (12.4%)	21 (9.7%)	
Former	5403 (39.8%)	196 (37.0%)	160 (47.3%)	85 (39.4%)	
Antihyperglycemic Therapies					
Metformin	11174 (82.2%)	408 (77.0%)	234 (69.2%)	150 (69.4%)	<0.001
Sulfonylurea	6125 (45.1%)	268 (50.6%)	147 (43.5%)	105 (48.6%)	0.055
Pioglitazone/thiazolidinedione	370 (2.7%)	11 (2.1%)	8 (2.4%)	7 (3.2%)	0.753
Insulin	3106 (22.9%)	132 (24.9%)	111 (32.8%)	59 (27.3%)	<0.001
Cardiovascular Medications					
Statins	10914 (80.3%)	395 (74.5%)	259 (76.6%)	151 (69.9%)	<0.001
Aspirin	10736 (79.0%)	375 (70.8%)	249 (73.7%)	158 (73.1%)	<0.001
ACE inhibitors/angiotensin receptor blockers	10694 (78.7%)	429 (80.9%)	265 (78.4%)	167 (77.3%)	0.052
Beta blockers	8613 (63.4%)	356 (67.2%)	213 (63.0%)	140 (64.8%)	0.343
Diuretics	5445 (40.1%)	310 (58.5%)	151 (44.7%)	114 (52.8%)	<0.001

Data are median (IQR) or n (%). CABG coronary artery bypass graft surgery; CAD coronary artery disease; NYHA New York Heart Association; BP blood pressure; eGFR estimated glomerular filtration rate; ACE angiotensin-converting enzyme.

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Supplementary Table 3. Multivariable risk factors associated with cause-specific mortality (Cox proportional hazards model, multivariate analysis)

Risk factor	HR with 95% CI	P-value
Sudden death		
eGFR per log ₁₀ (mL/min/1.73 m ²) higher	0.33 (0.18-0.58)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.40 (0.22-0.74)	0.0036
NYHA II vs. NYHA I	0.93 (0.46-1.88)	0.8338
NYHA III vs NYHA I	1.42 (0.59-3.45)	0.4321
NYHA IV vs. NYHA I	5.43 (1.16-25.5)	0.0318
History of PCI	0.61 (0.43-0.87)	0.0066
Female vs. male	0.65 (0.44-0.95)	0.0265
HbA _{1c} (%), per 1% increase	1.41 (1.02-1.96)	0.0389
Heart failure death		
Age, per 5-year increase	1.39 (1.17-1.64)	<0.0001
Prior MI	2.28 (1.33-3.89)	0.0027
Asymptomatic (no CHF) vs. NYHA I	0.29 (0.12-0.70)	0.0057
NYHA II vs. NYHA I	0.85 (0.31-2.34)	0.7505
NYHA III vs NYHA I	1.50 (0.51-4.45)	0.4612
NYHA IV vs. NYHA I	5.88 (0.68-50.62)	0.1070
eGFR per log ₁₀ (mL/min/1.73 m ²) higher	0.33 (0.13-0.80)	0.0142
Systolic BP ≤ 135, per 5-mmHg increase	0.87 (0.77-0.98)	0.0211
Acute MI or stroke death		
Age, per 5-year increase	1.26 (1.12-1.43)	0.0002
History of cerebrovascular disease	1.80 (1.23-2.63)	0.0025
Systolic BP > 135, per 5-mmHg increase	1.11 (1.07-1.43)	0.004
Asymptomatic (no CHF) vs. NYHA I	0.47 (0.22-1.00)	0.0486
NYHA II vs. NYHA I	0.96 (0.40-2.31)	0.9287
NYHA III vs NYHA I	2.19 (0.86-5.58)	0.0989
NYHA IV vs. NYHA I	Not estimable	Not est.
Presumed or other cardiovascular deaths		
Age, per 5-year increase	1.15 (1.06-1.26)	0.0011
History of PCI	0.66 (0.49-0.91)	0.0102
History of cerebrovascular disease	1.35 (1.00-1.82)	0.0502
Unknown causes of death		
Age, per 5-year increase	1.28 (1.17-1.40)	<0.0001
NYHA IV vs. NYHA I	16.48 (4.64-58.5)	<0.0001
NYHA III vs NYHA I	1.94 (0.78-4.84)	0.1556
NYHA II vs. NYHA I	1.57 (0.74-3.35)	0.2413
Asymptomatic (no CHF) vs. NYHA I	0.71 (0.36-1.39)	0.3158
Weight ≤ 90kg, per 5-kg increase	0.87 (0.82-0.93)	<0.0001
Female vs. male	0.64 (0.47-0.89)	0.0071
eGFR per log ₁₀ (mL/min/1.73 m ²) higher	0.55 (0.34-0.91)	0.0192

MI myocardial infarction; CHF congestive heart failure; NYHA New York Heart Association; eGFR estimated glomerular filtration rate; PCI percutaneous coronary intervention; BP blood pressure. Other variables in the heart failure death model include: Systolic BP > 135, per 5-mmHg increase (HR 0.99; 95% CI 0.86-1.13; p=0.85). Other variables in the acute MI/stroke death model include: Log of eGFR (mL/min/1.73 m²) (HR 0.53; 95% CI 0.27-1.03; p=0.059); Systolic BP ≤ 135, per 5-mmHg increase (HR 0.94; 95% CI 0.71-1.10; p=0.28). Other variables in the unknown causes of death model include Weight > 90 kg, per 5-kg increase (HR 1.01; 95% CI 0.86-1.19; p=0.88)

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Supplementary Table 4. Sensitivity analysis of risk factors associated with cardiovascular death including unknown deaths

Risk factor	HR (95% CI)	P-Value
Age, per 5-year increase	1.24 (1.18-1.30)	<0.0001
History of cerebrovascular disease	1.28 (1.09-1.52)	0.0033
Prior myocardial infarction	1.37 (1.17-1.60)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.60 (0.44-0.83)	0.0021
NYHA II vs. NYHA I	1.20 (0.83-1.72)	0.3372
NYHA III vs NYHA I	1.59 (1.03-2.44)	0.0356
NYHA IV vs. NYHA I	5.46 (2.32-12.9)	0.0001
History of PCI	0.65 (0.55-0.76)	<0.0001
White vs. other race	0.53 (0.38-0.76)	0.0004
Black vs. other race	0.70 (0.40-1.21)	0.2039
Asian vs. other race	0.74 (0.49-1.13)	0.1662
Latin America vs. North America	1.22 (0.85-1.74)	0.2872
Asia Pacific/Other vs. North America	1.25 (0.93-1.67)	0.1447
Western Europe vs. North America	1.06 (0.78-1.44)	0.7069
Eastern Europe vs. North America	1.61 (1.24-2.09)	0.0003
Female vs male	0.69 (0.58-0.82)	<0.0001
eGFR per log ₁₀ (mL/min/1.73 m ²) higher	0.50 (0.38-0.65)	<0.0001
qHbA _{1c} (%), per 1% increase	1.28 (1.10-1.49)	0.0013
Systolic BP ≤ 135, per 5-mmHg increase	0.93 (0.89-0.97)	0.0004
Systolic BP > 135, per 5-mmHg increase	1.03 (0.99-1.06)	0.1387

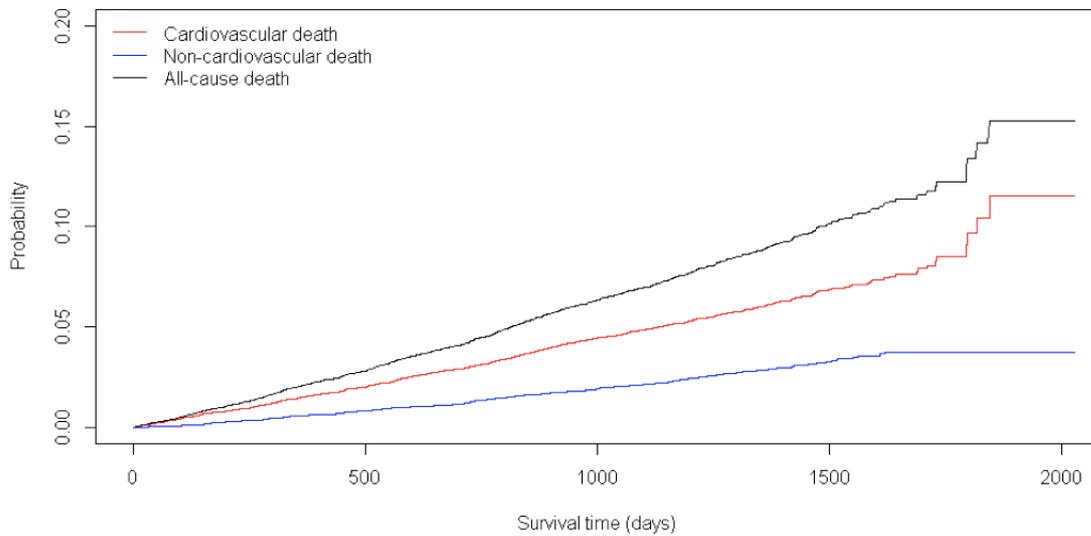
Supplementary Table 5. Fine–Gray Model for cardiovascular death (competing risk adjusted for non-CV and unknown death)

Risk factor	SHR* (95% CI)	P-Value
Age, per 5-year increase	1.17 (1.10-1.25)	<0.0001
History of cerebrovascular disease	1.29 (1.06-1.58)	0.0122
Prior myocardial infarction	1.45 (1.20-1.75)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.54 (0.37-0.78)	0.0010
NYHA II vs. NYHA I	1.14 (0.76-1.71)	0.5147
NYHA III vs NYHA I	1.61 (1.01-2.58)	0.0467
NYHA IV vs. NYHA I	2.96 (0.90-9.75)	0.0747
History of PCI	0.63 (0.52-0.77)	<0.0001
Latin America vs. North America	1.65 (1.16-2.37)	0.0060
Asia Pacific/Other vs. North America	1.32 (0.98-1.79)	0.0696
Western Europe vs. North America	1.02 (0.72-1.46)	0.8939
Eastern Europe vs. North America	1.49 (1.10-2.03)	0.0103
Female vs. male	0.63 (0.51-0.78)	<0.0001
eGFR per log ₁₀ (mL/min/1.73 m ²) higher	0.49 (0.35-0.69)	<0.0001
qHbA _{1c} (%), per 1% increase	1.28 (1.07-1.53)	0.0076
Systolic BP ≤ 135, per 5-mmHg increase	0.93 (0.88-0.97)	0.0028
Systolic BP > 135, per 5-mmHg increase	1.04 (1.00-1.08)	0.0502
Baseline weight ≤ 90 kg, per 5-kg increase	0.92 (0.87-0.96)	0.0007
Baseline weight > 90 kg, per 5-kg increase	1.04 (0.99-1.08)	0.1103

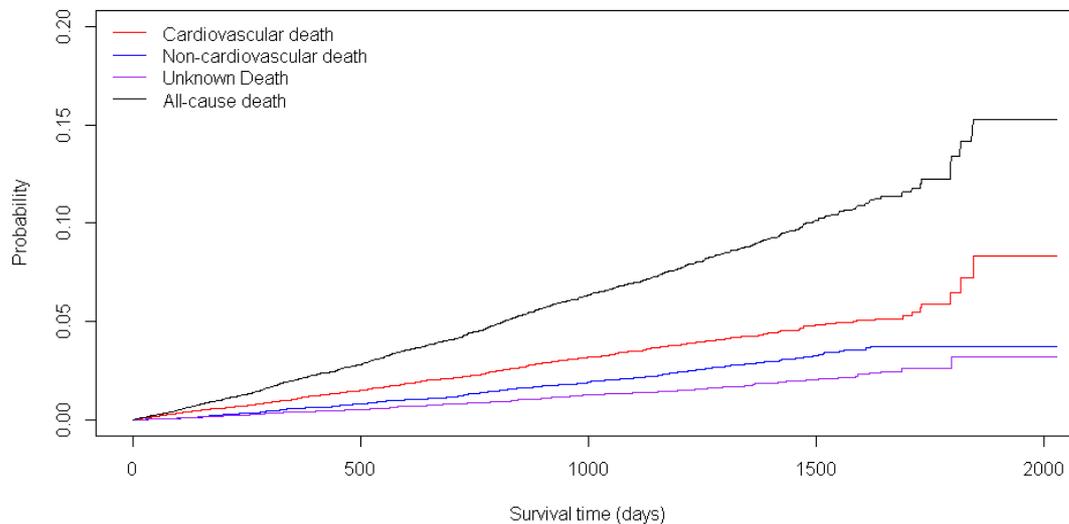
*Sub-distribution hazard ratio.

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Supplementary Figure 1. Cumulative incidence of all-cause, cardiovascular and non-cardiovascular mortality (cardiovascular death includes unknown causes of death)



Supplementary Figure 2. Cumulative incidence of all-cause, cardiovascular, non-cardiovascular, and unknown mortality



The first table below lists the baseline covariates that were used in the stepwise selection as possible risk factors for each endpoint analysis. Bolded are covariates with missing data. The PROC MI model specifications and Fully Conditional Specification method that were utilized are described. The final table reflects the unique missing data patterns from our dataset for the covariates used in the endpoint analyses; this provides the missing data pattern as well as its frequency within the dataset.

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Characteristic	All Patients (N=14671)
Demographics	
Age, median (25th percentile, 75th percentile), n	65 (60, 71), 14351
Female	4297/14671 (29%)
Race Groups	
White	9957/14671 (68%)
Black	447/14671 (3%)
Asian	3265/14671 (22%)
Other	1002/14671 (7%)
Not Hispanic or Latino	12873/14671 (88%)
Hispanic or Latino	1798/14671 (12%)
Region Groups	
Latin America	1471/14671 (10%)
Asia Pacific/Other	4565/14671 (31%)
Western Europe	2076/14671 (14%)
Eastern Europe	3965/14671 (27%)
North America	2594/14671 (18%)
Medical History and Baseline Labs	
Duration of Diabetes in yrs, median (25th percentile, 75th percentile), n	10.0 (5.0, 16.0), 14659
Baseline HbA1c (mmol/mol), median (25th percentile, 75th percentile), n	55 (51, 60), 14666
eGFR mL/min/1.73cm², median (25th percentile, 75th percentile), n	73.0 (60.0 88.0), 14528
Hemoglobin, median (25th percentile, 75th percentile), n	137.00 (127.00 147.00), 9623
Prior Cardiovascular Disease	10863/14671 (74%)
History of CAD	10863/14671 (74%)
Cerebrovascular Disease	3588/14671 (24%)
Peripheral Artery Disease	2433/14671 (17%)
Prior Myocardial Infarction	6255/14671 (43%)
Prior CABG	3664/14671 (25%)
Prior PCI	5714/14468 (39%)
Prior Congestive Heart Failure	2643/14671 (18%)
History of Hypertension	12648/14671 (86%)
NYHA Classification at Baseline	
I	535/2643 (20%)
II	1312/2643 (50%)
III	360/2643 (14%)
IV	13/2643 (0%)
Not Available	423/2643 (16%)
Systolic BP mmHg, median (25th percentile, 75th percentile), n	134 (124 145), 14629
Diastolic BP mmHg, median (25th percentile, 75th percentile), n	79 (70 84), 14629
Baseline Weight kg, median (25th percentile, 75th percentile), n	83 (71 96), 14599
Baseline BMI, median (25th percentile, 75th percentile), n	29.5 (26.3 33.3), 14534
Smoking History	
Never	7149/14671 (49%)
Current	1678/14671 (11%)
Former	5844/14671 (40%)

PROC MI Model Specifications

Data Set	WORK.FORIMP2
Method	FCS
Number of Imputations	25
Number of Burn-in Iterations	20
Seed for random number generator	16218

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FCS Model Specification

Method	Imputed Variables
Regression	qhba1c DIABDUR SBPBL DBPBL WGHTBL blgfr AGEIMP blhgb
Logistic Regression	PCIHXFN NYHAGR1N
Discriminant Function	female RACEGR1N REGGR1N hispanic MIHXFN CABHXFN SMOKGR1N CBVHXFN PADHXFN CHFHXFN

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Missing Data Patterns

Group	Covariates										Number of Cases
	HbA1c	Duration of Diabetes	Systolic BP	Diastolic BP	Weight	eGFR	History of PCI	Age	Hemoglobin	NYHA Classification	
1	X	X	X	X	X	X	X	X	X	.	2981
2	X	X	X	X	X	X	X	X	.	.	911
3	X	X	X	X	X	X	X	X	X	X	317
4	X	X	X	X	X	X	X	X	.	X	65
5	X	X	X	X	X	X	X	.	X	X	39
6	X	X	X	X	X	X	.	X	X	.	35
7	X	X	X	X	X	X	X	.	X	.	18
8	X	X	X	X	X	X	X	.	.	.	11
9	X	X	X	X	X	X	.	X	.	.	10
10	X	X	X	X	X	.	X	X	X	.	10
11	X	X	X	X	X	X	X	.	.	X	7
12	X	X	X	X	X	.	X	X	.	X	3
13	X	X	X	X	X	.	X	X	.	.	3
14	X	X	X	X	.	X	X	X	X	.	2
15	X	X	X	X	X	X	.	X	.	X	1
16	X	X	X	X	X	X	1
17	X	X	X	X	X	.	X	X	X	X	1
18	X	X	X	X	.	X	X	X	.	.	1
19	.	X	X	X	X	X	X	X	X	.	1